EMJ UROLOGY

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+ PENILE RECONSTRUCTION: CURRENT THOUGHTS, TECHNIQUES, AND OUTCOMES

+ ARTICLES

Urothelial Carcinoma: Highlights and Reviews on Various Pathologies

A Review of Rare Associations of Horseshoe Kidney: Highlight of a Rare Clinical Case of Polycystic Horseshoe Kidney, Liver Cyst, and Uterine Prolapse

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*PSA doubling time of ≤10 months, despite ADT.[1]
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†Data taken from the TITAN study evaluating ERLEADA® + ADT vs ADT alone in a broad population of patients with mHSPC. OS and rPFS were dual primary endpoints of the TITAN study. OS at 2 years: 82.4% with ERLEADA® + ADT vs 73.5% with ADT alone. rPFS at 2 years: 68.2% with ERLEADA® + ADT vs 47.5% with ADT alone.[3]

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been conducted with ERLEADA. It is unknown whether apalutamide/metabolites are excreted in human milk. ERLEADA should not be used during breast-feeding. Based on animal studies, ERLEADA may decrease fertility in males of reproductive potential. It is not known whether apalutamide or its metabolites are present in semen. 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Mild or moderate inhibitors of CYP2C8 are not expected to affect the exposure of apalutamide. ***Medicinal products that inhibit CYP3A4:*** No initial dose adjustment is necessary when ERLEADA is co-administered with a strong inhibitor of CYP3A4 (e.g., itraconazole, ketoconazole, ritonavir, clarithromycin) however, a reduction of the ERLEADA dose based on tolerability should be considered. Mild or moderate inhibitors of CYP3A4 are not expected to affect the exposure of apalutamide. ***Medicinal products that induce CYP3A4 or CYP2C8:*** No dose adjustment is necessary when ERLEADA is co-administered with inducers of CYP3A4 or CYP2C8. **Potential for apalutamide to affect exposures to other medicinal products:** Apalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected. The reduction in plasma concentrations can be substantial, and lead to lost or reduced clinical effect. There is also a risk of increased formation of active metabolites. ***Drug metabolising enzymes:*** *In vitro* studies showed that apalutamide and N desmethyl apalutamide are moderate to strong CYP3A4 and CYP2B6 inducers, are moderate inhibitors of CYP2B6 and CYP2C8, and weak inhibitors of CYP2C9, CYP2C19, and CYP3A4. When substrates of CYP2B6 (e.g., efavirenz) are administered with ERLEADA, monitoring for an adverse reaction and evaluation for loss of efficacy of the substrate should be performed and dose adjustment of the substrate may be required to maintain optimal plasma concentrations. In humans, ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9. Concomitant use of ERLEADA with medicinal products that are primarily metabolised by CYP3A4 (e.g., darunavir, felodipine, midazolam, simvastatin), CYP2C19 (e.g., diazepam, omeprazole), or CYP2C9 (e.g., warfarin, phenytoin) can result in lower exposure to these medicinal products. Substitution for these medicinal products is recommended when possible or evaluation for loss of efficacy should be performed if the medicinal product is continued. If given with warfarin, INR should be monitored during ERLEADA treatment. When substrates of UDP glucuronosyl transferase (e.g., levothyroxine, valproic acid) are co-administered with ERLEADA, evaluation for loss of efficacy of the substrate should be performed and dose adjustment of the substrate may be required to maintain optimal plasma concentrations. ***Drug transporters:*** Apalutamide was shown to be a weak inducer of P glycoprotein (P gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. When substrates of P-gp (e.g., fexofenadine, colchicine, dabigatran etexilate, digoxin), BCRP/OATP1B1 (e.g., lapatinib, methotrexate, rosuvastatin, repaglinide) are co-administered with ERLEADA, evaluation for loss of efficacy of the substrate should be performed and dose adjustment of the substrate may be required to maintain optimal plasma concentrations. Based on *in vitro* data, inhibition of organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3) and multidrug and toxin extrusions (MATEs) by apalutamide and its N-desmethyl metabolite cannot be excluded. No *in vitro* inhibition of organic anion transporter 1 (OAT1) was observed. ***GnRH Analog:*** In mHSPC subjects receiving leuprolide acetate (a GnRH analog), co-administration with apalutamide had no apparent effect on the steady-state exposure of leuprolide acetate. Medicinal products which prolong the QT interval: Since androgen deprivation treatment may prolong the QT interval, the concomitant use of ERLEADA with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g., quinidine, disopyramide) or class III (e.g., amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics (e.g. haloperidol), etc. should be carefully evaluated. Paediatric population: Interaction studies have only been performed in adults. **LEGAL CLASSIFICATION:** Medicinal product subject to medical prescription. **MARKETING AUTHORISATION NUMBER(S):** EU/1/18/1342/001, EU/1/18/1342/002, EU/1/18/1342/003. **MARKETING AUTHORISATION HOLDER:** Janssen-Cilag International NV. **PACKS & PRICE:** *Country specific* Products mentioned in this document may not be registered in all countries. Prescribing Information may vary per country. Health Care Providers must refer to their country prescribing information. Prescribing information generation date or last revised: February 2020. Based on 27 January 2020 EU Summary of Product Characteristics.

References: 1. Smith MR, *et al. N Engl J Med.* 2018;378:1408–18. 2. ERLEADA® (apalutamide) Summary of Product Characteristics. Janssen-Cilag International NV, Beerse, Belgium, February 2020. 3. Chi KN, *et al. N Engl J Med.* 2019;81(1):13–24.

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Erleada® (apalutamide) tablets

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Spencer Gore, CEO

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VIEW IN FULL ←

Aims and Scope

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EMJ Urology 8.1

Welcome

I am pleased to be delivering to you EMJ's latest journal in Urology, our eighth volume since the launch in 2012. Our authors and editorial team have been hard at work to deliver to you the latest research and medical news via our selection of peer-reviewed papers and research articles, featuring our Editor's Pick, as well as interviews with clinicians.

Our Editor's Pick for this edition is the review presented by Brazio et al., who discuss the increased availability and incidence of penile reconstructive surgeries. The authors examine surgical techniques, including choice of reconstructive flaps and potential complications, and the wider recognition of gender dysphoria and greater accessibility of gender-affirming surgery. This review is particularly poignant for the plastic surgeons amongst you, as well as urologists.

Additional articles in *EMJ Urology* include the review by Dr Gokhan Calik and Dr Jean de la Rosette on bladder pain syndrome, and the data regarding disease progression, remission, prevention, and the risk factors for the development of associated symptoms over time. A condition which has, in its past, caused significant challenges in clinical practice, the authors hope to present and critique the contemporary literature. Additional review topics include urothelial carcinoma pathogenesis and micro-fragmented adipose tissue injections for the treatment of vaginal atrophy, vulvovaginal dystrophy, and stress urinary incontinence.

"We are enormously grateful to the many people working hard throughout this time, and we congratulate those accumulating the knowledge that will help get us all through this"

The ongoing, evolving situation involving the COVID-19 pandemic will inevitably have affected almost all of our readers' day-to-day lives. We are enormously grateful to the many people working hard throughout this time, and we congratulate those accumulating the knowledge that will help get us all through this. Please keep yourself and others safe, and I wish you all well.

Spencer Gore

Spencer Gore

Chief Executive Officer, EMG-Health

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Foreword

Dear colleagues,

It is with great pleasure that I welcome you to the new edition of *EMJ Urology*.

The COVID-19 pandemic has made 2020 a testing time for all, notably for the healthcare community who have been under increasing pressure worldwide to tackle this challenge. The European Association of Urology (EAU) Congress was postponed earlier this year, along with many other events, which makes the sharing of the latest developments in urology, in formats such as this, more important than ever.

The Editor's Pick in this issue is the review paper by Brazio et al. entitled 'Penile Reconstruction: Current Thoughts, Techniques, and Outcomes'. As recent years have seen increased availability, and consequently occurrence, of penile reconstructive surgeries, the techniques for this surgery have been improved to reduce the incidence of complications. Brazio et al.'s paper reviews phalloplasty surgical techniques, such as the different approaches to the reconstructive flap. With the aforementioned increase in penile reconstructive surgeries, this article is beneficial to those working in urology, and more specifically to plastic surgeons.

This is just one of several interesting papers in this issue of *EMJ Urology*. Dick et al.'s paper 'Urothelial Carcinoma: Highlights and Reviews on Various Pathologies' offers insight into the most common variations of urothelial carcinoma, and Cassell et al. review a clinical case of anomalies in a patient with horseshoe kidney in their article 'A Review of Rare Associations of Horseshoe Kidney: Highlight of a Rare Clinical Case of Polycystic Horseshoe Kidney, Liver Cyst, and Uterine Prolapse'. These are just a few of the papers in this issue that will add great value to those working in the field of urology.

I would like to take this opportunity to thank all of the contributors for this issue and to everyone in the healthcare industry who is helping to enable open-access education, such as this.

Best wishes,

Prof Roger Dmochowski

Vanderbilt University Medical Center, Nashville, Tennessee, USA

Penile Reconstruction: Current Thoughts, Techniques, and Outcomes

EDITOR'S PICK

Our Editor's Pick for *EMJ Urology 8.1* is this review paper by Brazio et al. Availability and incidence of penile reconstructive surgeries has increased, with techniques refined over recent years to reduce complication rates. This article provides a detailed review of surgical techniques, including choice of reconstructive flaps and potential complications. As greater numbers of reconstructive surgeries are performed, this review provides valuable insight for urologists and plastic surgeons.

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Abstract

Phalloplasty has matured considerably over the last decades in reconstructive options and technical refinements, thanks to increasing recognition of gender dysphoria. The primary goals of performing a phalloplasty are to facilitate sexual penetration, protective sensation, orgasm, standing micturition, and natural aesthetic, ideally in few stages and with minimal morbidity. Radial forearm free flap, anterolateral flap, and metoidioplasty are the most common options, each with a unique profile of complications, aesthetic, and functional outcomes. Choices for reconstruction must be tailored to the individual patient's goals and available tissue characteristics.

INTRODUCTION

Phalloplasty may be performed for penile trauma, congenital defects, or for gender dysphoria.[1,2] While phalloplasty for trauma[3] or for microphallus[4] remains relatively rare, phalloplasty has seen a steady rise in recent years with increasing recognition of gender dysphoria.[5,6] An estimated 0.6% of the world's population identifies as transgender. Gender-affirming genital surgery is on the rise: from 2006 to 2011, 83.9% of patients undergoing gender-affirming surgery underwent genital surgery.[6]

Generally speaking, goals of phalloplasty include the facilitation of sexual penetration, protective sensation, orgasm, standing micturition, and natural aesthetics.[7] Additionally, the ideal choice of reconstructive method would have few stages and minimal morbidity.[8]

PREOPERATIVE EVALUATION

As with any elective reconstructive procedure, initial discussion with the patient should focus on their priorities for surgery, as well as setting expectations for potentially suboptimal outcomes and relatively high risks and rates of complications.

Gender-affirming phalloplasty in particular merits careful consideration. A detailed discussion of preoperative evaluation for gender-affirming surgery is beyond the scope of this article. Evaluation requires co-ordination between specialists from various fields including social work, psychiatry, endocrinology, urology, and plastic surgery. Version 7 of the Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People by the World Professional Association for Transgender Health (WPATH) for phalloplasty/genital surgery[9] specifies the preoperative requirements for surgery.

For nongender-confirming surgery, careful assessment of the preoperative penile functional and anatomical deficit, especially for cases after trauma, is paramount for the choice of reconstruction. In some rare instances, transplantation may also be an option.[10] Combined with a physical exam of potential donor sites, initial discussion allows honing into a method of reconstruction. If a microsurgical method is planned, the patient should be in good enough health to safely undergo a long procedure. Depending on the donor site, preoperative weight loss, hair/tattoo removal, and other preparations may be necessary.

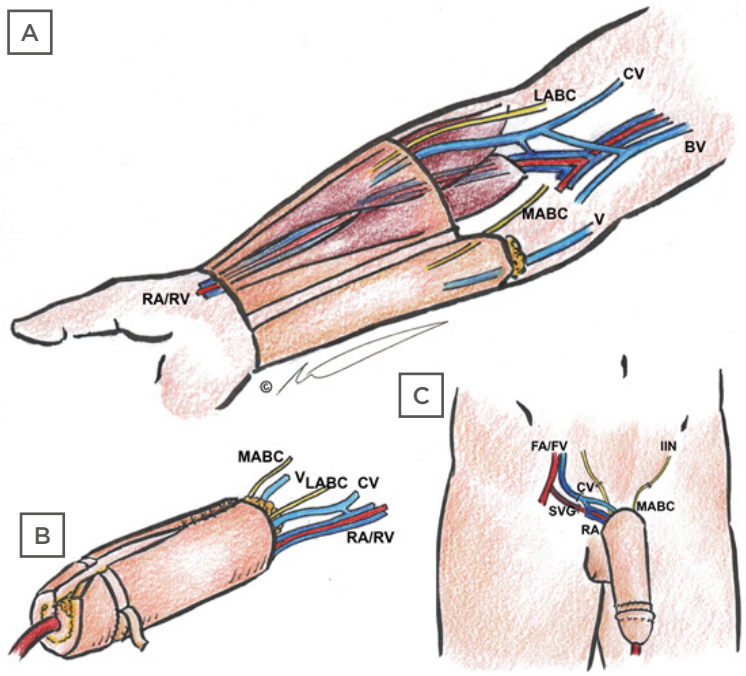

Figure 1: Schematic views of radial forearm flap phalloplasty.

(A) Anatomy of the flap in the arm including urethral (ulnar) segment with cuff of subcutaneous fat, external (radial), and de-epithelialised segments, the radial artery and vein emerging between brachioradialis and flexor carpi radialis muscles, lateral and medial antebrachial cutaneous nerves, cephalic and basilic veins, and unnamed superficial vein. **(B)** Fabrication of tube-in-tube neourethra showing partial tubularisation, as well as skin grafting from the de-epithelialised segment behind the neocoronal ridge in preparation for coronaplasty. **(C)** *in situ* appearance after single-stage phalloplasty showing anastomosis of the cephalic vein and radial artery to femoral vein and femoral artery via saphenous vein graft, respectively; as well as coaptation of the medial antebrachial cutaneous nerve to the ilioinguinal nerve.

