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EMJ

Science Versus COVID-19: What Have We Learnt So Far?

Editor's Pick

Thromboembolic Storm in the Recovering Stage of COVID-19: A Case Report

Interview

David Oliver

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"this 2-year mark since COVID-19 broke out on a global level is an excellent opportunity for looking back and marvelling at how far the world has come in tackling this disease."

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Aims and Scope

EMJ is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

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EMJ Welcome letter

Dear Readers,

Welcome to the first flagship issue of *EMJ* for 2022, which has a mini-focus on COVID-19. With infection rates and COVID-19-related deaths showing declining trends across Europe, it appears that we have reached a new, more controlled phase in the pandemic and have learnt a number of lessons.

While the toll on public health has been immense and the aftermath of the pandemic is yet to be fully understood, this 2-year mark since COVID-19 broke out on a global level is an excellent opportunity for looking back and marvelling at how far the world has come in tackling this disease. To this end, *EMJ* presents an article outlining the key scientific advances since the start of the pandemic. Alongside this is an interview by David Oliver touching on the effect of COVID-19 on elderly populations, as well as a series of interesting COVID-19 case reports. Our journal also features a number of articles of interest to different specialists, with topics ranging from prediabetes, T cell therapies, and Paget disease, to antidrug antibodies in patients with inflammatory bowel disease.

It would, of course, be a great omission if we failed to acknowledge the war in Ukraine and the ongoing situation faced by people in the country. *EMJ* is hosting a feature by European Organisation for Rare Diseases (EURORDIS), which outlines the challenges faced by patients with rare diseases in Ukraine and proposes actions to manage the situation. We hope that this feature will help raise awareness among healthcare professionals, and that these actions will facilitate healthcare delivery to this population.

Once again, I would like to thank the people who have helped bring this issue to fruition, both within EMJ and externally. I do hope you enjoy reading this issue, and we look forward to receiving your manuscripts for consideration.

Evgenia Koutsouki, PhD.

Editor

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Foreword

Dear Colleagues,

I am delighted to welcome you to the latest issue of *EMJ*, which hones in on the theme of COVID-19 and what we have learnt as a scientific community over 2 years of the pandemic from a range of therapeutic perspectives. A collection of compelling articles also features, sharing the latest insights across healthcare.

The Editor's Pick for this issue is a fascinating case report titled 'Thromboembolic Storm in the Recovering Stage of a COVID-19: A Case Report' by Jervis et al. This timely report covers a case of severe COVID-19 infection and subsequent development of adverse thromboembolic complications. The article explains the key symptoms of this rare presentation, as well as discusses the mechanisms behind the episode and opportunities for future research.

Delve into this issue for interesting articles on the topic of adverse manifestations during COVID-19 recovery. Alkindi et al. tackle a case of reactive hip arthritis and avascular necrosis following severe infection, stressing the advent of multisystem involvement and varied clinical presentations. Our feature article titled 'Science Versus COVID-19: What Have We Learnt So Far?' gives an in-depth understanding of the key lessons learnt as a scientific community following a 2-year feud with the pandemic. From the impact on epidemiology and public health, to the developments in treatment and prevention, this feature showcases the overwhelming response of healthcare as a whole to the unprecedented eruption of COVID-19.

The field of diabetes care is ever-developing and this issue of *EMJ* includes an insightful review by Francois and Oetsch that explores prediabetes and its associated challenges, delving into potential treatments and future directions. Mahmoud et al. present research on the phenomenon of clinical inertia in discharge planning in a retrospective study of patients with diabetes in a Libyan tertiary care hospital, highlighting how it challenges therapeutic success.

I would like to thank the authors, peer-reviewers, and researchers for their continued efforts and commitment in producing this journal as we share this excellent round-up of original and timely research.

Markus Peck-Radosavlijevic

Professor of Medicine, Chairman of the Department of Gastroenterology and Hepatology, Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria

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1. VerMilyea M, Hall JMM, Diakiw SM, et al. Hum Reprod. 2020;35(4):770-784.

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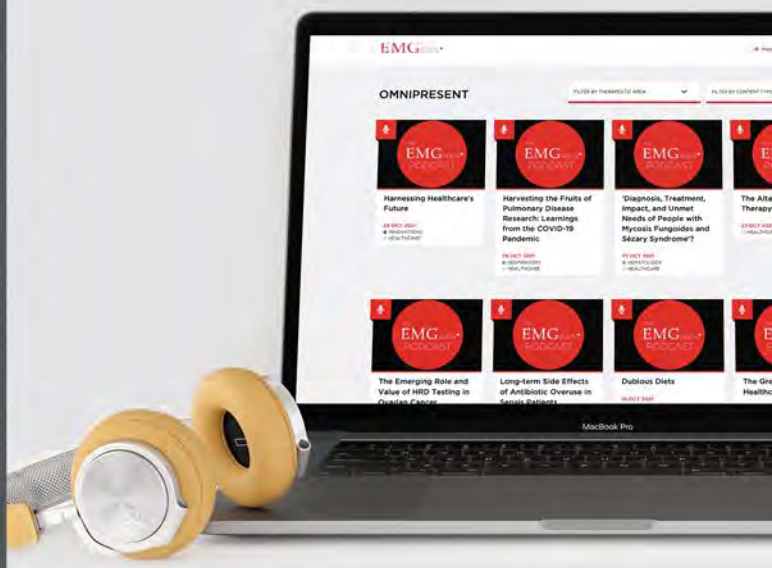

EMG HEALTH

Interview

David Oliver

NHS Consultant in Geriatrics and Acute General Medicine, Royal Berkshire NHS Foundation Trust, UK; Former President and Honorary Secretary, British Geriatrics Society; Former Clinical Vice-President, Royal College of Physicians; Former National Clinical Director for Older People (England), Department of Health; King's Fund Fellow; Nuffield Trust Trustee, London, UK; *British Medical Journal* columnist; and freelance medical writer

David Oliver shared his thoughts with EMJ on his leadership and policy experience, his passion for advocacy in healthcare, and his work in bedside geriatric and internal medicine care.

Q1

What initially motivated you to specialise in the field of geriatrics?

In my first Senior House Officer job working in emergency medicine, I realised that I was happiest working in adult internal medicine. When I became a medical Senior House Officer studying for my MRCP and rotating through different disciplines, I had my best training experience and role models in geriatric medicine, and so I chose higher speciality training and dual accreditation in geriatrics and general internal medicine. I like the fact that it combines a very solid grounding in adult internal medicine with advocacy and special interest for a somewhat previously neglected group of patients: those with frailty, multiple long-term conditions, and often a component of functional or cognitive impairment. It is also about working in multidisciplinary teams, across the interface of acute and community care systems, and is a very person-centred discipline with wonderful colleagues who are generally far more ego-free and collaborative than in some disciplines.

Geriatric Medicine was described by Rowan Harwood as "part acute medicine, part primary care, part rehab medicine, part old-age psychiatry, part social care, and part palliative medicine." We also provide much of the stroke care in the UK and have to be conversant with relevant ethical and legal issues. It is a very broad discipline with lots of subspecialities within it. But, like emergency medicine, general practice, and acute medicine, we are 'expert generalists'.

I also find older people endlessly fascinating, and enjoy trying to support their carers.

Q2

You regularly write articles on the topic of healthcare policies. How do you hope that patients' lives will be impacted through policies, as compared to guidelines, colleges, and societies, or healthcare services themselves?

Healthcare politics and policies have a very tangible impact on the working lives of doctors, other clinical staff, and services for patients. Of course, clinical guidelines, evidence-based medicine, and clinically-led quality improvement projects are important, but everything we do as practitioners in a system like the National Health Service (NHS), which is centrally funded and centrally accountable, is influenced for better or worse by health policy.

Policy decisions affect funding, workforce planning, capital spending on building and facilities, social care policy,

"We should not passively accept the conditions, but actively try to change and challenge them. The medical profession has a long history of doing just this, especially around public health."

immigration policy, public health, local government, socioeconomic inequalities, and wider determinants of health and healthcare access.

The Health Secretary and Number 10, the Department of Health and Social Care, national NHS leadership bodies, public health agencies, and regulators all exert a major influence over service delivery, as do their equivalents in devolved UK nations.

Doctors and nurses persistently top the league table of professions the public trust. The NHS is consistently the institution the British public say makes them most proud. I would say that a key part of medical professionalism, and a key role of medical colleges, unions, and specialty societies, is advocacy, lobbying, influencing, and communicating directly with the public in the media as credible voices.

We should not passively accept the conditions, but actively try to change and challenge them. The medical profession has a long history of doing just this, especially around public health.

There are also many doctors working within government or its agencies, or co-opted onto official advisory groups. During my time as National Clinical Director for Older People in the Department of Health, I learnt a great deal about how government works from the inside and is influenced from the outside. If you take on one of these roles, you do have to work with and within the system, but you can still influence policy considerably from inside. There are numerous examples of this in action, not least during the pandemic response.

Q3

How do you currently use social media platforms to educate, and what do you hope to achieve through doing this?

I have written a weekly column for the *British Medical Journal* (*BMJ*) since 2014. I also write for other specialist healthcare publications and a range of national newspapers and news sites. I have also blogged for the King's Fund, where I am a visiting fellow; for the Nuffield Trust, where I am a trustee; for the British Geriatrics Society (BGS); and Royal College of Physicians (RCP). I write professionally as a member of the Medical Journalists' Association, and make a modest second income from writing, but I also often write for free.

In terms of social media platforms, I am only on Twitter and have been for 8 years. I learn a great deal about healthcare, health policy, and medical practice from all the accounts I follow. For me, it is important to follow a diverse range of individuals and organisations within healthcare, health journalism, health policy, and health research.

I regularly share key articles, papers, and threads with my followers; some are my own,

but largely they are written by others. I think Twitter can be a great engagement forum for collective views, debate, and mutual education. It can also make experts, including doctors, more accessible and visible and able to engage with the public.

Clearly, Twitter can also become a fractious and polarised environment; I have fallen foul of that myself, and learnt from some mistakes. I would commend all doctors using the platform, or other social media, to look at the social media guidance set out by the British Medical Association (BMA), the General Medical Council (GMC), the medical defence organisations, or Royal Colleges. You shouldn't go far wrong if you adhere to the advice.

I would also encourage people to mute whole threads or individuals, or block them freely if anything is becoming abusive or personal; and not to amplify disinformation, misinformation, and conspiracy theories by engaging or sharing. Check the self-description and recent posts of anyone you follow back or engage with.

Q4

With a range of academic publications to your name, as well as your columns and blogs, what do you believe to be the current gaps in literature that merit greater attention?

That is a huge question, which I can't do full justice to here. But I think there are some key issues about the fairly near future of healthcare that merit attention. One is a greater focus on evidence from disciplines like health services research, improvement, or implementation science about real-world change that address questions conventional clinical trials cannot readily address. There should be greater focus on how we address workforce numbers, training, skills, and flexible roles; on the role of multidisciplinary teams and systems of care across organisational and professional boundaries; and the interface between ethical and legal issues and medical practice. There is also the growing role of technology, and its upsides and downsides, including artificial intelligence, telecare, and telehealth in medicine, and the growing importance of genome research and 'precision medicine'. There is scope for research on how we tackle wider determinants of health and healthcare inequalities, and preventable disease, as well as improving ageing, so that people live fewer of their later years in poor health or with inadequate support to live the best life they can.

I also feel we should aim to have the same strong empirical evidence base for nursing, social work, allied health professionals, and the role of multidisciplinary teams that we have for medical interventions.

Finally, whilst reams have already been written about COVID-19 and our response, I think there is still much learning to be set out about how we learn from the pandemic and prepare our systems for future ones.

Q5

How has your involvement as a writer for numerous publications contributed to the increased awareness of geriatric healthcare?

Whether you are writing an academic paper, a literature review, a book chapter, or writing as a medical journalist or policy commentator, you have to make sure you have researched, referenced, attributed, and fact-checked any statements that go beyond personal opinion. Even opinions and debating points need to be backed by the evidence. You will very soon be challenged by critics if you can't back up your statements, and so the writing leads you to explore the literature and get better informed. You also learn when you are challenged or corrected.

I spent around a year of my non-clinical time writing a major King's Fund Paper, 'Making health and care systems fit for an ageing population', which was densely referenced, and I learnt a great deal in the process of writing. Delivering 48 *BMJ* columns each year for 7 years has been a similar learning experience.

Q6

What changes did you implement during your time as President of the British Geriatrics Society (BGS)? What role do societies and associations play in modern healthcare?

Leadership in any medical membership organisation is never down to one elected officer. We are only in the post for a short period and it is a team effort, building on strategy and priorities developed by others, and not possible without the employed staff and executives. You can put some of your own stamp on the role, though. For me, this was around expanding, increasing, and diversifying the membership, which already included most registrars and consultants in geriatric medicine, to have far more nurses, allied health professionals, including advanced care practitioners, and more doctors from other disciplines such as general practice, emergency medicine, and old-age psychiatry. This, in turn, livened

"I think Twitter can be a great engagement forum for collective views, debate, and mutual education. It can also make experts, including doctors, more accessible and visible, and able to engage with the public."

up our committees, conferences, and publications, and broadened our expertise. The new recruits have been among the most enthusiastic contributors to the society's work.

Also during my time, we helped professionalise and rebrand the communications and policy work, the website, publications, blog, and social media presence. Though the credit is far wider than my personal role, my background in policy, communications, and media work, and my interest in public engagement probably helped a little.

Q7

How do you feel that the field of geriatrics has been affected by the COVID-19 pandemic?

As a specialty, we have a major stake in healthcare for care home residents and in 'hospitals without walls' services to support people in care homes, their own homes, in community hospitals, with 'hospital at home' rapid response supported discharge, or with virtual ward-type models. COVID-19 has put these services very much in the spotlight and, as part of this, the BGS has produced a series of good practice resources such as 'Right place, right time' and 'Healthcare for care home residents'. They are also one of the lead organisations in updating the *Silver Book* on emergency care for older people.

We continue to have a key stake in acute care and deliver a high quantity of all-age acute and general internal take-based, ambulatory, and ward-based medicine. Geriatricians found themselves looking after large numbers of patients with COVID-19. In my case, I was one of two consultants for a 28-bed 'Hot' (all-COVID-19) ward for many months during the 2020 and 2021 waves. There has been a great deal of empirical learning about the clinical presentation and the course of COVID-19 in people who are older and frailer, and the outcomes and usefulness of interventions; for instance, non-invasive ventilation. Older people with frailty sometimes experience COVID-19 differently to younger people with better underlying health.

COVID-19 also sparked much-needed debate and scrutiny on the use of frailty scales to prioritise, or even ration, treatment in cases of mismatch between capacity and demand, and in decisions about do not attempt cardiopulmonary resuscitation orders or treatment escalation.

Q8

You recently authored an article discussing clinical service innovations following the pandemic. What would you say was the most noteworthy clinical innovation to develop from COVID-19? Do you think that these new strategies will continue as the immediate impact of COVID-19 improves?

The rapid development, testing, and rollout of vaccines could provide a template for years to come in the advent of further pandemic respiratory viruses. Likewise, the large clinical trials of various pharmacological treatments, both preventative and disease-modifying, and the huge learning across international health systems about the groups most, or least, likely to benefit from ventilation or organ support.

We have also shown that virtual wards can work for selected patients with respiratory infections and symptoms, and at some scale. We have demonstrated the value of specialist support for care home residents needing some traditional hospital-level interventions and strengthened the case for more explicit advance care planning and treatment escalation plans. We have shown that if we provide local health and care systems with the resources and permissions, they can help far more medically stable patients leave hospital more quickly and avoid their being stranded, and can also reconfigure their own local services at some speed. Not every innovation or improvement should rely on central agencies. Left to their own devices, local clinicians and managers can adapt quickly in the face of challenges.

Q9

What would you say has been the greatest achievement of your career? And what do you hope to focus on for the next few years ahead?

Working as an NHS doctor for 33 years and a consultant for 24 years has been the most important thing for me. I am committed to the NHS as an institution, and to medicine as a profession and a career. All the other things are a wonderful add-on. But I was especially proud to be president of the BGS, an organisation that has been so instrumental in my own career and has done so much to help improve care for older people over many years since the NHS was founded. ■

Urgent Support and Aid Needed for Ukrainian Patients with Rare Diseases and their Families

Michael Wilbur, Anna Kole
EURORDIS-Rare Diseases Europe, Plateforme Maladies Rares, Paris, France

Citation: EMJ. 2022; DOI/10.33590/emj/22F0309.

AT THE BEST OF TIMES, the 30 million people living with rare diseases in Europe require specific actions and support to achieve equitable access to health and social needs. In times of crisis, relief efforts must include specific consideration for the needs of this vulnerable population.

The urgent need regarding people with a rare disease in Ukraine is for help to get vulnerable families safely out of the country and help to get essential medicines and supplies in.

There are an estimated 2 million people in Ukraine living with a rare disease. There are >6,000 rare diseases. They are heterogenous conditions, but what unites them is that they are not well understood (experts are also rare), difficult to diagnose, and most often do not have a cure. Those affected by a rare disease typically require frequent and complex care. Many also have disabilities that make movement very difficult. In the context of a war, these families have extreme difficulty leaving their homes without support to access care or retrieve food and supplies needed for survival, even when these are available.

Because it requires highly specialised clinical knowledge to care for a rare disease where some treatment is available, many families who were able to relocate to the West of the country can no longer access therapies that were only available in Kyiv or other areas providing specialised care. To seek safety in another country, many require additional support for transport within Ukraine to the border; once on the other side of the border, they may need adapted accommodation and very quick access to specialised care in a new country (where access to such treatments and care may not be widely understood by first responders and local healthcare professionals).

Preliminary exchanges with patient organisations in Ukraine have revealed evidence of shortages of medications and supplies already for a number of rare diseases. It is understood that in some cases, treatments procured and paid for by Ukraine before the war have no safe channel to

get in. In many cases, including cystic fibrosis, epidermolysis bullosa, and Angelman syndrome for example, there are organised patient groups on both sides of the border who are willing and able to help with collection and transfer of badly needed materials, but there is as of yet no official corridor and no major aid organisation willing to get involved with this effort in a systematic way. EURORDIS-Rare Diseases Europe[1] is liaising with agencies on their behalf as it is extremely difficult for this rare and dispersed vulnerable population to get on the radar of agencies and authorities as individual communities.

This means that if and when the 'aid corridor' agreed by Russia and Ukraine is put into effect, there will be little or no opportunity for patients with rare diseases to benefit.

Because many Ukrainians have family or friends already living in Poland, and because of language skills and a large, shared border, many Ukrainians are moving into Poland. Poland has been welcoming to Ukrainian refugees, and they have the same access to care as Poles and have been offered free train travel within Poland. However, patients with rare diseases need more support beyond other refugees, for example to find their specialty centres and access to specialised treatments: a role that patient organisations are mobilising to help with within Poland and other countries. It is also anticipated that many further refugees will go to other countries within the European Union (EU), and so expert centres need to anticipate and ideally facilitate the arrival of Ukrainian refugees.

There have been very impressive examples of grassroots efforts of patient groups supporting vulnerable patients to cross the border safely and access appropriate accommodation and care on the border. Organisations like Fundacja SMA,[2] Debra International[3] and EB Polska,[4] and Edu[5] and NoRo[6] in Romania have mobilised effective networks to support dozens of families to safely cross into Poland, Romania, and elsewhere and to access care on the other side.

"In times of crisis, relief efforts must include specific consideration for the needs of this vulnerable population"

However, there are many vulnerable patients with rare diseases in Ukraine who would like to leave but are unable to because:

- They need specialised transport to accommodate their medical devices or disability;
- They cannot get 'fast tracked' across the border and their care needs mean they cannot wait in long lines overnight (there are reports of some border crossings having waits of 2–3 days); and
- Men aged 18–60 years are not allowed to leave the country. In cases where a man is the carer of his spouse, or where a child's care requires two parents, there is no option for the parents to be separated. In Ukraine, many women do not have driving licenses and so cannot travel by car alone. There are also cases where a man is the sole carer of a child.

The immediate priorities therefore include:

1. For large aid agencies to facilitate moving vulnerable people with rare diseases safely and quickly out of Ukraine and to facilitate groups to legally get essential supplies into the country; and
2. For Ukrainian authorities to recognise the specialised needs of this population, including the immediate need for exemption for men who have a son, daughter, or partner with a rare disease to leave the country. The exemption for children should be regardless of the age of the child, as many fathers still need to care for their disabled children even when they are >18 years of age. This exemption will mean the family can safely leave the country if that is their need.

EURORDIS are currently reaching out to Ukrainian authorities, along with our member patient organisations there. We are also reaching out to the World Health Organization (WHO),[7] Red Cross,[8] Doctors without Borders (Médecins Sans Frontières),[9] and United Nations Office for the Coordination of Humanitarian Affairs (UN OCHA)[10] amongst others, to help us with this.

We are continuing to help patient organisations to connect to each other to exchange knowledge and information.

EURORDIS recognises and appreciates that there is an exemption in place for fathers of disabled children <18 years of age, and there have been some examples that show that this exemption is being respected by Ukrainian border guards when evidence is provided. But we need to be able to assure families who are afraid to risk making the long journey to the border that they will be allowed to cross, and expand this exemption so that it reflects the reality of caring for someone with a rare and complex condition. ■

Further resources

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Science Versus COVID-19: What Have We Learnt So Far?

Katherine Colvin
Editorial Manager

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TWO YEARS AGO, the COVID-19 pandemic emerged and swept through the world, going on to have a profound human and health toll and a devastating impact on world economy. Two years on, the global scientific community has amassed a staggering and unprecedented volume of information about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its resulting disease state COVID-19. By mid-February 2022, there have been a staggering 414.5 million confirmed cases of COVID-19, leading to 5.8 million deaths, with 10.2 billion vaccine doses administered worldwide.[1] A PubMed search of "COVID-19 OR SARS-CoV-2" reveals an impressive >24,000 publications sharing insights into this new clinical entity. The speed of knowledge gained to aid understanding of epidemiology, pathophysiology, clinical manifestations and complications, and prevention and treatments is a result of awe-inspiring global displays of collaboration, transparency, and selfless dedication from the scientific, healthcare, and pharmaceutical communities. While it would be a mighty feat to summarise 24,000 studies-worth of clinical insights, highlights from some of the lessons learnt so far serve to celebrate the work of these communities in combatting this pandemic.

EPIDEMIOLOGY AND PUBLIC HEALTH

Gene sequencing of the SARS-CoV-2 virus, shared transparently and swiftly with the global community, led to rapid amalgamation of epidemiological data on the transmission of the virus and cases of COVID-19.[2] This provided an early evidence base that helped to shape public health strategies and to develop testing capabilities to diagnose and track cases as the virus grew to pandemic levels. While some questions surrounding transmission and prediction of clinical severity remain, particularly among vulnerable populations and children, the transmission of SARS-CoV-2 is generally well-understood: respiratory transmission and infection via droplets, personal contact, contaminated surfaces, and fomites have all been identified as contributing to the transmissibility of the virus.[3] It is this droplet and respiratory transmission that was the basis for effective implementation of mask strategies as a cornerstone of public health interventions. Understanding of the role of droplet spread led to the development of 'social distancing' strategies, while the impact of some airborne transmission contributed to the advice for ventilation and avoidance of overcrowding in public spaces and at events, as well as periods of lockdowns.[3,4] Comparing mutational patterns in gene sequencing across different global regions and over time built an understanding of the virulence of SARS-CoV-2, showing that mutations

in SARS-CoV-2 accumulate at a slower rate than other RNA viruses, including HIV and influenza.[3]

PATHOGENS AND PATHOPHYSIOLOGY

Electron cryomicroscopy, alongside genetic sequencing, enabled an intimate understanding of the structure of the SARS-CoV-2 virus to then inform approaches to diagnosis, the development of treatments, and an understanding of immediate and possible long-term complications. SARS-CoV-2 is a single-stranded RNA virus with a double-layered lipid envelope that includes the widely recognisable spike glycoprotein, which plays a significant role in entry to host cells and initiation of clinical infection.[3] The virus enters via mucosal surfaces of the face and upper respiratory tract, with angiotensin-converting enzyme 2 (ACE2) receptors serving as the binding site for viral particles. Binding to ACE2 receptors reduces levels of ACE2, impairing the renin–angiotensin–aldosterone system so that signalling is diverted via the angiotensin II pathway; upregulation of this angiotensin II pathway can lead to severe dysfunction of inflammatory processes and circulation.[3] ACE2 receptors are found in the tissues of the endothelium, gut, kidneys, lung, heart, and vasculature, which is why SARS-CoV-2 can lead to multisystem clinical presentations.[3,5] Direct cytopathic effects of the virus, coupled with build-up of angiotensin II in the tissues, are thought to be the mechanism of direct lung damage in COVID-19, while the endothelial inflammation triggered by the angiotensin II pathway is believed to underpin the thrombotic, haemorrhagic, and coagulopathic impacts of the disease, leading to cardiovascular events, stroke, and pulmonary embolism in severe cases.[3]

THE ILLNESS AND ITS COMPLICATIONS

While many cases of infection with SARS-CoV-2 remain asymptomatic, posing great challenges to ongoing public health strategies, the exact proportion of asymptomatic versus symptomatic cases varies based on different studies and may be underreported where asymptomatic cases are not tested. Of those patients with symptomatic COVID-19, >80% have mild disease, which presents in 98% of cases within 12 days of exposure to the virus.[6] Mild cases have variable presentations, but may be characterised by fever, respiratory symptoms including cough, altered taste or smell, or myalgia. There is no statistically

"highlights from some of the lessons learnt so far serve to celebrate the work of these communities in combatting this pandemic."

reliable symptom to differentiate COVID-19 from other illnesses; however, the constellation of cough, shortness of breath, and altered taste or smell account for the most common symptoms, while fever is too variably described in the literature to be a reliable marker.[6,7] Severe disease is often described as cases affected by hypoxia or >50% lung involvement on radiographic imaging, and affects approximately 15% of patients; critical disease, characterised by shock, multi-organ injury, or respiratory failure, affects up to 5% of patients.[6] Severe COVID-19 or worse prognosis in symptomatic cases have been associated with several risk factors, including age >75 years, obesity, history of transplant, and comorbid conditions including diabetes, cancer, hypertension, or previous cardiac or pulmonary disease.[6] Several biomarkers that are associated with poorer prognosis have also been identified over the past 2 years of treating and investigating COVID-19.[6]

Identifying and understanding complications of COVID-19 has been an area of significant study over the evolving pandemic, and will be profoundly important for the years and possibly decades ahead as these complications contribute to health outcomes globally. Cardiac, neurologic, gastrointestinal, and haematologic or thrombotic complications predominate, contributing significantly to acute burden of disease, morbidity, and mortality in COVID-19.[6] While evidence for longer-term complications continues to mount, patient cases and physiological understanding suggest that they include heart failure, myocarditis, lung fibrosis, stroke, venous thromboembolism and arterial thromboses, and mood impairments.[8] It is likely that these complications, particularly cardiac and respiratory complications, will make up a great burden of disease sequelae for COVID-19; research is ongoing and long-term impacts are still to emerge, although pathophysiological understanding of these sequelae is growing rapidly.[8]

TREATING COVID-19

Treatment of COVID-19 has understandably been a focal area of study for bedside clinicians, pharmacologists, biological scientists, and governing bodies of medical colleges, associations, and organisations worldwide. The World Health Organization (WHO) has maintained 'living guidelines' for both clinical management and therapeutic treatments throughout the pandemic, showcasing the transparent, collaborative, and fast-paced efforts that have been a hallmark of the global pandemic response.[9,10] The advice for clinical management of COVID-19 is determined by both clinical severity and underlying risk factors or vulnerability, with mild cases recommended for supportive management of symptoms in home-based settings, while those patients at risk of severe disease may be considered for sotrovimab or casirivimab and imdevimab, although studies to date suggest that casirivimab and imdevimab may not be effective against the omicron BA.1 variant of the virus.[10] Severe disease is treated with oxygen therapy, intravenous corticosteroids, prophylaxis for venous thromboembolism, and either baricitinib or an IL-6 blocker (tocilizumab or sarilumab).[10] This clear guidance has evolved over time as >5,000 global clinical trials evaluated various therapeutic options, including ACE-inhibitor therapies, antimalarial agents, antiretroviral medications, and new therapeutic options identified based on pathophysiological understanding of the virus and its behaviour. Knowledge of best treatment practices in COVID-19 is still growing, particularly with the development of new viral variants as well as appraisal of the impact of current treatment practices against longer-term complications and sequelae.[10]

VACCINATION

At least 18 vaccines have been developed to prevent cases or reduce risk of severe illness in COVID-19, and the WHO has advocated that the most effective pathway forward in addressing the impacts of the pandemic is to promote and support worldwide high levels of uptake of reliable vaccination.[11] The vaccines developed to address COVID-19 fall into three categories by method of action: mRNA vaccines, viral vector vaccines, and inactivated or protein subunit vaccines.[12] The development of these new vaccines demonstrated an unprecedented speed of pharmaceutical innovation, clinical trial undertaking, and global roll-out that has been widely celebrated as a marker of the great success of the scientific community in facing this

pandemic. The mRNA vaccines in particular were the first mRNA-based vaccines to be successfully developed and were very effective and well-tolerated; this may represent future avenues for mRNA-based interventions for both vaccination and therapeutics.[12]

All of the vaccines developed were found to be well-tolerated and effective against COVID-19, such that the benefits of vaccination greatly outweigh the risks of vaccine-related adverse events.[12] For the 18 vaccines developed, the quality of research evidence is variable, but the most reliable evidence bases support the efficacy of the most widely provided vaccines;[12] real-world studies have further supported the efficacy of these new vaccines against COVID-19.[13]

LEARNINGS BEYOND COVID-19

The scientific developments forged in response to the pandemic have seen benefits span beyond combatting COVID-19 alone. The rapid identification of current therapeutics to trial for treatment in COVID-19 and the speedy development and roll-out of new vaccines have provided key learnings to help fuel faster future pharmaceutical pipelines and provide groundwork for drug repurposing potential in some rare diseases.[14] Virtual healthcare systems and telehealth grew substantially in response to the pandemic, which can support the provision of care to those with impaired access to health resources due to geography, mobility, or vulnerability in open healthcare settings.[15] The success of the mRNA vaccine shows fantastic proof-of-concept that may lead to the adaptation of mRNA vaccination to address other conditions, including chronic diseases such as diabetes, asthma, and cystic fibrosis, immunotherapy in cancer, and bone remodelling in musculoskeletal conditions.[16] Perhaps the greatest lesson to carry forward from the COVID-19 response is the powerful value of global collaboration of the scientific community to meet complex challenges and benefit health worldwide. While the impact of COVID-19 on day-to-day hospital and outpatient care continues, appreciating the vast knowledge base gathered shows how healthcare services are now far better equipped to combat the disease and help care for patients than 2 years ago. ■

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C5a, complement component 5a;GC, glucocorticoid; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; SoC, standard of care.

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Contraindications: TAVNEOS is contraindicated in patients with a history of a hypersensitivity reaction to TAVNEOS or any of its excipients.

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VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA

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Thromboembolic Storm in the Recovering Stage of COVID-19: A Case Report

EDITOR'S PICK

COVID-19 presents itself in countless ways and can lead to many complications in patients. As our understanding of the disease develops from a case-by-case perspective, increasing evidence shows the incidence of adverse effects, including those of endothelial damage and subsequent complications. This timely case report highlights a relevant case of thromboembolic storm in a patient with severe COVID-19 infection, the initial presentation and treatment decisions, as well as emphasises key messages for healthcare professionals.

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Abstract

A previously well 77-year-old male was admitted to hospital on Day 5 of COVID-19 symptoms, with a moderate infection. They progressed into the severe COVID-19 category, requiring the use of non-invasive ventilation. From a respiratory point of view, they made a good recovery from moderate-to-severe COVID-19 pneumonitis. On Day 16 since symptoms started, they developed widespread thromboembolic disease, affecting their right central retinal artery, spleen, kidneys, peripheral vasculature, and gut causing widespread ischaemia, which unfortunately led to their death. There is emerging evidence of endothelial damage (COVID-19 endotheliitis), resulting in thromboembolic complications. Whilst much of the COVID-19 focus is on the respiratory complications, this highlights a case of a thromboembolic storm induced by severe acute respiratory syndrome coronavirus 2 infection in the absence of the more typical vascular complications of COVID-19 (pulmonary emboli and deep vein thrombosis).

BACKGROUND

COVID-19 was first identified in Wuhan, Hubei Province, China, in late 2019 and led to a worldwide pandemic, with limited understanding of how the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus caused disease. COVID-19 pneumonitis was the most commonly identified presentation but, over the course of 2020, the haematological effects of the

SARS-CoV-2 virus became more evident, leading to improved protocols for anti-coagulation prophylaxis and a lower threshold for considering CT angiograms to investigate persistently unwell or deteriorating patients with COVID-19. COVID-19 is an emerging health emergency, with a lack of knowledge and literature compared to other common respiratory viral infections. The sharing of clinical experience in the medical literature, to demonstrate key complications in COVID-19 and to aid in the treatment of COVID-19, is vital to improve survival rates. Thromboembolism is a complication of COVID-19 that all healthcare individuals must be aware of; there must be a low threshold of suspicion for thromboembolism in COVID-19 and treat accordingly. It is important to consider the future management of patients with COVID-19, including whether thrombolytic therapy or enhanced prophylaxis are indicated.

INITIAL PRESENTATION

A fit and active 77-year-old male was admitted with a 5-day history of fever, productive cough, and hypoxia during the winter peak of the COVID-19 pandemic. Despite an initial negative screening test, clinical presentation, and chest radiograph findings warranted a repeat PCR test, which confirmed COVID-19 infection. Their medical history included seropositive rheumatoid arthritis treated with methotrexate, diet-controlled Type 2 diabetes (HbA1c: 65 mmol/mol [<48]), with a normal range BMI, hypertension, and hypercholesterolemia. They had never previous been in atrial fibrillation, had a cardiovascular event, pulmonary emboli, or deep vein thrombosis.

They were categorised as a moderate case of COVID-19 infection, with no evidence of pulmonary embolism on CT-arterial portography (CTPA) on Day 6 of symptom onset and a typical COVID-19 blood profile. The CTPA showed ground glass opacification, characteristic of COVID-19. Admission ferritin level was 2,500 µg/L (20–300) and his D-dimer was 2,700 ng/mL (<500). C-reactive protein was raised at 300 mg/L (0–5). White cell count (WCC) was at $6.0x10^9$ /L (4.2–10.6), with a lymphopaenia ($0.3x10^9$ /L [1.1–3.6]). Procalcitonin was 0.33 µg/L (values <0.5 practically excludes infection). Activated partial thromboplastin time was 29 secs (25–35). Platelets were $236x10^9$ /L (130–370) and remained within normal range throughout admission (ruling out heparin induced thrombocytopaenia).

