Coagulopathy and Hyperinflammation in COVID-19

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MORTALITY in novel coronavirus disease 2019 (COVID-19) is impacted by haematological complications and therefore, addressing these may improve patient survival. In shared presentations at the 25th European Hematology Association (EHA) Annual Congress, expert haematologists discussed clinical and scientific findings in the global experience of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, analysed data to articulate current understanding, and provided insights for care and management of affected patients. The final stage of a three-part programme was a presentation titled "Treatment of COVID-19: Current and Future", which included detailed examinations of thrombosis management, immunotherapy, and the value of haematologists' expertise in combatting this current pandemic.

COVID-19, a disease resulting from SARS-CoV-2 infection, generally results in mild-to-moderate illnesses in those affected. However, 15% of symptomatic patients develop severe interstitial pneumonia, with 5% going on to develop profound and life-threatening complications including acute respiratory distress syndrome, sepsis, hyperinflammatory syndromes, and multiorgan failure. Clinical complications of COVID-19 include myocarditis, acute myocardial infarction, heart failure, venous thromboembolism, and cerebrovascular events. These vascular and thromboembolic complications suggest a coagulopathic impairment requiring specialist haematological examination and input.

THROMBOSIS

COVID-19-Associated Hypercoagulopathy

In contrast to the typical disseminated intravascular coagulation (DIC) pattern seen in trauma or bacterial sepsis, COVID-19 is associated with a clinical coagulopathy but mild thrombocytopenia and minimal prolongation of the activated partial thromboplastin time or prothrombin time. In her presentation to the virtual congress, Prof Anna Falanga, of the University of Milano-Bicocca, Milan, Italy and Hospital Papa Giovanni XXIII, Bergamo, Italy, outlined the coagulopathy seen in patients infected with SARS-CoV-2: "What is really interesting is that in this infection, there is a clear association of D-dimer levels with the severity of the disease." Prof Falanga went on to discuss findings across several international studies

where a consistent association of D-dimer levels with both severity of infection and poorer prognosis has been observed. However, she noted that great variability in the D-dimer levels has been reported between studies. Similarly, platelet levels have been associated with disease severity but reported levels vary between studies.

In her analysis of the currently available body of evidence, Prof Falanga went on to discuss the coagulation markers in patients in intensive care, with a pattern of results more consistent with a hypercoagulability of a severe inflammatory state, rather than acute DIC. In the pathogenesis of this hypercoagulability, the severe inflammatory state seen with COVID-19 causes a profound derangement of the haemostatic system. The impact of the cytokine storm, the hyperinflammatory host immune response triggered by SARS-CoV-2, leads to direct tissue damage, secondary tissue damage from shock states, acute respiratory distress syndrome, and multiorgan failure. The inflammatory cytokines also promote massive infiltration of the lung tissue by neutrophils and macrophages and activate blood clotting. This activation of blood clotting occurs by cytokines inducing activation of vascular endothelium, platelets, and leukocytes, resulting in dysregulation of thrombin generation. Excessive thrombin generation, with subsequent fibrin formation, has both a systemic and local lung effect in the setting of severe pneumonia, where deposition of fibrin leads to direct tissue damage and to microangiopathy.

Viral Effects on the Endothelium

In her discussion of the pathophysiology of COVID-19, Prof Falanga elaborated on the mechanisms of action and direct effects of SARS-CoV-2. SARS-CoV-2 can also interact with the endothelium directly, causing microvascular dysfunction and leading to organ ischaemia. SARS-CoV-2 also exploits the angiotensin-converting enzyme receptor-2 to infect host cells. As this receptor is expressed on endothelial cells across multiple organs, the multiorgan complications of SARS-CoV-2 can be partly explained by the direct effect of the virus on the endothelium by way of this receptor. This interaction leads to immune cell recruitment which can trigger systemic endothelial dysfunction, shifting the balance of the vasculature toward vasoconstriction, and leading to organ ischaemia, tissue oedema causing further inflammation, and a procoagulant state. Prof Falanga emphasised the research findings supporting this understanding; the inflammation-associated endothelial changes directly triggered by SARS-CoV-2 are supported in autopsy studies of patients, revealing the presence of viral elements within endothelial cells and diffuse endothelial inflammation.

The hypercoagulability seen in COVID-19 is a consequence of the inflammatory response to severe infection but is also a consequence of the direct effect of SARS-CoV-2 on the endothelium. The severity of coagulation derangement is

associated with poorer prognosis in affected patients. Prof Falanga discussed a retrospective study that has shown that prophylactic low-molecular-weight heparin is associated with a reduction in mortality risk; as a result, it is currently recommended by multiple scientific societies, including the International Society on Thrombosis and Haemostasis (ISTH) and Italian Society for the Study of Hemostasis and Thrombosis (SISET), as well as by the World Health Organization (WHO).

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Venous Thromboembolism

The coagulopathy seen in COVID-19 is also demonstrated through evidence of venous thromboembolism (VTE) in affected patients. Prof Falanga continued her presentation by examining the published body of evidence. She noted that there are conflicting data on the incidence of VTE in patients with COVID-19; rates range from 0–8% in general medical wards to 16–35% in patients in intensive care units, with VTE events often occurring in the presence of adequate low-molecular-weight heparin prophylaxis. In autopsy studies, a VTE incidence rate of up to 58% has been identified in patients with COVID-19 where VTE was not suspected prior to death. A larger study comparing data from 1,765 patients across multiple studies found that VTE occurred in approximately 20% of patients with COVID-19; cumulative incidences were noted to be up to 49% in cases of hospitalisation. A post hoc meta-analysis of this study determined that the proportion of VTE occurrance is much greater in patients in intensive care, and that there is both publication bias and heterogeneity of data affecting the validity of these findings.