BV: basilic veins; CV: cephalic veins; FA: femoral artery; FV: femoral vein; IIN: ilioinguinal nerve; LABC: lateral antebrachial cutaneous nerves; MABC: medial antebrachial cutaneous nerves; RA: radial artery; RV: radial vein; SVG: saphenous vein graft; V: unnamed superficial vein.

SURGICAL TECHNIQUES AND OUTCOMES

Radial Forearm Free Flap

Free radial forearm flap (RFF) is most commonly used for contemporary phalloplasty.[11] Biemer et al.[12] reported its use in transgender males in the early 1980s incorporating a portion of the radius as a stiffener, coapting nerves for sensation, and fabricating the urethra with a skin graft. In 1984, Chang and Hwang[13] reported a single stage tube-within-a-tube design of the RFF, which decreased urethral complications from previous methods of reconstruction.[14] Further refinements have been added in the three decades since (Figure 1).

Preoperatively, an Allen's test should be performed. Patients should undergo complete preoperative electrolysis or laser hair removal of the donor side arm to minimise hair on the final construct; if this is impossible, flap design should place the neourethra in an area with the least amount of hair (usually the ulnar half of the forearm).

While there are variations on the design, the authors prefer centrally placing the neourethra in continuity with a neoglans to avoid circumferential meatal suture lines without sacrificing length.[13,15] The dimensions of the flap depend on the patient's desires and the available tissue; the thicker the tissue, the wider the flap to allow tube-within-a-tube construction. Minimum dimensions are 15x17 cm. A proximal extension of the neourethra of 4–5 cm should be incorporated in gender-affirming surgery.[14] This allows for more anterior and cephalad position of the base of the neophallus without tension on the urethral anastomosis.

The radial artery and venae comitantes are identified distally at the wrist and followed proximally, preserving septocutaneous perforators while ligating muscular and periosteal branches. Care is taken to include the superficial venous system, which is drained by the cephalic vein radially. Ulnar superficial branches may be included, but the basilic vein should be preserved if possible, to preserve venous outflow of the arm. The artery is dissected proximally until the bifurcation of the brachial artery. Venae comitantes are dissected until the two veins coalesce into one. If this dissection is continued more proximally, the coalesced vena comitans will join the cephalic vein via the profundus cubitalis vein, which allows for drainage of superficial and deep venous systems through one large calibre vessel. Dual venous anastomosis and outflow is an important tool to limit congestion and partial flap necrosis. The medial, lateral, and possibly posterior antebrachial cutaneous nerves, are identified and dissected an additional 3–4 cm proximal to the skin paddle to allow for tensionless coaptation at the recipient site.[15,16]

The femoral or the deep epigastric system can be used for flap inflow and outflow.[16,17] The authors prefer the femoral system, creating an arteriovenous loop using 20 cm or more of the great saphenous vein, and anastomosing to the superficial femoral artery in end to side fashion. Large saphenous vein tributaries are usually available for secondary drainage via the basilic vein. Epineurial neurorrhaphy is performed between the lateral antebrachial cutaneous nerve and the dorsal nerve of the penis/clitoral or the deep pudendal nerve, allowing for erogenous sensation. If medial or posterior antebrachial cutaneous nerves are included in the flap, they can additionally be coapted with the ilioinguinal or other sensory nerves to provide tactile sensation. The medial antebrachial cutaneous nerve may be less preferable if it innervates the urethral segment.[14,15,18]

The skin over the shaft of the clitoris is incised to identify the dorsal clitoral nerves before the clitoris is de-epithelialised and buried at the base of the neophallus.[19] Finally, urethral lengthening is performed by inverting and tubularising the adjacent mucosal surface of vagina and labia minora in continuity with the native urethral opening. This allows the neophallus construct to sit in a more appropriate anterocephalad position on the pelvis after urethral anastomosis.[14] The urethra is anastomosed end-to-end over a Foley catheter. De-epithelialised edges around the proximal neourethra can be used to reinforce the anastomosis.

There are many variations of RFF phalloplasty; some prefer to create the neoglans through the Norfolk procedure consisting of a rolled skin flap and split-thickness graft.[19] Part of the radial bone can be harvested as osteocutaneous free flap for rigidity rather than placing a prosthesis.[16,17] Exact

nuances depend on the surgeon experience and preference.

Compared to other methods of reconstruction, RFF are relatively well reported in the literature and demonstrate overall favourable subjective and objective results.[20-22] However, a paucity of high quality, comparative data on long-term surgical outcomes should lead to a provisional perspective on reported results.[11]

The aesthetic quality of the phallus has been rated highly by RFF phalloplasty patients, higher than surgeon or independent observer ratings.[20-22] In a recent systematic review, 70–80% reported overall satisfactory aesthetic outcome of the neophallus, usually 7.5–14.0 cm in length.[2,11] The RFF can maintain exquisite sensitivity.[2] Erogenous and tactile sensitivity have been maintained, with a significant portion of patients engaged in sexual activity being able to achieve an orgasm.[21,23]

The primary disadvantage of the RFF is donor-site morbidity, requiring a large skin graft for coverage. Many patients choose other methods for this reason because the RFF donor site scar can be associated with social stigma.[2,11,24-26] Other disadvantages include length and complexity of a microsurgical procedure, potential for total and partial flap loss, as well as other less common but certainly possible donor site morbidities, including possibly permanent hand dysfunction, prolonged hand swelling and lymphoedema, and need for regrafting of the arm defect.[2,24]

The complication rate of RFF phalloplasty is reported as higher than other reconstructive options.[2,24] Urethral complications are the most common, as they are with other methods, with urethral fistula rates of 15–77% and stricture and stenosis rates of 21-51%.[27] Other common complications include wound healing issues, need for anastomotic revision, partial flap necrosis, and complications related to prostheses.

Anterolateral Thigh Flap

The anterolateral thigh (ALT) flap is a reliable option for reconstructive phalloplasty. It provides adequate shape and bulk, sensation, a long vascular pedicle, possibility for erectile prosthesis placement, minimal donor site morbidity, colour match, and a concealable scar.[28-30] The standard technique for ALT flap design and perforator location can allow consistent dissection.[31]

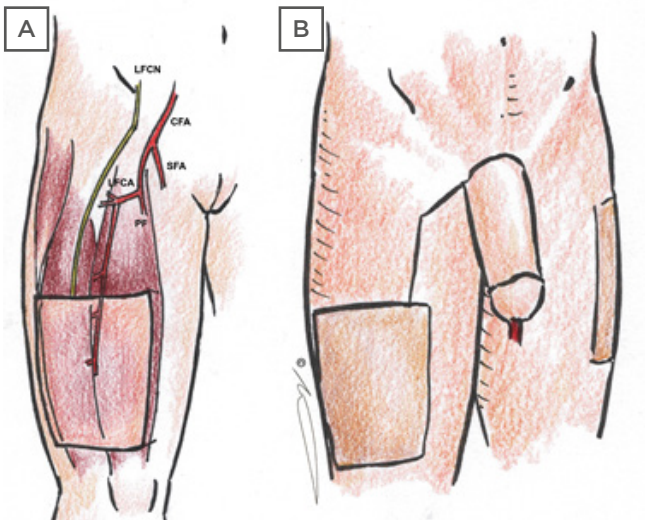

Figure 2: Schematic views of anterolateral thigh phalloplasty.

(A) Anatomy of the flap in the leg (without tube in tube urethral design), showing lateral femoral cutaneous nerve branch, common femoral artery , superficial femoral artery, profunda femoris, lateral femoral circumflex artery, and from lateral to medial the tensor fascia lata, vastus lateralis, and rectus femoris muscles. **(B)** Relative size of neophallus, showing flap donor site with skin graft, skin graft donor site on contralateral leg, and optional connecting scar from flap donor site to inset in pedicled technique.

CFA: common femoral artery; LCFN: lateral femoral cutaneous nerve; LFCA: lateral femoral circumflex artery; PF: profunda femoris; SFA: superficial femoral artery.

It is a good alternative for patients who do not qualify for a RFF due to a positive Allen's test or previous forearm surgery. Ideal patients should have a thigh pinch thickness <1.5 cm if a single-stage urethral lengthening is planned; otherwise, patients should undergo a two-stage approach.[32]

The free ALT phalloplasty was initially reported as an alternative to the RFF.[28] The authors specifically recommended a triangular skin flap on the pubic area with a distal 3 cm base and vertex 4 cm proximally at the midline. This allows the tubularised ALT to remain loosely approximated at the base of the neophallus to minimise pedicle compression and avoid flap defatting which can compromise circulation and sensation. The free ALT phalloplasty flap is rectangular, between 10x12 and 11x14 cm. The vascular pedicle is the descending branch of the lateral circumflex femoral artery. The ALT should be harvested from medial to lateral to preserve perforators through the vastus lateralis and superficial sensory branches of the lateral femoral cutaneous nerve.[30] Flap reinnervation is via the dorsal pudendal nerve or ilioinguinal nerve. The typical recipient vessels are the same as with RFF.[28] To minimise urethral stricture, triangular flaps from the neourethra interdigitate with the native urethra.[30] The pedicle must be monitored for compression during tubularisation of the flap.

If the flap does not use a tube-in-tube urethroplasty,[14] the perineal tissue can be used to construct a lining flap for the neourethra. The base of the flap for the neourethra is immediately above the clitoris; a 2x14 cm flap is created in the space between the clitoris and labia minora.[28] It is rolled around an 18 French units (Fr) catheter and transposed upward to line the single-tube ALT flap. The donor site is closed primarily. After 6–12 months, the second stage can proceed with the neourethra anastomosis to the native urethra in the same setting as erectile prosthesis implantation.

An alternative to a free ALT flap is a pedicled ALT flap, which offers similar benefits without the need for microvascular anastomosis (Figure 2).[30,33,34] The flap is raised as described above. To maximise lateral circumflex femoral artery pedicle length via the descending branch, the included perforators should be as distal as possible (until 5–6 cm proximal to the superior patella edge), and the pedicle dissected to the origin at the profunda femoris artery.[32] A tunnel is created beneath the rectus femoris that becomes subcutaneous at the medial edge of the sartorius and the flap is carefully passed through the tunnel.[30,35] The dorsal pudendal nerve or ilioinguinal nerve is identified and neurorrhaphy performed to the preserved lateral femoral cutaneous nerve on the ALT flap. Although penile implants are typically placed in a later stage, immediate placement has been described with a chimeric flap design incorporating a 3 cm strip of fascia lata to wrap the implant.[33,36] A modification to the flap design using a semicircular extension at the distal portion, known as the mushroom flap, resembles more closely the glans of the native male penis,[37] but may add excessive bulk in all but the thinnest patients.

Tissue expansion of the donor site may minimise scarring and need for skin grafting, as well as improve the flap perforator's vascular territory.[35] Expansion takes between 4 weeks to 6 months. This can allow primary closure and minimisation of donor site contour deformities, avoiding the need for fat grafting.[35] Other authors have urged caution, however, with an expander complication rate of 53% for pre-expanded RFF and ALT flaps, and only a 31% primary closure rate of the donor site.[38]

Complete flap loss is rare; however, partial flap loss does occur and can be morbid.[32] It often involves the periphery of the flap (distal tip or base) and in areas where the tissue is folded on itself, such as the neourethra. Other outcomes have shown that the majority of patients can urinate standing (66.7%), are capable of penetrative intercourse (60.0%), and satisfied with the neophallus (100.0%); while the most common complications are fistula formation (22.2%) and stricture or stenosis (6.7%).[2]

Metoidioplasty

Metoidioplasty, first described in 1996,[39] comes closest to the reconstructive surgery concept of replacing 'like with like'. It uses the tissues of the external female genitalia to recreate their male analogs, paralleling the developmental processes that give rise to male external genitalia. The clitoris is first hypertrophied using systemic testosterone therapy. The clitoris is then surgically lengthened in a manner similar to chordee repair, with urethral reconstruction requiring the use of mucosal flaps

or grafts, combined with local clitoral skin or labial flaps. Scrotoplasty and scrotal implants can be performed in the same stage or later.[40,41]

The operation begins by degloving the clitoris through a transcoronal incision and transecting the clitoral suspensory ligaments. Great care must be taken not to damage the dorsal clitoral nerve or the corpora cavernosa. The urethral plate is divided between urethral plate and clitoris to repair the chordee and allow lengthening of the neophallus. In a simple metoidioplasty, no urethroplasty is performed. This variant allows erogenous sensation and the appearance of a microphallus, but does not allow standing micturition.[40]

More complete metoidioplasty can be performed using several techniques. Ring metoidioplasty involves lengthening of the ventral urethral plate by the interposition of a 'ring flap' from the inner surfaces of the labia minora and a proximal neourethral flap of vaginal epithelium (Figure 3). This is then closed over a Foley catheter flaps to form a longer tubular structure. This repairs both the clitoral chordee and hypospadias, and therefore allows standing micturition.[42]

The 'Belgrade' metoidioplasty achieves further urethral lengthening using a buccal mucosal flap to lengthen the ventral urethral plate, followed by a closure with a longitudinal dorsal clitoral skin flap[43] or labial flaps.[44]

In a direct comparison, final closure with labia minora flaps achieved greater urethral length of 10.8 cm, as well as higher percentage of voiding while standing, and lower incidence of fistula compared with dorsal clitoral skin flap.[45] Major complications include urethral fistula (7–15%) and stricture (2–3%).[40,46] Initial assumptions about metoidioplasty outcomes have not been universally borne out. Twenty-four percent of Belgrade metoidioplasty patients underwent additional phalloplasty procedures in long-term follow-up, leading the authors to conclude that it could not be considered a true single-stage procedure.[47] It was also initially believed that metoidioplasty would not allow penetrative intercourse;[39] however, up to 53% of metoidioplasty patients report successful penetration in recent studies.[11]

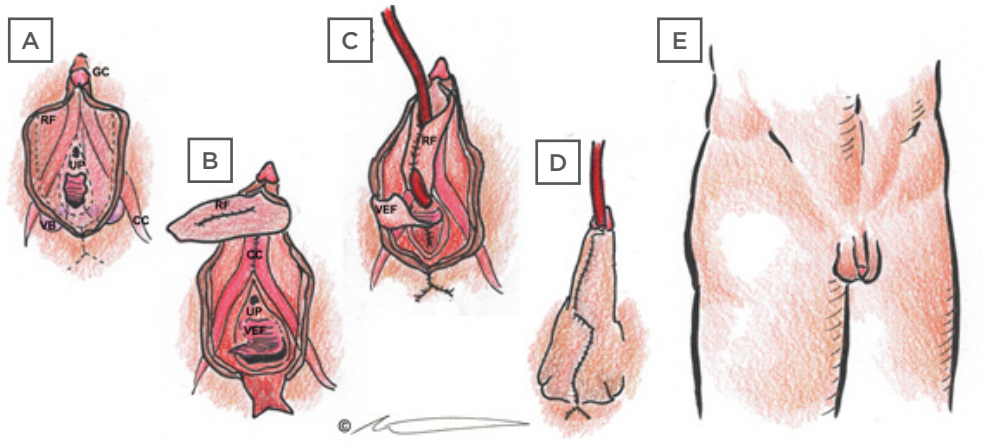

Figure 3: Schematic views of metoidioplasty using labial ring flap.