The hospital policy included starting dexamethasone for patients with symptoms, which started less than 10 days previously and who are saturating at <90%; remdesivir in severe cases before Day 10 of symptoms; enhanced thromboembolism therapy for all (based off weight and platelet level); and antibiotic therapy (amoxicillin 2 g intravenous three times daily and doxycycline 200 mg orally once daily) is not indicted unless there was a superimposed bacterial infection or for patients with sepsis.

Dexamethasone was commenced. Their oxygen requirements increased, and they subsequently progressed to a severe infection (meeting the criteria for acute respiratory distress syndrome) with non-invasive ventilation commenced on Day 10 of symptoms (when the patient was outside the window for remdesivir). Serial procalcitonin levels were all <0.5 µg/L. Subsequently, oxygen requirements were weaned and by Day 15 they no longer required oxygen supplementation.

CASE PRESENTATION

Abdominal Pain: Renal and Splenic Infarcts

On Day 16 of symptoms, the patient developed moderate right upper quadrant abdominal pain and had evidence of a neutrophilia (WCC: $20.9x10^9$ /L, with neutrophils: $20.2x10^9$ /L [2.0–7.1]), plus an increasing C-reactive protein of 157 mg/L and a cholestatic picture, with a raised alkaline phosphatase of 170 U/L (30–130) and an alanine aminotransferase of 64 U/L (0–45). An ultrasound of the liver showed a fatty liver but was otherwise normal.

On Day 18 of symptoms the patient reported ongoing, now generalised, abdominal pain and had evidence of abdominal distension with reduced bowel sounds on examination. Inflammatory markers and neutrophil counts increased, and with a lactate at the upper limit of normal (2 mmol/L [0.5–2.0]), an abdomen CT was performed. This demonstrated new multiple splenic infarcts (Figure 1), which were not seen on admission CTPA and a probable wedge infarct within the interpolar segment of the right kidney

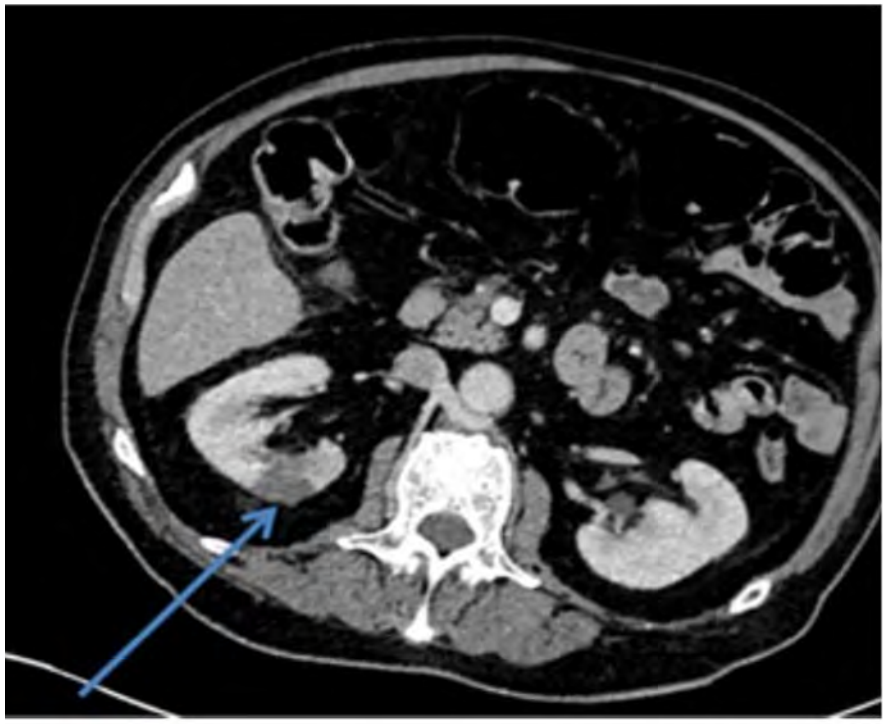

Figure 1: CT-arterial portography.

Day 18 (one slice): wedge infarct within the interpolar segment of the right kidney. This can be seen as a hypodense wedge-shaped region labelled by the arrow.

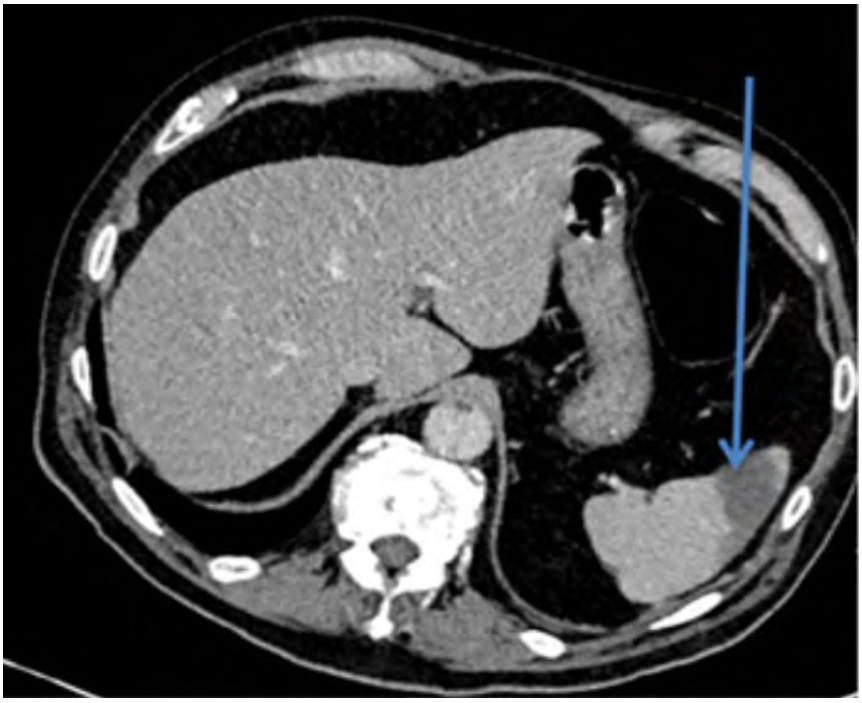

Figure 2: CT-arterial portography.

Day 18 (one slice): one of the splenic infarcts. An arrow labels a hypodense region in the spleen. The hypodense region represents infarcted splenic tissue.

(Figure 2). Parts of the caecum were distended with mild inflammatory changes seen.

Unilateral Visual Loss: Right Central Retinal Artery Occlusion

On Day 18, they also reported a 2-day history of right eye visual loss; an ophthalmologist advised likely central retinal artery occlusion but as it was >24 hours since onset of visual loss, no acute intervention was indicated. A CT of the brain demonstrated no acute cortical infarct but some hyperdensity along the interhemispheric falx. With specialist advice from neurology and haematology, their enoxaparin was increased from 40 mg twice daily (as per hospital protocol [enhanced prophylaxis in COVID-19]) to an enhanced treatment dose of 150 mg once daily (normal treatment dose being 1.5 mg/kg; 120 mg in this case) and aspirin 75 mg was commenced. A CT venogram demonstrated a complete filling defect in the right internal carotid artery. Neurosurgeons advised it was likely longstanding and he was not on any medical interventions.

In light of the thromboembolic events, it was pertinent to consider possible sources. Serial blood cultures grew gram negative rods (*Bacteroides ovatus*) on Day 19 of symptoms. Dental sources were ruled out. As per microbiology, no antibiotics were commenced. A transthoracic echocardiogram was normal, with no valvular abnormalities. A full rheumatological screen was negative.

Bilateral Foot Pain: Bilateral Popliteal Artery Occlusions

On Day 20 of symptoms, the patient developed bilateral cold, painful feet with dusky discoloration of their toes and absent pulses distally to the popliteal arteries. An urgent ultrasound with Doppler flow demonstrated complete occlusion of the left superficial femoral artery and the right popliteal artery (Figure 3). Enhanced treatment dose enoxaparin was switched to a heparin infusion and the patient was transferred to a vascular surgery centre.

Blood results had also worsened, with a WCC of $38x10^9$ /L, a D-dimer of 3,800 ng/mL, a ferritin of

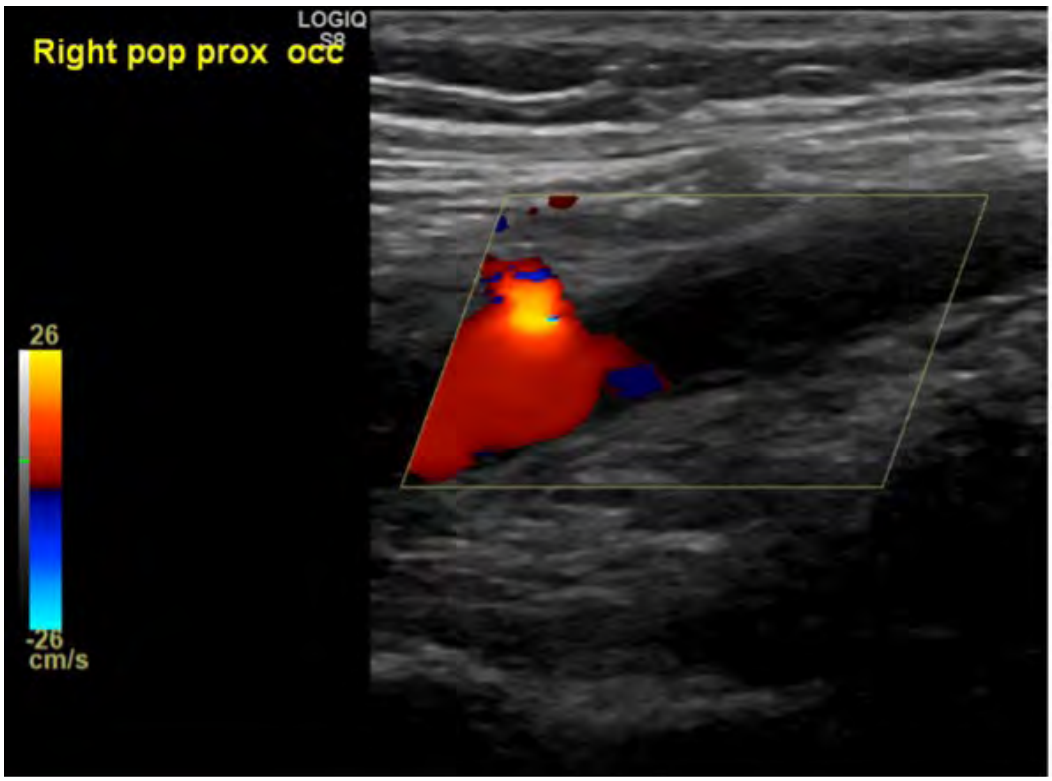

Figure 3: Ultrasound right lower limb with Doppler flow.

Popliteal artery occlusion noted; no flow in the calf arteries demonstrated more distally.

5,800 µg/L, and a blood film showed neutrophilia with toxic granulations and platelet clumps.

Bleeding per Rectum: Ischaemic Colitis

The patient had two episodes of malaena on arrival at the vascular centre, with new onset fast atrial fibrillation and abdominal tenderness. A triple phase CT with CT angiogram in the emergency department demonstrated free floating thrombus in the proximal left subclavian artery and aortic mural thrombi at multiple levels; embolic thrombi within the distal tributaries of the superior mesenteric artery, likely to account for the ischaemic colitis, was also seen. Also noted was a grossly oedematous caecum with haemorrhagic content inside the bowel wall. There was no active contrast extravasation; however, a contained perforation of the caecum and appendix was likely. Unchanged ischaemic insults to the right kidney and spleen with no pulmonary emboli were also noted; however, persisting ground glass opacification and organised pneumonia was seen.

These features represent multiple ischaemic events secondary to a catastrophic thromboembolic storm (also referred to as red rain).

Surgery: Colectomy and Embolectomy

On Day 21, the patient underwent a right hemicolectomy, which showed extensive ascending colon infarction and caecal perforation. This was followed by bilateral lower limb embolectomies and transverse popliteal arteriotomies. Although significant fresh thrombii alongside inflammatory material were retrieved, by this time, irreversible ischaemia with fixed mottling had developed across his toes.

Outcome

Unfortunately, intra-operative deterioration required both increasing inotropic requirements and ventilator support. The patient was transferred to the intensive care unit but sadly succumbed to the burden of disease on Day 22.

DISCUSSION

Consequences of acute COVID-19 infection are far-reaching and can impact all organ systems. As a relatively new virus, the impact on the respiratory system is well appreciated, has been extensively studied, and reported. However, it has become increasingly apparent that COVID-19 is more than a chest infection, with wide ranging multi-system effects and systemic inflammation reported in several organs, including the kidneys, brain, and gut. The understanding, identification, and treatment of thromboembolic disease, particularly pulmonary embolism, has significantly improved since the first wave of COVID-19 infection, experienced in the UK in March–April 2020. Despite sequential uptitration of anticoagulation, from enhanced thrombo-prophylaxis (enoxaparin 40 mg twice daily), to enhanced treatment dose (enoxaparin 150 mg once daily), to a heparin infusion, the authors patient progressed to thromboembolic storm.

A recent publication discussed the mechanisms behind the increased thrombosis leading to increased mortality and morbidity.[1] The mechanisms included immune-mediated thrombotic mechanisms; complement activation; macrophage activation syndrome; antiphospholipid antibody syndrome; hyperferritinaemia; and renin-angiotensin system dysregulation.

In addition, severe damage to endothelial cells in COVID-19 results in coagulation activation.[2] The RECOVERY trial by Oxford University, UK, concluded that tocilizumab (often used in rheumatoid arthritis) reduced deaths in patients hospitalised with COVID-19.[3] Coagulation activation could be more common in a patient with an underlying inflammatory condition, such as rheumatoid arthritis in this case.

Neutrophil extracellular traps formation is a feature of COVID-19 infection.[4] The marked neutrophilia in this patient is very likely to have contributed to the appearance of neutrophil extracellular traps, which are essential for immune-mediated thrombosis.[5] Detection of neutrophil extracellular traps markers (such as cell-free DNA and myeloperoxidase) in a patient's plasma at several time points during a COVID-19 infection may be beneficial for patient outcomes in the future. Unfortunately, the authors do not have access to stored patient plasma, which is a limitation of this manuscript.

The mechanism behind the thromboembolic storm episode requires further research. The

thrombotic episodes tend to be proportional to the severity of COVID-19 infection with an incidence of 31% in patients admitted to the intensive care unit.[6]

Pre-publication, interim results from a multiplatform, international, randomised control trial (ATTACC, ACTIV-4A, and REMAP-CAP),[7] suggest that the timing of anticoagulant therapy could be vital in COVID-19. It has concluded that therapeutic dose heparin reduces mortality when initiated in individuals with moderate infection; and when an individual is severely ill, there is a 98.5% probability that initiating treatment dose heparin is harmful when compared to thromboprophylaxis.

Furthermore, the potentials of thrombolytic therapy could be considered in the future.[1] Specialist input from haematology with continuously updated guidelines, protocols, and individual case management, is vital in patients with COVID-19. With the increasing prevalence and understanding of thromboembolic disease, international guidance for the prevention and management of thromboembolism is essential for best practice in clinical decision-making processes.

Other case reports detailing thromboembolic storms in COVID-19 exist.[8] Culminating information and data across the globe is fundamental to developing the scientific and medical knowledge; knowledge will result in more effective treatment of an acute COVID-19 infection.

TAKE HOME MESSAGES

- To be aware of varied and evolving presentations of moderate-to-severe COVID-19.
- Keep a low threshold of suspicion for thromboemboli in moderate-to-severe infection.
- Ongoing grading of severity of infection and appropriate dosing of anticoagulant therapy is vital.
- Coagulation activation in those with underlying inflammatory conditions could result in increased morbidity and mortality and, therefore, need to be explored as part of an anti-coagulation protocol.

PATIENT'S PERSPECTIVE

'Deeply shocking' is the sentiment that the patient's partner wanted to portray to readers. On admission, their fully fit partner could walk for miles a day. The patient subsequently deteriorated, despite a lack in oxygen requirements. Furthermore, the patient was due to have their vaccine dose on the day that they sadly passed away. With the roll-out of a global vaccination programme, these deaths can be potentially prevented. Finally, the patient's partner would like to extend their gratitude to the entire healthcare service, unselfishly working throughout the pandemic.

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Utility of Evidence-Based Clinical Decision Support in Reducing Unwarranted Variations in Diagnosis and Treatment of Breast and Lung Cancer

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Abstract

Advanced healthcare delivery prolongs life, but it is also associated with preventable patient harm such as misdiagnosis, suboptimal treatment, and avoidable care-associated injuries. While best practice guidelines are an important tool in reducing unwarranted variation in clinical decision-making, their utility in routine care is limited by the complexity and quality of recommendations, which a clinician is expected to remember or quickly access.

Well-designed, evidence-based clinical decision support (CDS) tools can help clinicians incorporate an often overwhelming reservoir of evidence into their decision-making process. They work best when integrated into standard clinical workflow, so that they do not rely on human memory for their accurate execution. This review focuses on the use of CDS systems in breast and lung cancer, summarising recent findings in the areas of cancer screening, diagnosis, management, and image analysis.

By integrating a vast array of complex data into healthcare workflow, CDS systems allow clinicians to leverage data to provide the best services, timely decision-making, and health-related quality of life for patients with cancer.

However, to realise the full potential of CDS, further well-designed trials are needed to evaluate such tools in real clinical environments, and existing guidelines need to be converted into algorithms that can be interpreted by computers.

ADVANCED HEALTHCARE DELIVERY PROLONGS LIFE, BUT AT WHAT PRICE?

It is clear that the delivery of advanced healthcare prolongs life. The global average life expectancy has almost doubled since 1900, driven by higher standards of living, public health interventions, and improvements in healthcare.[1] However, advanced healthcare provision is associated with preventable patient harm, including patient safety incidents, misdiagnosis, delayed diagnosis, and suboptimal treatment. Such events represent a serious problem across all healthcare settings.[2]

Clinician diagnostic and treatment decisions vary widely. When this variation is associated with deviation from best practice, evidence-based knowledge, unique individual patient needs, or patient preferences, it can appropriately be labelled 'unwarranted'. Unwarranted variation can be associated with morbidity and mortality (Figure 1).[3]

In one retrospective review of patient records (N=14,407) in primary care in England, UK, the rate of significant and probably avoidable harm was 35.6 per 100,000 patient-years. Most of these incidents (61%) were due to misdiagnosis, 26% due to medication-related problems, and 11% due to delayed referrals. In most cases (80%), incidents could have been identified sooner, or prevented altogether, if the practitioner had followed evidence-based best practice guidelines.[4]

Outpatient diagnostic errors occur in approximately 12 million adults in the USA every year. Roughly half of these errors are estimated to be potentially harmful.[5] In outpatient settings, delayed cancer diagnosis is considered one of the most harmful types of diagnostic errors.[5] One study found that opportunities to diagnose lung cancer were missed in 38% of patients (N=587), resulting in significant diagnostic delays.[6]

A meta-analysis of global observational studies found that the pooled prevalence for preventable patient harm was 6%, mainly related to medication or other treatments. Twelve percent of events of preventable patient harm were severe or fatal.[7] The real incidence rate of patient harm may be even higher, as automated measures of patient safety almost certainly fail to identify all adverse events. An alternative method, the Global Trigger Tool, was developed by the Institute for Healthcare Improvement (IHI). When applied to hospital records from three large tertiary care centres in the USA, results indicated that adverse events occurred in 33% of hospital admissions.[8] While this study did not formally judge whether each harm event was avoidable, the study's authors estimated that at least half of all events detected fell into that category. They also noted that more than 9% of all hospital admissions directly resulted from outpatient care-associated harms (unpublished data).

Although progress has been made in improving the quality of healthcare globally, the World Health Organization (WHO) reports that 10% of patients are still adversely affected during treatment in high-income countries, and a considerable proportion of patients globally do not receive appropriate, evidence-based care.[9]

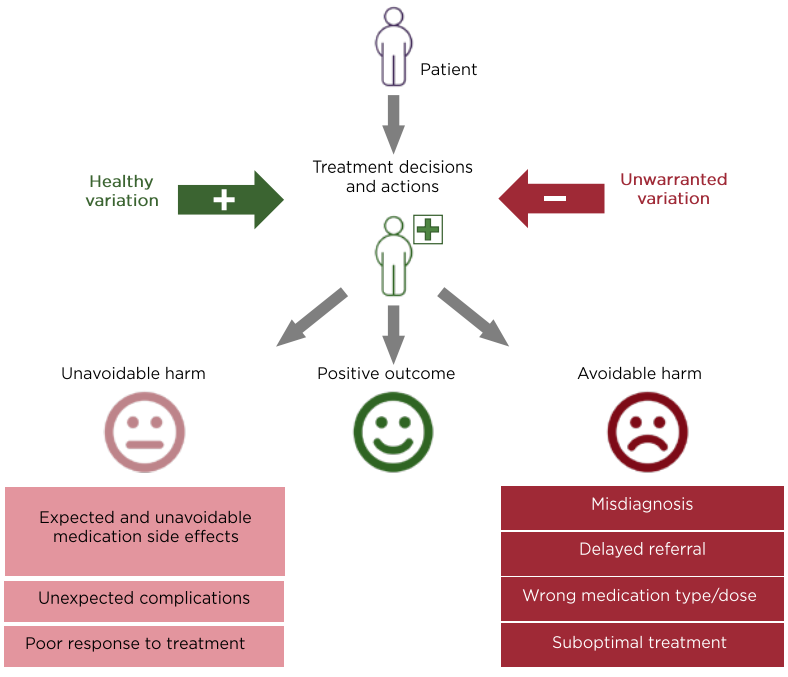

Figure 1: A graphical illustration of variation in treatment decisions and adverse outcomes in healthcare.

Unwarranted variation in patient care, and the resultant patient harm, is a substantial price to pay. However, we do not have to pay that price.[10] CDS has the potential to substantially reduce unwarranted variation.

CAN WE JUST FOLLOW THE PUBLISHED BEST PRACTICE GUIDELINES?

Best practice guidelines are an important tool to improve clinical decision-making.[11] They have been developed for many cancers and other disease conditions, directing clinicians to the applicable options for a specific patient. However, their utility in routine care is limited by deployment methods, and the quality of the recommendations.

Guidelines are mainly deployed through clinical training; clinicians are expected to remember them. However, cancer is a complex, heterogenous disease that affects patients of all ages and backgrounds, making decision-making difficult.[12] In addition, rapid advancements in therapy and our understanding of cancer presents a significant challenge for oncologists. For instance, over 4 million cancer-related papers have been published in peer-reviewed journals,[13] with over 178,000 published in 2020 alone.

Unfortunately, this approach to guideline deployment results in roughly half of all patients not receiving recommended care.[14-16] Because of the vast array of options for patients with cancer, it is unrealistic to expect clinicians, relying on memory alone, to be able to select the most appropriate treatment for a specific patient at a specific stage of their cancer journey, without significant time outlay. Indeed, literature suggests that when clinicians have only their training, expertise, and experience to rely on, they struggle with cognitive limitations and biases.[3]

Ideally, all best practice guidelines would be based on high-quality evidence. However, expert consensus often plays a large role. A limited pool of well-designed studies means that recommendations are often dependent on the individual experts involved.[17] An evidence review of 421 clinical practice guidelines found them to be of widely variable quality; only 23% could be considered high quality.[18]

Well-designed, evidence based CDS tools may help clinicians to incorporate the often overwhelming reservoir of evidence into their decision-making process.[3] This is especially true if such tools have the potential to learn, modifying guidelines 'on the fly' based on data collected during their use.[19]

WHAT IS CLINICAL DECISION SUPPORT AND HOW CAN IT HELP?

The WHO defines CDS as: "The provision of knowledge and patient-specific information presented at appropriate times to enhance front-line healthcare delivery."[9] CDS encompasses all tools that support healthcare, including clinical guidelines, computerised alerts and reminders, and documentation templates.[9] This article will focus on computerised CDS systems for oncology, many of which can be automated by embedding in electronic health records (EHR) or mobile devices.

CDS tools should facilitate the decision-making process, helping clinicians to adhere to guidelines, to quickly diagnose and/or identify the most suitable treatment for a specific disease, and to gather all the relevant information about the patient and their tumour, so that the best treatment decisions are made from the start (Figure 2). The fundamental elements that a CDS tool must consider include tumour characteristics, patient characteristics, prior therapy, molecular profiling results, combination therapy options, and dosage.[20] Many algorithms for prediction or classification have been implemented in CDS systems to diagnose different diseases, and most of these systems have a way of 'learning' from the data,[21] offering the opportunity to refine guidelines based on patterns in data or clinician feedback. In addition, CDS systems have been developed to assist clinicians with the interpretation of imaging data, such as CT scans or MRIs, with the intention of reducing unwarranted variability.[22,23]

CDS systems support clinicians by removing the need to rely on human cognition, as guidelines and protocols are built into standard clinical workflow.[3] This implementation strategy is critical to the success of any CDS system.[24-26]

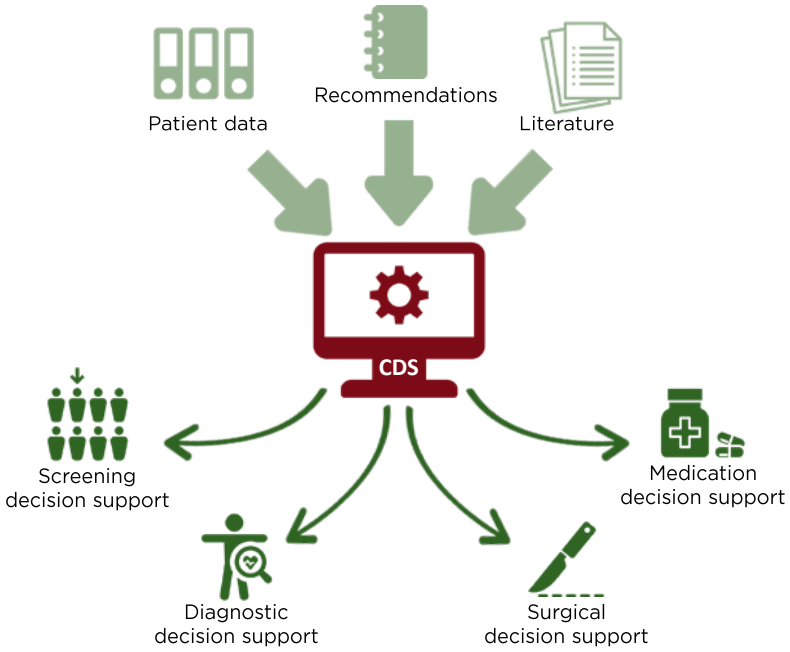

Figure 2: A graphical illustration of how clinical decision support systems are intended to support healthcare practitioners.

CDS; clinical decision support.

RECENT RESEARCH INTO THE UTILITY OF CLINICAL DECISION SUPPORT SYSTEMS FOR CANCER

Due to the vast literature available for cancer, the author focused on the use of CDS systems in breast and lung cancer, which have the highest global incidence and highest global mortality, respectively,[27] and which represent the huge complexity in treatment decisions for cancer.

Cancer Screening

CDS systems can help primary care practices to identify patients at high risk of cancer, who may benefit from screening tests. For example, in a recent study carried out in the USA, a CDS system implemented algorithms derived from the 2018 National Comprehensive Cancer Network (NCCN) guidelines for genetic evaluation of hereditary cancer. The system was integrated into an EHR and evaluated in a single-centre pilot study (N=143,012). It identified 5,245 (3.7%) patients who met criteria for genetic evaluation. Genetic councillors contacted 71 of those patients, of whom 35% scheduled an appointment, resulting in the identification of pathogenic variants in cancer predisposition genes in two patients.[28]

Cancer Diagnosis

The first step in the clinical management of cancer is to definitively diagnose the disease. Therefore, supporting clinicians to reduce delayed diagnosis or misdiagnosis, as well as increasing identification of early-stage cancer, has the potential to improve outcomes. A systematic review of studies using CDS systems for cancer diagnosis in primary care between 1998–2018 found that three out of nine studies showed improvements in diagnostic decision-making, three out of nine demonstrated positive effects on secondary outcomes, and one out of nine reported a reduction in time to diagnosis.[24]

For example, one CDS system that assists radiologists in diagnosing lung cancer from CT scans showed superior nodule-detection sensitivity compared to state-of-the art analysis programs.[29] Another CDS tool is currently in use in Birmingham Children's Hospital, UK, to support

non-invasive diagnosis in children presenting with solid body tumours. Early findings suggest that the tool makes the interpretation and analysis of advanced MRI more comprehensive and accessible to clinicians.[30]

In Baltimore, Maryland, USA, a CDS algorithm categorises lung cancer nodules as malignant or non-malignant using Fleischner Society recommendations, along with smoking history, sex, and nodule location. It can stratify malignancy risk beyond the Fleischner categories and may help clinicians provide more personalised treatment recommendations.[31]

Finally, a retrospective study in a primary care centre in Saudi Arabia compared clinical outcomes for adults in the 3.5 years before and after implementation of EHR-integrated CDS systems. Findings indicated that CDS systems led to significant increases in breast cancer diagnosis.[32]

Cancer Management

Cancer is a complex disease with many therapeutic options.[33] Therefore, treatment decisions require co-ordinated expertise from diverse health professionals. Multidisciplinary team (MDT) meetings are routinely held to meet this need, but they can be affected by difficulties in transferring expertise across centres, and in evaluating the quality of decision-making.[33] CDS systems can support the MDT process by presenting patient data and suggesting the most suitable treatments according to best practice guidelines, potentially using previous cases as evidence.

Clinical decision support systems can improve treatment guideline adherence

For example, an online tool that customises NCCN guidelines for non-small-cell lung cancer (NSCLC) to patients' clinical and pathologic features was tested at a tertiary care centre in California, USA. Patients seen after the use of the tool (N=76) were more likely to receive smoking cessation counselling and less likely to receive adjuvant therapy than patients seen prior to the use of the tool (N=157), suggesting that the CDS tool increased guideline-concordant care.[34]

Similarly, a CDS system increased adherence to NCCN breast cancer guidelines by 0.5% (p=0.003) in China (N=1,977 patients). Oncologists changed their initial treatment decision in 5% of patients, citing consideration of the CDS system recommendations, patient factors highlighted by the system, and the decision logic provided as reasons for the change.[35] Another CDS tool that combined three breast cancer clinical practice guidelines was tested in Spain and France. In 17% of cases (24 out of 138), clinicians modified their decisions after using the tool, and an external expert determined that in most cases (75%), the new decisions were more appropriate.[36]

Using an alternative approach, a CDS system was developed in the Netherlands to help multidisciplinary tumour boards construct a shared mental model of individual lung cancer cases. A simulated tumour board using eight primary lung cancer cases found that the system was helpful for accurate diagnosis and classification, helped to cross-validate diagnostic findings, and facilitated cancer staging.[37]

Clinical decision support tools can predict complications

Accurate assessment of complication risks can support the decision-making process of an MDT. For example, a CDS system incorporating machine learning showed the potential to improve the prediction of significant weight loss following radiotherapy in patients with lung cancer (N=37). In four cases, physicians changed their original prediction after reviewing the CDS system's output, resulting in an improvement in accuracy (from 0.54 to 0.59).[38]

In a larger study, the utility of a CDS tool to make relapse risk predictions for breast cancer was assessed in patients for whom adjuvant chemotherapy was uncertain. Use of the tool resulted in changes to initial chemotherapy decisions in 36% of cases (72 out of 200).[39]

Similarly, an evidence-based neutropenia-risk algorithm developed to assist oncologist decisions regarding cytotoxic chemotherapy was tested on a retrospective cohort of patients with newly diagnosed cancer in the USA (N=126). Mean predicted risk in high-, medium-, and low-risk groups were similar to observed event rates over the following year.[40]

Clinical decision support systems can support clinical interpretation of genomic mutations

The interpretation of genomic mutations to inform treatment decisions is a formidable task,[41] and several CDS systems have been developed to support these decisions. For example, a tool that reports a '21-gene recurrence score' for patients with early-stage breast cancer was assessed across four centres in Spain (N=401). Use of this tool reduced the rate of chemotherapy prescription from 56% to 25%, reducing unnecessary chemotherapy.[42] However, since each CDS has a different way of classifying variants and identifying potential treatments, they can produce disparate results. A comparative analysis of three genomic-mutation CDS systems was performed on a cohort of 48 patients in Austria, with breast, colorectal, or lung cancer. The frequency of concordant actionable recommendations was only 4.3–28.0%, depending on the systems being compared, suggesting that further development and testing of CDS algorithms is needed.[41]

Clinical decision support tools have the potential to predict therapeutic response

Individual patients can respond quite differently to the same treatment, and accurate prediction of this response could support MDT decision-making. A CDS algorithm based on machine learning was developed in South Korea to combine clinical characteristics related to response to anti-programmed death protein 1 therapy in patients with NSCLC. Compared to separate predictions based on the individual characteristics, the CDS algorithm showed a significantly greater prediction performance.[43]

Can clinical decision support systems accurately model multidisciplinary team treatment decisions?