Prof Falanga went on to discuss the mechanisms involved in VTE in patients with COVID-19. The VTE events in COVID-19 resulting in pulmonary vessel occlusion could result from macrothrombosis via embolisation of deep-venous thrombosis, or from microthrombosis via thrombotic microangiopathy of the pulmonary vascular bed. It has been postulated that the diffuse, bilateral pulmonary inflammation seen in COVID-19 causes a localised microangiopathy, distinct from DIC; this novel, pulmonary-specific pathophysiological process has been termed pulmonary intravascular coagulopathy. Autopsy studies have revealed platelet–thrombin microthrombi in the lungs, which is consistent with a coagulopathy process.

The coagulopathy processes of COVID-19, resulting from both severe inflammation and direct effects of SARS-CoV-2 on the endothelium, contribute to the severity of illness, incidence of complications, and mortality risk of COVID-19. Algorithms for determining correction of coagulopathies and use of prophylactic low-molecular-weight heparin have been proposed by published studies, but further assessment into the outcomes of such interventions is required. Prof Falanga closed her presentation by reiterating that treatment of the underlying infection remains the primary intervention for improving coagulopathy in COVID-19.

IMMUNOTHERAPY

There are two immunotherapeutic strategies by which haematological expertise can help to address COVID-19, as discussed by Prof Hermann Einsele, Medical Clinic and Polyclinic II at the University Hospital Centre for Internal Medicine, Würzburg, Germany. Prof Einsele outlined an early immunotherapy strategy, making use of convalescent plasma to improve clearance of the virus and improve infection outcomes, and a late immunotherapy strategy, which aims to reduce the hyperinflammatory syndrome of life-threatening COVID-19.

The first Nobel Prize in Physiology or Medicine, awarded to Emil Behring in 1901, recognised the use of convalescent plasma therapy. Prof Einsele reviewed the available evidence on the use of convalescent plasma therapy for patients with COVID-19. Currently, its use in COVID-19 remains investigational, with data mostly limited to case reports and further study needed. One randomised controlled trial of 103 patients undertaken in China found that, based on viral nucleic acid PCR testing, 33.3% of patients

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receiving convalescent plasma had cleared the viral infection at 24 hours, compared to 11.8% without the plasma therapy. At 72 hours, 90.5% of patients in the plasma group had cleared the virus, compared to 41.2% of those in the control group. The time to clinical improvement was not significantly different between the two groups overall or within the subset of patients classed as having life-threatening disease, although patients with clinically severe disease improved at a faster rate when receiving convalescent plasma therapy. However, Prof Einsele emphasised that this study did not standardise therapy for COVID-19, which may have impacted the reliability of the results.

Peripheral blood screening has revealed evidence of the hyperinflammatory state associated with COVID-19. In a further review of the published global evidence, Prof Einsele explained that the pattern of change in inflammatory profiles maps to clinical severity; a low lymphocyte count and low platelet count in the early phase of infection is associated with a more severe infection and worse outcome. Similarly, high C-reactive protein, IL-6, IL-1, lactate dehydrogenase, creatine kinase, and ferritin in the early phase of the infection are each associated with severe disease. Other patterns emerging in published research were highlighted by Prof Einsele in his presentation to the congress. CT imaging in COVID-19 cases links the severity of hyperinflammation and cytokine release measured by blood testing with the severity of pulmonary infiltration on imaging. Secondary haemophagocytic lymphohistiocytosis (sHLH) can occur with severe COVID-19 and lead to fulminant hypercytokinaemia, multiorgan failure, and death; pulmonary involvement occurs in approximately 50% of patients with sHLH. Hallmark features of sHLH include hyperferritinaemia, fever, and cytopenias, which are also recognised in severe COVID-19 infection. This further suggests that mortality in COVID-19 may relate to virally driven hyperinflammation. In addressing this hyperinflammation, reduction in viral load has been found to improve inflammatory markers.

Prof Einsele went on to consider possible avenues of treatment for these processes of hyperinflammation and associated poorer clinical outcomes. The increased activation of Th1 cells and inflammatory monocytes seen in COVID-19, more pronounced in life-threatening infection, could potentially be addressed with tocilizumab or anakinra immunotherapy. Prof Einsele noted that previous experience with CAR T-cell therapy in oncology has revealed a typical cytokine release syndrome with high fevers and high inflammatory reactions; in oncological and haematological pathologies, this cytokine release syndrome is treated with tocilizumab. Tocilizumab may, therefore, be a potential treatment strategy in COVID-19 to address pathogenic T cell- and inflammatory monocyte-mediated hyperinflammation.

CONCLUSION

Severe infection and life-threatening complications in COVID-19 result, in part, from a substantial hyperinflammatory response and cytokine cascade, generating a coagulopathy and contributing to mortality. Addressing coagulopathy with blood product management, microangiopathy and thromboembolism risk with low-molecular-weight heparin prophylaxis, and hyperinflammatory syndromes with immunotherapy agents are all late-stage interventions, using haematological expertise to minimise mortality risk in the sickest patients. Using patterns of inflammatory markers and coagulation profiles to risk-stratify patients for early intervention may help mitigate this risk earlier in the disease course. However, the best strategy for preventing life-threatening complications and COVID-19-associated deaths is early treatment of the viral infection itself, an area of ongoing global effort.