(A) Anatomy of natal female after hormone induced clitoral hypertrophy, showing glans clitoris, ring flap from labia minora inner surface, urethral plate, crus clitoris/corpus cavernosum, and vestibular bulb. **(B)** Elevation of ring flap after excision of vestibular bulb and midline suture of corpora cavernosa, with partial elevation of vaginal epithelial flap. **(C)** Full elevation of vaginal epithelial flap in preparation for anastomosis to ring flap, which has been tubularised around a Foley catheter. **(D)** Completed metoidioplasty with external surfaces of labia minora closed to form external surface of neophallus. **(E)** Relative size of metoidioplasty and scrotoplasty.

CC: corpus cavernosum; GC: glans clitoris; RF: ring flap; UP: urethral plate; VB: vestibular bulb; VEF: vaginal epithelial flap.

Other Surgical Techniques

While the above techniques have become the preferred approaches for penile reconstruction, several other techniques have previously been used. These include the suprapubic phalloplasty, groin flaps, latissimus, free fibula flap, and transplantation.

The suprapubic phalloplasty is typically a multi-stage procedure.[48,49] The first stage involves design of the flap where the base of the flap is near the desired location of the penis, ideally including the superficial external pudendal vessels, prior to tubularisation of the abdominal skin. The second stage creates the neourethra from perineal epithelium or clitoris. Additional stages may involve tissue expansion prior to flap design and keeping the tubularised flap attached in the first stage and then releasing the abdominal skin of the neophallus on one side.[49]

The groin flap can be performed as a one or two-stage operation. For the single-stage operation, the groin flap can include the superficial circumflex iliac artery and the posterosuperior iliac spine to create a composite flap where the iliac crest bone provides rigidity.[50] This composite flap is tubed around the neourethra, tunnelled from the donor site to the pubic symphysis, with the neourethra anastomosed to the native urethra in the same stage. The two-step procedure uses the superficial circumflex iliac artery and deep circumflex iliac artery,[50] which provides the blood supply to the mobilised iliac bone.[51] A prefabricated urethra from a full thickness skin graft is placed within the composite flap and the surrounding soft tissue is tubularised with the superior and inferior edges remaining attached. The second stage divides the superior edge and transposes the flap to the pubic region. Suprapubic and groin flaps have fallen out of favour because of inconsistency for sensation, atrophy of the neophallus, limited ability for standing micturition, and inability to engage in sexual intercourse.[49,50]

The latissimus dorsi muscle has been used as a functional pedicled musculocutaneous flap or free innervated flap.[2] The innervated flap requires tonic contraction for erection formation.[52] In addition, the flap does not allow for a tube-within-a-tube penile urethra and often requires several stages.[53]

The osteocutaneous free fibula flap provides an autologous option that achieves the rigidity of a penile implant.[2] Sensation is provided via the lateral or posterior sural cutaneous nerves that are harvested with the peroneal artery. The neourethra is prefabricated and inserted in a subcutaneous plane along the lateral leg where the planned osteocutaneous fibula flap will be taken. In the second stage, the osteocutaneous fibula flap is wrapped around the neourethra and transferred to the pubic region. It can be difficult to anchor the fibula to the pubic bone, and over time the fibula is prone to atrophy.[54] Because of these disadvantages it is less commonly employed. As with other techniques, urethral stricture is the most common complication.

Vascularised composite penile transplantation has rarely been performed. It is the most complex of all the options for phalloplasty reconstruction, but can provide near-normal erections with orgasm and urinary transport.[55,56]

Penile Implants

While penile implants are commonly used for erectile dysfunction in native males, their application to reconstructive phalloplasty involves additional challenges.[57] Protective sensation of the neophallus is required to avoid peri-implant trauma resulting in infection or exposure. Therefore, any flap being considered for implants must be successfully neurotised. The implant must also have a stable tissue bed to support the construct. In a natal male, the implant is contained within the corpora cavernosa and supported by the proximal penis. In reconstructive phalloplasty, the implant must be anchored, usually with a hinged or flexible construct to the pubis. As with other penile implants, implants for phalloplasty may be inflatable or semi-rigid. Complication rates are high: in a series of 1,056 patients, 36% experienced complications, only 84% achieved penetration, and only 60% still had their original implant at a mean follow-up of 3 years. New device development is already focussing on these unique considerations, and specific prostheses are being tested for use after phalloplasty.[58]

Table 1: Summary of advantages and disadvantages to common methods of penile reconstruction.

Operation	Advantages	Disadvantages
Radial forearm free flap	Good size match for natural appearing neophallus Tube-in-tube urethral reconstruction	Forearm donor site scar, possible pain and functional morbidity Higher reported urethral complication rate
Metoidioplasty	Reliable erogenous sensation and ability to orgasm Lower complication rate Inherent erectile function No secondary donor site Ability to convert to phalloplasty later (Possibly) improved standing micturition and ability to achieve penetration	Microphallus appearance
Anterolateral thigh flap	May be used as pedicled flap Large neophallus without forearm donor site	Decreased sensation Increased bulk Single stage and tube in tube urethral reconstruction generally not possible

DISCUSSION

Choice of Reconstructive Method

Overall patient satisfaction after phalloplasty is high.[2] The increasing awareness of phalloplasty is also improving available patient information and helping to educate patients preoperatively, leading to more informed decisions.[59] Radial forearm appears to be the new standard in phalloplasty, followed by metoidioplasty and ALT flap (Table 1). Few studies have attempted to directly compare the outcomes of different methods. One meta-analysis comparing metoidioplasty with RFF revealed respective 87% versus 70% aesthetic satisfaction, 0.43 versus 0.88 complication per patient, 100% versus 69% erogenous sensation, 53% versus 43% ability to achieve penetration, and 89.1% versus 75.0% standing micturition.[11] The ALT flap is essentially a second-line option for patients who would like a larger neophallus but want to avoid a forearm donor site, and are relatively thin.

In interpreting subjective outcomes of phalloplasty (especially aesthetics), self-selection by patients must be given significant weight.

While complication and functional profiles do differ between different methods, fundamentally each of the major choices will have a different aesthetic outcome, and the patient who chose a particular method will have done so with that outcome in mind.

The radial forearm usually comes closest in appearance to a natural-appearing phallus but has a significant aesthetic donor-site morbidity that must be acceptable to the patient. The metoidioplasty may have the best functional outcomes, but in appearance resembles a microphallus. The ALT flap is too thick to support tube-in-tube neourethra creation in all but the thinnest patients, and even then, may have excessive girth to be aesthetically acceptable to some.

Avoiding Urethral Complications

Urethral complications (leak and stricture) bear special mention as the most common problem with penile reconstruction.[2,24,27,60] Strategies for avoidance of urethral complications involve basic surgical principles of avoiding of tension and optimising perfusion to the urethral segment. With tube-in-tube designs, perfusion can be improved by including secondary venous drainage on the urethral portion of ulnar side of the forearm, by fashioning the urethral segment of the flap longer proximally, and by leaving a cuff of fat even more proximal to this to avoid devascularising the proximal skin edge. Recent data suggests that single-stage urethroplasty[60] and the use of paravaginal tissue flaps[27] may also decrease the incidence of urethral complications.

CONCLUSION

Penile reconstruction has matured considerably over the last decades in reconstructive options and technical refinements, thanks to increasing recognition of gender dysphoria. Free RFF, ALT flap, and metoidioplasty are the most common options, each with a unique profile of complications, aesthetic, and functional outcomes. Urethral complications remain the largest barrier to operative success. Choices for reconstruction must be tailored to the individual patient's goals and available tissue characteristics. Analysis of the larger numbers of penile reconstructions now being performed will enable ongoing improvement in outcomes and better options for patients.

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A Review of Rare Associations of Horseshoe Kidney: Highlight of a Rare Clinical Case of Polycystic Horseshoe Kidney, Liver Cyst, and Uterine Prolapse

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Abstract

Horseshoe kidney is the most common renal fusion anomaly occurring in 0.15–0.25% of the general population. Horseshoe kidney is usually asymptomatic but may present with disease-like infections, urolithiasis, malignancy, polycystic disease, and other associated anomalies that may require intervention. Polycystic horseshoe kidney is rare, its association with uterine prolapse has not been reported in the literature, and it can only be postulated as an associated risk factor for uterine prolapse when found in the pelvis. The authors reviewed rare associations of horseshoe kidney and the management of these associated anomalies and disease conditions with the clinical vignette of a 60-year-old female with low-lying/lumbo-pelvic polycystic horseshoe kidney and hepatic cyst, and concomitant uterine prolapse requiring total abdominal hysterectomy at a Senegalese Hospital.

INTRODUCTION

Horseshoe kidney is the most common renal fusion anomaly occurring in 0.15–0.25% of the general population.[1-3] The male to female ratio is 2:1,[3] and although horseshoe kidney has been reported in identical twins and siblings, there is currently no established genetic link.[4] Horseshoe kidney is also seen in individuals with chromosomal anomalies and in 7% of those with Turner's syndrome.[5] The incidence of horseshoe kidney exists in three age groups:[4] in children, the pathology is diagnosed as part of a congenital anomaly; in young adults, it is diagnosed as a component of delayed puberty, for example in Turner's syndrome; and in adult patients, horseshoe kidney is diagnosed incidentally following a transabdominal

ultrasound, intravenous urogram, or CT scan for detection of other diseases.[4]

In 90% of cases, fusion occurs along the lower pole moiety; however, in 5–10% of patients, fusion may occur along the upper pole giving the appearance of an inverted horseshoe kidney.[4] The isthmus of the horseshoe is usually a fibrous band or parenchymatous renal tissue connecting the horseshoe kidney at lumbar vertebrae 2–4 (L2–L4).[4] Horseshoe kidney is a developmental variance usually occurring between 4 to 6 weeks of intrauterine life. The fusion of the lower pole of the kidney during this period creates a U-shaped kidney that is prevented from ascending to its normal level at the fourth lumbar vertebra by the inferior mesenteric artery originating from the aorta at the third lumbar vertebra.[4] Subsequently, the normal posterior rotation of the kidney is not possible, leaving the renal pelvis in an anterior plane.

Horseshoe kidney is usually asymptomatic but association with ureteropelvic junction obstruction, infection, and urolithiasis has been frequently reported,[6] and other rare associations including polycystic horseshoe kidney, malignancies, and vascular anomalies have been reported. The incidence of renal pelvis cancer associated with horseshoe kidney has been estimated at 19.8%,[2] and renal cell carcinoma has accounted for approximately 50.0% of malignancies found in horseshoe kidney.[3] The incidence of renal cell carcinoma is, however, the same in the population with nonfused kidney.[3]

Evidence has revealed that horseshoe kidney is associated with both venous and arterial anomalies. Based on results from several reports, there could be aberration of the renal artery to the horseshoe kidney along the following arterial vasculature: internal iliac artery (1.94%), iliolumbar artery (2.90%) and phrenic artery (0.97%), common iliac artery (40.0%), median sacral artery (2.90%), external iliac artery (0.97%), and the inferior mesentery artery (no data available).[4] Venous anomalies associated with horseshoe kidney are ten times more common than those in the general population. Some variations include double inferior vena cava (IVC), left-sided IVC, and preisthmic IVC.[4]

Polycystic horseshoe kidney is a rare association with a prevalence of 1 in 134,000 to 1 in 8,000,000 cases;[7] however, polycystic kidney disease and horseshoe kidney have separate aetiopathogeneses. Polycystic kidney disease itself is an autosomal dominant genetic disease and a major cause of renal failure. Studies have implicated two genes: *PKD1*, located on the short arm of chromosome 16 and accounting for 95% of cases; and *PKD2*, localised on chromosome 4, which accounts for 5% of cases.[7]

Polycystic horseshoe kidney plus liver cyst with associated uterine prolapse has not been reported in the literature. The exact incidence of uterine prolapse is unknown but accounts for 20% of women awaiting urogynaecological surgery in the UK.[8] Multiparity, race, older age, family history, increased BMI, constipation, menopause, and increased intra-abdominal pressure have been reported as established risk factors for uterine prolapse.[8] Nevertheless, there have been no published data on horseshoe kidney as a potential aetiologic factor. Horseshoe kidney, an anomaly itself, may not require any intervention except for the treatment of coexisting anomalies, disease, or complications. Frequent complications that may warrant intervention include ureteropelvic junction obstruction, suppurative infection, and obstructing urolithiasis. Other rare associations or complications that may need further management include malignancies, vascular anomalies, or polycystic disease.

This review emphasises rare associations of horseshoe kidney and management of associated anomalies with the clinical case of a 60-year-old female with low-lying/lumbo-pelvic polycystic horseshoe kidney with hepatic cyst and concomitant uterine prolapse requiring total abdominal hysterectomy at a Senegalese hospital.

CLINICAL CASE

A 60-year-old female (gravida 5 para 5; BMI 29 kg/m^2) presented to the obstetrics and gynaecology outpatient department with history of intermittent vaginal bulge for >5 years with associated dysuria that resolved with reduction of the bulge. The prolapse

occurred while standing or working but reduced manually during bed rest. Her fourth pregnancy was complicated by prolonged and obstructed labour that necessitated assisted vaginal delivery. There was no family history of hypertension or renal disease ascertained.

Her physical exam revealed a Stage 4 pelvic organ prolapse approximately 8 cm beyond the vaginal introitus. The prolapsed uterus was pinkish with areas of hyperaemia but no sign of ulcerations. Estimation using the Pelvic Organ Prolapse Quantification (POPQ) was not documented. Further examination with a contrast CT scan showed an incidental finding of a hepatic cyst of 8.0x7.5 cm in diameter in segment, fusion of the right and left kidney along the midline of vertebral bodies L4, L5, and S1, with a 4x4 cm cyst in the upper pole of the left kidney with multiple smaller cysts bilaterally.