Several studies have investigated how well recommendations made by CDS systems align to actual treatment decisions made by MDTs.[33,44,45] In Australia, a machine learning model was tested on breast cancer cases (N=1,065). The model more accurately predicted MDT decisions regarding adjuvant cancer therapy than a simple application of guidelines did, suggesting that it has the potential to facilitate the transfer of expert knowledge to more remote centres.[33]

In a similar study, concordance between CDS-based treatment recommendations and an MDT for patients with breast cancer (N=638) was assessed in a single centre in India. Results suggested a high level of concordance overall (93%), though it was significantly lower in older patients.[44]

Finally, a study in South Korea investigated the alignment of treatment recommendations from a CDS system versus an MDT in cases of lung cancer (N=405). Results indicated that recommendations were highly concordant (92% agreement) in general. Concordance was lower for patients with Stage II NSCLC and limited disease small-cell lung cancer (83% and 85%, respectively), suggesting that patient preference may be more important in these disease stages.[45]

Clinical Decision Support for Image Analysis

CT and MRI represent advanced techniques for lesion detection, disease staging, and the assessment of therapeutic response.[46] Molecular classification of cancers, and the potential for non-invasive tumour subtyping, are increasingly important. That means that advanced image processing and the integration of imaging and clinical data are increasingly required.[22]

CDS systems have been developed to assist clinicians in diagnosing cancer using CT or MRI. For example, a deep-learning system designed to support CT-based lung cancer diagnosis outperformed a current state-of-the art analysis program.[29] A team at Birmingham Children's Hospital is evaluating another CDS tool that analyses advanced MRI data to support non-invasive diagnosis in children presenting with solid body tumours. Early findings suggest that the tool facilitates discrimination between benign and malignant tumours with high sensitivity and specificity.[30] Additionally, a CDS system has been developed to analyse multiparametric MRI and clinical data to determine the probability that a patient is harbouring clinically significant pancreatic cancer. Initial evaluation suggests that this system has comparable sensitivity and specificity to an experienced radiologist.[23]

A machine learning approach is also being used to develop a radiomics model for the preoperative prediction of microsatellite instability status from rectal cancer MRIs. This Chinese clinical trial hopes to show that a non-invasive model could be applied in CDS systems to improve diagnostic, predictive, and prognostic accuracy.[47]

Machine learning techniques are often applied to image processing because of the volume and complexity of the associated data. However, the training of these systems represents a challenge. Training requires vast amounts of quality data to validate performance.[22]

To address this issue, the International Association for the Study of Lung Cancer (IASLC) is developing the Early Lung Imaging Confederation (ELIC). ELIC will provide access to large numbers of high-quality CT images and associated de-identified clinical information, using a cloud-based infrastructure. The IASLC hopes that this image library will help to improve the reliability of CT-based CDS systems worldwide.[46]

Utility of Clinical Decision Support to Predict Outcomes in Cancer

Several systematic reviews have been conducted over the past 5 years to assess the impact of CDS systems in cancer. Beauchemin et al.[12] reviewed studies of CDS systems used to support therapeutic decision-making in cancer, finding that 56% (five out of nine) demonstrated a significant improvement to process outcomes, and 67% (four out of six) demonstrated significant improvements in patient outcomes.[12] A similar review conducted by Klarenbeek et al.[48] analysed 61 publications that evaluated the impacts of higher level CDS systems (those using automated clinical guidelines, artificial intelligence, data mining, or statistical methods). In this review, CDS systems were associated with significant improvements for process outcomes and guideline adherence; however, very few of the studies assessed clinical outcomes, and none identified significant improvements with the use of CDS.[48]

Unfortunately, the quality and utility of CDS systems can be quite variable. Very few are backed up by strong validation data to demonstrate their performance in actual practice. For example, a systematic literature review of systems available for incurable metastatic NSCLC found that few had been validated with recent, external, clinical data, and their calibration and discrimination were often poor.[49]

LIMITATIONS AND NEXT STEPS

The literature raises several potential facilitators and barriers to the implementation of CDS systems for cancer, summarised in Table 1.

Implementation strategy is critical to the success of a CDS system.[24-26] For example, one CDS

Table 1: Potential facilitators and barriers to the implementation of clinical decision support systems for cancer.

Facilitators or benefits	Barriers
Easy access to well-structured patient data[48]	Clinicians' trust in the CDS system[24]
Reduction of MDT preparation time and/or meeting duration[48]	Negative impact on workflow[24,25]
Increased efficiency of workflow[48]	Insufficient adaptability of the system to local and contextual needs[25]
Integration with clinical protocols[50]	Potential requirement for ongoing technical assistance[21]
Simple and transparent overall reasoning structure[50]	
A focus on supporting the diagnostic journey; suggesting the next step, rather than just knowing the direction of a pathway[51]	

CDS: clinical decision support; MDT: multidisciplinary team.

system implemented in an outpatient cancer clinic in Norway to support pain management failed to reduce pain intensity, or significantly change opioid prescriptions. This failure was attributed to poor implementation of the system in the clinic.[52] Part of the difficulty in successful implementation is the potential for a CDS system to be perceived as a threat to clinical judgment by some clinicians, and fear of implementing new technology.[53] Adequate training for the clinicians who will use the CDS system is essential to ensure effective use.

To begin to realise the full potential of CDS in cancer, several steps need to be taken. First, further well-designed trials are needed to evaluate CDS in real clinical environments.[24,50,53] There is a paucity of data evaluating clinically relevant outcomes in oncology, and rigorous evaluation is critical to understand the best way to implement CDS systems to improve patient outcomes.[54] Second, existing guidelines need to be converted into algorithms that can be interpreted by computers,[55] and several attempts have already been made to address this issue.[56,57] Finally, the issue of missing data in EHRs needs to be addressed, since many machine learning algorithms require complete datasets.[58] One approach to this problem was suggested by Baron et al.,[58] who developed a metamodel that produces an aggregate output from cancer modules for which a patient has complete data. The metamodel better predicted survival than many of the individual models. Its performance was similar to that of imputation methods that address missing data, which can be subject to bias.[58]

CONCLUSIONS

Cancer care delivery could be dramatically better than it is. Unwarranted variation results in a considerable waste of resources, indicating that better care can be delivered more efficiently and at lower cost. Effective precision oncology requires the consideration of a vast array of complex data. By integrating these data into CDS systems, we can leverage rapidly increasing knowledge to provide the best possible healthcare services, timely decision-making, and health-related quality of life for patients with cancer. To realise the full potential of CDS systems, we need to address well-documented limitations in current clinical best practice guidelines and data representation; conduct further well-designed trials to demonstrate the utility of CDS systems in cancer care; and improve our understanding of the best way to implement CDS systems into healthcare systems.

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ST Elevation Myocardial Infarction in Patients with COVID-19: Case Series

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Abstract

Severe acute respiratory syndrome coronavirus 2, or COVID-19, has triggered an unprecedented pandemic situation across the globe. Patients with COVID-19 frequently experience a range of clinical complications driven by their health status, comorbidities, and disease responsiveness. Patients with COVID-19 also encounter cardiovascular conditions that potentially increase their risk for mortality. Few clinical studies reveal the development of ST segment elevation myocardial infarction (STEMI) in patients with COVID-19.

New York City, USA, continues to witness and report a high incidence and prevalence of COVID-19 infections. New York City's healthcare centres and hospitals have treated more than 6,000 cases of COVID-19 pneumonia in their inpatient and intensive care units.

The authors conducted a retrospective study of patients admitted to NYC Health + Hospitals, Queens, New York City, USA, with confirmed COVID-19 reverse transcriptase-PCR test findings between 29th March 2020 and 1st May 2020. The authors used a retrospective case series design to evaluate the association between laboratory-confirmed COVID-19 infection and hospitalisation for acute myocardial infarction. They utilised a series of ECGs to record and analyse STEMI patterns across patients with COVID-19. This study aimed to determine the risk/incidence of STEMI in patients with COVID-19, and its impact on their clinical presentation, angiographic findings, and clinical outcomes. The authors hypothesised STEMI as a significant COVID-19 complication, with the potential to impact the long-term prognostic outcomes of patients with COVID-19.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) predominantly leads to COVID-19.[1] The spike glycoproteins over the envelope of the positive-sense single-stranded RNA coronaviruses give them a crown-shaped appearance. The coronaviruses belong to the *Coronaviridae* family, *Orthocoronavirinae* subfamily, and order *Nidovirales.* The 16–140 nm size, pleiomorphic form, elliptical structure, and ability to tolerate lower temperatures of SARS-CoV-2 add to its virulence and pathogenicity. COVID-19 progresses with cough and fever symptoms; however, its clinical manifestations trigger mild respiratory illness in 80% of affected patients. More than 15% of patients with COVID-19 develop severe pneumonia and shock, requiring hospital-based care. Nearly 5% of patients with COVID-19 develop life-threatening complications, requiring medical management in intensive care units (ICU).[2]

Patients with SARS-CoV-2 frequently encounter cardiovascular complications, including Type 1 or 2 myocardial infarction (MI), myocardial injury, ST segment elevation, myocarditis, worsening or new-onset heart failure, cardiogenic shock, severe arrhythmias, and venous thromboembolic episodes.[3] The authors aimed to evaluate the clinical presentation, angiographic findings, and clinical outcomes of STEMI in patients with COVID-19.

The authors identified six patients with COVID-19 with STEMI, who presented initially to a non-percutaneous coronary intervention (PCI)-capable hospital and were transferred to a PCI-capable facility or managed with fibrinolytics. ST segment elevation in some patients developed during their clinical presentation; however, other patients developed it during the course of their hospitalisation. Patients with COVID-19 who underwent cardiac catheterisation had a poor prognosis due to their obstructive and non-obstructive patterns. The multifactorial aetiology and pathophysiology of myocardial injury in these patients warranted further investigation to inform their diagnostic and treatment management.

METHODS

The authors present six cases in this article. Permission was obtained from the Icahn School of Medicine at Mount Sinai Institutional Review Board, New York City, USA (No.: STUDY-21-00049).

RESULTS

Case 1

A 59-year-old male with a history of hypertension arrived at the emergency department (ED) with 2 days of subjective fever and light-headedness. Reverse transcriptase (RT)-PCR testing confirmed the SARS-CoV-2 antigen. The patient encountered decompensation shortly after admission due to multiorgan dysfunction and acute hypoxic respiratory failure, requiring mechanical ventilation. An ECG on the day of admission demonstrated left ventricular hypertrophy and a dilated right ventricle (RV) that appeared hypokinetic on limited views. The left ventricle was not well visualised, but appeared normal in limited views.

The next day, the patient experienced cardiac arrest, followed by the return of spontaneous circulation. The ECG findings revealed sinus rhythm, with a rate of 71, and intraventricular conduction delay; 2 mm ST elevation in leads II, III, and augmented vector foot (aVF); 5 mm ST elevation in leads V4–6; and 2 mm ST elevation in leads I and augmented vector left (aVL), which are consistent with an acute inferolateral STEMI. The decision was then made to administer thrombolytics as the patient became haemodynamically unstable to be transferred for a primary PCI after they had a cardiac arrest. The repeat ECG (Figure 1A) showed 1 mm ST elevation in lead II and aVF, 1 mm depression in lead I and aVL, and 4 mm ST elevation in leads V4–6.

The patient's condition did not favour transfer as they remained haemodynamically unstable and, subsequently, the alteplase infusion was continued. The patient's respiratory and renal functions deteriorated within a few hours of medical management, resulting in intolerable cardiac arrest, and, eventually, the patient expired.

Case 2

An 80-year-old female who was overweight and with a history of hypertension arrived at the ED with subjective fever, cough, and diarrhoea for the last 2 weeks. The patient was found to be COVID-19 positive via an RT-PCR test. The clinical findings revealed a marked elevation in inflammatory markers and bilateral multifocal pneumonia, as seen on their chest X-ray. The D-dimer was elevated to 911 ng/L. ECG on admission showed sinus tachycardia with supraventricular premature complexes and probable old inferior MI. The pro brain-type natriuretic peptide value of 5,308 pg/mL exceeded the normal reference range of 300–900 pg/mL.[4]

The patient was transferred to the ICU for worsening hypoxemic respiratory failure secondary to bilateral pneumonia. The patient developed a pneumothorax, requiring chest tube placement and invasive positive pressure ventilation. Repeat ECG showed ST elevations in leads II, III, aVF, and V4–6, with depressions in leads I and avL (Figure 1B). The cardiac troponin-I level of the patient increased from 0.05 to 2.16 within 4 hours of ICU admission, which exceeded the normal limit of 0.03 ng/mL.[5] The patient's instability restricted her transfer for emergency catheterisation due to a reduction in preload after intrathoracic pressure elevation.[6] The subsequent ECGs after alteplase administration revealed slight improvement in persistent ST elevations.

An ECG after thrombolytics showed an ejection fraction (EF) of 60% with Grade I (mild) left ventricular diastolic dysfunction, dilated RV cavity size, and reduced RV systolic pressure. The pulmonary artery systolic pressure was recorded as 62.76 mmHg. No left ventricular wall motion abnormality was identified; however, subsequent ECGs revealed the resolution of ST elevations and inferior Q waves. The patient's treatment course was complicated by atrial fibrillation, with a rapid ventricular response. The rate control was achieved with amiodarone; however, the patient ultimately expired within a few days of medical management.

Case 3

A 62-year-old female with a medical history of cerebral palsy and dementia was brought in by the emergency medical services from a nursing home after developing respiratory distress and hypoxia (oxygen saturation: 85% at room air). The preliminary emergency room assessment revealed fever, tachycardia, and hypoxia requiring intubation. Telemetry monitoring did not reveal any arrythmia. Cardiology was consulted in the ED for STEMI on ECG. The ECG (Figure 1C) showed 2 mm ST elevation in leads II, III, and aVF; 5 mm ST elevation in leads V2–6; and 1 mm ST elevation in lead I. The initial troponin was recorded as negative; however, neither a repeat troponin nor an initial ECG was obtained.

The COVID-19-related RT-PCR testing showed a positive result, while the D-dimer was elevated to 35,807 ng/dL (exceeding the reference range of 0.4–250.0 ng/mL). The chest X-ray showed extensive right mid–lower lung field (pulmonary) consolidation, and nonspecific left basilar markings. The patient's transfer to another medical facility with PCI capability was also constrained due to haemodynamic instability. The patient received loading doses of aspirin and plavix; however, the patient experienced cardiac arrest and eventually expired in the ED before arriving at the ICU.

Case 4

A 71-year-old male with a history of Type 2 diabetes and hypertension was brought in by the emergency medical services with altered mental status. The patient appeared afebrile but was found to be hypoxic, with oxygen saturation levels of 85%. The chest X-ray was remarkable for bilateral patchy infiltrates. Laboratory workup revealed diabetic ketoacidosis. The patient was admitted to the ICU for further management.

The diabetic ketoacidosis was resolved in ICU; however, the patient required increasing oxygen requirements, and was intubated and placed on mechanical ventilation. The post-intubation ECG revealed ST elevations in the lateral leads with reciprocal depressions in the inferior leads, and severe sinus bradycardia competing for junctional escape (Figure 1D).

Care was escalated and arrangements were made for transferring the patient to another facility for PCI. Loading doses of aspirin and ticagrelor were administered and followed by therapeutic anticoagulation with heparin. The patient, however, experienced polymorphic ventricular tachycardia, which was seen on

telemetry, and arrested before being transferred. Return of spontaneous circulation was achieved after one round of cardiopulmonary resuscitation. The patient was eventually transferred for cardiac catheterisation.

Another ECG revealed new, inferior ST elevations and the resolution of lateral ST elevations. A left heart catheterisation revealed a large proximal right coronary artery (RCA) thrombus, complete thrombotic occlusion of the right posterior descending artery, and a non-occlusive thrombus in the right precordial leads, which restricted the administration of PCI. The decision to withhold PCI relied on the concern for distal embolisation and the underlying thromboembolic process. The anticoagulation protocol was eventually continued that included aspirin, ticagrelor, and cangrelor infusion. The ECG confirmed wall motion abnormalities, including severe hypokinetic left ventricular apex, hypokinetic mid-inferior and inferolateral walls, and severe hypokinetic RV, without any evidence of pulmonary hypertension. The patient continued to decompensate with multiorgan failure and, eventually, expired on the Day 6 of hospitalisation.

Case 5

A 58-year-old male with a history of diabetes and hyperlipidaemia arrived at the ED after 4 days of subjective fever and cough. A chest X-ray revealed ill-defined bibasilar opacities suggestive of multifocal pneumonia. The COVID-19 RT-PCR testing showed a positive result and the patient developed acute onset of chest pain shortly after admission. The ECG revealed Q waves and ST elevation in inferior leads and Q wave in leads V5–6, with ST depression in augmented vector right and aVL (Figure 2A). The patient was transferred to another facility for urgent left heart catheterisation and was found to have RCA occlusion combined with emboli showering to distal territories. Three stents were placed in the RCA and aspiration thrombectomy was performed. The patient developed worsening hypoxic respiratory failure, requiring mechanical ventilation. Aspirin, clopidogrel, and atorvastatin were continued, while therapeutic anticoagulation with enoxaparin was started post-catheterisation.

A follow-up ECG revealed Q waves and persistent ST elevations in the inferior leads. The subsequent ECG demonstrated an EF of 30%, hypokinetic mid-anterolateral and mid-inferolateral wall, severe anterior apical and apical lateral wall hypokinesis, a severely hypokinetic apical septum, and a left ventricular thrombus. The patient was transitioned to intravenous heparin and continued with aspirin and clopidogrel, based on the concern for COVID-19 related myocarditis versus stress cardiomyopathy, due to the pattern of wall motion abnormalities revealed on the ECG. However, the patient's condition deteriorated, and they expired on the Day 10 of their hospital stay.

Case 6

A 40-year-old female, with a medical history significant for Type 2 diabetes, hypertension, and psychiatric disorder, arrived at the ED with a productive cough and shortness of breath for 6 days and severe, constant, and non-radiating retrosternal chest pain for 24 hours. The patient was admitted with the impression of acute hypoxic respiratory failure, requiring supplemental oxygen, likely secondary to COVID-19. The SARS-CoV-2 infection was confirmed via an RT-PCR.

The ECG on admission indicated sinus tachycardia (Figure 2B). The initial troponin finding was negative; however, the patient complained of worsening chest pain the following day and a repeat ECG revealed acute ST elevation in leads II, III, aVF, and V2–6, and reciprocal ST depressions in lead I and aVL (Figure 2C). The patient was loaded with aspirin, clopidogrel, and started on atorvastatin. The therapeutic anticoagulation was administered with heparin and the patient was transferred for cardiac catheterisation. A thrombotic lesion was found in the ostium of the left anterior descending artery, requiring PCI. The high thrombus burden attributed to the distal left circumflex coronary artery was treated with intracoronary alteplase.

The point of care ultrasound indicated a severely reduced EF of 10–15%, with diffuse wall motion abnormalities. The patient's course of treatment was complicated by cardiogenic shock, requiring mechanical ventilation during the PCI procedure. The Impella® (Abiomed, Danvers, Massachusetts, USA) was subsequently placed for reversing the cardiogenic shock (cardiac index: 1.7 on pulmonary artery catheter). The patient's clinical course, however, did not improve, and they expired 2 days later.

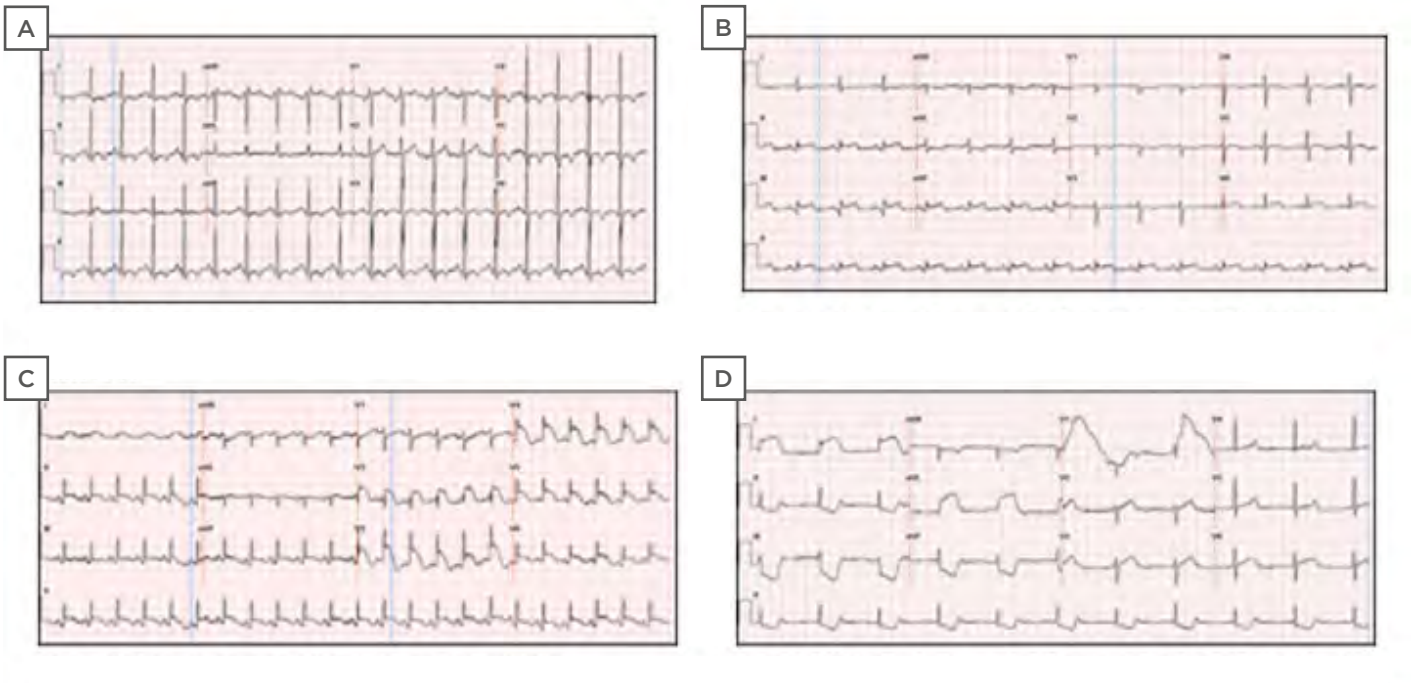

Figure 1: ECG ST segment elevation in four patients (cases 1–4) with COVID-19.

A) ECG ST segment elevation in lead II and aVF, and a 1 mm depression in lead I, aVL, and 4 mm ST segment elevation in leads V4–6. **B)** ECG showed ST segment elevation in leads II, III, aVF, and V4–6 and ST depressions in lead aVL. **C)** ST segment elevation in leads II, III, aVF, and leads V2–6. **D)** ECG post-intubation revealed ST segment elevations in the lateral leads, reciprocal ST segment depressions in the inferior leads, and severe sinus bradycardia competing for junctional escape.

aVF: augmented vector foot; aVL: augmented vector left.

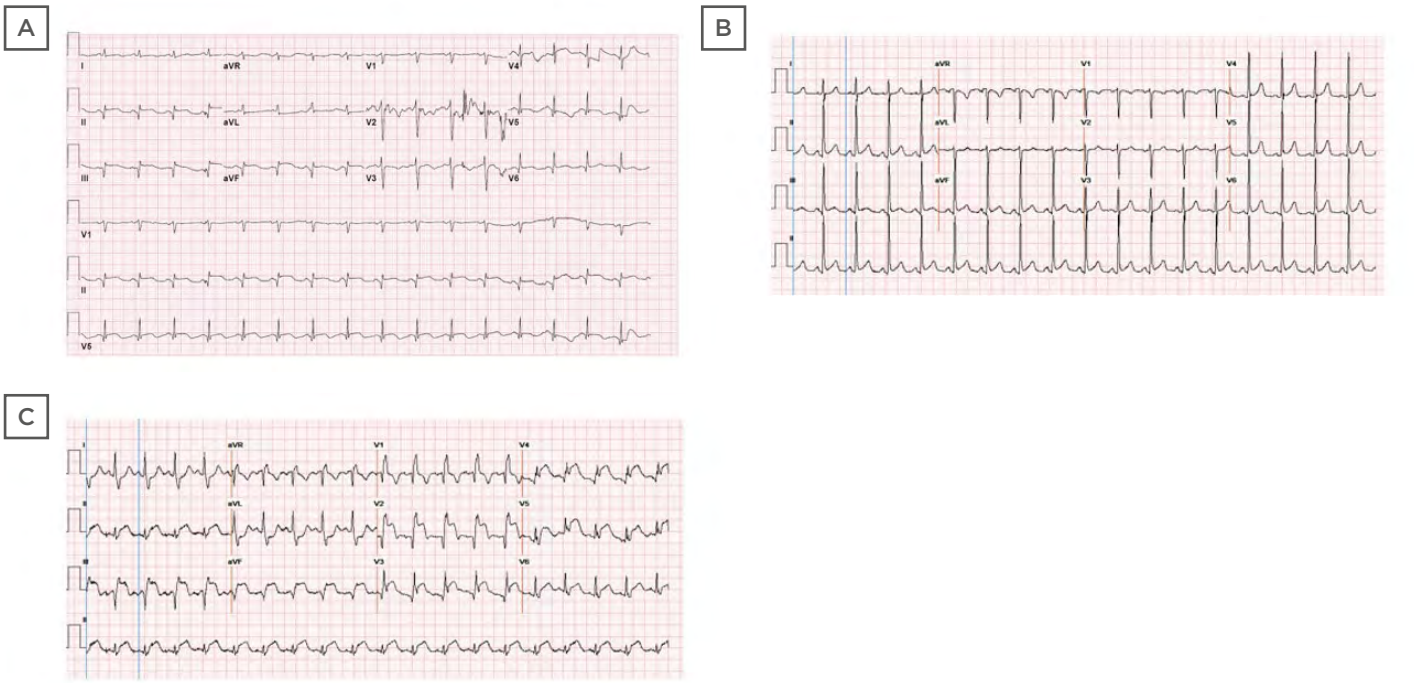

Figure 2: ECGs of two patients (Cases 5 and 6) with COVID-19.

A) ECG revealed Q waves and persistent ST elevations in the inferior leads. **B)** Initial ECG on presentation demonstrated sinus tachycardia. **C)** Repeat ECG revealed acute ST segment elevation in leads II, III, aVF, and V2–6.

aVF: augmented vector foot.

DISCUSSION

Several studies have highlighted a constellation of observed cardiovascular consequences that appear unique to COVID-19. The evidence of myocardial injury attributing to troponin level elevation was found to be common among patients hospitalised for COVID-19. The potential causes that trigger this troponin elevation include stress cardiomyopathy, hypoxic injury, and an ischemic injury from a systemic inflammatory response syndrome. The clinical observations confirm a wide variety of findings in patients with COVID-19 based on their ST elevations on ECG and emergent angiography status. The findings vary from classic obstructive coronary artery disease, non-obstructive coronary artery disease, normal epicardial coronary arteries, and/or left ventricular dysfunction due to myocarditis or stress-induced cardiomyopathy.[7]

The authors identified six patients with COVID-19 with ST segment elevation, indicating the onset of acute MI. They determined a marked variation in the baseline characteristics and clinical presentation of the included patients. They further tracked the development of severe COVID-19 manifestations that potentially complicated medical management of treated patients. Details regarding pertinent history, baseline characteristics, laboratory, and ECG findings are outlined in Table 1. The authors postulate that the symptomatology, signs, and manifestations of COVID-19 may have concealed the classic symptoms and presentations of acute MI, thereby leading to its underdiagnosis. The ECG findings concerning the selected patients revealed normal or abnormal wall motions. The COVID-19 candidates for cardiac catheterisation prevalently developed obstructive pulmonary disease. The authors' observations further revealed marked elevations in the D-dimer levels of the treated patients.

A clinical study revealed elevated D-dimer levels in patients who underwent primary PCI for STEMI. The higher D-dimer levels correlated with larger MI size, suggesting that D-dimer may be a diagnostic marker of advanced myocardial injury.[8] Myocarditis has been shown to mimic acute coronary syndrome and has been associated with COVID-19 with high mortality. It is challenging to differentiate myocarditis from acute coronary syndrome in the acute setting. Endomyocardial biopsy is the gold standard for the diagnosis of myocarditis, but it is an invasive procedure that, at the peak of the pandemic, posed several limitations to the patient and the healthcare worker. The cases above who presented with dynamic ECG changes with preserved left ventricular EF were suggestive of unobstructed coronaries, raising the concern for myocarditis.

The clinicians continue to observe several plausible factors concerning cardiac injury throughout the COVID-19 pandemic. The arteriovenous thrombosis is a hallmark of severe COVID-19 infection and correlates with vascular injury and prothrombotic cytokines released due to intense systemic inflammatory responses.[9] The prothrombotic and procoagulant states may potentially elevate the risk of coronary thrombosis at the sites of plaque disruption. The factors contributing to coronary thrombosis include the production of neutrophil extracellular traps (from intraplaque and circulating neutrophils), increased platelet activity, elevated accumulation of procoagulants or tissue factor, impaired fibrinolysis, and overall disruption of anticoagulant function of the endothelium.[10] The clinical studies postulate cytokine storm, hypoxic injury, and coronary spasm or microthrombi as the significant factors with the potential to trigger myocardial injury in patients with COVID-19.[11]

An Italy-based systematic pathological analysis correlated Type 2 MI with the development of microthrombi in the coronary vasculature of patients with COVID-19. The pathologists revealed marked differences in composition between microthrombi and intramyocardial thromboemboli in subjects who were COVID-19-negative and coronary thrombi retrieved from patients with STEMI who were COVID-19-positive/negative.[12] The previously reported clinical studies also highlight the impact of acute infections on the MI predisposition of patients with COVID-19. The medical literature additionally provides evidence concerning the attribution of systemic viral infections or influenza to the development of acute MI and inflammation.[13] Plausible evidence correlates STEMI events with the systemic inflammatory responses triggered by COVID-19 infection.

Table 1: Baseline characteristics and case details of six confirmed patients with COVID-19 and acute myocardial infarction.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	59	84	62	71	58	40
Gender	Male	Female	Female	Male	Male	Female
BMI (kg/m^2)	27.67	26.52	NC	24.91	26.98	33.28
Race	N/A	N/A	N/A	N/A	Non-Hispanic	African American
Risk factors	Hypertension, overweight	Hypertension, overweight	Cerebral palsy, dementia	Diabetes, hypertension	Diabetes, hyperlipidaemia	Diabetes, hypertension
Presenting symptoms	Subjective fever, light-headedness	Cough, fever, diarrhoea	Respiratory distress	Altered mental status	Subjective fever, cough	Chest pain, shortness of breath, cough
Antiplatelet therapy	ASA (325 mg)	ASA (325 mg)	ASA (325 mg)	ASA (325 mg)	ASA (325 mg)	N/A
Troponin T (ng/mL) Follow-up* Peak	0.079 0.155 0.217	0.050 0.082 2.160	<0.010 N/A N/A	0.079 N/A N/A	<0.010 0.060 N/A	<0.010 0.384 N/A
Time to STEMI presentation	0 days	5 days	0 days	1 day	8 days	0 days
Findings on chest radiography	N/A	Bilateral infiltrates (right greater than left)	Extensive right to mid–lower lung field consolidation, nonspecific left basilar markings	Patchy opacities in the chest bilaterally, with relatively peripheral distribution	Ill-defined bibasilar opacities	Patchy airspace disease within the mid and lower lung zones bilaterally
Pro-BNP (pg/mL)	1,092	5,308	N/A	N/A	N/A	N/A
D-dimer (ng/mL)	1,064	5,679	35,807	14,559	1,036	7,658
LDH (U/L)†	>900	741	N/A	3,398	1,368	2,824
CRP (mg/L)	>300.00	179.40	N/A	N/A	136.69	35.90
ECG interpretation	IVCD, STE II, III, aVF, V2–6, I, aVL	STE II, III, aVF and V4–6	STE II, III, aVF, V2–6	STE	STE II, III, aVF	STE II, III, aVF, V2–6

Table 1 continued.

ECG findings	No WMA	No WMA	NP	WMA	WMA Apical LV thrombus	WMA Severe reduced EF
Coronary angiography	NP	NP	NP	Complete thrombotic occlusion of RCA and RPDA	RCA occlusion	100% stenosed (thrombotic), ostial LAD lesion
Treatment	Alteplase, ASA, clopidogrel	Alteplase, ASA	ASA, clopidogrel	Systemic anticoagulation	ASA, clopidogrel, thrombectomy, PCI	Thrombectomy, PCI, ASA, Brilinta, cangrelor, Impella
Outcome	Cardiac arrest	Cardiac arrest	Cardiac arrest	Ventricular tachycardia, torsades, arrest	Cardiac arrest	Cardiogenic shock

*Follow-up laboratory values typically obtained within 6–12 hours of initial results.

†Reference range: 135–225 U/L.

ASA: aspirin; aVF: augmented vector foot; aVL: augmented vector left; BNP: brain-type natriuretic peptide; CRP: C-reactive protein; EF: ejection fraction; IVCD: intra ventricular conduction delay; LAD: left anterior descending; LDH: lactate dehydrogenase; LV: left ventricle; N/A: not applicable; NC: not calculated; NP: not performed; PCI: percutaneous coronary intervention; RCA: right coronary artery; RPDA: right posterior descending artery; STE: ST segment elevations; STEMI: segment elevation myocardial infarction; WMA: wall motion abnormality.

The COVID-19-related clinical guidance by the American College of Cardiology (ACC) reveals that COVID-19 complications commensurate with SARS, Middle East respiratory syndrome, and influenza analogues. Pre-COVID-19 data regarding the influenza virus suggest that patients with acute respiratory infections are highly predisposed to atherosclerotic plaque rupture and eventual MI, under the impact of profound inflammatory responses and haemodynamic changes.[14,15]

The standard treatment protocol for patients with STEMI includes invasive revascularisation (within 90 minutes of hospital presentation), or fibrinolytic therapy in the absence of invasive revascularisation (after 90 minutes of hospital presentation). Fibrinolytic therapy has recently gained much attention, based on its potential to treat COVID-19-related STEMI in medical centres without cardiac catheterisation facilities. The challenges concerning medical management of STEMI in COVID-19 reciprocate with the unstable presentations of undetermined aetiologies. Furthermore, the clinical correlation between ST segment elevation and its potential causes in patients with COVID-19 appears highly challenging in emergencies. The clinical studies have yet to determine the mortality attribution of ST segment elevation in COVID-19 scenarios. Future studies also need to evaluate the risks and benefits of fibrinolytic therapy in the setting of COVID-19. The current body of evidence appears clueless regarding the MI predisposition of patients with COVID-19 following their acute or short-term post-infection period. Patients with COVID-19 experience a high predisposition for aggressive inflammatory responses that potentially increase their risk for hypercoagulability. However, future studies still need to determine the long-term prognosis of acute coronary syndrome in patients with COVID-19.

The authors' study has several limitations. Firstly, they relied on the findings of a single hospital, which challenged the generalisability of findings across other hospital settings with cardiac

catheterisation capabilities in New York City. The reporting of incomplete data in the selected case reports increased the risk of information bias to many folds.

Secondly, the authors may have missed many cases concerning ST elevation MI and inappropriate treatments due to the surge of patients in the ED. Thirdly, the ECGs were not performed on many patients periodically, despite their troponin elevation, due to the probable masking of their symptoms by concurrent respiratory failure. The awareness of these limitations could have improved the medical management and treatment outcomes of patients with COVID-19.

CONCLUSION

Exploring the significant unknowns regarding the short and long-term sequelae of COVID-19 infection among hospitalised patients is key to improving treatment outcomes. Respiratory tract symptoms mostly determine the clinical course of COVID-19 infection, yet there appears to be a unique interplay between coronavirus disease and acute coronary syndrome. The recognition of ST elevation MI as a complication of COVID-19 may inform its diagnostic monitoring, and help to determine prognostic outcomes. This case series highlights the importance of clinical surveillance and laboratory testing in the subgroup of patients with COVID-19, to analyse their atypical symptomatology, and avoid potential delays in recognising their treatment modalities. The authors determined a critical knowledge gap concerning baseline characteristics, comorbidities, revascularisation strategies, and outcomes of admitted patients with COVID-19-related ST elevation MI. Their findings advocate the standardisation of diagnostic and therapeutic protocols to enhance the medical management of patients with COVID-19 with STEMI.