Consultation with the urologists and general surgeons showed that she had a polycystic horseshoe kidney and a liver cyst that had been asymptomatic for years. The vital signs were all stable during the examination (blood pressure: 130/80 mmHg; pulse rate: 96 beats per minute; respiratory rate: 18 breaths per minute). Serum creatinine, blood urea nitrogen, complete blood count, coagulation profile, liver function test, and liver enzymes were normal. Her blood urea nitrogen was 15.00 mg/dL, albumin was 4.00 g/dL, creatinine was 0.95 mg/dL, and alanine transaminase was 30.00 U/L, aspartate transaminase was 36.00 U/L, and lactate dehydrogenase was 191.00 U/L. Routine urine analysis showed proteinuria (1+) and haematuria (1+) with a normal number of red blood cells in high power field.

With a multidisciplinary team, she underwent a total abdominal hysterectomy for a Stage 4 pelvic organ prolapse. Significant intraoperative findings revealed that the horseshoe kidney was abnormally lower in the pelvis and descended deeper during ventilation. It was assumed at the time that the repetitive descending of the horseshoe kidney may have previously contributed to the uterine prolapse. Her postoperative recovery was unremarkable. Follow-up laboratory tests have since shown a normal renal function and liver function.

METHODOLOGY

This review of horseshoe kidney with a literature search conducted from 2000 to 2019 used the search engines Google, Google Scholar, African Journal Online, and PubMed. The English-language literature was explored using the search term "horseshoe kidney", and appended associations ("polycystic horseshoe kidney", "polycystic horseshoe kidney + uterine prolapse", "horseshoe kidney + pyelonephritis", "horseshoe kidney + malignancy"). A total of 23 publications, two review articles, and 21 case reports of rare associations of horseshoe kidney were retrieved and included in the study. Other usual or frequent associations of horseshoe kidney such as horseshoe kidney plus uteropelvic junction obstruction, and horseshoe kidney plus urolithiasis, were excluded from the study. A total of 21 case reports of horseshoe kidney (20 published reports and one clinical vignette) were selected and reviewed for the study including polycystic horseshoe kidney, horseshoe kidney plus pyelonephritis, and horseshoe kidney plus malignancy. A total of 21 publications and case reports were reviewed for age, gender, associations, diagnostic modalities, and treatment. The data is represented in Tables 1 and 2 and a qualitative analysis is reported in the main text of the results. The clinical vignette of a 60-year-old female with polycystic horseshoe kidney associated with liver cyst and vaginal prolapse requiring total abdominal hysterectomy at a Senegalese hospital was highlighted specifically in the review as shown in Figures 1A–F.

RESULTS AND DISCUSSION

Horseshoe Kidney and Associated Infections

A total of 21 case reports of horseshoe kidney (20 published reports and one clinical vignette) were reviewed. The age of diagnosis ranged from 22.0 years to 83.0 years, with an average of 53.4 years. There were three reports of horseshoe kidney with associated infections: xanthogranulomatous pyelonephritis and renal calculi,[9] emphysematous pyelonephritis and ureteric stones,[10] and pyonephrosis and xanthogranulomatous pyelonephritis.[6]

Table 1: Age, sex, horseshoe kidney with associated ureteropelvic junction obstruction, vascular anomalies, infection, or polycystic kidney disease, and imaging modalities and treatment options.

Study	Age (years)	Sex	Horseshoe kidney and associations	Diagnostic modalities	Treatment
Tsuru et al.[1] 2016	53	M	UPJO and left duplex collecting system	Three-dimensional CT scan, ureteroscopy and cystoscopy	Laparoscopic pyeloplasty
Basson et al.[9] 2013	≥18	N/A	Right XP and renal calculi	CT scan	N/A
Gargouri et al.[10] 2014	67	F	Left emphysematous pyelonephritis and left pelvic ureteric stone	CT scan and 99m-Tc-DMSA	Antibiotics, PCD, and ureterolithotripsy
Fernandez et al.[6] 2018	64	F	Left staghorn calculi, massive pyonephrosis, and XP	CT scan and renal scintigram	Antibiotics, PCD, and left laparoscopic heminephrectomy
Özsin et al.[11] 2018	65	M	Aortoiliac occlusive disease	Intraoperative, multislice CT scan, and CT angiogram	Aortobifemoral bypass
Guvendi et al.[12] 2016	41	F	Left renal vein compression	CT scan and CT angiogram	N/A
Batista Peres et al.[13] 2006	36	F	Polycystic HSK and liver cyst	Ultrasound and CT scan	N/A
Shahreyar et al.[7] 2005	47	F	Bilateral polycystic HSK	Ultrasound	Bilateral nephrectomy and transplantation
Jehangir et al.[14]2006	22	F	Bilateral polycystic HSK and renal calculi	Ultrasound and CT scan	N/A
Ram et al.[15] 2013	32	M	Polycystic HSK and liver cyst	Ultrasound and CT scan	N/A
Ghonge et al.[16] 2014	45	M	Polycystic HSK and liver cyst	CT scan	N/A
Yildiz et al.[17] 2019	54	F	Polycystic HSK and multiple liver cysts	Ultrasound and CT scan	N/A
Present study	60	F	Polycystic HSK and liver cyst and uterine prolapse	CT scan	TAH

DMSA: dimercapto succinic acid; F: female; HSK: horseshoe kidney; M: male; N/A: not available; PCD: percutaneous drainage; TAH: total abdominal hysterectomy; UPJO: ureteropelvic junction obstruction; XP: xanthogranulomatous pyelonephritis.

The latter two cases of horseshoe kidney and pyelonephritis were managed with antibiotics, percutaneous drainage, and ureterolithotripsy,[10] and antibiotics, percutaneous drainage, and laparoscopic heminephrectomy, respectively.[6]

Emphysematous pyelonephritis is a severe acute necrotising fasciitis of the renal parenchyma. The most common risk factor is diabetes (for 80% of cases) followed by obstruction from urolithiasis.[10] *Escherichia coli* is the most common isolated organism followed by *Klebsiella* species. The diagnosis is confirmed by CT scan.[10] Fulminant cases require a nephrectomy, admission to an intensive care unit, and antibiotics. Xanthogranulomatous pyelonephritis is an unusual form of chronic pyelonephritis which results from granulomatous destruction of the renal parenchyma and abscess formation, occurring in 1% of pineal parenchymal infections.[9]

Table 2: Age, sex, horseshoe kidney with existing malignancies, diagnostic modalities, and treatment options.

Study	Age (years)	Sex	Horseshoe kidney and malignancy	Diagnostic modalities	Treatment
Ito et al.[2] 2018	75	M	Urothelial Ca of left renal pelvis	CT-guided biopsy	Chemotherapy and left hemiureteronephrectomy
Suzuki et al.[18] 2018	78	M	Urothelial Ca of right renal pelvis	CT scan and MRI	Robotic RNU and Isthmusectomy
Natsuyama et al.[5] 2019	62	M	Urothelial Ca of left distal ureter and aberrant renal artery	CT scan and indocyanine green near-infrared fluorescence	Laparoscopic left nephroureterectomy and bladder resection
Ohtake et al.[19] 2018	83	F	Left RCC	CT scan	Laparoscopic PN
Yamamichi et al.[20] 2019	63	M	Left clear cell RCC	3D CT scan	Robot-assisted PN
Scavuzzo et al.[21] 2017	37	F	Right clear cell RCC and pregnancy	Ultrasound and MRI	Radical nephrectomy
Nikoleishvili et al.[3] 2017	69	M	Left clear cell RCC	Ultrasound and CT scan	Laparoscopic PN
Tijani et al.[22] 2017	69	F	Left clear cell Ca and aberrant renal artery	CT scan	Open radical nephrectomy and isthmusectomy

Ca: carcinoma; F: female; M: male; PN: partial nephrectomy; RCC: renal cell carcinoma; RNU: radical nephroureterectomy.

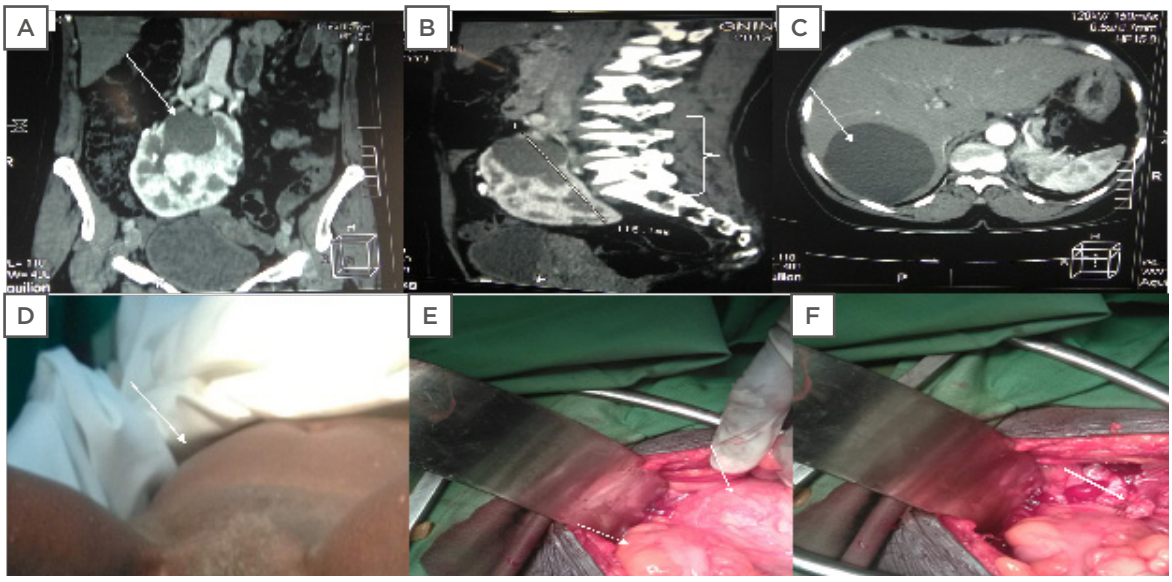

Figure 1: CT scan and clinical and intraoperative evidence of polycystic horseshoe kidney.

A) A 4x4 cm renal cyst in the left upper pole moiety of the horse kidney with multiple smaller cysts. **B)** The polycystic horseshoe kidney at the L2-S1 vertebrae. **C)** An 8.0x7.5 cm simple cyst in Segment VII of the liver. **D)** A uterine prolapse. **E)** The left arrow shows the sigmoid colon and the right arrow reveals the intraoperative picture of the horseshoe kidney descending into the pelvis during ventilation. **F)** The white arrow shows the empty space in the pelvis after ascent of the horseshoe kidney.

They are more common in females and result from infected obstructing urolithiasis. Features of lipid-laden and foamy macrophages are pathognomonic microscopic characteristics.[9] CT scans may reveal a nonfunctioning kidney, obstructing renal calculus, contracted renal pelvis, and inflammatory changes in the perinephric fat.

Horseshoe Kidney and Associated Vascular Anomalies

Özsin et al.[11] and Guvendi et al.[12] reported horseshoe kidney with concurrent aortoiliac occlusive disease and left renal vein compression, diagnosed with multislice CT and CT angiography, respectively. Tsuru et al.[1] also reported a rare case of horseshoe kidney with ureteropelvic junction and duplicated collecting system in a patient who underwent a laparoscopic pyeloplasty. Reports from published literature have shown that abdominal aortic aneurysm is frequently associated with horseshoe kidney; the true incidence of concurrent aortoiliac occlusive disease remains unknown, however. Many variations in the renal collecting system as well as renal vasculature, with the presence of varying renal accessory vessels occurring with a horseshoe kidney, have been reported.[11] Ordones et al.[23] reported that these vascular aberrations and duplications could be useful in rare cases of horseshoe kidney transplant. Multislice CT and CT angiography have been helpful in delineating the horseshoe kidney and their associated vasculature. Intervention in these patients without proper insight of the renal vasculature could lead to renal parenchymal necrosis, or major haemorrhage.

Horseshoe Kidney and Associated Malignancies

Reports of horseshoe kidney were associated with three cases of urothelial carcinoma;[2,5,18] two affecting the renal pelvis, and one involving the distal ureter associated with an aberrant renal artery. There were five reports of horseshoe kidney with renal cell carcinoma,[3,19-21] predominantly clear cell variants.[3,21,22] CT was mostly used for diagnosis. Treatment options were generally laparoscopic or robotic. Partial nephrectomy,[3,19,20] radical nephrectomy,[21,22] hemi-nephroureterectomy,[2] and radical nephroureterectomy with bladder resection[5,18] were all management options. The treatments were based on staging and oncological principle of the various histologies. The incidence of tumours arising from renal fusion anomalies is approximately 5–13%; however, 50% of these tumours are proven to be renal cell carcinomas. Although the risk of nephroblastoma and urothelial cancer seem to be higher in renal fusion anomalies, the incidence of renal cell carcinoma appears to be similar to the general population.[3] Preoperative imaging of the blood vessel with CT angiogram is essential to avoid perioperative complications. The surgical options are open, laparoscopic, or robotic partial/radical nephrectomy based on the oncological principle, institutional capacity, and surgeon's expertise.

Polycystic Horseshoe Kidney, Associations and Clinical Case

There were seven cases of polycystic horseshoe kidney,[8,13-17] including the case highlighted in Figures 1A–F. Five of the seven cases of polycystic horseshoe kidney were associated with single or multiple liver cysts.[13,15-17] Shahreyar et al.[7] reported on a case of polycystic horseshoe kidney with renal insufficiency that necessitated bilateral nephrectomy and renal transplantation; the outcome of the intervention was not elucidated in the report. Polycystic horseshoe kidney is the combination of two different renal anomalies: horseshoe kidney is a fusion disorder during embryogenesis while polycystic disease of the kidney is a genetic disease of autosomal dominant inheritance. Adult polycystic kidney disease is the third most common aetiology of end-stage renal failure.[16] Remarkably, the patient in the current study maintained a normal renal function both before and after surgery as well as subsequent follow-up.

The case of polycystic horseshoe kidney reported in this review was associated with a liver cyst as well as a uterine prolapse requiring a total abdominal hysterectomy. The horseshoe kidney as reported in the clinical vignette was discovered incidentally by CT, similarly to other cases of renal fusion anomalies reported in adults (usually asymptomatic). The horseshoe kidney shown in Figures 1A–F was at a much lower level of vertebral segment (L4–S1), as shown on contrast enhanced CT scan. The

usual position of a horseshoe kidney is in the hypogastrium at the second to fourth lumbar vertebrae. After its ascent, it is arrested by the inferior mesenteric artery at the third lumbar vertebra during the 7–9th week of gestation. Moreover, it was observed to have protruded deeper into the pelvis intraoperatively during ventilation. This association has never been reported to the authors' knowledge, and neither has a pelvic kidney been reported as a risk factor for pelvic organ prolapse in females.