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Reactive Hip Arthritis and Avascular Necrosis After Severe COVID-19 Infection: A Case Report and Comprehensive Review of Literature

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Abstract

COVID-19 has variable clinical presentations, severity, and multisystem involvement. Some patients have encountered arthralgia and myalgia symptoms. Reactive arthritis is an emerging musculoskeletal manifestation post-COVID-19 infection. The authors report a 29-year-old male, previously healthy, who developed acute left hip arthritis 8 weeks after recovering from severe COVID-19 pneumonia. It was associated with bilateral avascular necrosis of femoral heads, with medullary bone infarctions at both proximal tibias. Human leukocyte antigen-B27 was positive and synovial fluid culture, autoimmune workup, crystals, and infectious aetiologies were negative. The patient's clinical condition improved with the use of non-steroidal anti-inflammatory drugs and physiotherapy. To the best of the authors' knowledge, this is the first case reported of hip arthritis and avascular necrosis following the COVID-19 infection. In addition, the authors reviewed the literature for the reported reactive arthritis cases post-COVID-19 infection and management outcomes.

INTRODUCTION

The incidence of the COVID-19 infection is increasing globally, with an estimated mortality rate of 3.5%. The cardinal presenting symptoms of COVID-19 infection are fever, cough, and shortness of breath. Gastrointestinal symptoms, and musculoskeletal complaints (arthralgia and myalgia) have been encountered in 15–30% of patients.[1] The clinical severity ranged from mild disease to severe pneumonia, multi-organ failure, and death. Cytokine storm or cytokine release syndrome might contribute to extra-pulmonary involvement of COVID-19 such as acute kidney injury, venous thrombosis, neurological complications, and hepatic and myocardial injury.[2]

Reactive arthritis is an emerging musculoskeletal (MSK) manifestation post-COVID-19 infection. The authors report a case of acute arthritis in the left hip and bilateral avascular necrosis (AVN) of femoral heads, with medullary bone infarctions at both proximal tibias developed 8 weeks after severe COVID-19 pneumonia.

CASE DESCRIPTION

A 29-year-old athletic male from Jordan, who was previously healthy, tested positive for COVID-19 on 20th May 2020, with initial presenting symptoms of fever, myalgia, breathing difficulty, and a cough. They were a non-smoker and did not drink alcohol. There was no previous allergy and no family history of rheumatologic diseases.

The patient's clinical condition deteriorated with development of acute respiratory failure due to respiratory distress syndrome and severe COVID-19 pneumonia. They required mechanical ventilation and prolonged critical care in another hospital. They were treated with combination of experimental anti-COVID-19 therapies, including favipiravir (1,600 mg orally twice daily [BID] on Day 1, and 600mg orally BID for 10 days), hydroxychloroquine (400 mg orally BID on Day 1, then 200 mg orally BID for 4 days), tocilizumab (400 mg intravenously [IV] once), and methylprednisolone (40 mg given IV daily for 5 days). They had nosocomial infection (urosepsis) and were treated successfully with broad-spectrum antibiotics (ertapenem). The patient required physiotherapy for critical illness neuropathy and chest physiotherapy, with gradual improvement. They were discharged on 3rd August 2020 in a stable clinical condition with mild left hip pain.

On 3rd November 2020, the patient presented to the authors' hospital with a 2-day history of fever, shortness of breath, worsening productive cough, and severe left hip pain, with limited mobility. The patient noticed mild non-traumatic left hip pain after their first hospital discharge, which got worse over time. A review of systems was negative for back pain, other joint involvement, skin rash, oral or genital ulcers, diarrhoea, and eye redness. They had no recent contact with sick individuals or recent travel. In the emergency department, they were febrile (38.1 °C), had sinus tachycardia (116 beats/min), and were in mild respiratory distress (respiratory rate of 25 breaths/min). Their blood pressure was 115/75 mmHg and BMI was 22.02 kg/m^2. There was evidence of bilateral crackles involving the upper and middle zones of the lungs. Their cardiovascular exam was normal. A MSK examination revealed tenderness in left hip area, with limited range of movements. Other physical examinations were unremarkable.

Their laboratory investigations revealed normal liver, kidney, and thyroid function tests, and for uric acid. Inflammatory markers were elevated, including C-reactive protein (66.000 mg/L), erythrocyte sedimentation rate (102.000 mm/hour), and D-dimer (2.680 mg/L) levels (Table 1). Deep venous thrombosis and pulmonary embolism were ruled out by an ultrasound Doppler of lower legs and a CT pulmonary angiography, respectively. They had evidence of post-COVID-19 pulmonary changes, including peribronchial consolidation in the upper lobes and traction bronchiectasis (Figure 1A and B). They were admitted as case of acute pneumonia and was started on oral amoxicillin-clavulanic acid (1 g every 8 hours for 5 days) and albuterol/ipratropium via nebuliser.

Baseline imaging tests for the left hip were not taken previously. The left hip X-rays were normal. MRI with gadolinium of the hip showed left hip joint effusion, with peripheral synovial enhancement, AVN of subtrochanteric femoral heads, and medullary bone infarctions located in distal right femur and both proximal tibias (Figure 1C and D).

Autoimmune workup was negative as well as infectious tests (including HIV, hepatitis B and C virus, Brucella, mycoplasma, and tuberculosis [Table 1]). Blood and sputum cultures were negative. On Day 6 of admission (after 1 day of completing the antibiotic course), the patient's left hip pain did not improve, and they underwent ultrasound guided aspiration of the left hip effusion. Fluid analysis revealed turbid, yellow fluid, red blood cell count of 18,000 cells/mm^3,

Table 1: Laboratory results of the authors' patient.

Laboratory testing	Results	Normal range
Sodium (mmol/L)	136	136–145
Potassium (mmol/L)	4.2	3.2–5.5
Bicarbonate (mmol/L)	24	22–29
Creatinine (µmol/L)	81	62–106
Urea (mmol/L)	3.3	2.8–8.1
Ferritin (µg/L)	232	30–400
WBC ($x10^9$/L)	12.3	4.5–11.0
Lymphocytes ($x10^9$/L)	3.46	1.50–4.00
Haemoglobin (g/L)	139	132–173
Platelets ($x10^9$/L)	372	140–400
Procalcitonin (ng/mL)	0.03	≤0.50
CRP (mg/L)	66	≤5
D-dimer (mg/L)	2.680	0.129–0.523
AST (IU/L)	17	≤40
ALT (IU/L)	14	≤41
Vitamin D level (nmol/L)	35	50–150
Serum uric acid (µmol/L)	371	N/A
Brucella titre	<1:80	*B. abortus*: <1:80 *B. melitensis*: <1:80
ESR (mm/hour)	102	0–20
Antinuclear antibody	Negative	N/A
Rheumatoid factor (IU/mL)	15	≤14
Anti-CCP antibodies (units/mL)	0.0	<0.5
Anti-cardiolipin IgG (CU)	<2.6	≤20.0
β_2 glycoprotein IgG (CU)	<6.4	≤20.0
HLA-B27	Positive	N/A
Anti-hepatitis B surface antibody	Negative	N/A
Anti-hepatitis C virus antibody	Negative	N/A
Sickle cell screen	Negative	N/A
Culture results	Blood: negative Sputum: negative Synovial fluid: negative	N/A

ALT: alanine aminotransferase; AST: aspartate aminotransferase; *B. abortus*: *Brucella abortus*; *B. melitensis*: *Brucella melitensis*; CRP: C-reactive protein; CU: chemiluminescent units; CCP: cyclic citrullinated peptide; ESR: erythrocyte sedimentation rate; HLA: human leukocyte antigen; N/A: not applicable; WBC: white blood cell.

white blood cell count of 45,684 cells/mm^3, 91% neutrophils, no crystals, and the culture was negative. Orthopaedic and rheumatology teams were consulted, and the patient was treated with anti-inflammatory medications (40 mg of parecoxib given IV for 4 days, then naproxen 500 mg BID) for reactive left hip arthritis and AVN.

X-rays of the lumbosacral spine and sacroiliac joints were normal. On Day 8 of admission, they underwent left femoral head core decompression by the orthopaedic team. In addition to regular physiotherapy, their clinical condition improved dramatically within 2 weeks of hospitalisation period. They were discharged home on naproxen 500 mg BID

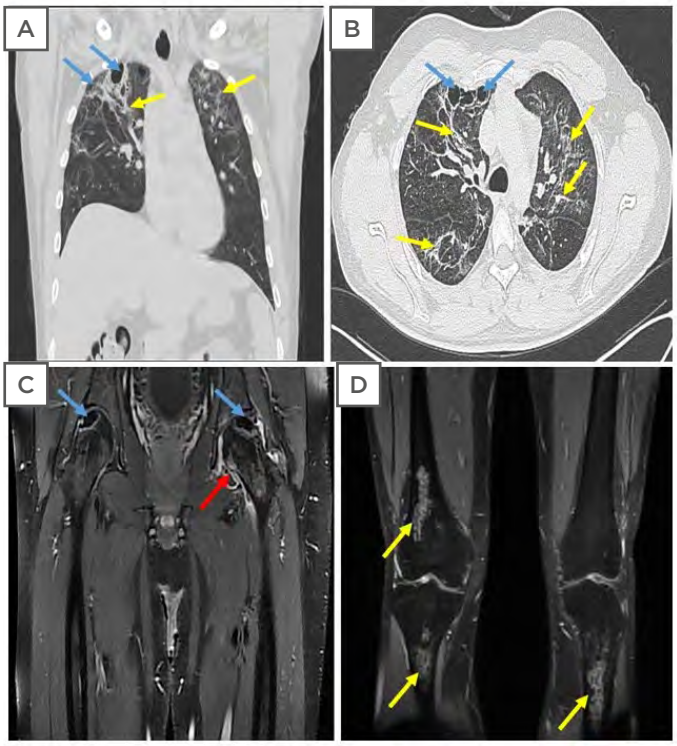

Figure 1: CT and MRI scans of the patient.

A) and **B)** Chest CT after 2 months following severe COVID-19 pneumonia showing parenchymal distortion, fibrotic changes (yellow arrows), and multiple subpleural cysts (blue arrows). **C)** and **D)** MRI of the bilateral femurs (coronal T1 fat-saturated post-contrast images), geographic abnormal signals involving bilateral superolateral femoral heads (blue arrows); left hip joint effusion (red arrow), with peripheral synovial enhancement; and medullary serpiginous abnormal signals in the distal right femur and bilateral proximal tibias in keeping with multi-focal medullary bone infarctions (yellow arrows).

and an albuterol inhaler. The human leukocyte antigen (HLA)-B27 came back positive after discharge on Day 14. After a 2-week follow up at telemedicine clinic, the patient reported no pain at left hip joint and good mobility with use of naproxen. At the rheumatology clinic follow-up after 6 weeks, the patient was in a stable clinical condition and non-steroidal anti-inflammatory drug (NSAID) therapy was stopped.

DISCUSSION

Reactive arthritis is a form of spondyloarthropathy, with reported incidence of 0.6–27.0 per 100,000 in population-based studies.[3] It affects mostly young males (aged 20–50 years) and occurs 1–6 weeks following symptoms of a gastrointestinal or genitourinary (GU) infection. About 50% of cases are associated with HLA-B27.[4] The underlying pathophysiologic process is not well established and linked to an immune-mediated activated cytotoxic-T cells following an infection, inflammatory cytokines production, synovial injury, and molecular mimicry.[5,6]

Reactive arthritis manifests as asymmetrical oligoarthritis, mainly involving peripheral or axial joints of lower extremities. Extra-articular manifestations associated with reactive arthritis include MSK (enthesitis, tendinitis, dactylitis), eye (conjunctivitis, episcleritis, anterior uveitis), GU (urethritis, cervicitis, cystitis, prostatitis, circinate balanitis), mucosal and skin involvement (mucosal ulcers, keratoderma blennorrhagica, erythema nodosum), nail changes, and, rarely, cardiac involvement (conduction, aortic valve abnormalities).[6,7] The systematic approach and screening for multisystem involvement is essential for the diagnosis of reactive arthritis.

The most commonly reported infections associated with reactive arthritis are HIV,

bacterial GU infections (*Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma hominis,* and *Ureaplasma urealyticum*), and gastrointestinal infections (*Salmonella, Shigella, Campylobacter jejuni, Yersinia enterocolitica,* and *Clostridium difficile*). *Chlamydia pneumoniae* can be associated with acute respiratory infection and reactive arthritis.[6,8] Screening for relevant infectious aetiologies in reactive arthritis is required. Inflammatory mediators might be elevated with negative culture results. Testing for HLA-B27 and other autoimmune work-up is needed. In the acute phase, plain radiographs might be normal or reveal non-specific joint findings. MRI or ultrasonography are more sensitive in detecting peripheral synovitis, enthesitis, and sacroiliitis.[4,6,9]

On the other hand, COVID-19 associated reactive arthritis is rarely reported. The authors had a review of 11 cases of post-COVID-19 reactive arthritis.[10] The authors conducted a literature review with a search from January 2020 to August 2021 and using PubMed, Google Scholar, and Mendeley. Search keywords were appropriate to the topic and not limited to: "reactive arthritis," "joint pain," "COVID-19," "SARS-CoV-2 infection," "effusion," and "musculoskeletal." A total of 25 cases fulfilled the inclusion criteria. The mean age of patients was 42.36 years and 56% of patients were males (Table 2).[4,9,11-31] The median duration of reactive arthritis diagnosis from COVID-19 infection ranged from 4 days to 8 weeks. Around half of the patients had mild COVID-19 infection (n=14 [56%]), while 16% of patients had either moderate or severe disease. Interestingly, there was similar range of joints involvement reported in COVID-19 reactive arthritis, including monoarticular involvement (36%), oligoarticular (2–4 joints; 32%), and polyarticular involvement (>4 joints; 32%). Seven patients had synovial fluid analysis reported as inflammatory with negative culture, crystals, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR result. The authors' patient had delayed left hip arthritis, occurring 8 weeks after COVID-19 infection.

Table 2: Characteristics of the 25 reported cases (including the authors' patient) of reactive arthritis post-COVID-19 infection.

Clinical data of patients (n=25)	Results (n=25)
Age (mean)	42.36 years old
Sex	Female: n=11 (44%) Male: n=14(56%)
Severity of COVID-19 infection	Mild: n=14 (56%) Moderate: n=4 (16%) Severe: n=4 (16%) N/A: n=3 (12%)
Prior history of rheumatologic disease	n=0
Time to onset of reactive arthritis (median)	4 days–8 weeks
Number of joints involved at time of diagnosis	Monoarticular: n=9 (36%) Oligoarticular (2–4 joints): n=8 (32%) Polyarticular (>4 joints): n=8 (32%)
Location of involved joints (upper versus lower limbs)	Upper joints: n=5 (20%) Lower joints: n=11 (44%) Both: n=9 (36%)
Enthesitis	Achilles: n=1 (4%)
Extra-articular involvement (eyes, skin, GI, GU, and others)	Skin rash, including erythematous itchy rash, urticarial rash, skin psoriasis, and palpable purpura: n=4 (16%) GU (balanitis): n=1 (4%) GI (diarrhoea): n=1 (4%) Dactylitis (foot): n=1 (4%)

Table 2 continued.

Inflammatory back pain	n=3 (12%)
AVN of bone	n=1 (4%)
HLA-B27	Of the 14 patients tested: n=5 (20%)
Autoimmune workup	Negative
Treatment of reactive arthritis	DMARDs: n=2 (8%) NSAIDs: n=10 (40%) Steroids: n=3 (12%) NSAIDs and steroids: n=10 (40%) Not provided: n=2
Outcomes of MSK symptoms	Improvement: n=25 (100%) Recurrence: n=2
Follow-up period (median weeks)	1.5–12.0

AVN: avascular necrosis; DMARD: disease-modifying anti-rheumatic drug; GI: gastrointestinal; GU: genitourinary; HLA: human leukocyte antigen; MSK: musculoskeletal; N/A: not applicable; NSAID: non-steroidal anti-inflammatory drug.

Extra-articular manifestations were identified in 40% of patients, including skin rash (erythematous itchy rash, urticarial rash, skin psoriasis, palpable purpura), diarrhoea, dactylitis, wrist tendinitis, Achilles enthesitis/tendonitis, and balanitis. Of all the patients, 12% had inflammatory back pain. Autoimmune workups were unremarkable in most of cases. HLA-B27 testing was completed in 14 patients and only five patients (20%) had positive results. Plain radiographs and MRI were used to identify extent reactive arthritis, with findings ranging from tenosynovitis, joint effusion, and sacroiliitis being noted in some patients who had tested positive for HLA-B27.

In this cohort, 40% of patients were managed with either NSAIDs alone, or a combination of NSAIDs and steroid (oral, intra-articular). Other patients were managed with corticosteroids (n=3 [12%]), while two patients (8%) with recurrent disease required disease-modifying anti-rheumatic drugs (certolizumab, sulfasalazine) and spontaneous resolution without medical therapy have been reported (n=2).

Favourable outcomes of COVID-19 reactive arthritis were noted in all patients. The median follow-up period ranged from 1 week to 3 months. A follow-up with the rheumatology team is helpful in such patients to indicate laboratory, radiological, and clinical improvement. In general, reactive arthritis is a self-limiting disease and patients who are positive for HLA-B27 have a high-risk of chronic recurrent disease and sacroiliac joint involvement.

Viral arthritis is another entity reported to affect around 1% of patients with acute inflammatory arthritis.[32] Fever, arthralgia, arthritis (monoarticular or polyarticular) and rash can develop during an acute viral infection. Various viral pathogens reported with different pattern of joints involvement such as parvovirus, Epstein–Barr virus, HIV, *Chikungunya virus*, *Zika virus*, and hepatitis B and C viruses.[17] Acute arthritis diagnosed in patients with COVID-19 is uncommon. López-González et al.,[33] reported 81 (26.4%) out of 306 patients with COVID-19 complained of arthralgia and myalgia at presentation. Four adult males (1.3%) developed acute arthritis (mean age: 60.25 years) and onset of arthritis ranged from 3–21 days. All the patients had prior history of recurrent crystals induced arthritis and they had a flare up of arthritis gout (n=3) and calcium pyrophosphate disease (n=1) during acute COVID-19 infection. The results of reverse transcriptase-PCR for SARS-CoV-2 RNA in synovial fluid were negative.[33]

AVN of bilateral femoral and multi-focal medullary bone infarctions involving right femur and both proximal tibias were noted in the authors' patient. Such distinctive abnormalities were not reported in association with the COVID-19 infection prior to the authors' case. There is compromised subchondral microcirculation leading to infarction of the bone due to various aetiologies. Systemic lupus erythematosus, alcohol, and sickle cell anaemia are among the differential diagnosis of AVN that were ruled out in the authors' patient.

Corticosteroid use has been associated with 10–30% of AVN cases in retrospective studies.[34] The use of corticosteroids in severe COVID-19 infection is supported by clinical trials.[35] A prolonged use of corticosteroids in COVID-19 infection might predispose to AVN. Furthermore, the cumulative dose of 2,000 mg of prednisolone or its equivalent has been associated with AVN development.[36] However, the authors' patient received only a 5-day course of IV corticosteroids (cumulative dose: 200 mg) and had no other risk factors for AVN. Larger follow-up studies need to be conducted to understand the risks of AVN following corticosteroid use in patients with COVID-19 patients. In addition, a severe COVID-19 infection might increase the risk for AVN due to hypercoagulation caused by cytokine activation syndrome.[37]

It is possible that AVN and reactive arthritis in the authors' patient were directly linked to the COVID-19 infection and exacerbated by an unidentified superimposed infection. The authors could not identify the organism causing pneumonia in the second hospital admission on sputum, blood, and respiratory viral panel PCR. The HLA-B27 positivity may been genetically predisposed the authors' patient to develop reactive arthritis post-COVID-19 infection.

CONCLUSION

Reactive hip arthritis and AVN are rare MSK manifestations after a severe COVID-19 infection. HLA-B27 positive testing might indicate a severe and delayed form of arthritis with risk of recurrence. NSAIDs, either alone or combination with steroids, had favourable outcomes.

Larger studies are required to delineate the potential risk factors, clinical involvement, and long-term management outcomes for reactive arthritis and AVN associated with the COVID-19 infection.

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Genome Editing as a Vehicle to Drive Successful Chimeric Antigen Receptor T Cell Therapies to the Clinic

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Abstract

Chimeric antigen receptor (CAR) T cells have emerged as an effective therapy for patients with relapsed and refractory haematological malignancies. However, there are many challenges preventing clinical efficacy and thus broader translation of this approach. These hurdles include poor autologous T cell fitness, manufacturing issues and lack of conserved tumour-restricted antigens to target. Recent efforts have been directed toward incorporating genome editing technologies to address these challenges and develop potent CAR T cell therapies for a diverse array of haematopoietic cancers. In this review, the authors discuss gene editing strategies that have been employed to augment CAR T cell fitness, generate allogeneic 'off-the-shelf' CAR T cell products, and safely target elusive myeloid and T cell cancers that often lack appropriate tumour-specific antigens.

INTRODUCTION

Haematologic malignancies are a heterogeneous group of cancers, which include leukaemia, lymphoma, and multiple myeloma. These diseases are a major global health burden, with an estimated 1.28 million new cases annually, representing approximately 6–7% of all global cancer cases.[1] Incidence of these malignancies have been on the rise, with a 26% and 45% increase in leukaemia and non-Hodgkin lymphoma, respectively, from 2006 to 2016.[2] Current standard treatments for haematologic malignancies include stem cell transplantation,

chemotherapy, and radiation therapy. These therapies have traditionally focused on reducing the burden of malignant cells, and an expanding palette of drugs targeting these tumour cells is now clinically available. Although the vast majority of newly diagnosed patients are expected to respond to initial treatments that incorporate novel targeted agents such as inhibitors of B cell signalling pathways, these strategies are rarely curative.[3] Further, despite these advances, and even in individuals who achieve deep molecular remissions, many individuals relapse with disease that becomes progressively more refractory to successive lines of therapy.[4,5] Prolonged treatment also has significant medical, social, and economic costs, and patients who become resistant have a very poor prognosis.

Cellular immunotherapies have emerged as exciting and effective therapeutic options for patients. CAR T cell therapy in particular has demonstrated remarkable clinical efficacy, leading to sustained remissions in a large percentage of treated patients with relapsed and refractory leukaemia and lymphoma.[6-8] With these therapies, a patient's T cells are typically engineered *ex vivo* to express a chimeric receptor containing an extracellular single-chain variable fragment fused to intracellular signalling domains, comprised of CD3ζ and costimulatory domains (e.g., CD28 or 4-1BB).[9] The single-chain variable fragment portion of the synthetic receptor binds antigens on the surface of tumour cells, initiating signalling through CD3ζ, enhanced by costimulatory signalling, to elicit T cell mediated cytotoxicity. The successes of several CAR T cell clinical trials have paved the way for five U.S. Food and Drug Administration (FDA)-approved CAR T cell therapies, three of which have also gained European Medicines Agency (EMA) approval. Four of these therapies (Kymriah [tisagenlecleucel], Yescarta [axicabtagene ciloleucel], Tecartus [brexucabtagene autoleucel], and Breyanzi [lisocabtagene maraleucel]) target CD19, a B cell lineage marker present on malignant and healthy B cells.[10] These therapies are approved for treatment of relapsed/refractory B cell acute lymphoblastic leukaemia (B-ALL), diffuse large B cell lymphoma, mantle cell lymphoma, and/or large B cell lymphomas.[11-14] Recently, Abecma (idecabtagene vicleucel) was also approved by the FDA as the first CAR T cell therapy to target B cell maturation antigen for patients with multiple myeloma who progress or do not respond to at least four prior lines of therapy.[15]

Despite the great success of CAR T cell therapies for B cell malignancies, much still needs to be done to generalise this approach for the treatment of various other haematologic cancers. The sub-optimal quality of starting autologous T cells across different patients, long manufacturing processes that inadvertently exclude individuals with rapid disease progression, high production costs, and logistical issues associated with manufacturing a living, self-replicating therapeutic agent represent major hurdles to the broader translation of this approach. Additional challenges that must be overcome include exhaustion and premature senescence of CAR T cells that occur post-infusion and often result in poor proliferation, persistence, and effector function. In the setting of research efforts to enhance the quality and availability of CAR T cell therapies that are currently only available as 'bespoke' products, precision gene editing has emerged to produce a new generation of CAR T cells that overcome many of the aforementioned challenges. Possibilities include genetic editing strategies to improve CAR T cell anti-tumour activity and proliferative capacity, generation of allogeneic CAR T cells to circumvent autologous T cell quality challenges and enable on-demand treatment for patients, and the potential to overcome on-target, off-tumour toxicity in the context of non-B-cell haematopoietic malignancies (Figure 1).

Gene editing has come of age over the past few decades through the development of a variety of site-specific programmable nucleases. These technologies (including zinc finger nucleases [ZFN], transcription activator-like effector nucleases [TALEN], and clustered regularly interspaced short palindromic repeats [CRISPR]-Cas9) create double-stranded breaks in the genome that can be repaired by the cell through two pathways, non-homologous end-joining (NHEJ) or homology-directed repair (HDR) (Figure 2). NHEJ is an error-prone repair pathway by which the non-homologous broken ends are ligated together, often resulting in insertions or deletions that can prevent expression of a functional protein or protein ablation. HDR occurs less frequently than NHEJ but allows for template-directed repair to facilitate site-specific

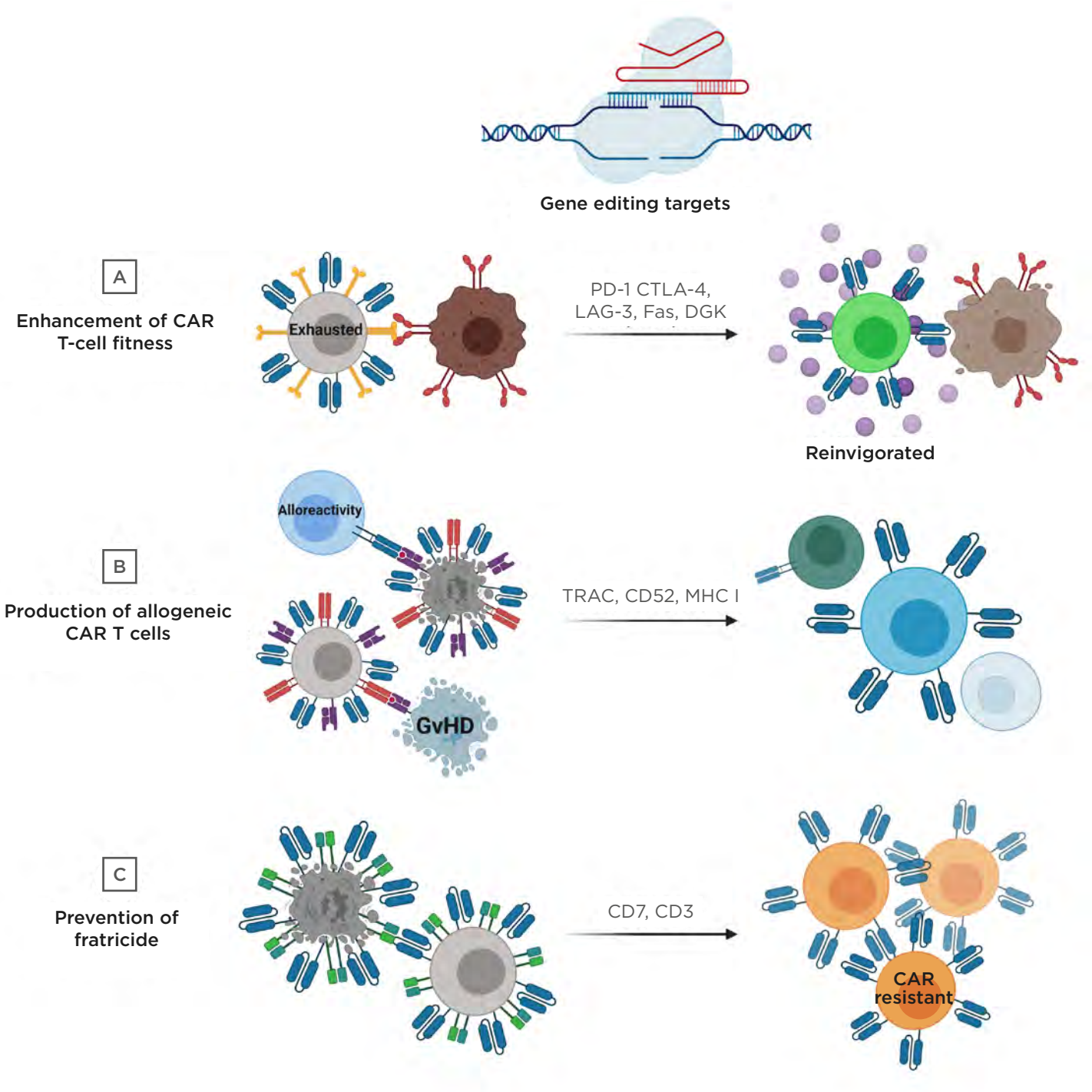

Figure 1: Gene editing strategies to improve chimeric antigen receptor T cell therapy.

A) Targeted genetic knockout of negative regulatory molecules (e.g., PD-1) can prevent exhaustion in CAR T cells and improve effector function. **B)** Unmatched donor-derived CAR T cells have the potential to cause GvHD and alloreactivity. To manufacture allogeneic CAR T cells that will not cause GvHD and can avoid eradication by recipient immune cells, the TCR and additional molecules can be knocked out. **C)** Engineering CAR T cell therapies targeting T cell lineage antigens can result in fratricide during the manufacturing process; however, this can be prevented by gene editing of the targeted antigen (e.g., CD7 or CD3).

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CAR: chimeric antigen receptor; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; DGK: diacylglycerol kinase; GvHD: graft-versus-host disease; LAG-3: lymphocyte-activation gene 3; MHC I: major histocompatibility complex Class I; PD-1: programmed cell death protein 1; TCR: T cell receptor; TRAC: T cell receptor α constant.

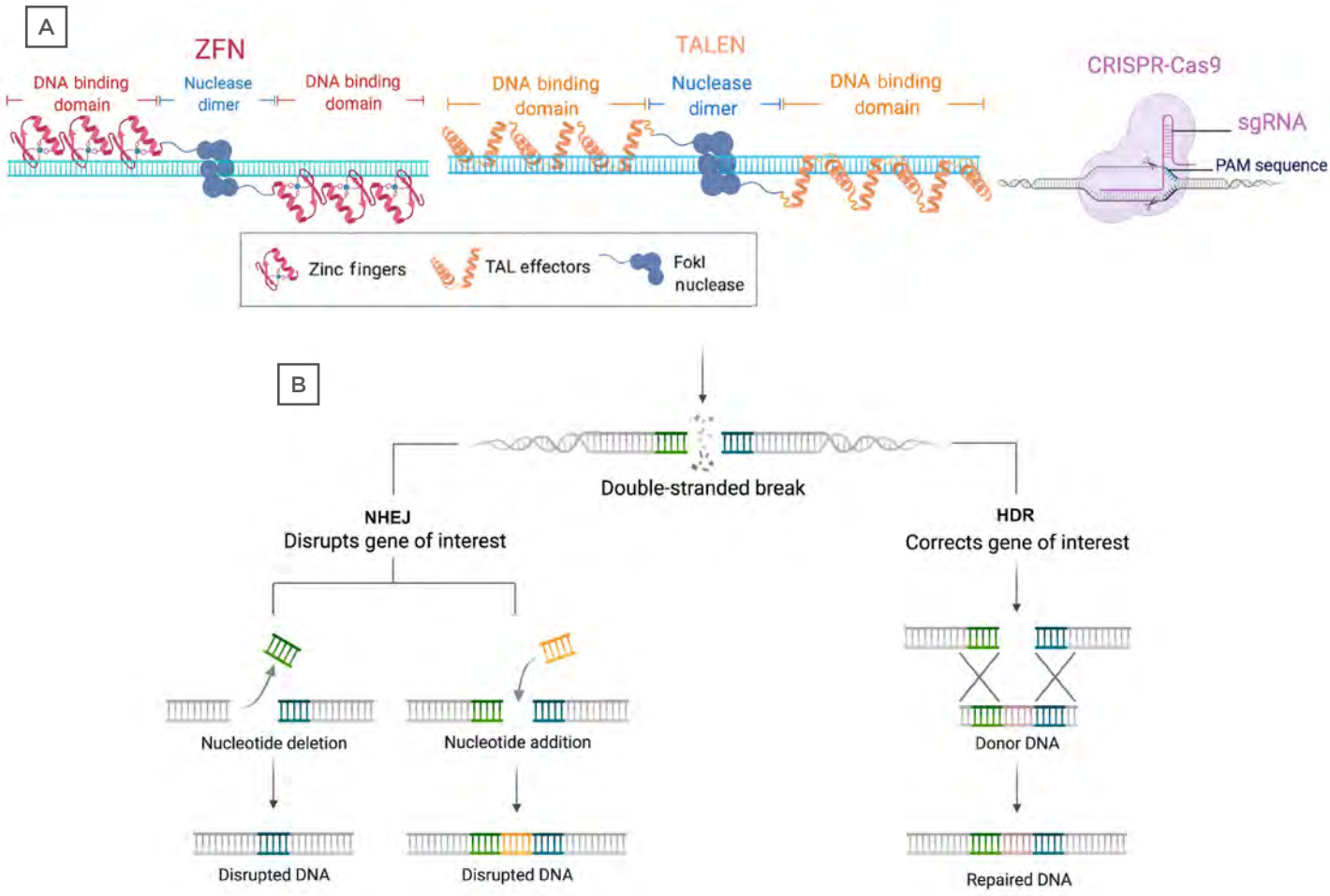

Figure 2: Programmable nucleases and DNA repair pathways.

A) The three major gene editing technologies include ZFNs, TALENs, and CRISPR-Cas9. Each programmable nuclease recognises DNA sequences through different mechanisms, including zinc finger binding domains (ZFNs), TAL effector binding domains (TALENs), or via a single guide RNA (CRISPR-Cas9). ZFNs and TALENs rely on *FokI* nucleases fused to the DNA binding domains that dimerise to produce double-strand breaks. The CRISPR-Cas9 system utilises the Cas9 protein, which can produce double-strand breaks without dimerisation. **B)** Following a double-stranded break due to a programmable nuclease, the DNA is repaired through either NHEJ or HDR. NHEJ can result in deletion or insertion of nucleotides around the break-site, leading to disruption of the target gene. HDR can use donor DNA for template-directed repair and results in insertion of a sequence of interest at the break-site.

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CRISPR: clustered regularly interspaced short palindromic repeats; HDR: homology-directed repair; NHEJ: non-homologuous end joining; TALENS: TAL: transcription activator-like effector binding domains; ZFN: zinc finger nuclease.

insertion of a genetic sequence of choice. Although each gene editing tool has been used for both NHEJ and HDR-mediated editing, these modalities have different features with distinct advantages and limitations, as discussed below.

A ZFN is a restriction enzyme fused to zinc finger motifs that can recognise a triplet codon sequence in DNA. Although ZFNs can have good editing efficiency, they are often difficult to engineer and exploit for multiplex gene editing and are not highly specific.[16] TALENs (consisting of TAL proteins fused to a nuclease) are much easier to engineer, have higher editing efficiency compared to ZFNs, and display very low off-target editing. However, they are difficult to deliver to cells and have limited high throughput editing capacity.[16] Finally, the CRISPR-Cas9 system consists of an RNA-guided endonuclease (Cas9), which is directed to DNA cut-sites with a

high degree of specificity and efficiency. As the Cas9 protein is directed by a single guide RNA (sgRNA), this system is simple to employ and can easily be used for editing multiple genes; however, conventional CRISPR-Cas9 systems tend to exhibit higher off-target editing rates compared with TALENs.[16]

STRATEGIES TO IMPROVE CHIMERIC ANTIGEN RECEPTOR T CELL FITNESS

Inhibitory receptors such as programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), lymphocyte-activation gene 3 (LAG-3), and T cell immunoglobulin and mucin domain 3 are natural regulators that limit T cell activation and prevent autoimmunity as well as severe inflammation. These molecules have also been demonstrated to hamper anti-tumour immune responses and potentiate tumour escape through binding to their cognate ligands overexpressed on malignant cells.[17] Antibodies employed to interfere with inhibitory receptor activation have proven effective for therapy of both liquid and solid tumours.[18] These therapies can act synergistically with CAR T cell therapies by preventing or reversing CAR T cell inhibition.[18] However, antibody-based checkpoint blockade therapies often require repeated administration to maximise efficacy and have been associated with severe toxicities, particularly autoimmune reactions.[19]

Genetic ablation of inhibitory molecules in CAR T cells is an alternative strategy that would avoid the systemic toxicities of conventional immune checkpoint blockade approaches. For example, knockout of *PDCD1* (gene coding for PD-1) has been widely employed for this purpose and the strategy has frequently augmented CAR T cell proliferation, cytotoxicity, and overall anti-tumour activity in multiple preclinical models of both haematopoietic and non-haematopoietic cancers.[20-23] It is important to note that these enhancements to antitumour efficacy are dependent on the expression of programmed death-ligand 1 (PD-L1) on tumour cells and most of these model systems require forced expression of PD-L1; however, Ren et al. found that over 90% of naïve prostate tumour (PC3) cells gain PD-L1 expression after encountering prostate stem cell antigen-directed CAR T cells, suggesting that PD-1 ablation may help avoid adaptive resistance resulting from upregulation of inhibitory ligands on tumour cells.[20] Additionally, PD-1 knockout appears to only restore anti-tumour function impaired by PD-1/PD-L1 interactions back to baseline levels, but does not enhance cytotoxic CAR T cell capacity against PD-L1 negative cell lines. There are also conflicting reports regarding the sustained T cell potency enhancing effects associated with PD-1 genetic ablation, with one study reporting a significant increase in terminally differentiated $CD8^+$ T cells and a long-term reduction in survival, proliferation, and durability of PD-1 knockout cells in a model of chronic virus infection.[24] Dissecting the effects of PD-1 ablation is difficult due to its complex role in both the negative regulation of T cell function as well as the maintenance of T cell effector activity, persistence, and memory differentiation.[25] Further investigation is required to determine if the benefit of short-term improvement in CAR T cell proliferation and anti-tumour function outweighs the potential for inducing T cell hypofunction due to PD-1 disruption. Despite these conflicting reports, many cellular therapy clinical trials are currently being conducted to include CAR T cell-intrinsic PD-1 inhibition strategies.

In addition to PD-1, disruption of other negative regulators of CAR T cell function, including LAG-3, CD95/Fas, and diacylglycerol kinase (DGK), have been investigated. Unexpectedly, genetic deletion of the LAG-3 inhibitory receptor in anti-CD19 CAR T cells does not improve antitumor efficacy.[26] However, CAR T cell-intrinsic CD95/Fas ablation has demonstrated some success. Although T cells utilise Fas signalling as a mechanism to induce apoptosis of cancerous and infected cell targets, this death pathway may also inhibit anti-tumour T cell activity.[27,28] Accordingly, blockade of Fas signalling restores anti-tumour T cell function, and CD95/Fas genetic ablation leads to reduced apoptosis and increased expansion of anti-CD19 CAR T cells.[27,29] Finally, ablation of DGK enhances CAR T effector functions, resulting in resistance against immunosuppressive factors, and increased durability of cytotoxic functions following repeated stimulation in models of glioblastoma and mesothelioma.[30,31] This was somewhat expected, as DGK is known to restrict T cell activation by the metabolisation of the second messenger, diacylglycerol, resulting in negative regulation of antigen receptor signalling.[32]

Ablation of multiple inhibitory pathways has the potential to provide CAR T cells with even more enhanced durability and potency. In this regard, the feasibility of multiplex editing has been demonstrated in preclinical studies.[20,29,33] A study by Ren et al. accomplished quadruple multiplex editing of CAR T cells, ablating *TRAC, B2M, PDCD1, and CTLA-4* simultaneously.[29] However, there are many safety considerations that must be taken into account when considering clinical translation of such a strategy. Notably, the consequences of genetic instability and translocations induced by multiple double-strand DNA breaks are not fully understood, particularly when introducing multiplex-edited cells in patients. In a Phase I clinical trial recently conducted by the authors, triple-knockout *TRAC*, *TRBC*, and *PDCD1* T cell receptor (TCR)-engineered T cells targeting cancer/testis antigen 1 was a safe and feasible therapy in patients.[34] This study demonstrated that although chromosomal translocations were observed during cell manufacturing, translocation frequency decreased after infusion. These translocations resulting from multiplex CRISPR-Cas9 editing were not associated with clonal expansion or abnormal proliferation of cancer/testis antigen 1 T cells, at least within 9 months following administration. However, additional clinical investigations with longer patient follow-up times need to be conducted to fully evaluate any potential safety risks.

In addition to ablation of negative regulators, genetic editing strategies can be used to integrate a variety of gene cassettes into a locus/loci of choice.[35] This allows for controlled integration of a transgene, limiting the potential risk of oncogenic transformation due to random insertional mutagenesis by a viral vector. Additionally, placing a transgene under control of an endogenous promoter may allow for more regulated expression of the transgene. For example, studies have investigated integrating CAR transgenes into the *TRAC* locus, leading to increased CAR expression and enhanced anti-tumour potency of the engineered cells.[36,37] In addition, Sachdeva et al. explored integration of proinflammatory IL-12P70 into the *CD25* or *PDCD1* locus, permitting regulated cytokine expression upon T cell activation. This strategy allows for tightly controlled expression of IL-12P70 following tumour cell recognition, thus augmenting anti-tumour activity through the combined proinflammatory effects of the cytokine and amelioration of PD-1-mediated negative regulation.[37] This approach can be generalised to knocking cassettes encoding a wide array of effector molecules into various target loci, opening up opportunities to direct location-specific anti-tumour mediator expression to potentiate CAR T cell therapy.

A variety of other potential gene editing targets to improve CAR T cell function are currently being explored, including modulation of proteins involved in T cell fate determination. The authors found that accidental ablation of tet methylcytosine dioxygenase 2 (TET2), a protein involved in DNA demethylation, skews CAR T cell differentiation toward a central memory state and confers enhanced proliferation and anti-tumour function.[38] In this 'bedside-back-to-bench' study, *TET2* disruption altered global and site-specific chromatin accessibility and transcription of genes involved in cell cycle progression and T cell receptor signalling. The resultant clonally expanded CAR T cells possessed properties of short-lived memory cells with potent effector functions and long-lived memory cells with long-term persistence. Despite this remarkable effect, *TET2* may not be a viable target for conventional gene editing due to its well-characterised function as a tumour suppressor. Future studies will evaluate the potential benefit of targeting alternative genes involved in regulation of T cell differentiation, effector function, and persistence to enhance the effectiveness of CAR T cell therapies.

THE PROMISE OF UNIVERSAL CHIMERIC ANTIGEN RECEPTOR T CELLS

The generation of 'off-the-shelf' allogeneic CAR T cell products has been a major goal in the cellular immunotherapy field. Engineering CAR T cells from healthy donors would solve many logistical issues, allowing for rapid treatment of patients and major reductions in manufacturing costs. Additionally, because these T cells would be derived from healthy donors, they may not be dysfunctional at the start of the manufacturing process, unlike the case with many conventional autologous cell therapy approaches. However, there are several challenges with developing this kind of therapy. To achieve safe and effective

treatment, universal CAR T cells must not induce graft-versus-host-disease (GvHD) and must be resistant to host-versus-graft alloreactivity. Many strategies have been investigated to accomplish these goals using gene editing technologies.

Elimination of GvHD has primarily been achieved through genetic disruption of endogenous TCR expression in CAR T cells. In the first proof-of-concept study of the feasibility of engineering allogeneic CAR T cells ZFNs were used to knockout the TCRα- or β-chain (i.e., through *TRAC* or *TRBC* targeting). This work revealed that TCR knockout does not significantly impact the cytotoxic functions or proliferative capacities of edited CAR T cells.[39] The study thus opened the door for development of allogeneic CAR T cells, with *TRAC* and/or *TRBC* genetic disruption being used in a multitude of preclinical and clinical investigations.[20,33,34,40-43,44] Investigators have also pursued approaches to permit site-specific integration of CARs into the *TRAC* locus to safely insert the synthetic receptor transgene while simultaneously eliminating GvHD, improving CAR expression and enhancing CAR T cell potency.[36,41]

In addition to prevention of GvHD, many studies have also investigated strategies to prevent endogenous recipient immune cells from eliminating allogeneic CAR T cells. One method has been to engineer CAR T cells that are resistant to lymphodepletion. TALEN-editing of *TRAC* and *CD52* leads to generation of CAR T cells that do not cause GvHD and are rendered resistant to alemtuzumab-mediated lymphodepletion targeted against $CD52^+$ wild-type alloreactive T cells. This strategy has been evaluated preclinically in the setting of B cell maturation antigen-directed CAR T cells for multiple myeloma.[40] In addition, this strategy has been used for the development of universal CD19-targeting CAR T cells (UCART19). UCART19 has demonstrated powerful clinical efficacy, achieving molecular remission in two paediatric patients with B-ALL.[43] Following the success observed in paediatric patients, UCART19 was then expanded to two multicentre Phase I clinical trials evaluating feasibility, safety, and efficacy in adult and paediatric patients with B-ALL (NCT02808442,[45] NCT02746952[46]). These trials showed cytokine release syndrome (CRS) as the most common adverse event (91% of patients; 14% had Grade 3–4 CRS) and limited GvHD (10% of patients), demonstrating a manageable safety profile.[44] Fourteen of the 21 patients had a complete response or complete response with incomplete haematological recovery at 28 days post-UCART19 infusion. Progression-free survival was 27% at 6 months, demonstrating initial clinical efficacy of UCART19 cells in aggressive B cell leukaemia.

An additional strategy to avoid host destruction of allogeneic CAR T cells is elimination of human leukocyte antigen Class I expression to prevent recognition of CAR T cells by recipient T cells. Disruption of human leukocyte antigen-A has been shown to allow for allogeneic CAR T cell escape from host T cell-mediated killing.[47] Other studies have targeted *B2M*, a component of major histocompatibility complex Class I molecules. Multiplexing *B2M* knockout with *TRBC* and *PDCD1* disruption leads to CAR T cells with reduced alloreactivity, elimination of GvHD, and enhanced *in vivo* anti-tumour activity.[20] Multiplex editing combining knockout of the endogenous TCR together with a molecule to prevent alloreactivity (e.g., CD52 or *B2M*) will be required to manufacture an off-the-shelf allogeneic CAR T cell product, and inclusion of additional genetic edits are likely needed to enhance clinical efficacy.

CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY FOR NON-B CELL MALIGNANCIES

Antigen-directed treatment of haematologic malignancies is challenging due to the sparsity of conserved tumour-specific targets. CAR T cell therapies for haematologic malignancies typically target cell lineage markers, such as CD19 for B cell malignancies. Thus, CAR T cell therapy for these neoplasms results in destruction of both malignant and healthy cells, which can result in severe toxicity. Targeting B cell malignancies has had greater success compared to other haematologic neoplasms due to well-tolerated and effectively managed B cell aplasia.[48] However, the targeting of other haematologic malignancies such as myeloid and T cell leukaemias can result in lethal toxicities due to on-target, off-tumour effects. Current gene editing research in the context of cellular therapies has, therefore, been directed toward developing strategies to avoid these limitations.

Myelotoxicity is a prominent concern when translating CAR T cell therapies to treat myeloid malignancies. One strategy to avoid CAR T cell-mediated destruction of healthy myeloid cells is to knockout the targeted lineage antigen in haematopoietic stem cells (HSC) and transplant these cells into patients after CAR T cell therapy. This allows for repopulation of the myeloid compartment with CAR-resistant cells. Studies have investigated this approach for anti-CD33 CAR T cells and found that genetic ablation of CD33 in haematopoietic stem and progenitor cells can be used for HSC transplantation. This strategy led to generation of a CAR-resistant myeloid system that allows for selective targeting of cancer cells without myelotoxicity.[48,49] The method could be translated to other therapies targeting myeloid malignancies such as CD123-directed CAR T cells. CD123 is overexpressed on a variety of haematologic malignancies, and CD123 CAR T cells are being investigated for treatment of myelodysplastic syndrome, blastic plasmacytoid dendritic neoplasm, and acute myeloid leukaemia, with a clinical trial currently underway for relapsed/refractory acute myeloid leukaemia (NCT03190278[50]).[51,52] Implementation of subsequent HSC transplantation with CD123 deficient cells could prevent toxicities associated with destruction of healthy $CD123^+$ myeloid cells and offers a feasible treatment for myeloid malignancies.

CAR T cell therapies for T cell malignancies have proven difficult to translate clinically due to targeting of T cell lineage antigens shared by both normal and malignant cells, which are also expressed on CAR T cells. This leads to 'fratricide' during the CAR T cell manufacturing process, in which CAR T cells induce cytotoxicity of other engineered T cells. One strategy for fratricide-resistant CAR T cell generation is genetic depletion of CD7 in CD7-targeting cells. Preclinical studies have demonstrated anti-tumour efficacy of allogeneic CAR T cells with *CD7* and *TRAC* knockout.[53] The use of an allogeneic system reduces the risk of generating CD7-negative, CAR-resistant leukaemic T cells, which is a major safety concern with an autologous product. Initial clinical evaluation of an allogeneic CD7-targeting CAR T cell product has demonstrated safety and efficacy in two patients with T cell acute lymphoblastic leukaemia (T-ALL).[54] Accordingly, a Phase I clinical trial is being initiated with autologous CRISPR-edited, CD7-targeting CAR T cells for T-ALL and T cell non-Hodgkin lymphoma (NCT03690011[55]). In addition to CD7-targeting CAR T cells, CD3-targeting CAR T cells have been investigated for certain T cell malignancies. A study showed that ablation of *CD3* and *TRAC* led to the generation of CD3e-CAR resistant T cells, allowing for the production of CD3e-targeting CAR T cells for T cell leukaemias.[56] Although this system would solve manufacturing issues, more research is needed to investigate the feasibility and management of potential T cell compartment depletion in patients with T-ALL with such an approach.

CHALLENGES AND EXPANDING OPPORTUNITIES WITH GENOME EDITING OF CHIMERIC ANTIGEN RECEPTOR T CELLS

Despite the promise that gene editing has shown in both preclinical and clinical studies, there are many challenges and concerns that need to be addressed to ensure the safety and reliability of this strategy. Some of these obstacles include severe clinical adverse events due to disruption of negative regulatory pathways, low knockout efficiencies, genetic instability caused by double strand DNA breaks, and the risk of off-target editing.

Major adverse events have been observed in the context of CAR T cell therapies, including neurotoxicity and CRS. Severe CRS can be fatal and is characterised by a massive production of proinflammatory cytokines, particularly IL-6.[57] Inhibitors of IL-6 are used for the management of severe CRS during CAR T cell treatment; however, there is concern that administration of these inhibitors could negatively impact the anti-tumour activity of CAR T cells.[57] When developing edited CAR T cells that disrupt negative regulatory pathways such as PD-1 there is concern for potential development of more severe CRS. As the understanding of the pathophysiology of CRS continues to expand, new genetic editing strategies have emerged to prevent or diminish CRS. For example, neutralisation of granulocyte-macrophage-colony-stimulating factor (GM-CSF) leads to a

reduction in toxicities associated with CAR T cell therapy, particularly neuroinflammation and CRS.[58] One study found that genetic ablation of GM-CSF in CAR T cells results in a drastic decrease in production of a variety of several proinflammatory cytokines, without impacting the anti-tumour function or proliferation of the engineered cells *in vitro*.[59] An additional study found that GM-CSF-deficient CD19 CAR T cells have enhanced anti-tumour potency, leading to improved survival in xenogeneic mouse models.[58]

To address issues of poor editing efficiency, improved CAR transgene delivery methods and editing platform advancements have been under investigation. Traditional viral transduction of CAR T cells followed by introduction of CRISPR-Cas9 editing machinery typically produces a heterogeneous cell population, in which not all CAR T cells are edited. This poses a problem for universal CAR T cell approaches, as knockout of the endogenous TCR is necessary to prevent GvHD, as discussed above. To improve the generation of universal CAR T cells, Georgiadis et al. created a Terminal-TRAC CAR T system in which a self-inactivating lentiviral vector delivered the CAR transgene and sgRNA targeting *TRAC*, coupling CAR integration with CRISPR-Cas9 editing.[42] This ensures that all T cells transduced with the CAR are *TRAC* deficient, eliminating safety concerns associated with incomplete TCR knockout in the CAR$^+$ population. In addition to employing plasmid-delivery systems to eliminate safety concerns of incomplete editing in universal CAR T cells, improved plasmid delivery methods have been used to develop simplified engineering processes and achieve more efficient genome editing. Hu et al. utilised a platform of nucleofection to introduce plasmids encoding a CD133-targeted CAR and CRISPR-Cas9 machinery for *PDCD1* knockout to achieve CAR integration and gene editing in a single reaction.[23] This simplified strategy of simultaneously delivering the CAR transgene and CRISPR-Cas9 editing machinery provides an efficient process for engineering cells that would be more desirable for manufacturing compared to the current multi-step process. Plasmid-based delivery can also enhance gene editing efficiency. A limiting factor of editing efficiency by CRISPR is fast degradation of sgRNAs compared to Cas9 protein or mRNA, and higher editing can be achieved by constitutive expression of the sgRNAs. By using a CAR lentiviral vector incorporating TRAC-sgRNA, Ren et al were able to achieve high percentages of CD3-disrupted cells.[29] This system can be used for multiplex editing as well, with triple- and quadruple-knockouts targeting *TRAC*, *B2M*, *Fas*, *PDCD1*, and/or *CTLA-4*.[29]

Editing technologies such as CRISPR-Cas9, TALENs, and ZFNs achieve gene knockouts through double-stranded breaks in the DNA. These breaks are mended through an error-prone DNA repair pathway, resulting in insertions and deletions which ideally prevent expression of functional protein. This process allows little control over how the cell is edited and has an increased risk of off-target editing. As such, base editing has emerged as a potentially more precise alternative to classic CRISPR-Cas9 editing. Base editors consist of a catalytically inactive Cas9 nuclease fused to DNA deaminase that can introduce site-specific point mutations through conversion of nucleotide bases without double-stranded breaks.[60] This allows for enhanced control over genetic disruption through altering bases to introduce premature stop codons or affect splice sites.[61-63] Additionally, because base editing does not result in double stranded breaks in the genome, it is a safer option to prevent translocations associated with multiplex editing. Webber et al. utilised base editing to create allogeneic CAR T cells by introducing premature stop codons or impacting splice sites in *PDCD1*, *TRAC*, and *B2M*.[64] This study revealed that multiplex base editing in primary human T cells resulted in reduced double stranded breaks and undetectable translocations without altering CAR T cell function.

In addition to chromosomal translocations, off-target editing is a major safety concern when translating CRISPR-Cas9 technology into the clinic. There are numerous methods to evaluate off-target editing, including homology-dependent and homology-independent approaches, which are often used in combination. Homology-dependent methods involve computational strategies that evaluate potential off-target sequences based on presence of a protospacer adjacent motif sites and similarity to the sgRNA sequence. Homology-independent methods are empirical measurements of off-target editing throughout the whole genome that employ a variety of assays coupled with next-generation sequencing.

Some homology-independent approaches are genome-wide unbiased identification of double-stranded breaks enabled by sequencing (GUIDE-seq), discovery of *in situ* Cas off-targets and verification by sequencing (DISCOVER-seq), circularisation for *in vitro* reporting of cleavage effects by sequencing (CIRCLE-seq), cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq), and Digenome-seq.[65-69] The challenge with using these assays is obtaining genome-wide coverage with enough sensitivity to detect rare off-target events and avoiding biases in the evaluation of off-target editing. Each of these methods possesses unique strengths and weaknesses and can be used in parallel to evaluate off-target editing more deeply. A recent comparison of three homology-independent methods (GUIDE-seq, CIRCLE-seq, and CITE-seq) showed similar accuracy in the detection of off-target CRISPR-Cas9-mediated gene editing.[70] The authors gave guidance in assessing off-target effects and suggested that GUIDE-seq may be the more appropriate tool to evaluate *ex vivo* engineered cells, such as CAR T cells. Additionally, novel techniques for evaluating off-target effects are actively being developed and optimised such as amplification-free long-read sequencing.[71] Thus, clinical translation of gene-edited cellular therapeutics will likely incorporate a variety of strategies to accurately detect off-target mutations and thus allay associated safety concerns.

CONCLUDING REMARKS

Despite the clinical successes of CAR T cell therapy in the setting of certain haematological malignancies, further development of this approach is necessary to achieve similar efficacy in other cancers. Gene editing has the potential to greatly improve CAR T cell therapies by enhancing T cell fitness, enabling the manufacture of off-the-shelf products, and allowing for treatment of T cell and myeloid cell cancers. Advances in multiplex gene editing are particularly exciting, as several modifications will allow for development of robust allogeneic CAR T cell treatments for many different diseases. However, safety concerns must be addressed to effectively integrate single and multiplex gene editing into the production of cellular therapeutics. The advent of more precise gene editing technologies such as base editing has the potential to produce safe and efficient multiplex editing strategies for this purpose. These innovations enable greater control over genetic modifications to CAR T cells, addressing many potential safety issues associated with genomic instability and off-target editing. Developments in the next few years in the areas of feasibility, safety, and efficacy of gene-edited CAR T cell products will ultimately determine how far reaching this approach will be in the broader battle against cancer.

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Prediabetes: Challenges, Novel Solutions, and Future Directions

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Abstract

Prediabetes: Prediabetes is a salient state of hyperglycaemia and/or hyperinsulinaemia that often precedes a diagnosis of Type 2 diabetes (T2D). It is projected that by 2040, almost 8% of the global population will have prediabetes, with approximately 70% progressing to T2D within their lifetime. Abnormal glucose tolerance increases the risk of associated complications, including cardiovascular disease, stroke, and microvascular diseases, all of which are major contributors to the global healthcare burden. T2D alone is predicted to cost the healthcare system upwards of 490 billion USD by 2030, thus addressing this growing burden is vital.

Challenge One. Diagnosis and classification: Diagnosis poses a challenge and there is debate between leading world expert panels regarding thresholds, notably between the World Health Organization (WHO) and American Diabetes Association (ADA) for impaired fasting glucose. Hyperinsulinaemia may also go undetected as this is not currently routinely tested or used as diagnostic criteria. This has been largely due to cost and lack of consensus data for appropriate diagnostic threshold; however, with disease burden costs estimated to be close to half a billion USD by the end of the decade, an in-depth cost analysis for benefits-costs of early detection and treatment or prevention is warranted.

Challenge Two. Health messaging and public perception: Prediabetes can revert to normoglycaemia with diet and lifestyle interventions. This, however, is not conveyed well in public health messaging. In addition to public perception about the likelihood of disease progression to T2D, prediabetes is not considered a disease state, which may also influence public perception regarding perceived urgency of treatment and necessity for intervention.

Challenge Three. Intervention and treatment: Diet and lifestyle interventions are heralded as best practice when it comes to prediabetes management, and metformin for those at greatest risk of future T2D. Synergistic use of the available novel and promising interventions including low carbohydrate diets, higher protein diets, time restricted feeding, and high intensity interval training may help time-poor individuals achieve improvements in risk-factors including weight loss and glycaemic control (HbA1c and fasting plasma glucose). As large-scale feasibility and adherence are major obstacles to contend with in the rollout of diet and lifestyle interventions, personalised approaches, coupled with counselling based on social cognitive theory, may be increasingly utilised to target specific groups and individuals as programmes can be tailored to meet specific needs and preferences.

SHOULD PREDIABETES BE TAKEN MORE SERIOUSLY?

Diagnosis

Prediabetes is a salient state of hyperglycaemia and/or hyperinsulinaemia that persists for years, often preceding a diagnosis of Type 2 diabetes (T2D). The diagnostic criteria for prediabetes is difficult to define and still debated. The American Diabetes Association (ADA) and the World Health Organisation (WHO) agree on a diagnosis for impaired glucose tolerance (IGT) and HbA1c but differ in their criteria for impaired fasting glucose (IFG). Both entities consider a 2-hour 75 g Oral Glucose Tolerance Test (OGTT) result 7.8–11.0 mmol/L (140–199 mg/dL) or HbA1c 5.7–6.4% (39–47 mmol/mol) to diagnose prediabetes. The diagnosis for IFG varies, with the ADA using a lower threshold of 5.6–6.9 mmol/L (100–125 mg/dL) compared to the WHO using a higher threshold of 6.1–6.9 mmol/L (110–125 mg/dL). While in theory, a lower threshold should provide earlier detection and an increased window for prevention, research has indicated that the lower threshold does not mirror actual risk for T2D development,[1] nor may it provide significant gain in T2D prevention.[2] The higher threshold appears a more accurate indicator of disease progression.[3]

Disease Classification

Prediabetes can also be classified or termed 'intermediate hyperglycaemia', which is the preferred terminology of the WHO.[3] The term 'prediabetes' indicates a pre-disease state, whereas 'intermediate hyperglycaemia' alludes to a mild disease and one that has independent consequences of a T2D diagnosis. Although at present prediabetes is not considered a mild disease, the shift towards acceptance as an independent pathological entity is supported by inclusion in the 2015 International Statistical Classification of Diseases and Related Health Problems (ICD).[4] This inclusion is important for public perception as it conveys the medically supported need for treatment or intervention. Treatments need not be pharmaceutical. Treatment and prevention should instead take the form of diet and exercise lifestyle intervention by allied health professionals.[5] These pathways reduce the over medicalisation and unsustainable burden for healthcare systems. This paper acknowledges the importance of treating intermediate hyperglycaemia an independent state but will use the more commonly accepted term 'prediabetes' to minimise confusion.

Consequences

Prediabetes has far-reaching complications, with approximately 25% developing T2D within 3–5 years[6] and 70% progressing within their lifetime.[7] In 2010, the estimated global expenditure for T2D was 376 billion USD[8] and is expected to rise beyond 490 billion USD by 2030.[8] In 2015 it was estimated that 6.7% of the world's population had prediabetes, with an estimate of 7.8% projected by 2040.[9] The predictions for prediabetes are significantly higher (35–39%) in regions such as Catalonia,[10] China,[11] and the USA.[12] Furthermore, according to the Centers for Disease Control and Prevention (CDC [2020]) 84% of cases are undiagnosed. Similar numbers are seen in Australia as one in four adults are thought to be living with undiagnosed prediabetes/T2D.[13] As those with prediabetes are at increased risk of cardiovascular disease (CVD), stroke, and microvascular diseases, including retinopathy, nephropathy, and neuropathy,[14] diagnosing and treating abnormal glucose tolerance early in the diagnostic process is essential to minimise the future burden of disease.

A prediabetes diagnosis does not guarantee disease progression. Approximately 5–10% of those diagnosed revert back to normoglycaemia each year[6] and this may be spontaneous.[15] A recent cohort study found that participants who returned to normoglycaemia after a IFG diagnosis were younger and had lower BMI.[10] As BMI is a modifiable risk factor, interventions focusing on diet and exercise for weight loss have been the focus of research; however, pharmaceutical trials have also been undertaken with varying success.

WEIGHT LOSS AND THE ROLE OF DIET AND EXERCISE INTERVENTIONS IN PREDIABETES MANAGEMENT

Findings from the DQDPS

The DQDPS is a 6-year lifestyle intervention in China that saw 576 patients with prediabetes across 33 clinics randomised into one of four

intervention or control groups.[16] The researchers compared changes in OGTT and fasting plasma glucose between those randomised to diet only, exercise only, or the combination of exercise and diet intervention. After 6 years, 32% had returned to normoglycaemia, 21% remained with IGT,[17] and 47% progressed to T2D.[17] The majority (68%) who progressed to T2D were from the control, with progression 25% lower in the interventions.[16] Those who progressed to T2D had higher baseline BMI and fasting plasma glucose when compared with those who remained IGT or returned to normoglycaemia.[17]

Five hundred and forty participants were followed-up for 24 years, making this a 30-year landmark study for the long-term effects of diet and exercise intervention in prediabetes. At the 24-year follow-up, those who remined with IGT had a median delay for T2D onset of 10 years, a 34% lower incidence of CVD, and 52% lower incidence of microvascular disease when compared to those who progressed to T2D during the 6-year trial. Those who reverted to normoglycaemia during the trial had a median delay for T2D onset of 15 years, a 37% lower incidence of CVD, and 66% lower incidence of microvascular disease.[17] These findings demonstrate that diet and exercise interventions have significant long-term effects not only on T2D progression but also on associated risk factors and complications. As a lower BMI had favourable outcomes, diet and exercise interventions with a weight loss focus are likely most beneficial.

Weight Loss

Obesity is a key risk factor in the development of prediabetes and T2D. Weight loss of 5–10% can reduce 3-year incidence of T2D by 60%[18] and, thus, is a clinically relevant target for diet and exercise interventions. Low engagement[19] and difficulty maintaining lifestyle changes[20] are often reported as major barriers to successful long-term behaviour change and weight loss. While many traditional dietary recommendations feature low-fat and calorie restriction,[21] the ADA care guidelines were updated in 2019 to include low carbohydrate diets as another strategy to improve glycaemia.[20]

Low-Carbohydrate Diets

Low-carbohydrate diets have gained recent traction due to promising results for weight loss, improved HbA1c, and remission for both prediabetes and T2D.[22] Additionally, despite some negative publicity concerning the safety of low-carbohydrate diets, a recent meta-analysis[22] reported no statistically significant or clinically important detrimental markers for CVD, including lipid profile or C-reactive protein when compared to low-fat calorie restricted diets. While the benefit of low carbohydrate diets for glucose control are largely attributed to the reduction in foods that raise blood glucose levels, consequently reducing insulin demands, another advantage of low carbohydrate diets over traditional dietary recommendations is their ability to increase feelings of satiety by reducing the hunger hormones insulin and ghrelin and increasing satiety hormones glucagon-like peptide 1 and peptide tyrosine tyrosine.[23] For example, when a low-fat, calorie-restricted diet containing 150 g of carbohydrate was compared to a low-carbohydrate, unrestricted-calorie diet containing less than 50 g net carbohydrate, it was found that the total calories consumed between the groups throughout the 3 month study were almost identical,[21] suggesting that the low-carbohydrate group naturally reduced their calorie intake. Interestingly, while consuming a similar energy intake, the low-carbohydrate group saw a mean weight loss of almost 6 kg, more than double the traditional treatment group. Additionally, this study also found 50% of low carbohydrate participants had a clinically significant decrease of 0.5% in their HbA1c, compared to 22.0% in the traditional dietary treatment group.

A 2020 pilot study[19] looked at adapting the CDC's National Diabetes Prevention Program (NDDP) to a low-carbohydrate diet-DDP (LC-DDP). The NDDP is an American lifestyle intervention programme designed to be affordable and accessible. The NDDP currently has a real-world success rate of 35% of participants meeting their weight loss goal of 5%. The LC-DDP pilot maintained the same delivery format as the NDDP, changing only the dietary advice from low-fat calorie restriction to a net carbohydrate intake of 20–25 g daily. This dietary change saw 50% of participants reach >5% weight loss after 6 months while reporting both diet enjoyment

and diminished cravings. After 12 months, 71% of participants reported still adhering to the low carbohydrate approach. The success of the LC-DDP indicates that low-carbohydrate diets are not only successful at achieving weight loss in the short term but are also acceptable and manageable long-term. Whilst a large proportion of the carbohydrates are replaced by fats, many low-carbohydrate diets also naturally increase protein as part of the macronutrient redistribution.

High Protein Diets

High-protein diets may also suppress hunger, increase satiety, and therefore assist in weight loss.[24] The satiating effects are achieved through the gut-endocrine axis as protein consumption reduces ghrelin and increases peptide tyrosine tyrosine.[25,26] Recently, Drummen et al.[27] found that a high-protein diet (25% protein) promoted initial weight loss and prevented weight regain over a 3-year follow-up period.[27]

A high protein diet (30% protein) followed for 6-months resulted in 100% reversal to normoglycaemia in people with prediabetes, compared with 33% in control.[24] Significant improvements in insulin sensitivity were also seen in the high protein group, as well as reduced CVD risk, oxidative stress, and inflammatory cytokines. In agreement, a recent systematic review reported improvements in insulin sensitivity and lipid profiles with a high protein diet across 13 studies in T2D.[28] Therefore, increasing protein and lowing carbohydrates is beneficial for weight loss and glycaemic control; however, meal timing may also be an important factor to consider.