There is a strong probability that the polycystic horseshoe kidney and the uterine prolapse could have been separate pathologies. The patient in the clinical vignette presented with many established risk factors including older age, multiparity, complicated assisted vaginal delivery from prolonged and obstructed labour, menopause, and increased BMI. However, the depth of the horseshoe kidney in the pelvis during ventilation intraoperatively could not have been easily discarded as a concurrent aetiological factor. Because increased intra-abdominal pressure has been identified as a causative agent,[4] it is difficult to assume that continuous abutting of the horseshoe kidney against the uterus during respiration could have contributed to the prolapse of the uterus through the introitus.

CONCLUSION

Horseshoe kidney is the most common renal fusion anomaly. It is usually asymptomatic but may present with associated anomalies or disease-like infections, urolithiasis, malignancy, polycystic disease, and other associations requiring intervention. Polycystic horseshoe kidney is rare. It is a common cause of end-stage renal failure, but the patient in the clinical vignette maintained a normal renal function. Moreover, the association of polycystic horseshoe kidney, liver cyst, and uterine prolapse has never been reported. Currently, the evidence is insufficient to reach a conclusion, and there is difficulty in assuming that continuous abutting of the horseshoe kidney against the uterus during ventilation could have contributed to the prolapse of the uterus through the introitus.

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Safety and Feasibility of Autologous Micro-Fragmented Adipose Tissue Injections for the Treatment of Vaginal Atrophy, Vulvovaginal Dystrophy, and Stress Urinary Incontinence: An Observational Case Series

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Abstract

Objective: Vaginal atrophy, vulvovaginal dystrophy, and stress urinary incontinence (SUI), common conditions in women, have detrimental effects on quality of life. Current treatments require ongoing use and are associated with risks, complications, and incomplete resolution of symptoms. The aim of this observational case series was to evaluate the safety and feasibility of autologous micro-fragmented adipose tissue injections for the treatment of vaginal atrophy, vulvovaginal dystrophy, and SUI in women.

Methods: Ten women affected by vaginal atrophy, vulvovaginal dystrophy, and/or SUI were injected into their affected areas with harvested and processed autologous micro-fragmented adipose tissue. Symptoms, diagnoses, previous treatments, and gynaecological surgeries were considered. Outcomes were measured using the Female Sexual Function Index (FSFI), the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF), the Vulvovaginal Symptoms Questionnaire (VSQ), and the Short-Form 12 (SF-12) health survey. Information gained from discussion and clinical examination at consultations was also used to measure outcomes.

Results: No adverse events or complications were reported during the intraoperative, recovery, postoperative, or follow-up periods. No signs of infection, pain, dysuria, skin irregularities, skin discolouration, discharge, or worsening of symptoms were reported. All 10 women reported an improvement of symptoms within 6–16 months of the planned follow-up period.

Conclusions: Autologous micro-fragmented adipose tissue injections appeared to be safe and feasible and may have a positive role in the treatment of the physical signs and symptoms of vaginal atrophy, vulvovaginal dystrophy, and SUI.

INTRODUCTION

Vaginal atrophy, vulvovaginal dystrophy, and stress urinary incontinence (SUI) are conditions that have significant implications for quality of life. They can occur at any time during a woman's life, but are most common in postmenopausal women, with a prevalence of up to 54.0%,[1,2] 1.7%,[3] and 31.0%,[4] respectively. Symptoms of vaginal atrophy and vulvovaginal dystrophy include vaginal dryness, decreased lubrication during sexual activity, irritation, itching, dysuria, dyspareunia, and postcoital bleeding. These symptoms, alongside the involuntary urination of SUI, can have a detrimental effect on urogenital health, sexual function, and psychological wellbeing.[5-8]

Vaginal Atrophy

Vaginal atrophy, also known as genitourinary syndrome of the menopause, is a common condition that is often under-diagnosed and under-recognised. The urogenital changes that cause the symptoms of vaginal atrophy occur as a result of a reduction in circulating oestrogen levels and therefore current treatments are targeted at replacing oestrogen through systemic or topical approaches. These treatments have been proven to have a therapeutic effect on the symptoms of vaginal atrophy, but the benefit of one modality over another is still debated. Furthermore, they require ongoing therapy and adherence is poor because of issues related to side effects, convenience, and worries surrounding increased risk of cancer with hormone therapies.[9,10] Additionally, <50% of women using prescribed treatments report satisfaction with the treatment and 10–20% of women report residual symptoms.[2,10]

Vulvovaginal Dystrophies

Vulvovaginal dystrophies such as lichen sclerosus, lichen planus, and lichen simplex are chronic inflammatory dermatoses with an unknown aetiology and are associated with an increased risk of the development of vulvar malignancies.[11,12] First-line treatment is limited to ultrapotent topical corticosteroids, but complete resolution is only reported in approximately 20% of patients and many experience skin thinning as a side effect.[13] Surgery is only indicated in cases of malignancy and postinflammatory sequelae, and for treatments such as photodynamic therapy and cryotherapy, relapse rates are high.[14]

Stress Urinary Incontinence

SUI describes the involuntary urination upon effort, exertion, sneezing, or coughing. The current nonsurgical therapies for SUI include physiotherapy, intravaginal devices, urethral inserts, and pharmacological treatment. However, these strategies require ongoing treatment and behaviour modification, which may reduce adherence to a regime. Furthermore, surgery to treat SUI can be associated with complications and recurrence of symptoms, and repeat surgery is required in up to 14.5% of women.[15]

Advancements in regenerative medicine over the last decade have revealed the potential for mesenchymal stem cells (MSC) to be used as a powerful therapeutic tool against tissue damage and degeneration. Not only do MSC possess multilineage potential, but the secretion of trophic factors act in a paracrine fashion to promote an antifibrotic, antiapoptotic, and angiogenic response in the recipient tissues, ultimately producing an anti-inflammatory and immunomodulatory healing effect.[16] Adipose tissue has been recognised as a reliable source for MSC[17,18] which can be easily harvested and processed using the Lipogems® system (Lipogems International S.p.A., Milan, Italy), where intraoperative mechanical manipulation provides micro-fragmented adipose tissue in a short period of time.[19] Furthermore, mechanical manipulation of adipose tissue results in greater preservation of trophic factors compared to traditional enzymatic methods used for harvesting adipose-derived stem cell.[20]

Autologous micro-fragmented adipose tissue injection is well established as a safe and effective treatment and has several clinical applications.[21-24] The use of autologous adipose tissue in the treatment of vaginal atrophy has provided some promising results, but evidence is limited.[25-31] Micro-fragmented adipose tissue was used by Fantasia et al.[27] for the treatment of vaginal atrophy in one woman and by Casarotti et al.[28] in three women. A significant improvement in symptoms was reported,

without any complications or adverse events. This uncontrolled observational case series reports on the safety and feasibility of the use of micro-fragmented adipose tissue injections for the treatment of 10 consecutive female patients with symptomatic vaginal atrophy, vulvovaginal dystrophy, and/or stress incontinence.

METHODS

Ethics

The procedure described in this observational case series was performed in accordance with Good Clinical Practice (National Institute for Health Research [NIHR]) and the General Medical Council (GMC) guidelines on research, patient consent to research, and future publication. The Lipogems system used to harvest and process the adipose tissue was a U.S. Food and Drug Administration (FDA)-approved product for the use of a number of surgeries, inclusive of gynaecological surgeries.

Patients

Ten women with a multitude of conditions, including vaginal atrophy, vulvovaginal dystrophy, and SUI, agreed to treatment by injection of autologous micro-fragmented adipose tissue. These patients had previously undergone various therapies with unsatisfactory symptom relief and sought out an alternative treatment modality. Patients were consulted by a gynaecological consultant and an anaesthetic consultant, in which suitability for the procedure and anaesthesia were assessed. Clinical diagnoses were made upon vulvovaginal examination. A decision to perform biopsy was made on a case-by-case basis and was not performed on every woman due to the risk of fibrosis and impact on the fragility of tissue to be injected.

Consent forms were sent to patients 2–3 weeks in advance of their procedure; they were advised on the risks and benefits of the procedure and made aware of any alternative treatments available, in line with GMC guidance on consent. All patients completed an online preassessment questionnaire to assess their health, BMI, and past medical history, which is displayed along with gynaecological diagnoses in Table 1.

Harvesting the Adipose Tissue

Harvest entailed tumescent liposuction, which was undertaken by an experienced (consultant grade) plastic surgeon. The most commonly used harvest (donor) site was the lower anterior abdomen, performed with the patient in a supine position. However, in patients with a lower BMI, the harvest was carried out with the patient in prone position, with donor sites including lumbar flanks, superolateral buttocks, and/or lateral thighs. The tumescent fluid comprised 0.9% normal saline and adrenaline (concentration of 1:500,000). The tumescent fluid did not include local anaesthetic because these (lidocaine and ropivacaine) are reported to have proapoptotic influences on adipose derived stromovascular fraction.[32]

A manual (nonautomated) and gentle (low vacuum and low shear) tumescent liposuction technique was adopted. A minimum of 200 mL of lipoaspirate was harvested from each patient; in slender patients more was required. The final processed fraction yield equated to approximately 10% of lipoaspirate volume, and therefore, approximately 20 mL of processed fraction was typically available for the operating gynaecologist.

At completion of tumescent liposuction harvest, each donor site used was infiltrated with approximately 50 mL of normal saline 0.9%, containing safe and appropriate concentrations of bupivacaine, tranexamic acid, and adrenaline. This step was employed to ameliorate postoperative donor site pain and bruising. Finally, donor sites were dressed with wound closure tape, simple gauze, and adhesive dressing, with application whenever possible (subject to fit) of a post-operative surgical compression band or garment.

Processing of the Adipose Tissue

The lipoaspirate was immediately processed, eliminating proinflammatory agents, such as oil from ruptured adipocytes and red blood cells, by filtering and washing. Sequential micro-fracturing ensured small and uniform particle size, which is subsequently important for smooth (low shear) injection. The trauma imparted to the cells during the micro-fracturing steps is important in promoting pericyte cell activation and MSC differentiation.

Table 1: Demographic data of the 10 patients treated with autologous micro-fragmented adipose tissue injections for the treatment of vaginal atrophy, vulvovaginal dystrophy, and stress urinary incontinence.

Patient	Age	BMI	Ethnicity	Parity	Symptoms and signs	Gynaecological diagnoses and duration	Previous gynaecological treatments	Previous gynaecological surgery	Comorbidities and allergies	Current medication
1	50	31.6	Bangladeshi	3+3	Vulvovaginal itching, stress incontinence, dryness	Lichen simplex chronicus, SUI, perimenopausal	Pelvic floor exercises, potent topical steroid	None	Peptic ulcer, iron deficiency anaemia	None
2	47	29.0	Indian	2	Dyspareunia, vulvovaginal itching	Lichen sclerosus, lichen planus	Vaginal dilators, potent topical steroid	None	None	None
3	60	48.0	Caucasian	1+2	Vaginal stenosis, dryness, pain and discomfort, inability to have sexual intercourse	Lichen sclerosus	2x oestrogen ring pessary	Adhesiolysis (2015 and 2016) for oestrogen ring insertion	Type 2 diabetes mellitus, peptic ulcer	Oral hyperglycaemic medication
4	45	26.2	Caucasian	0	Dyspareunia, pain	Premature menopause, vaginal atrophy	Systemic HRT, oestrogen vaginal inserts	3x Mona Lisa Touch® (HCA International Limited, London, UK) fractional CO_2 laser therapy	Asthma, latex allergy	Salbutamol inhaler
5	47	21.3	Middle Eastern	1+0	Dyspareunia, dryness	Premature menopause, vaginal atrophy	Systemic HRT	None	None	Systemic HRT
6	30	24.0	Caucasian	0	Dyspareunia, perineal thinness, multiple fissures, minimal fusion of labia minora, tightness	Nonspecific dermatitis, lichen sclerosus, VAIN-1	Potent topical steroid	Fenton's procedure to remove a ridge in the posterior fourchette	Asthma	None
7	44	18.3	Indian	2	Dyspareunia, fissures fused labia minora, perineal thinness	Lichen sclerosus	Potent topical steroid	LLETZ treatment (2011 and 2013)	Asthma, anaemia	Ventolin inhaler, beclomethasone inhaler, vitamin and iron supplements
8	62	26.6	Caucasian	1	Clitoral adhesions, cystic lesion	Lichen sclerosus, fibroids	Potent topical steroid	Total abdominal hysterectomy (for treatment of fibroids)	None	Topical oestrogen cream
9	47	25.7	Indian	2	Involuntary urination	SUI, overactive bladder	Medication for overactive bladder	Transvaginal tape	None	None
10	48	23	Caucasian	4+1	Dyspareunia, involuntary urination	SUI	ThermiVa® (Celling Biosciences, Austin, Texas, USA) radiofrequency treatment	None	Asthma, vitamin D deficiency	Salbutamol inhaler

HRT: hormone replacement therapy; LLETZ: Large loop excision of the transformation zone; SUI: stress urinary incontinence; VAIN: vaginal intraepithelial neoplasia.

This trauma is imparted to cells in the context of total fluid (normal saline) immersion, which in turn dissipates energy and reduces cell rupture rates because cells need to be activated rather than ruptured. The final fraction was expressed from the device in 10 mL syringes and after settling for 5 minutes, saline subnatants were discarded. The fractions were then decanted into multiple 1 mL Luer-lock syringes in preparation for injection by the operating gynaecologist.

Micro-Fragmented Adipose Tissue Injection

The genitourinary area was inspected and scored using the vaginal health index (VHI), and patients were placed in the lithotomy position for injection. If needed, the gynaecologist then performed a biopsy using small disposable punch biopsy forceps.