Time Restricted Feeding and Intermittent Fasting

While very low-carbohydrate diets can reinforce circadian rhythm and reduce oxidative stress and inflammation,[29] these benefits are in line with 'metabolic fasting'. Actual fasting through reduced eating windows and increased time between meals has been shown to have similar metabolic effects.[29] Fasts need not be long, and it appears meal composition and calorie content has minimal bearing on results.[29] In a tightly controlled study, Peeke et al.[29] provided identical calorie-controlled meals through the Jenny Craig Rapid Results programme to intervention and control groups for 8 weeks. The intervention group were instructed to fast for 14 hours (a pattern of 14:10), while the control group fasted for 12 hours (12:12). A statistically significant difference of 2 kg in weight loss was found between the groups simply by increasing the fasting window by 2 hours (-11 kg intervention versus -9 kg control). Another study found that time restricted feeding early in the day (6-hour eating window <3 p.m.) improved insulin sensitivity, β cell responsiveness, blood pressure, and oxidative stress in people with prediabetes when compared to a fasting pattern of 12:12.[30] Results from the above studies were intentionally independent of weight loss, demonstrating the benefits of intermittent fasting that extend beyond just weight loss.

Exercise

Exercise is considered a cornerstone therapy for weight loss and the management of lifestyle diseases such as prediabetes.[31] Exercise also provides benefits beyond weight loss, and overwhelming evidence suggests this is independent of exercise type.[32] Many regulatory bodies agree that 150 min of moderate to vigorous exercise per week is adequate;[33] however, 35% of those from more affluent countries do not meet this weekly requirement.[32] Often, 'lack of time' is cited as a key hurdle to maintaining a regular exercise pattern.[32] Recently research has experienced a shift towards exercise patterns that produce favourable outcomes while reducing the time burden. High intensity interval training (HIIT) is one way to achieve this.

High Intensity Interval Training

HIIT refers to short bursts of high intensity exercise interspersed with low intensity recovery or rest periods. A typical goal is to maintain approximately 90% of maximal effort (heart rate max) for a total of 10–15 min with periodised rests between exercise bursts.[33] A recent meta-analysis found HIIT increased cardiorespiratory fitness more than moderate intensity continuous training (MICT); however, both similarly improve HbA1c, blood pressure, lipid profile, BMI, or hip-to-waist ratio;[34] suggesting that similar health outcomes can be achieved through HIIT and shorter exercise duration. A 12-week pilot study[35] in 35 participants with prediabetes found a training intervention that included two

resistance/strength training sessions and either 30 min of HIIT or MICT for approximately 30 min 3 days per week, in line with the physical activity guidelines, similarly improved many of the above-mentioned markers of metabolic health.

The benefit of HIIT for long-term adoption is that there are countless ways it can be tailored to suit the individual. Usually cumulative intervals ≤15 min are considered low volume HIIT (LV-HIIT) and cumulative intervals ≥15 min are high volume HIIT (HV-HIIT).[32] A recent 12-week study in 77 participants who were overweight with prediabetes demonstrated a significant reduction with HV-HIIT and LV-HIIT for HbA1c of 1.27% and 0.87%, and fasting blood glucose of 0.9 mmol/L and 0.7 mmol/L, respectively.[33] Of interest, the HV-HIIT protocol was almost double the length of the LV-HIIT protocol (40 min versus 25 min). These findings of greater improvements; however, are consistent with a recent topical review suggesting that HV-HIIT≥LV-HIIT≥MICT across most measurable outcomes.[32] As the higher volume typically requires longer duration intervals (i.e., 4 min) this is not always a viable option for those with time constraints. The efficacy of LV-HIIT (i.e., 1 min intervals) must, therefore, be compared to that of HV-HIIT in the interest of maximising results in a shorter period.

The cardiometabolic benefits of exercise are conditional on continued engagement and participation for ongoing results.[31] Engagement in MICT is typically low[31] and while no studies have reported the efficacy of HIIT past 1 year, there is promising data that HIIT may be more sustainable than MICT in adults with prediabetes.[36] A recent study was conducted combining the use of counselling strategies based on social cognitive theory with either MCIT or HIIT.[37] After 1 year follow-up, females who received the counselling in self-regulatory techniques such as goal-setting, planning, and self-monitoring reported higher levels of continued exercise engagement.[38]

The authors know that both diet and exercise combined are essential elements of disease prevention. Whilst combining HIIT with a low-carbohydrate diet has been postulated,[39] there are yet to be studies combining the two strategies. It is hypothesised that combining these strategies will synergistically maximise the benefits of both approaches[39] and may prove to be an optimal diet and exercise combination for prediabetes and T2D.

PHARMACEUTICAL INTERVENTIONS FOR PRE-DIABETES

Pharmaceutical trials in prediabetes have had variable success across a range of new medications and those already approved for T2D management.[6,40,41] Pharmaceutical interventions for prediabetes are not currently routine based on limited efficacy, side effects, and/or cost.[42] Due to its relative low cost and safety, metformin is the exception and may be considered for those with a BMI of >35 kg/m^2, diagnosed <60 years, and previous gestational diabetes.[42] It is worth noting that unlike lifestyle changes such as exercise, pharmaceutical interventions do not demonstrate meaningful effects on many key outcomes for cardiovascular events or mortality,[40] including improvement in body composition or arterial stiffness.

Lifestyle modifications through diet and exercise remain the most effective preventive strategies for prediabetes;[40] however, they are often criticised as resource intensive and unsustainable. Pharmaceutical interventions are often cited as a viable inexpensive alternative,[40] yet lifestyle interventions are more cost effective than even metformin. Therefore, diet and lifestyle interventions remain the safest and most cost-effective treatment for prediabetes.

FUTURE DIRECTIONS

Diagnosis and Intervention

At least half of all prediabetes cases are thought to be undiagnosed.[13,43] Given early intervention can prevent ensuing disease, developing alternate methods to address prediabetes detection is paramount. One cost effective measure may be to increase the administration of existing T2D screening tools. A recent study[44] trialled pre-screening using the Finnish Diabetes Risk Score Calculator (FINDRISC) questionnaire as part of World Diabetes Day awareness. Of the 3,351 questionnaires administered to those without previously known prediabetes or T2D, as many as 15% reported a high-risk score (n=420). Laboratory diagnostics for HbA1c and fasting blood glucose

were administered to 397 of these and 40 subjects were diagnosed with T2D. Prediabetes was found in 213 subjects; more than half of those who returned a high-risk score on the pre-screening questionnaire.

Alternatively, the measurement of insulin resistance in diagnostic criteria may also be considered. One difficulty with prediabetes diagnosis is that hyperinsulinaemia can mask abnormal glucose levels for years.[45] Although more expensive, measuring plasma insulin is a much more accurate method of identifying insulin dysregulation and associated T2D risk. Increasingly, novel approaches such as plasma amino acid profiles and specific microRNA biomarkers are also emerging as possible future diagnostic criteria;[46,47] however, these are still largely in developmental phase. Improving diagnostics is only part of the puzzle, as improving lifestyle intervention strategies and rollout are crucial to pre-diabetes management post-diagnosis.

As large-scale feasibility and adherence are major obstacles in the rollout of lifestyle interventions,[37] personalised approaches may be increasingly utilised to target specific groups and individuals needs and preferences. For example, taking several elements from effective diet and exercise interventions such as the LC-DDP, or low-carbohydrate diet paired with tension and trauma release exercises and HIIT may be the most effective strategy for prediabetes.[39] However, these require people to change several aspects of their daily routine and may not be suited for higher-risk individuals.[32] The challenge may then be to find the minimum intervention required across each domain of diet and exercise to elicit beneficial results in either reversing prediabetes or delaying the onset of T2D. The establishment of a minimum benchmark would be beneficial for those who struggle with the long-term feasibility of more onerous intervention styles. By establishing recognised minimum requirements and best practice, allied health professionals could then work with individuals to create a tailored programme to best suit the needs of the individual. Effective short-term counselling based on social cognitive theory tailored to an individual's approach has the potential to promote long-term self-regulation and management, minimise ongoing financial barriers, and maximise independence.[37] Finally, public health campaigns communicating the reversable nature of prediabetes are also warranted as there appears to be a lack of messaging around positive future disease outcomes in this space.

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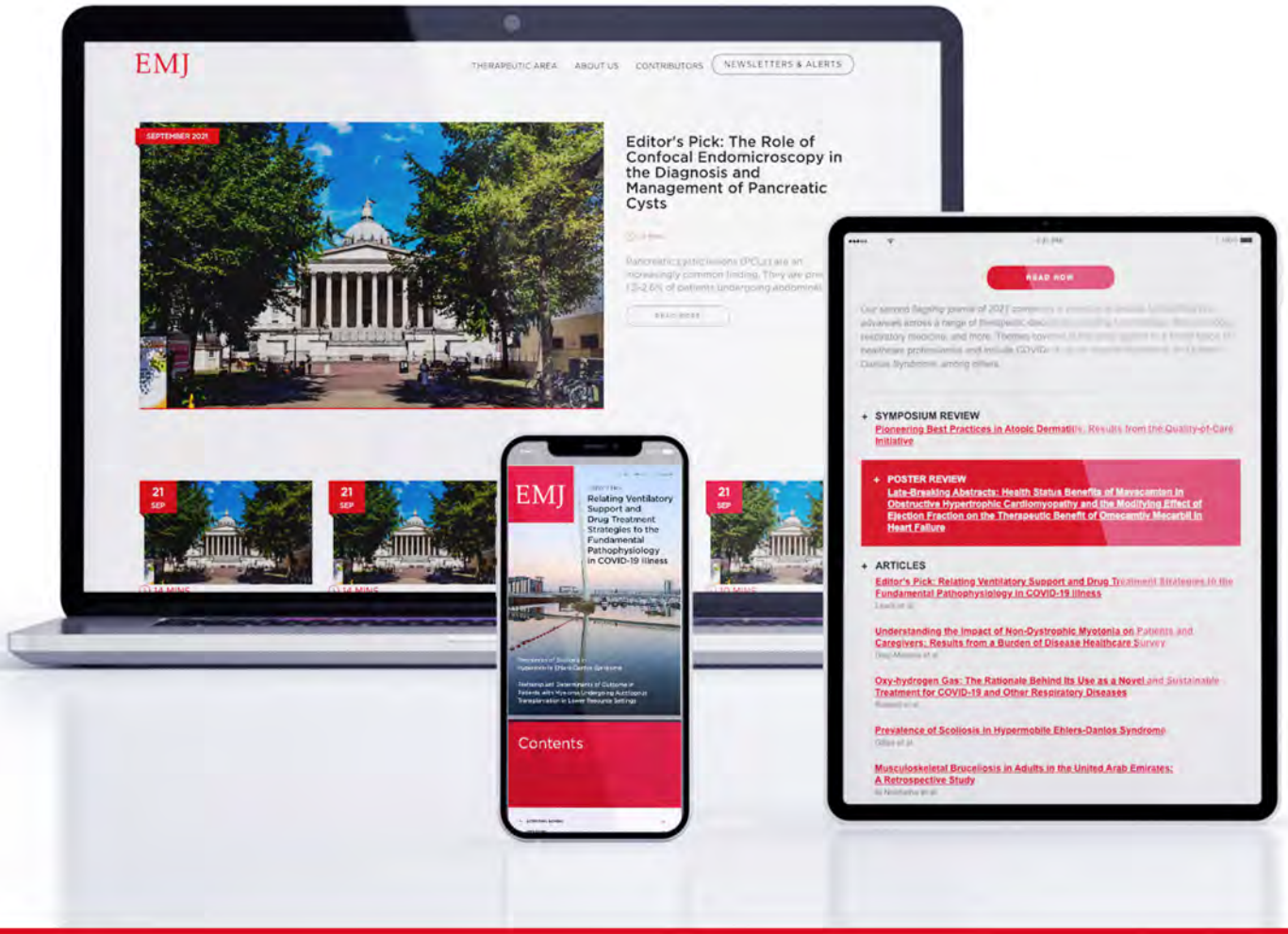

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Clinical Inertia of Discharge Planning Among Patients with Diabetes in Elhwari General Hospital

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Abstract

Background: Clinical inertia is defined as lack of treatment escalation in a patient warranting intervention, despite evidence-based goals for care. It is a major factor contributing to inadequate care for chronic diseases like diabetes, hypertension, dyslipidaemia, depression, and coronary heart disease.

Objective: To examine the effect of hospital admission on the glycaemic treatment of patients with diabetes discharged from the medical department of Elhwari General Hospital, Benghazi, Libya, and to assess the degree of clinical inertia in diabetic medicine.

Methods: A retrospective cohort study of patients who have the diagnosis of diabetes, hospitalised in the cardiology, respiratory, gastroenterology, rheumatology, and endocrinology departments for non-diabetic reasons in the Elhwari General Hospital.

Results: A total of 315 cases were reviewed. Among them were 289 patients (91%) with Type 2 diabetes and 29 cases (9%) with Type 1 diabetes. A glycated haemoglobin test (HbA1c) was available for 41 patients (13%) on admission. Out of 315 patients with diabetes, 171 (54%) had no change in their therapy during or at discharge from hospital. Out of 144 patients, 36 (25%) had changes in their treatment plan, but with no clear reason for the changes. Of the exercised interventions, the predominant change was intensification of therapy (116 out of 144 patients). The dominant triggers for change in management were admission hyperglycaemia (71 out of 144 patients; 49.3%) and pre-admission or hospital HbA1c (20 out of 144 patients; 13.8%). Hypoglycaemia constituted 11.8% (17 out of 144 patients) of cases for diabetic control change.

Conclusions: The authors' study shows that diabetic treatment inertia at a Libyan tertiary hospital was as high as 54.28%, where patients had no change in their therapy, and recent HbA1c was available for only 13.00% at admission.

INTRODUCTION

Diabetes is one of the most common chronic conditions. It affects a global population of approximately 425 million. The prevalence of diabetes is projected to increase to 629 million by 2045. The disease affects about 8.3% of adults worldwide, with the highest prevalence

between the ages of 40 and 59 years.[1] Diabetes is a progressive disease, which may lead to macrovascular, microvascular, and autonomic complications in the event of suboptimal control.[2] There is convincing evidence that early and tight glycaemic control leads to better long- and short-term outcomes, including a reduction in long-term macrovascular and microvascular complications.[3]

Despite good-quality evidence and recommendations, glycaemic control is often shown to be inadequate on a global scale. Russell-Jones et al.[4] showed that one-third of patients with Type 2 diabetes (T2D) in the UK failed to achieve target glycated haemoglobin test (HbA1c) levels of ≤7.5% (59 mmol/mol).

One of the most important causes for this is therapeutic inertia, previously known as clinical inertia, which is defined as the failure of healthcare professionals to advance or intensify treatment for patients with chronic conditions, despite available clinical guidelines.[4,5] It not only happens in diabetes cases, but also in other chronic conditions such as hypertension and hyperlipidaemia.

CAUSES OF DIABETIC (THERAPEUTIC) INERTIA

Factors causative of therapeutic inertia can be divided into healthcare provider-related factors, patient factors, and organisational and systemic factors.

Healthcare provider-related factors contribute to 50% of the causes of therapeutic inertia.[6] This includes time constraints, competing demands, inadequate training, lack of familiarity with the efficacy and safety of therapeutic regimens, lack of knowledge, and variations in guidelines and recommendations.[7]

Insulin is the most common and important therapy that healthcare professionals fail to initiate, intensify, and titrate.[8] The main reason attributed to the inertia is the fear of its side effects, specifically hypoglycaemia and weight gain, in addition to concern regarding patient acceptability of insulin as an injectable agent. Approximately 30% of therapeutic inertia may be attributed to patient factors. This includes concern regarding potential side effects, non-adherence, misunderstanding of treatment regimens, limited doctor-patient communication, low level of education, and presence of acute and terminal illnesses.[9]

The third group of causes of therapeutic inertia is related to organisational and systemic factors and contributes to 20% of causes of therapeutic inertia. This includes limitation in supply of medications, costs of medications, lack of individualised guidelines for patients, and insurance coverage.

THE IMPORTANCE OF DIABETIC INERTIA

Diabetes is a chronic, progressive condition. Therapeutic inertia impacts the health of patients and leads to higher levels of HbA1c and increased macro- and microvascular complications. It is vital to overcome therapeutic inertia, as there are benefits in terms of improved management of diabetes and reduced long-term costs, which will improve patients' outcomes and quality of life.[10] There are potential national healthcare benefits, including improving patient group outcomes, welfare, and social costs. For this reason, the authors conducted this study as the first of its kind about this problem.

METHODS

This was a retrospective cohort study, which included patients with diabetes hospitalised in the Elhwari General Hospital, Benghazi, Libya. These patients received medical therapy for different reasons (chest infection, cerebrovascular accident, urinary tract infection, etc.) in a medical ward over a period of 9 months. The information was collected from medical records and discharge notes. Treatment regimen was assessed before and during hospitalisation and at discharge to detect any change.

The primary outcome was a change in pre-admission and outpatients' prescriptions at hospital discharge, and the relation of this change to the type of diabetes, the type of diabetic treatment given before hospital admission, blood glucose at admission, pre-hospital or hospital HbA1c, and hospital hypoglycaemia.

The authors also examined the number of patients who had their treatment changed (intensified or decreased), and the reason behind the change, including admission blood sugar; pre-admission or in-hospital HbA1c; occurrence of in hospital hypoglycaemia, or admission with hypoglycaemia; and no clear causes for the change.

STATISTICAL ANALYSIS

A descriptive statistical analysis was carried out. Categorical variables were described with absolute and relative frequencies, and quantitative data were described as mean and standard deviation (SD), interquartile range, and median. The proportion of the study population with Type 1 diabetes (T1D) was presented as a per cent. Pearson chi-square tests were used to compare the proportions of patients with and without treatment intensifications. Independent student's t-tests were used to compare the mean, while the Mann–Whitney U test was used to compare the median between patients with and without treatment intensification.

RESULTS

A total of 315 patients with diabetes were included in this study. There were 140 males (44%) and 175 females (56%). Patients with T1D represented 9%, while 91% of patients had T2D. The mean age was 60.25 years (male: 62.08 years; female: 58.78 years), and the age range was between 18 and 93 years. Hospital stay duration was 2–30 days. Mean disease duration was 11 years. HbA1c was available for 41 patients (13%) during their hospital admission, or within 90 days before hospitalisation. HbA1c ranged between 4.9–15.5% (mean HbA1c: 8.9) with significant difference (p=0.004) between T1D (SD: 11.02+/-2.94) and T2D (SD: 8.4+/-2.04), but not between gender (male SD: 9.0890+/-2.5856; female SD: 8.895+/-2.4449; p=0.8). Of all the patients, 35% were smokers, and 60% had other comorbidities such as hypertension, dyslipidaemia, and/or chronic kidney disease (Table 1).

According to treatment before admission, 132 patients (42.0%) were on oral hypoglycaemic and 134 (42.5%) were on insulin. Around one-fifth of the study population was on both insulin and oral hypoglycaemic medications. In addition, six patients were on diet control, and there were 22 patients with no treatment, most of whom had refused treatment before (Table 2).

Out of 315 patients with diabetes, 171 (54.28%) had no changes in their therapy during their hospital stay or even at discharge, while 144 patients had changes in their treatment plan. Of note, the predominant change was intensification of therapy (116 out of 144 patients). There were no changes in the management plan for 28 patients. The main factor of change was admission blood sugar, which occurred in 71 out of 144 patients (49.3%); 69 patients had treatment intensification as they came in with hyperglycaemia; and for two patients, the dose decreased as their admission blood sugar was low. On the other hand, 16 out of 28 patients' treatment reduced at discharge as their admitted blood sugar was low. The second factor affected the change was the pre-admission or hospital HbA1c in 20 out of 144 patients (13.8%). Admission for hypoglycaemia constituted 11.8% (17 out of 144) of all causes of change. The majority of patients admitted with hypoglycaemia had a reduction of dose therapy, except one patient; surprisingly, the medical team intensified their treatment at the time of discharge without documenting the reason. The authors noticed that in a quarter of the patients (36 out of 144), there was no clear cause of change found in their files. The change in treatment according to the type of diabetes: 58.6% of patients had T1D and 44.4% had T2D (Table 3).

Regarding factors that affected treatment change, the authors found a significant relation with gender (X_2=6.159[a]; degrees of freedom: 2; p=0.046), and the type of treatment before admission (X_2=27.176[a]; degrees of freedom: 8; p=0.001). These two factors affected the decision of the treatment change. There was no relation between treatment change with other factors such as age, HbA1c, type of diabetes, or the duration of hospital stay. Half of the patients who were admitted on diet control had been prescribed treatment after their discharge, while of the patients previously on no therapy, 17 had treatment after discharge, and five were discharged without treatment without clear cause (Table 4).

Table 1: Patients' demographics.

Age (years)	
Mean (SD); range	60.25 (15.60); 18–93
Median (IQR)	62.00 (51.71)
Sex (n/N)	
Male	140/315 (44%)
Female	175/315 (55%)
Disease duration (years)	
Mean (SD)	11.2 (7.6)
Median (IQR)	10.00 (6.16)
Duration of hospital stay (days)	
Mean (SD)	6.8 (3.8)
Median (IQR)	6.0 (4.8)
Type of diabetes (n/N)	
T1D	29/315 (9%)
T1D	286/315 (91%)

IQR: interquartile range; SD: standard deviation; T1D: Type 1 diabetes; T2D: Type 2 diabetes.

Table 2: Type of treatment at admission and changes after discharge.

Pre-admission treatment	Frequency	Had treatment change after discharge
Oral hypoglycaemic	132 (42.0%)	51 (38.6%)
Insulin	134 (43.0%)	64 (47.8%)
Both	21 (7.0%)	9 (42.8%)
Diet control	6 (2.0%)	3 (50.0%)
No treatment	22 (7.0%)	17 (77.2%)
Total	315	144 (46.0%)

Table 3: Causes of treatment change.

Treatment change	Admission blood sugar	Pre- or hospital HbA1c	Admission or hospital hypoglycaemia	No clear cause of change	No change	Total
Intensification	69/116 (59%)	20/116 (17%)	1/116 (6%)	26/116 (22%)	0	116/315 (37%)
Decrease	2/28 (7%)	0	16/28 (57%)	10/28 (36%)	0	28/315 (9%)
No change	0	0	0	0	171	171/315 (54%)
Total	71	20	17	36	171	315

HbA1c: glycated haemoglobin test.

Table 4: Factors that affected treatment change.

Variables	p
Age	0.245
Sex	0.046
Type of disease	0.301
HbA1c	0.231
Duration of hospital stay	0.596
Type of treatment before admission	0.001
Disease duration	0.160

HbA1c: glycated haemoglobin test.

DISCUSSION

The aim of this study was to assess the prevalence of diabetic inertia in one of the main hospitals in Libya and, to the best of the authors' knowledge, this is the first study in this area.

The EDICT study demonstrated that the early intensive therapy of patients with newly diagnosed diabetes was more effective than conventional therapy.[11] This study showed that using triple therapy with metformin, pioglitazone, and exenatide was superior to conventional stepped therapy with metformin, followed by the addition of sulfonylurea and insulin glargine. In the patients who received triple therapy, there was a significant reduction in HbA1c (5.95%), compared with the group who received conventional therapy (6.50%; p<0.001). Furthermore, even with the greater fall in HbA1c in the triple-therapy group, the incidence of hypoglycaemia was 7.5-fold lower than the conventional therapy group, despite having a greater reduction in HbA1c. One of the major consequences of

therapeutic inertia is the extra cost on healthcare systems and public health due to the deterioration of patients who suffer from complications.[12]

The authors' study confirmed the presence of therapeutic inertia in Elhwari General Hospital. The frequency of therapeutic inertia in this study was comparable with that found in previous studies. From their data, the authors found that there were around 36% of patients with uncontrolled diabetes who had treatment intensification and the main trigger for change was the admission blood sugar level. In comparison to other studies, such as El-Kebbi et al.,[13] who showed that diabetes treatment was only intensified in 50% of patients with suboptimal T2D control. Similarly, the DICE study demonstrated that nearly 50% of patients with T2D in a primary care practice had an HbA1c above the target.[14] Griffith et al.[15] studied, suboptimally, patients with controlled diabetes with at least one hospital admission; they found that less than 25% of patients had treatment escalation or treatment change on their discharge, and few were allocated a follow-up visit. Therefore, there is compelling evidence that therapeutic inertia can lead to worse clinical outcomes.

In the authors' cohort, the inpatient measure of HbA1c to determine glycaemic control was used in the minority of cases (13%). From hospital records, the authors found during the study period that the HbA1c test was available in the hospital. Physicians were aware about the availability of the test. When hospital physicians were asked why the measure of HbA1c was not undertaken in all in patients with diabetes, reasons offered included: the result may delay patient discharge and that diabetes was irrelevant to the reason for admission. A reason offered by the group as a reason for not intensifying treatment, despite a suboptimal HbA1c measurement, was waiting for confirmation of persistent suboptimal glycaemic control (a second consecutive HbA1c measurement above the target), before intensifying treatment when patients were close to their glycaemic target. The approach of postponing treatment intensification until after two consecutive measurements of above-target HbA1c may justify some cases of therapeutic inertia. However, a study by Sidorenkov et al.[16] found that delay in therapy intensification due to waiting for two consecutive measurements of above-target HbA1c resulted in longer than recommended periods for treatment intensification for significant proportions of patients. Although a delay in therapy intensification may be justified for some patients, it took longer than recommended by existing clinical guidelines for significant proportions of patients to receive treatment intensification. Despite the availability of the test and results, other study groups faced the same issues of ignoring HbA1c as a useful resource.

Studies by López-Simarro,[17] Vinagre et al.,[18] and Gonzalez-Clemente et al.[19] demonstrated that the lack of treatment intensification in patients with poor glycaemic control (HbA1c: ≥7%) varies between 32.2% and 52.5%.[18,19] With regard to hospitalised patients, the comorbid prevalence of diabetes is around 35%, and the occurrence of hyperglycaemia during admission for non-diabetic reasons is associated with higher prevalence of morbidity and mortality.[20] A large UK cohort study found that one year delay in treatment intensification significantly increased the risk of myocardial infarction, stroke, and heart failure by 67%, 51%, and 64%, respectively.[21] Therefore, it is very important to address the issue of therapeutic inertia, and early and appropriate diagnosis and treatment of hyperglycaemia will lead to better health outcomes.

In contrast to other studies, the authors found no correlation between patient age, duration of hospital stay, or other comorbidities and the frequency of diabetic treatment intensification. Therapeutic inertia was present in this study in more than 54% of sampled patients. They also found treatment changes occurred, but without clear documentation for reason for change. In the majority of cases, no follow-up appointment for review of diabetic control was provided. Therefore, the authors think the cause of therapeutic inertia in their study was because of the healthcare provider, with some organisational factors.

Similarly with other studies, this study found that patients on more than one oral hypoglycaemic medication were less likely to be offered treatment intensification, despite an above-target HbA1c. Wan et al.[22] similarly showed that incremental number of oral anti-diabetic medications were associated with reducing chance for treatment intensification. In comparison to patients with

diabetes not on any pharmacological treatment, patients on dual or triple anti-diabetic therapy were 10 times less likely to receive treatment intensification.[21] Importantly, the use of multiple medications can lead to low adherence, higher rates of side effects, and may incur additional cost to patients and health systems.

Adopting proactive approaches to prevent inertia such as routine clinical audits, patient feedback systems, consistent follow-up procedures, effective use of clinical information systems, education of healthcare professionals, and ease of availability of guidelines are ways to tackle this issue. The results of this study were discussed with the diabetes team in the hospital; they have taken some actions, such as better referral systems, and providing junior doctors with some educational resources.

RECOMMENDATIONS

The authors recommend that all patients with diabetes who are hospitalised for any reason should be referred to the endocrinology team or diabetes experts for review if suboptimal glycaemic control is suspected or confirmed, in order to improve hospital outcomes and long-term health status. Developing clear guidelines even at the level of the hospital for referral to diabetic services, systems to support identification and management of hyperglycaemia, and the education of medical and nursing staff, by providing frequent lectures and workshops in order to raise the awareness about therapeutic inertia and their causes, is important. Having clear post-discharge follow-up systems and routine patient education about diabetes and its complications, in addition to giving adequate time for each patient, would also be helpful. This will reduce the resistance for future escalation of treatment and allow the monitoring of therapies and their side effects. HbA1c has been proved to be useful in disease monitoring and gives precious information in terms of disease progression and prognosis, so it should be used when available.

LIMITATIONS FOR THE STUDY

The lack of an organised electronic system, as most of the data was extracted from paper notes, meant that some records could not be accessed or were missing, and the authors struggled to collect the complete data. Moreover, some discharge notes were poor quality (i.e., illegible handwriting or the document was damaged) and, therefore, extraction of records was incomplete in some cases. As in other retrospective studies, some statistics could not be measured, or were confusing.

CONCLUSION

The authors' study shows that diabetic treatment inertia at a major tertiary hospital in Benghazi was high amongst patients with diabetes admitted to medical wards (54.28%). The therapeutic inertia in the study was likely due to doctors rather than the system or patients. HbA1c was carried out for only 13% of patients at admission and 25% (36 out of 144) had changes; however, there was no clear cause of change in their files. Patients on more than one oral hypoglycaemic medication were less likely to be offered treatment intensification, despite an above-target HbA1c. This work needs to continue with more patients in multicentre longitudinal studies.

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The Impact of Intermediate Antidrug Antibodies to Infliximab and Adalimumab on Clinical Outcomes in Patients with Crohn's Disease or Ulcerative Colitis

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Abstract

Background: The anti-TNF drugs adalimumab (ADA) and infliximab (IFX) are effective treatments for inflammatory bowel disease (IBD). However, 40% of patients lose response, often due to the development of antibodies-to-ADA (ATA) and antibodies-to-IFX (ATI). While low ATA/ATI titres (<200 ng/mL) are associated with better outcomes and high ATA/ATI titres (>1,000 ng/mL) are associated with poorer outcomes, the significance of intermediate ATA/ATI titres (200–999 ng/mL) is not well understood. This study aims to investigate the impact of intermediate ATA/ATI titres on outcomes in patients with IBD.

Methods: A retrospective chart review of 376 patients with IBD was conducted. The primary clinical outcome was persistence on anti-TNF therapy for 1 year after the measurement of ATA/ATI titres. The participants consisted of patients with IBD treated with IFX or ADA at the University of Maryland Medical Center's Inflammatory Bowel Disease Program between October 2016 and October 2019.

Results: Out of 322 patients with low titres, 271 persisted on their original anti-TNF, compared with nine out the 15 patients with intermediate titres (p=0.026) and one out the 10 patients with high titres (p<0.0001). The odds ratio of persistence when comparing intermediate titres to low titres was 0.26 (0.09–0.80), and when comparing high titres to low titres was 0.02 (0.00–0.14).

Conclusion: Patients with intermediate titres were more likely to lose response to anti-TNF drugs and require a change in anti-TNF therapy than patients with low titres. Although the sample size of patients with intermediate titres was small, providers should consider dose optimisation of anti-TNF drugs, with or without the addition of an immunosuppressant, when intermediate titres are present.

INTRODUCTION

Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, is a chronic autoimmune condition that involves the intestines.[1] IBD is characterised by chronic inflammation of the gastrointestinal tract, the pathogenesis of which involves an increase in the inflammatory cytokine TNF-α. This makes anti-TNF-α biologics such as adalimumab (ADA) and infliximab (IFX) effective options for the treatment of IBD.[2-5] Of all patients given ADA and IFX, about 30% are primary non-responders, meaning that they do not respond to treatment initially. Another 40% of patients lose response over time, meaning that they do respond to the treatment initially, but symptoms gradually return. One of the causes of loss of response is the development of antidrug antibodies.[6-11] This is a concern because most patients with IBD require long-term treatment and, with a limited number of treatments available, it is crucial to ensure that these drugs remain effective for as long as possible.

One of the ways that providers can optimise the treatment plan for a patient with IBD and prolong the benefits of a given biologic therapy like ADA or IFX is through therapeutic drug monitoring (TDM).[12-23] TDM involves taking routine measurements of the drug and antidrug antibody levels in a patient with IBD to ensure that the drug levels are therapeutic and the antidrug antibody titres are low or undetectable. While it is known that low antidrug antibody titres (<200 ng/mL) are associated with therapeutic ADA and IFX concentrations and better clinical outcomes,[5,24-32] and high antidrug antibody titres (>1,000 ng/mL) are associated with subtherapeutic ADA and IFX concentrations and poorer clinical outcomes,[6] the significance of intermediate antidrug antibody titres (200–999 ng/mL) are currently not well understood. At the authors' centre, the interpretation of antidrug antibody titres is at the discretion of the ordering provider. While there is no standard protocol in place, generally patients with low antidrug antibody titres are followed clinically for recurrent symptoms, such as signs of inflammation, and patients with high antidrug antibody titres are switched to a different anti-TNF drug or novel biologic, sometimes with the addition of an immunosuppressant when few therapeutic options remain. However, the approach to patients with intermediate antidrug antibody titres is unclear.

This study aims to address the gap in knowledge around intermediate antidrug antibody titres in order to give providers better guidance for managing patient treatments through TDM.

METHODS

This paper outlines a retrospective cohort study that took place at the University of Maryland Medical Center's Inflammatory Bowel Disease Program. The study participants consisted of patients with either Crohn's disease or ulcerative colitis who were being treated with ADA or IFX between 15th October 2016 and 15th October 2019 (Figure 1). The participants had at least one measurement of antibodies-to-ADA (ATA)/antibodies-to-IFX (ATI) and ADA/IFX during the study time period, with all assays done using LabCorp software (Laboratory Corporation of America Holdings, Burlington, North Carolina, USA) for comparability. Of the 376 patients identified, 157 patients were taking ADA and 219 patients were taking IFX. Of the 157 patients taking ADA, 113 had serial measurements and 44 had singlet measurements. Of the 219 patients taking IFX, 171 had serial measurements and 48 had singlet measurements.

The primary exposure variable examined was the patient's ATA/ATI titres, with thresholds as follows: low titres: <200 ng/mL; intermediate titres: 200–999 ng/mL; and high titres: ≥1,000 ng/mL.