Micro-fragmented adipose tissue was injected using a 20 gauge blunt cannula in 0.5–1.0 mL aliquots into the subcutaneous and subepithelial vaginal space. This was performed by an experienced gynaecologist (consultant grade) in a homogeneous and uniform manner following a patient-specific topographic map, which indicated the areas of genitourinary changes that were causing problems for each individual patient. Patients who experienced stress incontinence had additional injections into paraurethral areas using a temporary 12 French unit Silastic® (C.R. Bard, Inc, New Providence, New Jersey, USA) urinary catheter to assist in identification of the urethral anatomy. An average of 24.0 mL micro-fragmented adipose tissue was injected per case, ranging from 8.5 to 32.0 mL. Following the injections, unless contraindicated, a Voltarol® (GlaxoSmithKline, London, UK) suppository was given to the patients with prior consent. Total time for harvesting and processing adipose tissue into micro-fragmented adipose was 20–30 minutes, and the gynaecological injection phase lasted 20–30 minutes. The total operation time was under 1 hour for every case.

Recovery and Discharge

Patients were discharged the same day in accordance with the guidelines by the British Day Surgery Association (BADS) which ensures all women can freely pass urine. Patients were discharged with a prescription of paracetamol 1 g once daily, dihydrocodeine 30 mg once daily, lactulose 10 mL twice daily (to combat the constipating effects of dihydrocodeine only), and clotrimazole 1% w/w cream taken as needed in case of postoperative candidiasis. All women were provided with verbal and written advice regarding an abdominal binder to be worn, wearing abdominal dressings at the adipose harvest sites, and advice regarding time until resuming sexual activity, shaving, bathing, and heavy lifting.

Outcome Measures

All patients received a follow-up telephone consultation from a registered nurse 48 hours after their procedure to assess signs of infection, pain, dysuria, skin irregularities, skin discolouration, and discharge.

All patients received consultations with a consultant gynaecologist before the procedure, and at 2 weeks, 3 months, 6 months, and 1 year postoperation, as displayed in Figure 1. In addition to this, further consultations are planned for 2 years postoperation, or more frequently if required. These consultations involved a clinical examination, and outcomes were measured using the Female Sexual Function Index ([FSFI]: 2–36, in which 36 is a good result), the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form ([ICIQ-UI SF]: 0–21, in which 0 is a good result), the Vulvovaginal Symptoms Questionnaire ([VSQ]: 0–200, in which 200 is a good result), and the Short-Form 12 ([SF-12]: 10–70, in which 70 is a good result) health survey.

RESULTS

No intraoperative or postoperative adverse events or surgical complications were reported. During the recovery period, only one woman requested paracetamol for pain relief. The total time for this treatment as a day case from admission to discharge was 120–180 minutes per case. Postoperatively, no issues were reported relating to significant pain, discharge, signs of infection, or candidiasis. Mild donor site (tumescent liposuction) bruising, tenderness, and skin contours were in line with preoperative expectations and caused no significant concerns in any of the women in the cohort.

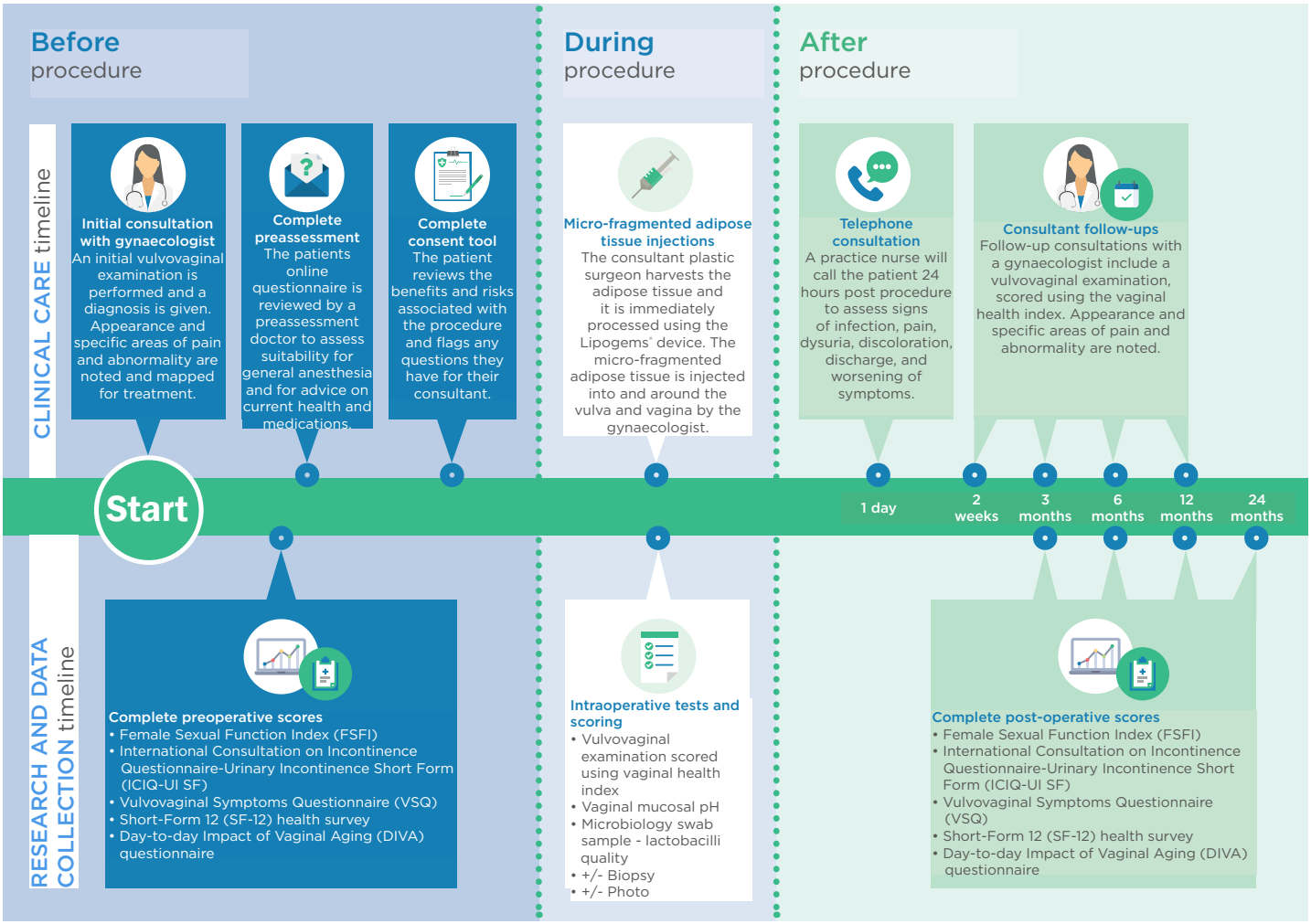

Figure 1: Follow-up and outcome measures for patients.

Patient 1

The patient presented with lichen simplex chronicus, vulvovaginal itching, SUI, and dryness, and upon examination there were signs of vaginal atrophy. The patient reported significant improvement of SUI and dryness at 6 months, with only occasional vulvovaginal itching. Examination revealed improvement of the appearance of the vulvar area with no vaginal atrophy. Unfortunately, this patient was not followed-up for scores.

Patient 2

The patient presented with lichen sclerosus with dyspareunia and vulvovaginal itching. The patient reported no dyspareunia at 3 and 6 months. At 16 months, the patient reported very mild dyspareunia, but complete resolution of vulvovaginal itching. A tender area of fibrosis was noted on the anterior vaginal wall on examination, but there was significant improvement in the appearance of the vulva, with no lichenification present. Overall, her scores had improved at 6 months: FSFI (21.5 to 29.1); VSQ (101 to 0); mental SF-12 (44 to 61). Her physical SF-12 decreased from 58 to 57. At 1 year, her scores demonstrated sustained improvement in her symptoms: FSFI (27); VSQ (14); mental SF-12 (56); and physical SF-12 (58).

Patient 3

The patient presented with lichen sclerosus and severe pain and discomfort, which precluded sexual intercourse. Vaginal examination was impossible due to stenosis and fibrosis; insertion of one finger was impossible due to pain. In the 6, 12, and 16 months following treatment, vaginal examination was possible with a small

speculum and the patient was able to insert vaginal dilators herself. There was still tightness of the vaginal wall as a result of fibrosis, but her ring pessary was more easily changed, with no pain, and the urethra was visible, which had previously been hidden by adhesions. Scores had improved at 6 months: FSFI (10.2 to 13.2); ICIQ-UI (10 to 7); VSQ (56 to 38); and physical SF-12 (48 to 54). Mental SF-12 decreased (61 to 580.

Patient 4

The patient presented with pain, dryness, and dyspareunia. Speculum examination previously caused severe pain and showed vaginal atrophy and dryness. There was complete resolution of dyspareunia and dryness at 3, 12, and 16 months, with only some occasional burning in the posterior fourchette. Speculum examination was performed without pain, and the vaginal wall appeared healthy and well lubricated. Scores had all improved at 6 months: FSFI (6.3 to 6.6); ICIQ-UI (4 to 0); VSQ (168 to 10); mental SF-12 (30 to 58); and physical SF-12 (34 to 41).

Patient 5

The patient presented with vaginal atrophy. Preoperative biopsy showed evidence of chronic inflammation, and the patient experienced dyspareunia and dryness. At 6-month follow-up this had improved significantly, and the patient reported a healthy discharge that was not present previously. This was also the case at 1 year and 16 months following treatment. Scores at 6 months and 1 year were the same: FSFI (5 to 20); VSQ (45 to 25); mental SF-12 (47 to 47); and physical SF-12 (29 to 29).

Patient 6

The patient presented with dyspareunia, chronic dermatitis, lichen sclerosus, and low-grade vaginal intraepithelial neoplasia. On examination, there was significant lichenification with raw skin around the perineum and fusion of the labia minora. No pain in the perineal area was reported at 6 months, but the patient had not been sexually active so could not comment on dyspareunia. Mild discomfort was reported around the labia minora where an inflamed pimple was found, and antibiotics prescribed. Vulvovaginal examination showed significant improvement, with no fissures or raw skin. Some scores improved at 6 months: VSQ (145 to 67) and physical SF-12 (57 to 59). Some scores mildly worsened: FSFI (4.4 to 3.6) and mental SF-12 (51 to 39). However, FSFI was difficult to measure because the patient had not been sexually active.

Patient 7

The patient presented with severe lichen sclerosus, dyspareunia and fissures following sexual intercourse, vulvovaginal itching, and dryness. Examination revealed labia minora fusion, perineal thinness, and raw skin on the perineum. Complete resolution of vulvovaginal itching, dryness, and dyspareunia was reported at 6 weeks and 9 months following treatment. Examination revealed a significant improvement in the appearance of the vulvovaginal area, with no evidence of lichenification. The authors were unable to obtain scores from this patient at 6 months, but there was improvement at 3 months: FSFI (4.4 to 5.3), ICIQ-UI (3 to 0), VSQ (89 to 55), and physical SF-12 (53 to 57). However, her mental SF-12 mildly decreased (56 to 47).

Patient 8

The patient presented with lichen sclerosus. Complete resolution of dryness was reported at 4 months, as well as significant improvement in vulvovaginal itching, but the patient could not comment on her dyspareunia because she had not had sexual intercourse due to other factors. On examination, the vulvovaginal area appeared healthier, particularly the labia majora, but there were still some small patches of lichen sclerosus around the anus. The following scores improved at 6 months: FSFI (3.8 to 8.4), VSQ (110 to 103), and mental SF-12 (32 to 38). However, there was a minimal decrease in physical SF-12 (60 to 59).

Patient 9

The patient presented with severe SUI. There was complete resolution of SUI at 2 weeks, though some symptoms returned at 3 months. However, SUI symptoms had significantly improved from her pre-operative state. Unfortunately, this patient was lost to follow-up after 3 months and therefore her scores are not available.

Patient 10

The patient presented with SUI and dyspareunia. Within 2 weeks the patient had noticed significant improvement of SUI, which was also reported at 1, 2, and 3 months follow-up. Additionally, the patient reported increased pleasure with sexual intercourse with no dyspareunia. Her scores improved at 6 months: FSFI (39.0 to 33.3), ICIQ-UI (8 to 5), physical SF-12 (40 to 55), and mental SF-12 (59 to 60).

DISCUSSION

Vaginal atrophy, vulvovaginal dystrophies, and SUI are conditions that can have detrimental effects on a woman's urogenital health, sexual function, and psychological wellbeing. Whilst current approaches can relieve symptoms, they require ongoing use, which can increase the risk of nonadherence. Additionally, some of the first-line treatment approaches currently used are associated with risks and complications, and do not always completely resolve symptoms.

This observational case series demonstrates the safety and feasibility of autologous micro-fragmented adipose tissue injections in the treatment of 10 women with vaginal atrophy, vulvovaginal dystrophy, and SUI. It is the largest case series to date that uses this procedure to treat women with these conditions. To the best of the authors' knowledge, it is the first case series that demonstrates the safety and feasibility of the described procedure for the treatment of vulvovaginal dystrophies such as lichen sclerosus and lichen planus, as well as SUI. Results are consistent with previous case reports of vaginal atrophy by Fantasia et al.[27] who treated one woman, and Casarotti et al.[28] who treated three women. Demonstration of the safety of this procedure is important in presenting a feasible treatment option for women who have found previous treatment modalities unsuccessful in resolving their symptoms. Additionally, where local and systemic hormonal therapies are contraindicated (women with previous gynaecological or breast cancers),[33] this treatment may act as a viable alternative.

The use of platelet-rich plasma (PRP) has been suggested for the treatment of the aforementioned conditions.[31] Casabona et al.[26] used a combination of PRP and micro-fragmented adipose tissue injection for the treatment of 15 women diagnosed with lichen sclerosus and Aguilar et al.[34] used a combination of PRP and hyaluronic acid, both with favourable outcomes.[26] The advantage of the method described in this case series is that it is a simple, one-step method that can be performed intraoperatively, but the small sample size in both case series limits the ability for statistical analysis. Additionally, fractional CO_2 laser therapy has been suggested as a treatment for vaginal atrophy. However, a comparative study has shown that autologous micro-fragmented adipose tissue injections are more effective in restoring healthy tissue, possibly due to the effect of trophic factors.[35]

For patients with vulvovaginal dystrophies such as lichen sclerosus and lichen planus, which are associated with vulvar malignancies, it is unknown whether early treatment lessens the risk of malignancy. Calcineurin inhibitors have been recently explored as a potential treatment, but there is concern surrounding the increased risk of potentiating malignant transformation due to their local immunosuppressive effects on tissue.[36,37] In the future, it will be important to evaluate the effect that treatment with autologous micro-fragmented adipose tissue injections has on risk of malignant transformation of these conditions, and whether early treatment can further reduce this risk.

Preliminary results are promising and encourage further research into the efficacy of the treatment, with a long-term follow-up. It will be important to evaluate efficacy with objective measures such as vaginal pH and cytological studies. Whether such a technique may exert a synergistic effect with current treatment modalities such as systemic and local treatments remains to be fully investigated.

This case series is limited by the low number of participants, and the wide variety of complaints and diagnoses among the 10 patients. A limitation to the procedure is that a day surgery operating theatre is required, as well as the presence of a consultant gynaecologist, a consultant anaesthetist, and a plastic surgeon to carry out the highly specialised procedure.

CONCLUSION

The results of this case series show the feasibility of using autologous micro-fragmented adipose tissue injections to treat women affected by vaginal atrophy, vulvovaginal dystrophy, and SUI. The technique appears to be safe, minimally invasive, and simple, with no adverse effects recorded, and preliminary results are promising with regards to efficacy.

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Bladder Pain Syndrome: A Review

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Abstract

Therapy of bladder pain syndrome (BPS) presents a significant challenge in clinical practice. Over the last 20 years, there have been important efforts directed at understanding the syndrome's aetiology and therapeutic challenges. Data regarding disease progression, remission, and prevention are very limited and little is known about the risk factors for the development of associated symptoms over time. Several visceral pain syndromes and systemic diseases often occur together in the same patient. Patients are currently treated by different clinicians on an empirical basis with a variety of different medications and other treatment interventions. Treatment approaches are local or systemic and range from behavioural, to pharmacological, and finally to surgical, which altogether are focussed on optimising quality of life. Treatment of BPS often requires a trial and error approach. The aim of this review is to analyse and present contemporary literature regarding BPS.

INTRODUCTION

Bladder pain syndrome (BPS) is a chronic bladder pain condition presenting in patients without any identifiable cause. This terminology is used instead of painful bladder syndrome, pelvic pain, or the most commonly used interstitial cystitis. Interstitial cystitis is not an appropriate term because research has shown that bladder inflammation (cystitis) is not clearly involved in the pathophysiology and the abnormal interstitium of the bladder is not reliably related to the disease.

The Society for Urodynamics and Female Urology (SUFU) defines this syndrome as "an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of identifiable causes."[1] Definitions that require longer duration of symptoms (e.g., 6 months) should not be taken into consideration because the prevention of withholding treatment in BPS patients is clinically important. Also, definitions from research studies should be omitted during the clinical practice as these may cause misdiagnosis or delayed diagnosis.

Vague characteristics of the disease have led studies to underestimate its prevalence, but it is generally accepted as a female-dominant disorder.[2] The diagnosis is generally made after the fourth decade of life but may be delayed depending on the clinical suspicion.[3] Prevalence rates vary greatly; in the NHANES III survey from the USA, the prevalence was recored as 470 per 100,000 population, which was 60 per 100,000

men and 850 per 100,000 women.[4] These numbers indicate that nearly 83,000 men and 1.2 million women have BPS in the USA. In Europe, prevalence figures are much lower: 8–16 per 100,000 women.[5] The patient's age should not be an exclusion criterion, as BPS is observed amongst children and adolescents.[6]

BPS should be a diagnosis of exclusion. The RAND Interstitial Cystitis Epidemiology (RICE) study investigating women with chronic bladder pain used exclusion criteria. Patients with bladder cancer, urethral diverticulum, spinal cord injury, stroke, Parkinson's disease, multiple sclerosis, spina bifida, cyclophosphamide treatment, radiation treatment to the pelvic area, tuberculosis affecting the bladder, uterine cancer, ovarian cancer, vaginal cancer, genital herpes, and pregnancy are all excluded.[7] During the diagnosis, similar exclusion criteria should be adopted for men also. In the RICE study, two definitions had been established for women based on either high sensitivity or specificity. The high sensitivity definition dictates pain, pressure, or discomfort in the pelvic area, alongside a daytime urinary frequency greater than 10 to avoid the discomfort and to be without fear of wetting. The high specificity definition includes two more criteria, specifically the presence of antibiotic treatment-refractory symptoms and absence of hormonal injections for endometriosis in women. High sensitivity criteria correctly identify BPS patients in 81% of cases with 54% specificity, whereas high specificity criteria correctly exclude non-BPS cases in 83% of cases with 48% sensitivity.[7-9]

Most patients with BPS feel pain or discomfort while holding urine and take relief after micturition.[10] It is important to define pain in a broad spectrum because some patients may deny pain but instead report pressure feeling.

In addition to pain, urgency, frequency, nocturia, dysuria, dyspareunia, bladder spasms, and suprapubic pressure sensation are common symptoms.[11] Patients usually define an increasing number of symptoms after the single initial symptom, such as dysuria, frequency, or pain. Symptoms vary from time to time and severity also changes. The onset of symptoms is generally gradual but some patients may define an abrupt onset without a triggering situation. Sudden intensifying symptom flares sometimes occur and may continue for several hours, days, or weeks. Symptoms may exacerbate during stress, menstruation, exercise, sexual intercourse, prolonged sitting, or following intake of certain foods or drinks.[12-14] Patients tend to hold their urine volume as low as possible and try to empty their bladder at the first opportunity; despite this, urinary incontinence is rarely observed. A possible aetiology may be related to bladder wall problems. Bladder impermeability to solutes stems from the glycosaminoglycan layer of the urothelial surface and defects in this impermeable surface expose the urothelium to urinary irritants, in turn leading to tissue damage, hypersensitivity, and pain.[15]

On physical examination, tenderness in the hip girdle, abdominal wall, urethra, and pelvic floor can be felt, as well as potential accompaning scrotal and penile tenderness in men. Significant pelvic prolapse, inguinal hernia, urethral diverticulum, uterine or cervical mass, prostate induration, and eroded or exposed vaginal mesh should be checked during the examination.

Impact on psychosocial functioning and quality of life is very typical in patients with BPS. BPS may cause depression, anxiety, loss of work–life balance, stress, panic disorder, and sexual dysfunction.[16] BPS patients may be reactive for these mental health situations, but there is also some evidence suggesting a genetic link between BPS and panic disorder.[17] There may be comorbidities associated with BPS, such as fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, Sjögren's syndrome, chronic headaches, and vulvodynia,[18] and common pathophysiology may exist. BPS may be part of a more generalised systemic disorder. Also, additional epidemiological studies suggest that many of these somatic symptoms are also present if the BPS patient is correctly assessed during the diagnostic workup. In addition to this, another hypothesis is that BPS may be a part of the continuum of painful versus non-painful overactive bladder syndrome.[19]

Quality of life is lower when compared to the controls;[20] because of this, social, educational, and career-related activities may not be pursued. Additionally, emotional distress, depression, and social isolation may be substantial.

There is an increased interest in BPS among the urology community because of the issue pertaining to quality of life and genitourinary function. The aim of this article is to provide contemporary knowledge to the general urologist.

ASSESSMENT

Costs

The economic burden of BPS on the healthcare system is immense. Direct costs associated with BPS include physician visits, prescription medications, outpatient procedures, and hospitalisation. These costs are greater than the mean annual per person direct costs of diabetes, depression, hypertension, and asthma.[21] Because of the chronic nature of the disease, these costs typically persist for years. Indirect costs of BPS include lost productivity while working or time away from work. This is a serious problem because the condition primarily affects those of working age (i.e., 25–50 years old).

Patient History

A history of pelvic pain irrelative with bladder filling, haematuria, severe urinary incontinence, prior surgery, pelvic trauma, recurrent urinary tract infections, irradiation, or neurological disorder may prompt for diagnostic cystoscopy and/or urodynamics. A 2-day voiding chart is recommended for all BPS patients. A frequent and low volume (<300 mL) voiding pattern is generally observed.

Urinary Tests and Instrumentation

Standard urine tests and post-void urine should be checked in all patients. A urine culture should be added if the urine test indicated an infection. Routine cystoscopy is not recommended but in the event of clinical suspicion for various situations (e.g., haematuria, unresponsiveness to previous treatment) it should be performed. There are two findings during cystoscopy: Hunner lesions, which are reddened lesions on the bladder mucosa with attached fibrin deposits that typically bleed after hydrodistention; and glomerulations, which are petechial red areas seen during the cystoscopy. In BPS patients these are of limited diagnostic value because they are nonspecific findings (e.g., one study found glomerulations in 45% of healthy patients), and their presence does not correlate well with symptoms.[22,23] An increased number of mast cells may be present on bladder biopsies.

Additional Tests

The potassium sensitivity test is best avoided because of the extreme pain felt during the procedure and the result not being specific to BPS.[24] Instillation of lidocaine to the bladder is also not reliable.

TREATMENT

As BPS is a chronic disorder, after the initial diagnosis all patients must be informed about the unavailability of curative treatment and that the goal is to provide relief of symptoms to achieve a good quality of life. Some studies suggest that BPS has a waning and waxing course with an average improvement over time, but other papers report patients with more improvement.[25,26] These conflicting results from different studies are not surprising because they were produced from different patient populations with varying purposes.

In BPS, initial measures applied to the patients should be patient education, treatment of comorbid diseases, and psychosocial support. The treatment strategy should start from the most appropriate conservative options and proceed to the less conservative therapies if symptom control is not enough. No single therapy is successful and continuously effective in all patients.[27] In order to optimise the quality of life, the treatment method should be tailored to the specific symptoms of each patient until the more effective therapies are available. After a reasonable period of the unsuccessful treatment trial, it is justifiable to advance to the next treatment level assuming consensus between the patient and the clinician. In instances where patients have a more complex presentation and/or have failed response to standard treatment approaches, urologists may need to co-operate with other clinicians such as gynecologists, gastroenterologists, pain specialists, physical therapists, primary care providers, nurse practitioners, and dietitians. Each treatment is individual, and if a patient rapidly develops

worsening symptoms it is wise to proceed to more aggressive therapies.

The American Urological Association (AUA) has issued clinical practice guidelines for the treatment of interstitial cystitis/BPS.[28]

First-Line Treatments

Self-care practices and behavioural modification should be discussed with the patient. Patients should be encouraged to cope with stress and manage stress-induced symptom exacerbations. Application of local heat or cold over the perineum or bladder; avoidance of activities, foods, or drinks that exacerbate the complaints; pelvic floor muscle relaxation; bladder training with urge suppression; fluid restriction; or additional hydration to alter the concentration and/or volume of urine can be recommended.[27,29] Foster et al.[30] reported that 45% of 136 BPS patients treated with these measures had a moderate-to-marked improvement at 12 weeks.

Stress increases BPS symptoms and effective coping with family, work, or post-traumatic experience is an important part of the management.[31] Clinicians should educate the patients about normal bladder function. They should try to explain what is known and not known about BPS and also make short comparisons between the benefits and risks of treatment alternatives. There are two facts that should be emphasised by the clinician: first, that there is no single treatment that is effective for the majority of patients, and second, that symptom control may require trials of various treatment options before seeing marked improvement.

Second-Line Treatments

Many BPS patients experience pelvic floor muscle tenderness and pain so appropriate manual physical therapy techniques may be applied. The benefits of physical therapy have previously been calculated as a 59% response rate in receivers versus 29% in non-receivers.[32] Pelvic floor strengthening exercises like Kegel should be avoided because they may worsen the symptoms.

There are no comparative studies of oral medications for interstitial cystitis/BPS; the choice of agent depends upon the risk of adverse effects and patient preference. Tricyclic antidepressants such as amitriptyline are believed to have analgesic properties and to also relieve the depressive symptoms associated with chronic pain. In a clinical randomised trial, oral amitriptyline (25 mg daily titrated over several weeks to 100 mg daily if tolerated) was reported to be superior to placebo (63% versus 4%) over 4 months.[33] Sedation, nausea, and drowsiness are extremely common adverse effects (up to 79% of patients) of amitriptyline therapy.

Pentosan polysulfate sodium (PPS) has a modest benefit in controlling BPS symptoms according to a randomised clinical study.[28] The proposed mechanism of action of PPS is that it reconstitutes the deficient protective glycosaminoglycan layer over the urothelium. In reality, however, only a tiny proportion of PPS is absorbed by the gastrointestinal tract and excreted in the urine of BPS patients.[34] Multiple randomised controlled trials have reported final outcomes of symptom reduction ranging from 21% to 56% in BPS patients, compared with 13% to 49% of patients under placebo. Adverse effects are not significant and seen only in 10–20% of patients. However, rare serious adverse effects on visual acuities such as metamorphopsia, blurred vision, and prolonged dark adaptation have been reported. PPS-associated maculopathy is a vision-threatening condition that can manifest in the setting of long-term exposure to the drug, and is a situation of ongoing interest in ophthalmology.[35]

Hydroxyzine is the most commonly used antihistamine for the treatment of BPS. The use of antihistamines for BPS is based upon the hypothesis that the pathogenesis process is hypersensitive in this condition. In one study, 23% of BPS patients treated with oral hydroxyzine (10–50 mg daily titration over several weeks if tolerated) for 6 months experienced symptom relief, however 13% of patients under placebo also felt symptom relief. This difference was not statistically significant.[36] Adverse effects (sedation, weakness) are common in up to 82% of patients but not serious.[37]

Cimetidine is used for its anti-inflammatory effect. Two observational studies have reported an improvement of symptoms in 44–57%

of patients at follow-up without significant adverse effects.[38,39]

Dimethyl sulfoxide has a mechanism of action that is thought to be multifactorial, including anti-inflammatory, analgesic, smooth-muscle relaxing, and mast-cell inhibitory effects.[40] Dimethyl sulfoxide is reserved for patients who have failed oral medications. Its use is limited because it is associated with a short-term exacerbation of symptoms and requires multiple hospital visits for bladder catheterisation.

Heparin and lidocaine are also second-line bladder instillation agents offering short-term relief and minimal side effects.

Third-Line Treatments

Cystoscopy under anesthaesia with hydrodistension (60–80 cm H_2O) for a short duration (10 minutes) is an appropriate technique in patients failing more conservative therapies. Observational studies have reported clinical relief to range from 30% to 54% at 1 month, 18% to 56% at 2–3 months, and 0% to 7% at 5–6 months. Significant adverse effects were not reported.[41-43] If Hunner lesions are present during cystoscopy then fulguration treatment should be applied. Post-treatment pain relief in patients is in the range of 75–86%.[44,45] There were no serious side effects but the patients should be informed about the re-treatment for when symptoms recur.

Fourth-Line Treatments

Intradetrusor botulinum toxin Type-A (BTX-A) and neuromodulation are fourth-line therapies for BPS. The mechanism of BTX-A therapy effect for BPS is likely in its ability to modulate sensory neurotransmission. Two studies reported high initial efficacy rates of 74% and 86% at 3 months.[46,47] The treatment effect is temporary and usually diminishes over a year.