The primary clinical outcome of interest was persistence on anti-TNF therapy for 1 year after the measurement of the ATA/ATI titres. Secondary clinical outcomes included the clinical response to therapy 1 year after measurement of ATA/ATI titres, the development of high ATA/ATI titres 1 year after measurement, the initiation of steroids within the 1-year study period, and a change in therapy made by the provider in response to the initial ATA/ATI titre measurement. Clinical response to therapy 1 year after the measurement of ATA/ATI titres was categorised into three groups: no response or worsening, partial response, and complete response, according to the physician's global assessment of disease activity. Additional sub-analyses evaluated the effect of

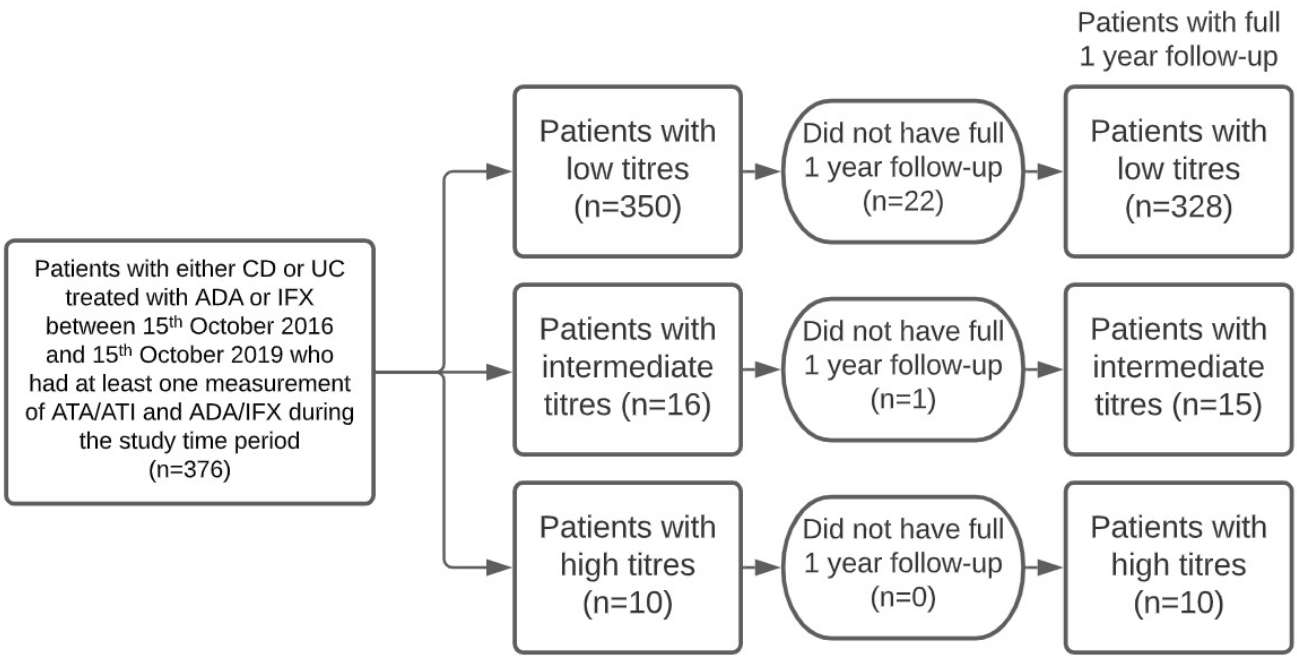

Figure 1: Schematic flow diagram of patient enrolment and analyses.

ADA: adalimumab; ATA: antibodies-to-adalimumab; ATI: antibodies-to-infliximab; CD: Crohn's disease; IFX: infliximab; UC: ulcerative colitis.

immunosuppressant use on the development of high ATA/ATI titres and clinical response. These clinical response rates were also categorised into three groups: no response or worsening, partial response, and complete response, according to the physician's global assessment of disease activity.

Groups were compared using parametric or non-parametric statistical analyses as appropriate. Baseline characteristics were described by the mean and standard deviation for continuous variables and by the number and percentage within the group for categorical variables. Comparisons of these variables were made using Student's t-test, chi-square test of homogeneity, or Fisher's exact test based on the type of variable and the normality of the data. A p value of 0.05 was considered significant for differences between groups. A final logistic regression analysis was performed to examine the relationship between exposure group and persistence on therapy after adjustment for confounding variables. Patients without 1 year of follow-up were excluded from the tables below.

RESULTS

In this study, 376 patients were identified (patients taking ADA: 157; patients taking IFX: 219): 350 patients with low titres, 16 with intermediate, and 10 with high titres. Participant baseline characteristics such as age, smoking history, and extraintestinal manifestations were similar. However, patients with intermediate (five out of 16) and high (two out of 10) titre antibodies were more likely to have a family history of IBD than those with low titre antibodies (35 out of 350; Table 1). Of the original set of patients, 22 of 350 low titre, one of 16 intermediate titre, and zero of 10 patients with high titres did not have a full 1 year of follow-up and were, therefore, excluded from subsequent analyses.

Persistence on Original Anti-TNF

It was found that 271 out of 322 (84%) patients with low titres persisted on their original anti-TNF treatment compared with nine out of 15 (60%) patients with intermediate titres and one out of 10 (10%) patients with high titres.

Table 1: Demographic and clinical characteristics of patients with inflammatory bowel disease who were treated with infliximab or adalimumab between 2016 and 2019 at the University of Maryland Medical Center's Inflammatory Bowel Disease Program.

Variable	Low (n=350)	Int (n=16)	High (n=10)	Total (n=376)	p
Age at diagnosis: mean (SD)	26.0 (13.3)	27.8 (16.4)	26.4 (11.1)	26.1 (13.3)	0.870 (ANOVA)
Age at first level: mean (SD)	38.0 (14.1)	40.9 (15.7)	39.4 (13.3)	38.2 (14.1)	0.70 (ANOVA)
Diagnosis (%)	N/A	N/A	N/A	N/A	0.5053 (Fisher's)
CD	259 (74.0)	12 (75.0)	8 (80.0)	279 (74.0)	N/A
UC	81 (23.0)	4 (25.0)	1 (10.0)	86 (23.0)	N/A
Indeterminate	10 (2.8)	0 (0.0)	1 (10.0)	11 (3.0)	N/A
Extraintestinal manifestations (%)	75 (22.0)	4 (27.0)	2 (20.0)	81 (22.0)	0.925 (Fisher's)
Family history of IBD (%)	35 (10.1)	5 (31.3)	2 (20.0)	42 (11.4)	0.019 (Fisher's)
Smoking status (%)	N/A	N/A	N/A	N/A	0.8542 (Fisher's)
Never	222 (63.4)	12 (75.0)	6 (60.0)	240 (63.8)	N/A
Current	42 (12.0)	3 (19.8)	1 (6.3)	48 (12.8)	N/A
Former	86 (24.6)	3 (30.0)	1 (10.0)	88 (23.4)	N/A
Prior IBD-related surgery (%)	N/A	N/A	N/A	N/A	0.763 (Fisher's)
None	203 (58.0)	8 (50.0)	5 (50.0)	216 (57.5)	N/A
One	142 (40.1)	8 (50.0)	5 (50.0)	155 (41.2)	N/A
Two or more	5 (1.4)	0 (0.0)	0 (0.0)	5 (1.3)	N/A
Duration of disease: mean (SD)	11.8 (9.4)	13.1 (11.4)	13.0 (5.4)	11.9 (9.4)	0.79 (ANOVA)
Use of immunosuppressant at baseline (%)	103 (30.0)	4 (25.0)	4 (40.0)	111 (30.0)	0.699 (Fisher's)
BMI: mean (SD)	28.2 (10.1)	30.9 (7.3)	28.3 (11.9)	28.3 (10.1)	0.58 (ANOVA)
Patients on IFX (%)	204 (58.3)	10 (62.5)	5 (50.0)	219 (58.2)	0.82 (chi-sq)
Initial drug level: mean (SD)					
IFX	11.1 (11.1)*†	4.9 (7.8)	0 (0.0)	N/A	Low versus int: 0.0350; int versus high: 0.0800; low versus high: <0.0001 (t-test)
ADA	7.1 (5.4)†‡	1.2 (1.4)	0.14 (0.3)	N/A	Low versus int: <0.0001; int versus high: 0.1200; low versus high: <0.0001 (t-test)

Table 1 continued.

Initial antibody level: mean (SD)					
IFX	15.7 (35.0)*‡	491.1 (221.7)§	4158 (5738.0)	N/A	Low versus int: <0.0001; int versus high: 0.0027; low versus high: <0.0001 (Wilcox Rank Sum) Low and high are not normally distributed (<0.0001; 0.0004), Int is distributed normally (0.1690) (Shapiro-Wilk)
ADA	14.5 (36.0)*‡	423.7 (142.5)§	2373 (1073.0)	N/A	Low vs int: <0.0001; int versus high: 0.0148; low versus high: <0.0001 (int versus high by t-test, others by Wilcox Rank Sum) Low is not normally distributed (<0.0001), Int and High are normally distributed (0.6500; 0.6400) (Shapiro-Wilk)

*Low titre group significantly different from intermediate titre group ($p<0.05$).
†Low titre group significantly different from high titre group ($p<0.0001$).
‡Low titre group significantly different from intermediate titre group ($p<0.0001$).
§Intermediate titre group significantly different from high titre group ($p<0.05$).
ADA: adalimumab; ANOVA: analysis of variance; CD: Crohn's disease; chi-sq: chi-square test; Fisher's: Fisher's exact test; IBD: inflammatory bowel disease; IFX: infliximab; Int: Intermediate; N/A: not applicable; SD: standard deviation; Shapiro-Wilk: Shapiro-Wilk test; t-test: Student's t-test; UC: ulcerative colitis; Wilcox Rank Sum: Wilcoxon Rank Sum test.

The odds ratio (OR) of persistence to original anti-TNF treatment when comparing intermediate titre to low is 0.280 (95% confidence interval [CI]: 0.096–0.827); when comparing high titre to low is 0.021 (95% CI: 0.003–0.169); and when comparing intermediate titre to high is 0.074 (95% CI: 0.007–0.746). Controlling for family history, the OR of persistence to original anti-TNF treatment when comparing intermediate titre to low is 0.260 (95% CI: 0.085–0.797), and when comparing high titre to low is 0.017 (95% CI: 0.002–0.143). When controlling for the above factors, the OR comparing high titre to intermediate was not significant (OR: 0.004; CI: <0.001–1.860; p=0.0785). In addition to the patients who did not have a full 1 year of follow-up, six out of 328 patients with low titres did not have data for their persistence on original anti-TNF treatment at 1 year and were, therefore, also excluded from this analysis.

Clinical Response to Therapy

In the low titre group, 45, 31, and 234 patients had no, partial, or complete response to therapy, respectively. In the intermediate titre group, six, zero, and eight patients had no, partial, or complete response, respectively; and in the high titre group, three, one, and three patients had no, partial, or complete response, respectively. The remaining patients with high titres did not have data at 1 year. The difference in the distribution of patients who showed no, partial, and complete responses was significantly different between the patients with low titres and intermediate titres (p=0.019), but not significantly different between patients with intermediate titres and high titres (p=0.440). There was a trend towards higher response rates in the patients with low titres compared with the high titres (p=0.061; Table 2). In addition to patients who did not have a full 1 year of follow-up, 18 out of 328 patients with low titres, one out of 15 patients with intermediate titres, and three out of 10 patients with high titres were excluded from the analysis because they did not have data for their clinical response at 1 year.

It was found that 30, 19, and 161 out of 210 patients with low titres not taking immunosuppressants at baseline and 15, 11, and 72 out of 98 patients with low titres taking immunosuppressants at baseline had no response, partial response, or complete response to therapy, respectively (p=0.76). The clinical response rates in patients with initially low antibody titres with and without baseline immunosuppressant use were not significantly different. Similarly, in patients with low titres, baseline use of immunosuppressants did not change the risk of persisting on initial anti-TNF compared to those who did not use immunosuppressants at baseline.

Furthermore, it was found that four, zero, and seven out of 11 patients with intermediate titres not taking immunosuppressants at baseline and two, zero, and one out of three patients with intermediate titres taking immunosuppressants at baseline had no response, partial response, or complete response to therapy, respectively (p=0.54). The clinical response rates in patients with intermediate titres with and without baseline immunosuppressant use were not significantly different. In patients with intermediate titres, baseline use of immunosuppressants also did not change the risk of persisting on the initial anti-TNF therapy compared with those who did not use immunosuppressants at baseline.

Table 2: Responses to anti-TNF therapy at 1 year in patients with inflammatory bowel disease who were treated with infliximab or adalimumab between 2016 and 2019 at the University of Maryland Medical Center's Inflammatory Bowel Disease Program.

Type of response	Low titre N (%)	Intermediate N (%)	High N (%)	Total N (%)
No response	45 (15)	6 (43)	3 (43)	54 (16)
Partial response	31 (10)	0 (0)	1 (14)	32 (10)
Complete response	234 (75)	8 (57)	3 (43)	245 (74)

Note: Patients with missing data for this outcome were excluded from analysis.

Risk of Developing High-Titre Antibodies

In this study, six out of 324 patients with low titres developed high ATA/ATI titres, compared with three out of 15 patients with intermediate titres (p=0.005). In addition to patients who did not have a full 1 year of follow-up, four out of 328 patients with low titres were excluded from the analysis because they did not have data for the development of high-titre antibodies at 1 year.

Of the 13 patients with intermediate titres who had subsequent drug levels, five patients had their original anti-TNF dose increased in response to their initial measurement. Of these five patients, three went into remission and saw a drop in ATA/ATI titre from intermediate to low, while two showed no change or worsening of symptoms. Moreover, four of the 13 patients had their original anti-TNF dose increased and were started on an immunosuppressant in response to their initial measurement. Of these four patients, three went into remission and saw a drop in ATA/ATI titre from intermediate to low, while one showed improvement in symptoms. However, three of these 13 patients had no change to their therapy in response to their initial measurement. Of these, two went into remission and one showed no change or worsening of symptoms and saw an increase in ATA/ATI titre from intermediate to high. One of the 13 patients was switched to a different anti-TNF treatment in response to their initial measurement but was lost to follow-up.

Additionally, three out of 220 patients with low titres not taking immunosuppressants and three out of 102 patients with low titres taking immunosuppressants developed high titre antibodies (p=0.39). Of the intermediate titre patients, two out of 9 patients not taking immunosuppressants and one out of 4 patients taking immunosuppressants developed high titre antibodies (p>0.99).

Impact of Antibody Titre on Management

It was found that 25 out of 325 patients with low titres started steroids due to IBD, compared with three out of 15 patients with intermediate titres (p=0.12). Patients with high titres are not included here because none of the 10 patients started steroids within the study period, and six of these 10 patients were already on a steroid regimen prior to TDM.

The distribution of change in therapy made in response to the initial ATA/ATI titre levels is significantly different between the patients with low, intermediate, and high titres: 142 out of 325 patients with low titres, one out of 15 patients with intermediate titres, and one out of 10 patients with high titres had no change in their therapy in response to the initial titre measurement. Furthermore, 52 out of 325 patients with low titres, six out of 15 patients with intermediate titres, and nine out of 10 patients with high titres changed or stopped their current anti-TNF treatment in response to the initial titre measurement (Table 3).

DISCUSSION

The data from this study indicate that the proportion of patients with intermediate titres who persist on their original anti-TNF therapy is lower than for patients with low titres. Clinical response rates seen in the patients with intermediate titres were different from the clinical response rates seen in the patients with low titres, but not different from the clinical response rates seen in the patients with high titres, suggesting that patients with intermediate titres have clinical response rates that more closely resemble those seen in patients with high titres. Patients with intermediate titres were also more likely to develop high ATA/ATI titres than patients with low titres. Altogether, these results suggest that patients with intermediate titres were more likely than patients with low titres to develop high ATA/ATI titres, lose response to anti-TNF treatment, thus requiring a change to anti-TNF therapy, and more closely resemble clinical response rates seen in patients with high titres. Thus, the identification of intermediate titre antidrug antibodies is a poor prognostic sign that warrants further intervention, which could entail a repeat assessment of antidrug antibodies before a subsequent infusion or injection, dose escalation, addition of an immunosuppressant, or both raising the dose and adding an immunosuppressant (Figure 2).

The finding from this study that patients with low titres persist more than patients with high titres on their original anti-TNF therapy is consistent

Table 3: Changes in therapy made in response to initial antibodies-to-adalimumab or antibodies-to-infliximab titres in patients with inflammatory bowel disease who were treated with infliximab or adalimumab between 2016 and 2019 at the University of Maryland Medical Center's Inflammatory Bowel Disease Program.

Type of change	Low titre N (%)	Intermediate titre N (%)	High titre N (%)	Total N (%)
No change	142 (44.0)	1 (6.7)	1 (10.0)	144 (41.4)
Increase anti-TNF dose	111 (34.4)	5 (33.3)	0 (0.0)	116 (33.3)
Add immunosuppressant	6 (1.9)	0 (0.0)	0 (0.0)	6 (1.7)
Increase dose and add immunosuppressant	12 (3.7)	3 (20.0)	0 (0.0)	15 (4.3)
Change or stop anti-TNF	52 (16.1)	6 (40.0)	9 (90.0)	67 (19.3)

Note: Patients with missing data for this outcome were excluded from analysis.

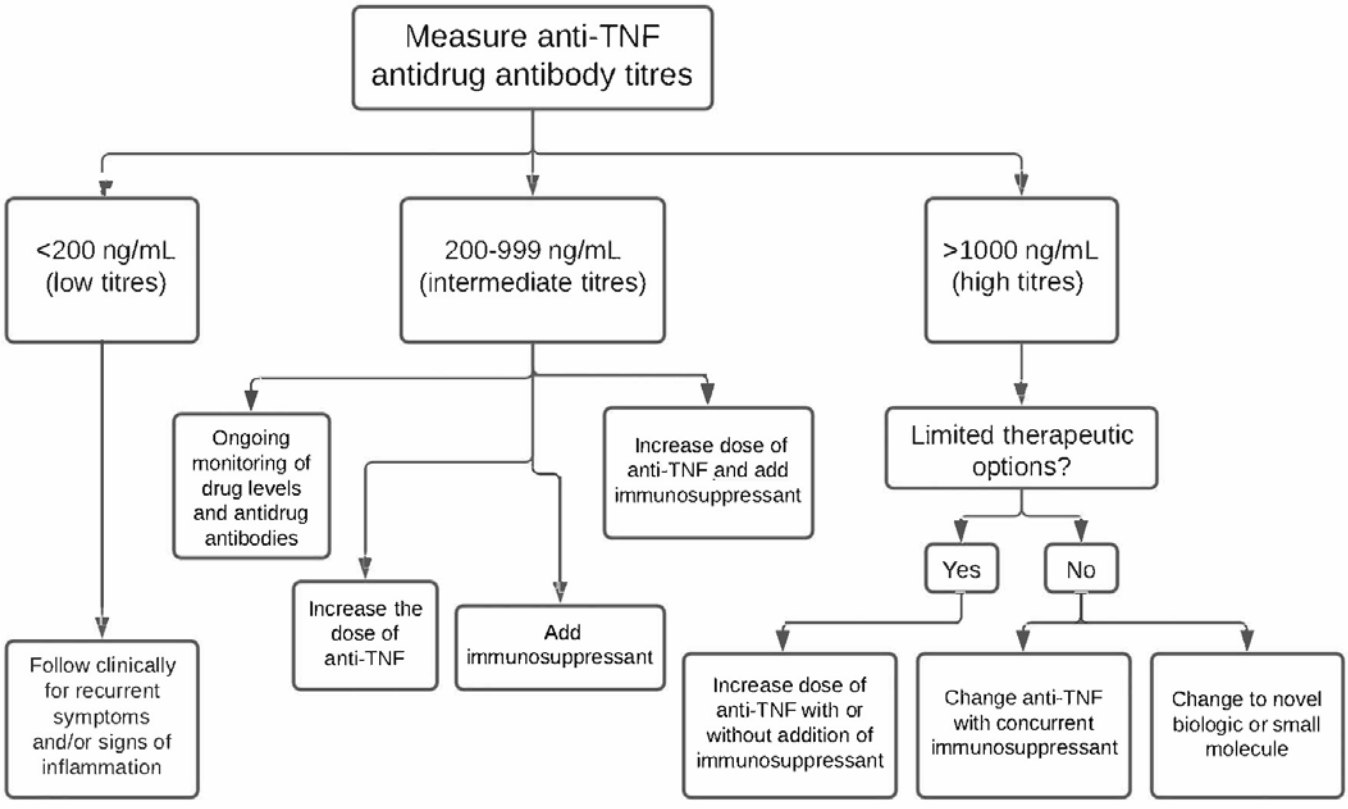

Figure 2: Clinical decision tree for patients with inflammatory bowel disease based on their antidrug antibody titre.

with de Boer et al.,[13] who found that patients with high titres frequently require switching to an alternative anti-TNF.[7] Although there was not quite a statistically significant difference in the distribution of response to therapy between patients with low titres and patients with high titres, there were more patients with low titres with complete response (251 out of 331) compared with patients with high titres with complete response (three out of seven), and fewer patients with low titres with no response (47 out of 331) compared with patients with high titres with no response (three out of seven). It was found that low ATA/ATI titres are associated with better clinical outcomes, such as a complete response, whereas high ATA/ATI titres are associated with poorer clinical outcomes, such as no response. These findings are consistent with Mazor et al.,[25] who found that high ATA titres are associated with disease activity.[8] In the management of rising ATA/ATI production, studies by both Ben-Horin et al.[22] and Vermeire et al.[23] found that concomitant immunosuppressive therapy suppresses the formation of ATI and restores clinical response in patients with IBD.[9,10] However, in the study outlined here, baseline immunosuppressant use did not seem to have a significant effect on the number of patients who went on to develop high ATA/ATI titres or the clinical response of patients. It is not clear whether adding an immunosuppressant at the time of identification of intermediate titres would have improved outcomes.

There are several strengths and few limitations in this study. The strengths include the overall sample size, the use of a single assay to measure IFX and ADA levels and antidrug antibodies, and carrying out adjusted analyses. A weakness of the study was its retrospective nature; nonetheless, most of the variables were collected with few cases of missing data. Additionally, as the University of Maryland is a referral centre for IBD care, these results may not be generalisable to the community at large. Lastly, a relatively small number of patients with intermediate antidrug antibodies participated, so the study was likely underpowered to identify small to moderate differences between the groups. This also limits the ability to study the specific interventions in response to antidrug antibody levels from this data. Nevertheless, to the author's knowledge, this is the largest study of intermediate antidrug antibody levels in the literature.

CONCLUSION

Patients with intermediate titres are more likely than patients with low titres to develop high ATA/ATI titres, lose response to anti-TNF, and require a change in anti-TNF therapy, meaning that these patients more closely resemble the clinical response rates seen in high titre patients. However, the authors suspect that the 'intermediate' antidrug antibody titres are not one monolithic group, and that there are likely to be more precise ranges of titres that put patients at a higher or lower risk of developing high antidrug antibodies titres later on.

Although the sample size of patients with intermediate titres in this study was small, based on these findings the authors suggest that patients with intermediate antidrug antibody titres undergo active changes in treatment. For example, providers should consider a dose escalation of IFX or ADA, with or without concurrent immunosuppressant repeat drug and antidrug antibody levels, to assess for rising titres.

A follow-up study with a greater sample size of patients with intermediate titres should be considered in order to strengthen the association that this study found between intermediate ATA/ATI titres and an increased risk of developing high ATA/ATI titres and a subsequent loss of response to treatment. Baseline immunosuppressant use did not impact the development of intermediate titre antidrug antibodies. Future studies should also stratify patients based on baseline immunosuppressant use and determine whether adding immunosuppressants in patients with intermediate titres reduces antidrug antibody titres and prevents a loss of response.

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Ewing's Sarcoma of the Lung as a Second Malignancy in Long-Term Survivor of Childhood Hodgkin's Lymphoma: A Rare Case Report and Literature Review

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Abstract

In patients with haematologic malignancies such as lymphoma and leukaemia, significant increases in survival have been seen, due to advances in treatment strategies. However, long-term survivors of these cancers still remain at a higher risk of developing second cancers during their lifetime, especially in the fourth decade. It is well known that immunodeficiency after radiotherapy, chemotherapy, or haematopoietic stem cell transplantation impairs the antitumour activity of the innate and adaptive immune systems, predisposing the immune system to fail to detect and eliminate newly mutated cells. Literature shows evidence of various malignancies in these survivors, including sarcomas; breast cancers; mesothelioma; and solid secondary malignancies like breast cancer, thyroid cancer, and bone or soft tissue sarcoma.

Here, the author reports a case of development of Ewing's sarcoma of the lung in an adult who is a long-term survivor of Hodgkin's lymphoma.

INTRODUCTION

Hodgkin's lymphoma (HL), first described by Sir Thomas Hodgkin in 1832, has evolved greatly in regard to its treatment. HL is a highly curable disease with a 5-year survival rate of approximately 88.3% overall, and more than 92.2% for localised disease.[1] Due to the advances in diagnosis and treatment, there has been an increase in the number of survivors of HL. Most live for decades after their initial diagnosis and treatment. However, survivors of HL are at increased risk for late effects, which may manifest as subsequent primary cancers, cardiovascular disease, pulmonary toxicity, or endocrine dysfunction.[2] These treatment effects can occur as late as the fourth decade after initial treatment.[3]

Ewing's sarcoma (ES), a malignancy of adolescents and young adults, has an incidence of approximately one in 1 million, and is characterised by the proliferation of small round

cells, expression of cluster of differentiation (CD) 99 in a characteristic membranous pattern, and non-random chromosomal translocations between the *EWS* gene on chromosome 22q12 and an *ETS* (E26 transformation-specific) family gene.[4] It is the second most commonly occurring sarcoma, arising from bone or soft tissue in children. Few case studies have been published on ES occurring secondary to cancer therapy, including multimodal therapy for haematologic malignancies.[5]

Here, the author reports a case of development of ES of the lung in an adult who is a long-term survivor of childhood HL.

CASE REPORT

A 28-year-old male non-smoker was admitted with complaints of recurrent haemoptysis and right side diffuse, dull aching chest pain. They had a known case of HL diagnosed at the age of 13 years, for which he received six chemotherapy cycles of adriamycin, bleomycin, vincristine, and doxorubicin, and no radiotherapy. The patient was kept under follow-up. On further evaluation, the patient also gave a history of recurrent cold and cough associated with occasional dyspnoea since childhood. The patient had no history of recent fever, weight loss, or loss of appetite. Chest X-ray posteroanterior view was suggestive of right middle lobe collapse (Figure 1A). Lung function showed severe obstruction with significant reversibility. An empirical diagnosis of uncontrolled bronchial asthma was made. The patient was further evaluated for allergic bronchopulmonary aspergillosis. Serum total IgE (940 IU) and specific IgE (0.34 IU) against *Aspergillus fumigatus* were raised. Allergic bronchopulmonary aspergillosis antifungals (voriconazole and caspofungin), oral corticosteroids, and inhaler therapy were prescribed. However, during follow-up, the patient continued to have haemoptysis, and repeat chest X-rays showed complete collapse of the right lung (Figure 1B). CT pulmonary

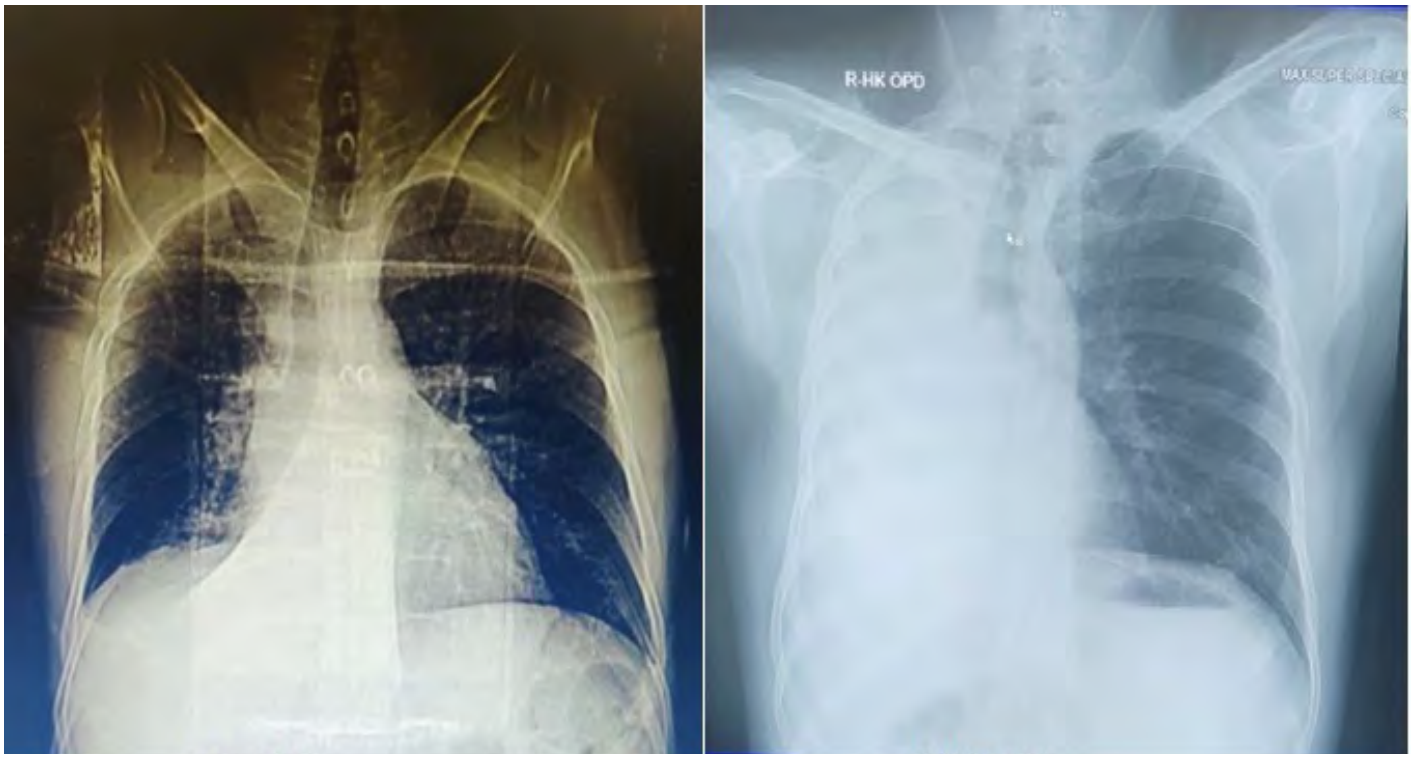

Figure 1: Chest X-ray of a patient with uncontrolled bronchial asthma, who had been diagnosed Hodgkin's lymphoma.

A) Chest X-ray at time of presentation showing right middle lobe collapse. **B)** Follow-up chest X-ray showing complete collapse of right middle side with mediastinal shift on same side.

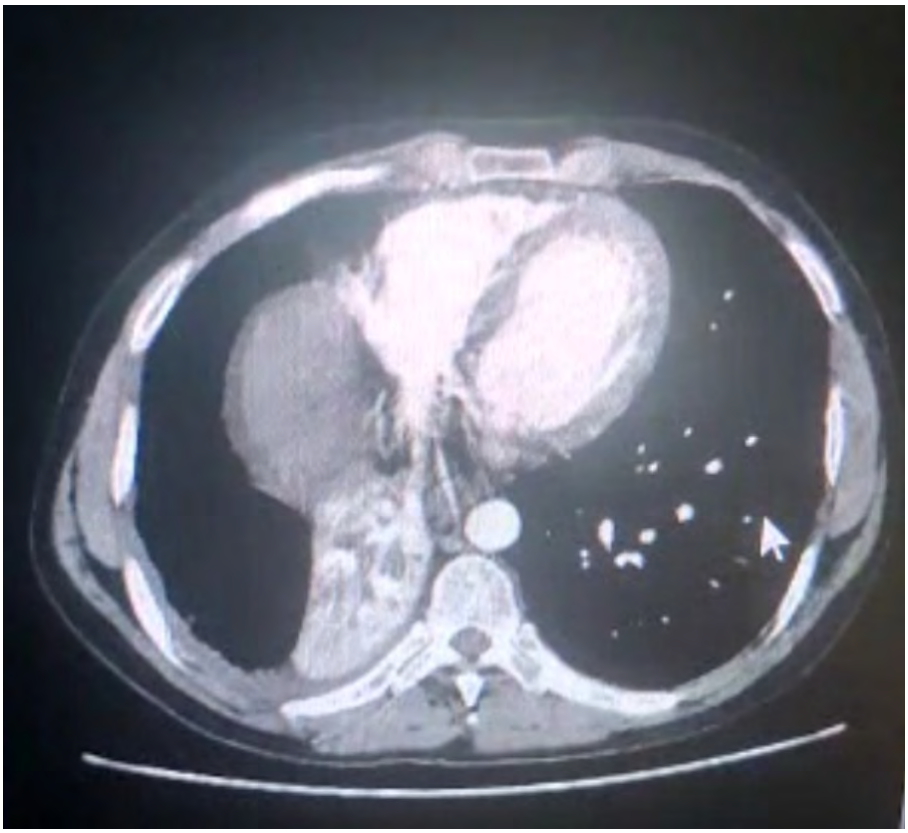

Figure 2: Mediastinal window of chest CT showing lobulated soft tissue density in the right hilar lesion.

angiogram was suggestive of a fairly-defined, poorly-enhanced lobulated soft tissue density in the right hilar lesion encasing the right bronchus and pulmonary artery, and causing narrowing of the right upper and middle lobe bronchi, and complete occlusion of lower bronchus with multiple patchy ground-glass opacities, likely to be right lower lobe complete collapse with alveolar haemorrhages (Figure 2).

The patient underwent fiberoptic bronchoscopy, which showed an intraluminal mass causing complete obliteration of the right main bronchus up to the carina. Bronchoalveolar lavage for malignant cells was inconclusive. Endobronchial biopsy showed infiltration of sheet of polygonal/round tumour cells in respiratory epithelium submucosa, with tumour cells having scant cytoplasm, a high nucleocytoplasmic ratio, and coarse chromatin with inconspicuous eosinophilic nucleoli. Endobronchial ultrasound-guided transbronchial needle aspiration showed singly scattered and clusters of markedly pleomorphic tumour cells with coarse chromatin, conspicuous nucleoli, and a scant-to-moderate amount of cytoplasm, which was positive for malignant cells (Figure 3A). On immunohistochemistry, it was positive for vimentin and CD99. They showed nuclear transducing-like enhancement of split expression and *FLT-1* positivity, and were negative for cytokeratin 7, cytokeratin 5/6, epithelial membrane antigen, leukocyte common antigen, PO, thyroid-specific transcription factor-1, synaptophysin, chromogranin, CD138, S-100, con, CD30, CD3, CD34, smooth muscle actin, and desmin. The Ki-67 proliferative index was approximately 10%, favouring a diagnosis of malignant round cell tumour, likely to be primitive neuroectodermal tumour. Further, in cytogenetics, fluorescence *in situ* hybridisation for *EWSR1* (22q12.2) gene rearrangement was positive in 68% of tumour cells (Figure 3B), whereas there was no evidence of translocation (X;18)(p11.2;q11.2)/*SS18* gene rearrangement (Figure 3C). A diagnosis of ES of the lung was made, and the patient planned for chemotherapy. However, the patient defaulted for further evaluation, and received alternative medicine for a period. The patient again presented with persistent cough and dyspnoea,

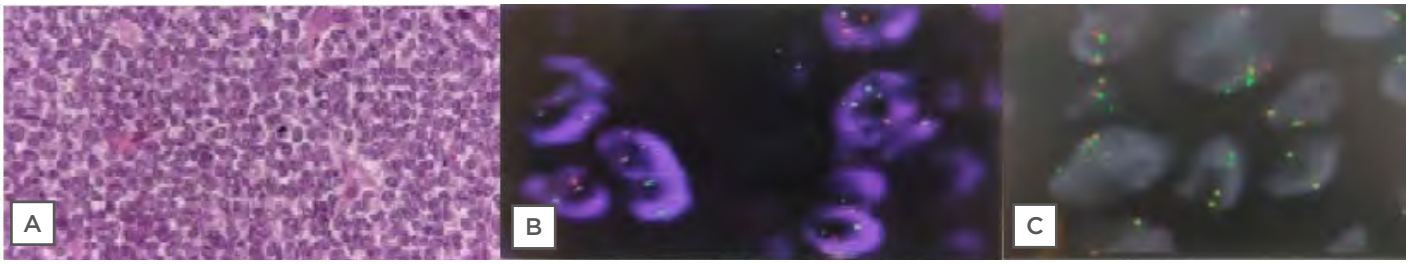

Figure 3: A series of tests leading to the diagnosis of Ewing's sarcoma of the lung.

A) Histopathology of EBUS-TBNA sample. **B)** FISH showing positive tumour cell for *EWSRI* gene rearrangement. **C)** Showing no evidence of translocation *SS18* gene rearrangement.

EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; FISH: fluorescence *in situ* hybridisation.

requiring intensive care unit admission. A PET-CT scan showed an ill-defined heterogeneously hypermetabolic pulmonary mass arising from the right lung field, with associated hypermetabolic collapse. Presence of hypermetabolic pleural, pulmonary, lymphatic, and skeletal metastasis was also seen, confirming diagnosis of Stage IV ES. Bone marrow aspiration and biopsy were performed as a staging workup, which showed trilineage haematopoiesis with normocellular marrow.

The patient was then treated with a regimen of vincristine, adriamycin, and cyclophosphamide (VAC). The patient had a symptomatic response to the first cycle of VAC, so another cycle was repeated. After the second cycle, the regimen was changed because the patient had already received 420 mg/m^2 of adriamycin (300 mg in six cycles of adriamycin, bleomycin, vincristine, and doxorubicin given during HL treatment, and 120 mg in two cycles of VAC). A new regimen containing vincristine, ifosfamide, and etoposide was given for two cycles, followed by two further cycles of irinotecan and temozolomide. The patient tolerated this therapy well; however, repeat PET-CT scans showed disease progression, with an increase in the size and metabolic activity of the primary and metastatic lesions, and with development of new nodal and soft tissue metastasis.

The patient was then treated with three cycles of the next line of chemotherapy, gemcitabine and docetaxel, but the disease progressed both radiologically and clinically. The patient was advised to undergo palliative radiotherapy in view of the recurrent cough and breathing difficulty, but refused to undergo radiotherapy, and was lost to follow-up.

DISCUSSION

There has been a significant increase in the survival of patients with haematologic malignancies as a result of advances in treatment strategies, including those for indolent and aggressive forms of lymphoma and leukaemia.[6,7] Long-term survivors of these cancers still remain at a higher risk of developing second cancer during their lifetime because of multifactorial causes.

Risk Factors Responsible for Second Cancer

There are numerous risk factors, such as age at treatment,[8] sex, phenotype of the first cancer, treatment modalities, radiation dose,[9] and chemotherapy[10,11] of the first cancer. Several treatment modalities for newly diagnosed malignancies have been implicated as risk factors for second malignancy, including various chemotherapeutic agents, radiotherapy, targeted therapy with monoclonal antibodies, and stem cell transplantation. Treatments are decided according to the phenotype, the line of differentiation, biological markers, and extent of the disease. Patients who received radiation therapy for first cancer are more prone to develop sarcomas, breast cancers, and mesothelioma compared with people who did not receive it.

The most frequently observed solid secondary malignancies are breast cancer, thyroid cancer, and bone or soft tissue sarcomas.[12] With extended follow-up of cohorts of young survivors of HL, increased risks of common adult carcinomas, including colorectal, lung, and gastric types, have emerged, and these cancers are being diagnosed at younger ages than observed in the general population.[13]

The use of treatment regimens based on a reduction in the field and dose of radiotherapy and alkylating chemotherapy has been introduced in order to reduce rates of long-term complications, while maintaining a high cure rate. Despite such modifications, a recent study from the Netherlands showed that this has not affected the risk of second cancers in individuals with HL.[3] Applebaum et al.[14] found that 12.1% of patients developed ES at the site of irradiation for the initial cancer.

Pathogenesis

It is well known that immunodeficiency after radiotherapy, chemotherapy, or haematopoietic stem cell transplantation impairs the antitumour activity of the innate and adaptive immune systems.[11] This predisposes the immune system to fail to detect and eliminate newly mutated cells carrying the ES translocation, allowing for the initiation of secondary ES.

The pathogenesis of ES is strongly linked to the presence of a translocation between the *EWSR1* gene and *ETS* gene family members. In 80% of cases, the partner gene is *FLI1*, with translocation (11;22)(q24;q12) leading to *EWS–FLI1*.[15] ES involves the expression of a germline predisposition syndrome, accounting for the strong predilection of ES to occur in young patients, similar to other genetically linked tumours.

Histology

Histologically, the tumour consists of a proliferation of small round cells with scanty and clear cytoplasm, round to oval nuclei, finely granular chromatin, and inconspicuous nucleoli. It is periodic acid–Schiff-positive due to the presence of cytoplasmic glycogen. Histologic differential diagnoses include small cell carcinoma, malignant lymphoma, alveolar rhabdomyosarcoma, and neuroblastoma. Tumours have a strong reactivity to CD99/MIC-2 and vimentin. In some cases, they may be positive for markers of neural differentiation, such as S100, neuron-specific enolase, and cytokeratins (in 20% of cases). Demonstration of translocation (11;22)(q24;q12) by fluorescence *in situ* hybridisation and/or reverse transcription-PCR is used to support the diagnosis.[16]

Treatment Options

There are only a few reports on ES as a secondary malignancy in the literature, mostly comprising single case reports or short series describing ES following treatment for unrelated tumours. As such, there are no defined guidelines or directions for managing such situations; hence, more experience is needed. The treatment of ES is aggressive, with the most effective approach being surgical resection with combination chemotherapy and/or high-dose radiation therapy. Prognosis is mainly related to the ability to achieve disease-free surgical margins, and the extent of anatomical spread to surrounding structures such as bone, pleura, and the epidural space.[17,18] The standard first-line treatment for patients with these tumours has been based on five drugs mainly included vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide. Pazopanib efficacy in pulmonary ES was reported, but it is not considered a standard therapy.[19]

CONCLUSION

The author has described an extremely rare case of pulmonary ES in a case of treated HL. Though rare, it should be considered in the differential diagnosis of patients with a history of HL. It is important for physicians and oncologists to follow-up patients with HL in the long term for accurate monitoring and quantification of the associated risks of second cancers and other late effects.

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Extramammary Paget Disease of Peristomal Skin Secondary to Bladder Urothelial Carcinoma

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Abstract

Extramammary Paget disease (EMPD) is a rare, cutaneous condition, which can present secondary to underlying carcinoma as an eczematoid rash that often mimics other conditions. Secondary EMPD should, therefore, be considered in the differential diagnosis where there is potential for malignant extension, particularly in post-operative tissue. This report describes a case of secondary EMPD of the peristomal skin in a patient with a distant history of cystectomy with ileal conduit for urothelial carcinoma, who developed an extensive eczematoid rash over 5 years after attempting several ineffective treatments. Early dermatologic referral for persistent inflammatory cutaneous disorders and appropriate histopathologic testing may reduce delays in the diagnosis of EMPD.

INTRODUCTION

Extramammary Paget disease (EMPD) is a relatively rare condition, with a reported incidence of 0.1–2.4 patients per 1,000,000 person years.[1] It most commonly presents in the vulvar region of White females between 50 and 80 years of age.[1] EMPD clinically presents as an erythematous eczematoid rash that clinically mimics inflammatory cutaneous disorders, which may result in a delayed diagnosis.[2] EMPD can be classified into primary and secondary, with the latter representing the spread of non-cutaneous internal carcinoma by direct extension or by epidermotropic metastasis. The most common carcinomas that cause secondary EMPD are anorectal and urothelial carcinomas.[2] Here, a case of secondary EMPD of the peristomal skin is reported in a patient with a distant history of cystectomy with ileal conduit for urothelial carcinoma, who developed extensive peristomal eczematoid rash over 5 years.

CASE DESCRIPTION

An 87-year-old male with a history of invasive transitional cell urothelial carcinoma of the bladder, left distal ureter status post-radical cystoprostatectomy, left distal uretectomy with ureteroureterostomy, and an ileal conduit

urinary diversion 14 years prior, presented at the authors' dermatology clinic with complaint of a peristomal rash that had persisted for many years. The patient reported that the rash had been present for at least 5 years and was getting larger and described it as pruritic and tender. The rash was initially attributed to urine leakage and had been treated as eczema and a fungal infection with wound and stoma care, as well as topical antifungals, unsuccessfully for years prior to presentation. The patient had been using wound cleanser spray, normal saline, nystatin powder, and miconazole. The dermatologic exam revealed a large erythematous plaque with areas of maceration around the stoma, involving most of the right abdomen extending to the pubis (Figure 1).

A shave biopsy was performed from around the peristomal lesion for histopathologic diagnosis. The biopsy showed infiltration of the epidermis, with large atypical epithelioid cells with enlarged hyperchromatic nuclei and pale cytoplasms in solitary units and nests (Figures 2 and 3). These cells showed diffuse and strong expression of cytokeratin 7 and GATA3, and focal expression of cytokeratin 20 (CK20), the CDX2 protein, and the BerEp4 antibody. The cells were negative for the proteins p63, carcinoembryonic antigen, Sox10, prostate-specific antigen, and thyroid transcription factor-1. No intracytoplasmic mucin was seen on the mucicarmine stain and a periodic acid–Schiff stain was negative for fungal organisms. The morphologic and immunohistochemical features are consistent with secondary EMPD, and consistent with the involvement of the patient's known urothelial carcinoma of the bladder.

These findings could represent local extension from recurrent cancer in the stoma itself, or metastasis. A biopsy of the stoma and urothelial tract, as well as CT scans of the chest, abdomen, and pelvis with and without contrast, were planned to assess for metastatic disease. However, soon after the diagnosis was made, the patient stated that they did not want to receive any invasive treatment or procedure and opted for do-not-resuscitate status. The patient was offered palliative therapy with topical imiquimod and radiotherapy, which they denied. This patient passed away years later from other systemic complications.

DISCUSSION

Currently, the exact mechanism underlying EMPD is unknown, but two widely known theories exist, namely the epidermotropic and transformation theories. The epidermotropic theory is more

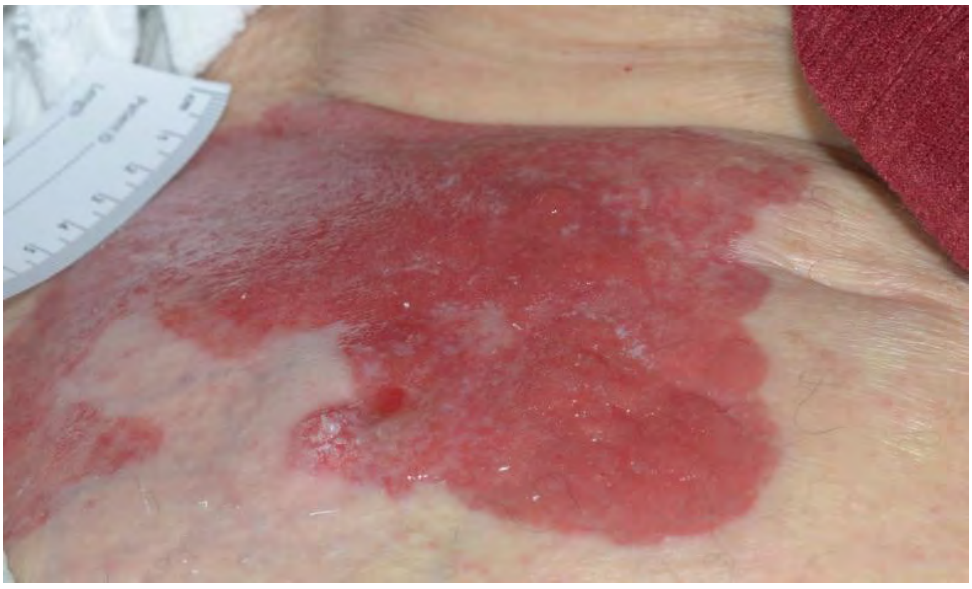

Figure 1: A peristomal, macerated, bright red plaque involving the right abdomen of the patient.
The stoma is seen in the central, lower portion of the image as an erythematous circular depression.

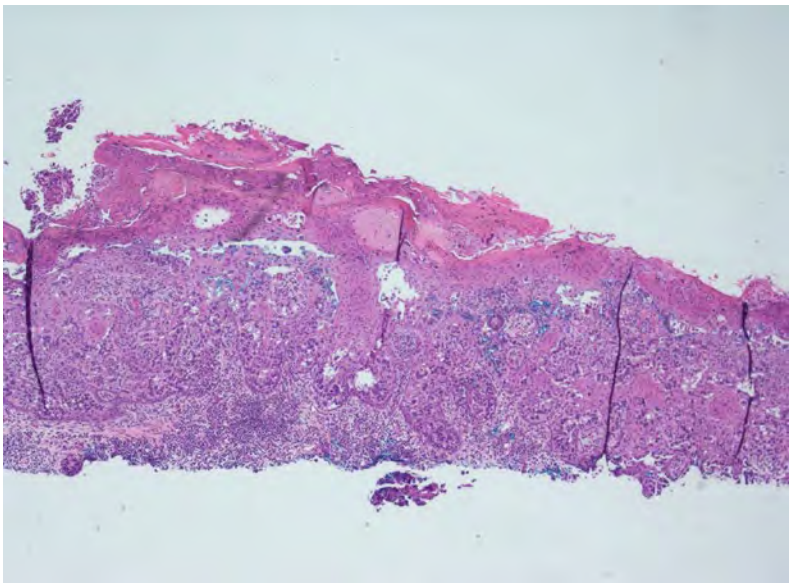

Figure 2: The epidermis displaying infiltration by large atypical epithelioid cells at low magnification (haematoxylin and eosin stain; original magnification: x40).

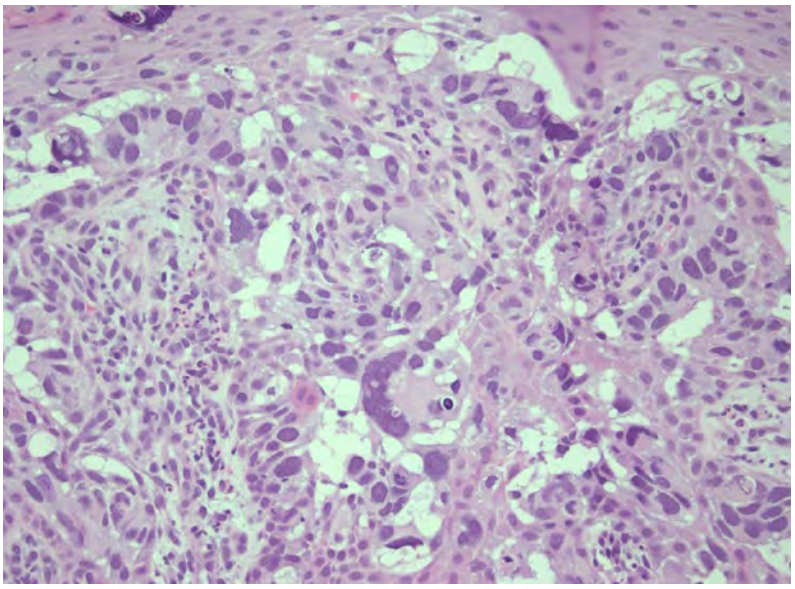

Figure 3: A high magnification (haematoxylin and eosin stain; original magnification: x400) view of lesion-displaying cells in solitary units and nests with enlarged hyperchromatic nuclei and pale cytoplasms.

commonly accepted and suggests the migration of adenocarcinoma cells into the epidermis, while the transformation theory postulates the *in situ* malignant transformation of basal keratinocytes.[3] However, there remains a lack of evidence for either theory and the pathogenesis of EMPD is considered controversial. There have been several studies that have sought to identify biomarkers and signalling pathways in an effort to guide the development of EMPD treatments. Specifically, the Musashi-1–mammalian target of rapamycin pathway has been cited as promoting the Paget cell conversion of keratinocytes, suggesting that the utility of rapamycin as a novel therapy would be effective in patients expressing this phenotype.[3] Similarly, human epidermal growth factor receptor 2 (and downstream molecules in the Ras–Raf–mitogen-activated protein kinase

kinase and phosphoinositide 3-kinase–protein kinase B–mammalian target of rapamycin pathways have been identified as potential targets for treatment.[4] Although the current understanding of EMPD is improving, more research is needed to determine the implication of these findings on treatment options for patients with EMPD.

EMPD largely affects body areas with a high concentration of apocrine glands, most commonly the genitals; EMPD has rarely been reported to occur in body areas that are less populated with apocrine glands such as the trunk and the cheeks.[2] A literature review composed by the authors revealed one similar case of secondary EMPD around a cutaneous ureterostomy stoma after radical cystectomy in an 85-year-old male.[5] This patient, presented by Kanda et al.,[5] similarly developed refractory dermatitis around a stoma on the abdominal skin. The time after the radical cystectomy and cutaneous ureterostomy were performed to the development of cutaneous manifestations was 4 years in this patient, which represents a similar time frame to that of the case study outlined in this article. The patient's cutaneous malignancy was cured by skin excision around the cutaneous stoma; however, they ultimately died of metastatic urothelial carcinoma.[5] Other cases exist of EMPD secondary to urothelial carcinoma, although the cutaneous manifestations presented on the apocrine-rich genital skin in these cases.[6,7]

Many different modalities of treatment exist for EMPD, depending on the presence or absence of metastatic disease and the surgical candidacy of the patient. In patients with primary EMPD, treatment typically consists of surgery with wide-local excision or Mohs micrographic surgery combined with adjuvant or neoadjuvant imiquimod.[8] In patients with secondary metastatic EMPD, such as the one presented here, systemic chemotherapy is typically used. However, the most effective regimen for metastatic disease has not yet been established; secondary EMPD is difficult to treat and is associated with poorer outcomes. Proposed chemotherapeutic regimens include utilising antimetabolites such as 5-fluorouracil, alkylating antineoplastics like cisplatin or carboplatin, and alkaloids, including paclitaxel or docetaxel.[8] Due to the patient's poor surgical candidacy and do-not-resuscitate status, they were offered topical imiquimod therapy for palliation only, which the patient denied.

The dermatologic exam of EMPD most commonly demonstrates a well-demarcated, erythematous plaque, with or without overlying secondary skin changes. Due to the variation in clinical appearance, the initial differential for EMPD may include many different infectious and non-infectious entities, including dermatophytosis, irritant or allergic contact dermatitis, and inverse psoriasis. Adding to the diagnostic difficulty is the fact that patients may be asymptomatic or present with non-specific symptoms such as pruritus, tenderness, and burning.[1] Given its ability to mimic several inflammatory conditions, the diagnosis of EMPD is often delayed by many years. Early recognition of EMPD is paramount given its tendency to demonstrate multifocal and discontinuous subclinical extension. It is, therefore, recommended that all patients with pruritic eczematous lesions on areas of apocrine gland-bearing skin who fail to respond to standard topical treatment after 4–6 weeks receive a skin biopsy of the affected area for diagnosis.[1,2]

CONCLUSION

In summary, it is important for the urologist and stoma care team to consider secondary cutaneous involvement by malignancy, regardless of the time passed postoperatively. Dermatology referral should be considered for most dermatological conditions that fail to improve or resolve as expected despite treatment, and this is particularly true of treated cancer patients with persistent peristomal rashes.

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Epidermodysplasia Verruciformis in a Patient with a Renal Transplant: A Rare Case Report

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Abstract

Acquired epidermodysplasia verruciformis is a rare condition that can occur in patients who are immunocompromised, particularly recipients of a renal transplant. In a patient who has had a renal transplant, acquired epidermodysplasia verruciformis has a greater propensity for developing non-melanoma skin cancer. It is critical to emphasise an early and accurate diagnosis, and regularly monitor this high-risk population.

INTRODUCTION

Epidermodysplasia verruciformis (EV) is a rare, autosomal recessive genodermatosis affecting the skin. It is characterised by an unusual susceptibility to the *human papillomavirus* (HPV) infection, especially with HPV5 and HPV8, without gender and race preponderance.[1,2] It can also be acquired and is more common in patients who are immunocompromised, such as those who have had a kidney transplant.[3]

The clinical feature is characterised by hypo- or hyperpigmented macules, skin-coloured flat-topped papules, and plaques with mild scaling that develop in children over the face, neck, trunk, and extremities.[1,4] According to reports, the risk of malignant transformation of skin lesions, particularly those on sun-exposed areas, is increased by 35–50%.[1,5]

The diagnosis of EV is usually clinical, and it can be confirmed by specific histopathological findings and EV-HPV identification using PCR.[6] There is currently no effective treatment for EV. However, early diagnosis, sun protection, life-long monitoring for malignant transformation, and therapeutic modalities such as acitretin, imiquimod, topical retinoids, cryotherapy, and others are available for the treatment of EV.[7]

Only a few cases of acquired EV, especially among recipients of a renal transplant, have been reported in the literature worldwide. The authors report a case of acquired EV in a patient who had a renal transplant, along with a review of the literature.

CASE PRESENTATION

A 24-year-old female patient who had had a renal transplant presented to the dermatology clinic with asymptomatic hypopigmented macules

with branny scaling and multiple flat-topped shiny papules over the forehead and cheek bilaterally. She was on systemic corticosteroid and mycophenolate mofetil and had consanguineous parents.

The lesions started on the forehead, gradually increasing in number to involve the cheek. There were no similar skin lesions among family members. Photosensitivity, joint pain, skin rashes, oral ulcer, fever, night sweats, and lymphadenopathy were not present. On examination, there were numerous hypopigmented macules, with mild scaling as well as numerous skin-coloured flat-topped papules and plaques over the forehead and cheeks on both sides. The size ranged from 0.5 to 1.0 cm, the shape was round to oval, and the surface was smooth with normal surrounding areas (Figures 1 and 2). Hair, nail, and mucous membrane were not involved, and systemic examination was normal. The patient's serological examination ruled out HIV infection.

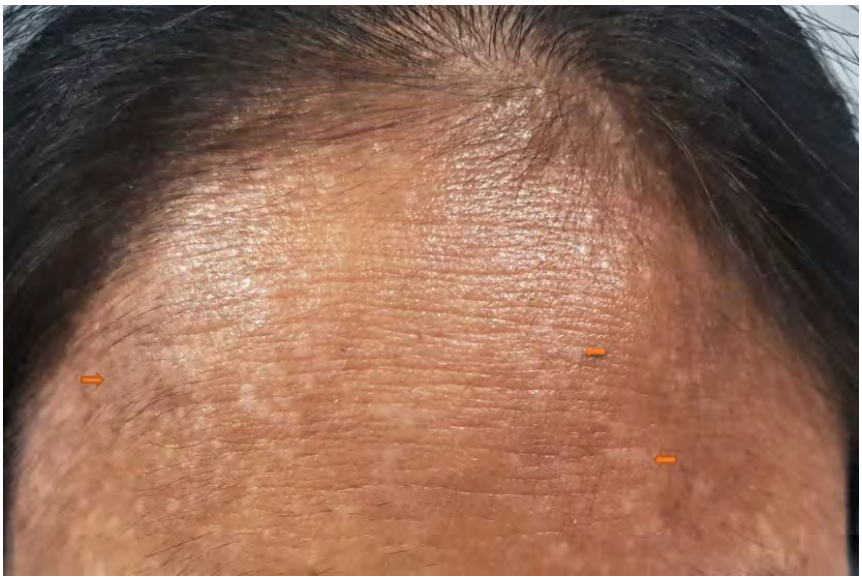

Figure 1: Multiple hypopigmented flat-topped papules and plaques present over the forehead (orange arrows).

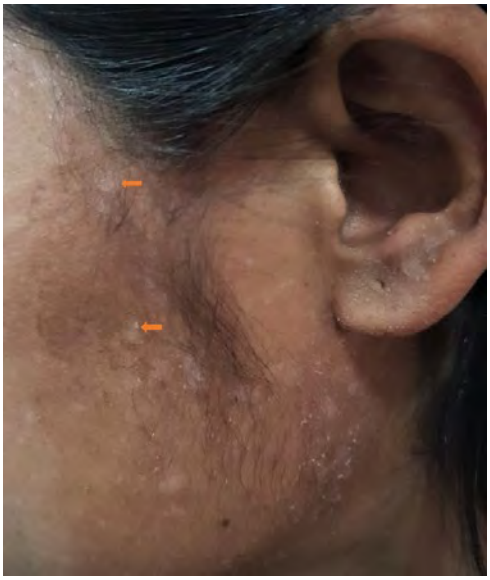

Figure 2: Multiple hypopigmented macules with scaling present over the lateral side of the face (orange arrows).

A punch skin biopsy was performed on the hypopigmented, slightly scaly macules over the forehead, which showed basket-weave hyperkeratosis; acanthosis; mild papillomatosis; prominent granular layer with vacuolisation of keratinocytes in the upper and lower epidermis; and a focal area showing enlarged or swollen keratinocytes in the upper layer, with pale bluish cytoplasm. The epidermal cells showed no dysplastic changes (Figure 3). Based on the clinical and histopathological features, a diagnosis of EV was made. The patient was given topical tretinoin gel and told to wear sunscreen on a daily basis, with regular follow-up.

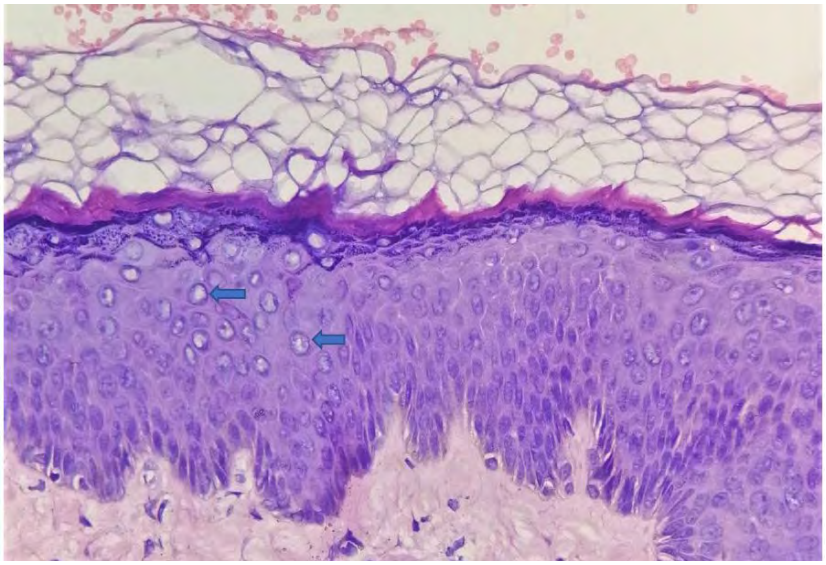

Figure 3: A histologic analysis of the forehead with a punch biopsy showed basket-weave hyperkeratosis, hypergranulosis, acanthosis, mild papillomatosis, and a large focal area affected with keratinocytes, with characteristic steel blue–grey cytoplasm, large nuclei, and clumping of keratohyaline granules (blue arrows) in the upper epidermis (haematoxylin-eosin stain; original magnification: ×40).

DISCUSSION

EV is a rare, autosomal recessive genodermatosis, which affects cell-mediated immunity and has no preference for gender, race, or geographic area.[1] There is an increased risk of non-melanoma skin cancer, mainly squamous cell carcinoma (SCC).[3] The disease can be sporadic, hereditary, or acquired, with the hereditary form being the most common. The acquired form can be seen in recipients of a renal transplant, Hodgkin's disease, systemic lupus erythematosus, and HIV infection.[3]

On chromosome 17q25, the *EVER1* or *EVER2* genes have been linked to impaired cell-mediated immunity and an unusually high susceptibility to a specific strain of HPV infection.[1] A higher lifetime cumulative sunlight exposure, X-ray irradiation, and immunologic defects in patients with EV are likely to induce mutations of the tumour suppressor gene protein (p53), leading to the development of skin malignancies in adult patients.[8,9] Transformation into non-melanoma skin cancer occurs in 35–50% of patients between the ages of 40 and 50.[4] Malignant transformation is caused by infection with specific strains of HPV, particularly HPV5 and HPV8. More than 30 EV-associated HPVs have been identified, including HPV5, HPV8, HPV12, HPV14, HPV15, HPV17, HPV19, HPV25, HPV36, HPV38, HPV47, and HPV50.[3,4,10] Skin malignancies normally develop after a long period of time, and they seldom metastasise or penetrate deeper tissues.[6]

In patients with EV, hypo- or hyperpigmented macules resembling pityriasis versicolor, verruca plana-like lesions, and seborrhoeic keratosis-like plaques are prevalent. These lesions typically start in childhood and affect the face, neck, extremities, and trunk, with mucous membrane involvement being rare.[1,3,9]

The clinical and histopathological examinations are used to diagnose EV. All clinical lesions of EV share common histopathological features, which include basket-weave hyperkeratosis of the stratum corneum, parakeratosis, acanthosis, and characteristic cytopathic changes of infected keratinocytes in the malpighian layer. Infected keratinocytes show characteristic cytopathic changes characterised by large cells with pale blue–grey cytoplasm and variable sized kerato-hyaline granules. Regardless of the infecting HPV strain, these findings are consistent across all EV-HPV infections.[6]

There is currently no effective treatment for EV. There are, however, certain medical and surgical treatments available. Topical and oral retinoids, imiquimod, cimetidine, interferon-α, electrocautery, and cryotherapy are some of the options. All of these therapeutic options, however, are ineffective against EV. In order to prevent skin cancer, patients must be educated about the disease's relapsing and persistent course, photoprotection, early detection, and excision of premalignant and malignant lesions with regular follow-up.[3,8]

CONCLUSION

Acquired EV is a rare entity and can be acquired in patients who are immunodeficient, especially in those who have had a transplant. Recipients of a renal transplant with acquired EV are at high risk of developing non-melanoma skin cancers.[11] As a result, it is critical for the treating physician to recognise and accurately diagnose acquired EV as early as possible, and to reduce the risk of early malignant transformation of skin lesions through strict sun protection and regular follow-up.

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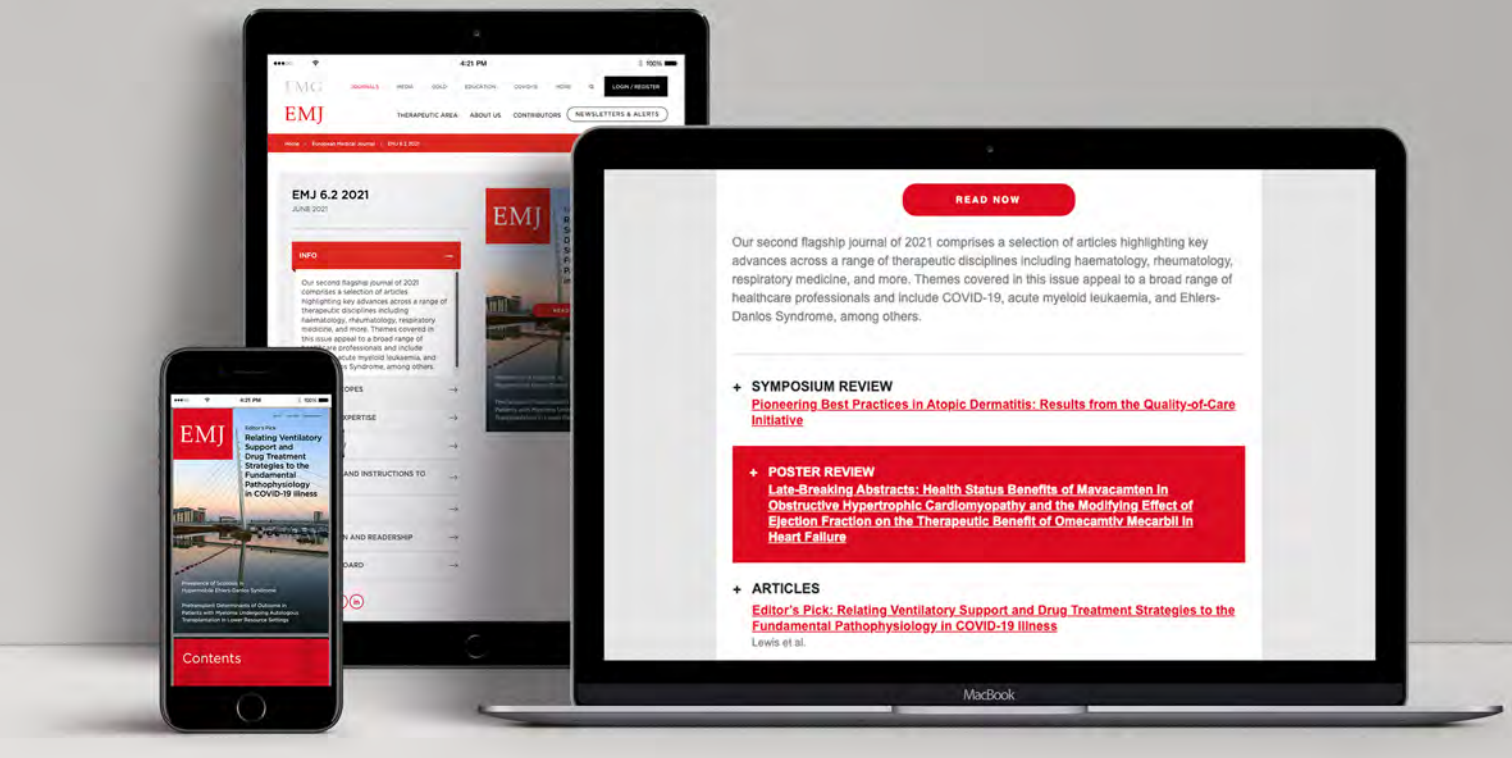

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