The patients who are willing to receive BTX-A treatment should be informed about the potential for chronic urinary retention and also be able to perform self-catheterisation if needed.

The sacral neuromodulation device consists of an implanted lead that lies along a sacral nerve root (usually S3) and is attached to an implanted pulse generator. Alternatively, the lead can be placed to stimulate the pudendal nerve. Observational studies suggest symptomatic relief; however, the rate of re-intervention is high. A small retrospective observational study with an average follow-up of 60 months suggested that treatment of BPS with an implant provides long-term symptomatic relief for most patients; however, this study and another showed a high rate of re-intervention. Reasons for re-intervention included device malfunction, treatment failure, or loss of benefit.[48,49]

Fifth-Line Treatments

The use of oral cyclosporine A has been reported to decrease the symptoms of some BPS patients, especially those with Hunner lesions. This agent is of limited use because of the severity of potential adverse effects, including nephrotoxicity, hypertension, immunosuppression, hair growth, gingival hyperplasia, paresthesias, abdominal pain, flushing, and muscle pain.[50] A randomised trial (N=64) to evaluate this therapy compared 6 months of treatment with oral cyclosporine A (1.5 mg/kg twice daily) to PPS (100 mg three times daily). Cyclosporine A showed significantly better results for improvement on a symptom scale (75% versus 19%) and reduction in urinary frequency (6.7 times versus 2.0 times per 24 hours).[51]

Sixth-Line Treatments

Treatment-refractory symptomatic patients, those with significant loss of life quality, and those that are motivated to undergo irreversible major surgery are candidates for this last-resort treatment. The informed consent process is critical. Carefully selected patients must understand that pain relief is not guaranteed and pain can persist even if the bladder is removed. Substitution cystoplasty and urinary diversion with or without cystectomy are surgical options for this group of patients. Small bladder capacity under anesthaesia and the absence of neuropathic pain are associated with better outcomes.[52,53]

Figure 1 summarises the treatment algorithm; however, all treatment stages should be tailored to the symptomatology of each individual patient at the discretion of the physician. Following the treatment algorithm step-by-step is not mandatory and some steps may be skipped or reversed during the course of the therapy.

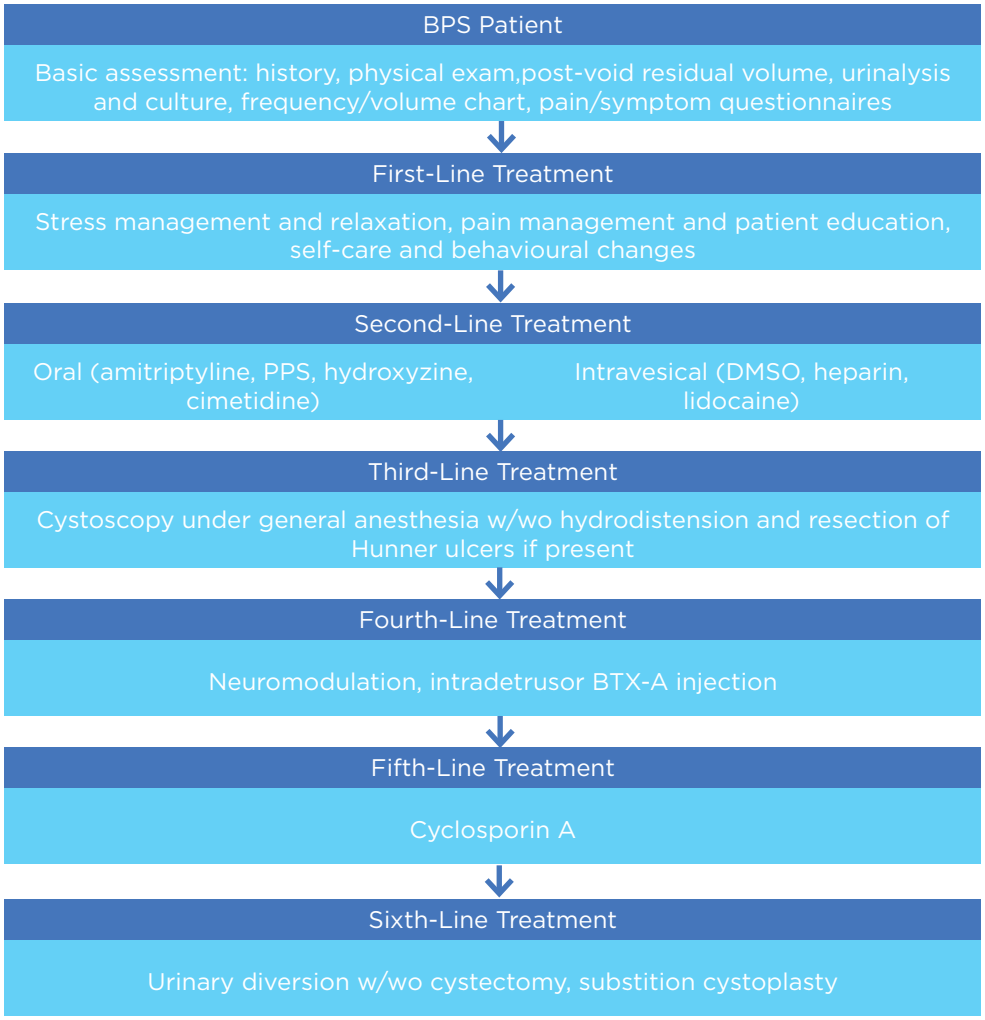

Figure 1: Treatment algorithm for bladder pain syndrome.

BPS: bladder pain syndrome; BTX-A: botulinum toxin Type-A; DMSO: dimethyl sulfoxide; PPS: pentosan polysulfate sodium; w/wo: with or without.

CONCLUSION

BPS is defined as an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of >6 weeks' duration, in the absence of identifiable causes. The characteristics of the bladder pain or discomfort in patients with BPS are variable, but the most common is an increase in discomfort with bladder filling and relief with voiding. BPS is a chronic pain syndrome and the aetiology is not well understood. Focus on biomarkers such as APF is the next area of research.

The initial diagnostic evaluation of most patients with BPS may be performed by a primary care physician. However, certain patients with bladder pain symptoms warrant referral to a specialist, such as a urologist or urogynecologist, for additional diagnostic testing. Treatment is not curative and the goal of management is to provide relief of symptoms to achieve an adequate quality of life. There are many therapeutic approaches for BPS and none are proven to be helpful for all patients. BPS is treated with a step-wise approach guided by individual patient characteristics and the risk for adverse effects associated with each type of treatment.

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Urothelial Carcinoma: Highlights and Reviews on Various Pathologies

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Abstract

Bladder cancers are the ninth most frequently diagnosed cancer worldwide. More than 90% of bladder cancers are of transitional cell origin and are classified as urothelial carcinomas (UC). UC remains amongst the most genetically diverse tumours and presents with numerous unique histological variants. The most common variants are squamous differentiated UC and glandular differentiated UC. Both of these variants tend to present at a later disease stage than conventional UC and are associated with worse patient outcomes. Rarer UC variants include trophoblastic differentiated UC, nested UC, micropapillary UC, plasmacytoid UC, and sarcomatoid UC. They also present at more advanced disease states than conventional UC, resulting in worse patient outcomes. Limited data is available for the pleomorphic giant cell UC and lipid-rich UC variants, but it suggests morbid outcomes with high patient mortality. The only UC variant with better prognosis than conventional UC is lymphoepithelioid-like UC. Proper identification of the histological variant of UC is important, as it aids the physician in clinical decision-making and can lead to better patient outcomes.

INTRODUCTION

The American Cancer Society estimates that there will be 80,470 new diagnoses of bladder cancer and 17,670 deaths from bladder cancer in the USA during 2019.[1] It is the ninth most frequently diagnosed cancer worldwide, of which the highest incidence is observed in men.[2] Most bladder cancers are epithelial in origin, and >90% are classified as urothelial (transitional) carcinoma (UC).[3] UC has a proclivity to differentiate, and the 2016 World Health Organization (WHO) Classification of Tumors of the Urinary System has identified many histological variants (Table 1).[4] The mainstay of treatment for muscle-invasive urothelial malignancy remains neoadjuvant chemotherapy followed by radical cystectomy; however, identifying the proper UC histological variant can guide treatment and provide more accurate prognoses. Urothelial cancer remains amongst the most highly genetically diverse tumours, which leads to substantial variation in histology.[5] With so many variant histologies, many cases require evaluation by a specialised genitourinary pathologist.[6] In this review, the identifying features of common UC histological variants and the expected patient prognoses are discussed. This is not a systematic review of the literature but a highlight of most common variants.

Table 1: Types of urothelial tumours.[4]

Urothelial Tumours
Urothelial carcinoma with divergent differentiation
Squamous differentiation
Glandular differentiation
Trophoblastic differentiation
Nested urothelial carcinoma
Micropapillary urothelial carcinoma
Lymphoepitheliod-like urothelial carcinoma (LELUC)
Plasmacytoid urothelial carcinoma
Sarcomatoid urothelial carcinoma
Pleomorphic giant cell urothelial carcinoma (PGCUC)
Lipid-rich urothelial carcinoma

Table 2: Studies comparing outcomes in squamous differentiation and stage-matched pure urothelial carcinoma.

Study	Patients with squamous differentiation	Cancer stages	Treatment	Significant difference in overall survival?
Nishiyama et al.,[18] 2004	38	All	RC	No
Xylinas et al.,[12] 2013	227	All	RC	No
Monn et al.,[19] 2015	68	All	RC	No
Li et al.,[20] 2017	227	pT1	TURBT	Yes
Sefik et al.,[14] 2018	17	MIBC	RC	No*
Minato et al.,[15] 2018	20	MIBC	RC	Yes
Marks et al.,[21] 2018	62	MIBC	RC	No

*There was a significant difference in postoperative tumour stage and upstaging was more likely.

MIBC: muscle invasive bladder cancer; pT1: primary tumour Stage 1; RC: radical cystectomy; TURBT: transurethral resection of bladder tumour.

UROTHELIAL CARCINOMA WITH DIVERGENT DIFFERENTIATION

UC with divergent differentiation is the most common variant of UC. The 2016 World Health Organization (WHO) classification lists subtypes for squamous, glandular, and trophoblastic differentiation.[4] It is recommended that the percentage of differentiated tissue be included in the pathology report.

Squamous Differentiation and Variants

Squamous differentiation is the most common subtype of UC with divergent differentiation and occurs in 14–40% of all cases of UC.[4,7,8] It is defined by the presence of intracellular bridges and keratinisation.[4] There is an association between human papillomavirus and squamous differentiation but the role of the virus in tumourigenesis is unclear.[9] Immunohistochemical markers for squamous differentiation include p63 (100%), HMCK (100%), CK14 (87%), CK7 (80%), S100P (78%), thrombomodulin (70%), desmoglein-3 (70%), GATA3 (35%), and uroplakin

III (13%).[10,11] The molecular subtype of squamous differentiated UC is basal.[6]

It is widely reported that squamous differentiation is significantly more likely to present with advanced tumour stage, lymph node metastasis, and lymphovascular invasion when compared to pure UC.[12-17] However, it is unclear if patients with squamous differentiation have a worse prognosis than patients with stage-matched pure UC.[12,14,15,18-21] Table 2 shows studies that examine overall survival in patients with squamous differentiation compared to patients with pure UC, and demonstrates inconsistent results. The comparison of squamous differentiation to stage-matched pure UC is interesting from an academic perspective but holds less weight for patients. Squamous differentiation typically presents at a later disease stage, which is associated with a worse outcome.

Partial sampling of squamous differentiation or poorly demarcated squamous differentiation can lead to erroneous classification as pure squamous cell carcinoma.[22] To further blur the lines, the two cancers are histochemically similar. The main difference is the 0% expression of GATA3 in pure squamous cell carcinoma compared to 35% expression in squamous differentiation.[11] Other aspects of a patient's history are usually required to aid diagnosis. For example, pure squamous carcinoma comprises 1.3% of bladder carcinomas in Western countries, but makes up 60.0% of cases where schistosomiasis is endemic.[23] In ambiguous cases, patients are given a diagnosis by a multidisciplinary team based on clinical history and the presence or absence of a clear-cut conventional UC component.[22,24] With increasing options for treatment, including immuno-oncologic therapies along with conventional chemotherapy, further studies will hopefully be directed at identifying the most effective systemic therapy option in these patients.

Glandular Differentiation and Variants

Glandular differentiation is the second most common subtype of UC with divergent differentiation.[4] It is estimated to comprise 6–18% of cases of UC.[6] Glandular differentiation is defined by the presence of glands within UC. The enteric variant of this tumour is easily confused with colonic adenocarcinoma as they may present similarly. Particularly in transurethral resection of bladder tumour (TURBT) specimens arising from the posterior of the bladder or with vesicoenteric fistulae, it can be unclear from which organ the primary malignancy arises. The mucinous variant presents as cells (occasionally signet ring-like cells) floating in extracellular mucin.[4,6,24] Immunohistochemical markers for glandular differentiation include S100P (100%), CK2 (100%), CK7 (90%), HMCK (90%), p63 (60%), GATA3 (50%), and uroplakin III (10%).[11] The molecular subtype of glandular differentiated UC is luminal.[6]

There is limited data regarding prognosis for individuals with glandular differentiation; most studies combine patients with glandular differentiation, squamous differentiation, or both, into one group. When compared to stage-matched pure UC, glandular differentiation +/- squamous differentiation is significantly more likely to present with lymphatic spread at time of diagnosis and extravesical disease at time of cystectomy.[16,17,25] However, the data is variable regarding overall survival in glandular differentiation +/- squamous differentiation compared to stage-matched pure UC. Wasco et al.[16] and Kim et al.[17] examined patients with any stage glandular differentiation +/- squamous differentiation who had received either a TURBT or radical cystectomy and found no difference in overall survival compared to stage-matched pure UC. Xu et al.[25] looked specifically at patients who received TURBT and chemotherapy for non-muscle invasive bladder cancer with glandular differentiation +/- squamous differentiation and found that glandular differentiation +/- squamous differentiation was an independent predictor of recurrence-free survival, but not progression-free survival. In the only study looking specifically at glandular differentiation, Zhao et al.[26] reported that primary tumour Stage 1 (pT1) glandular differentiation patients have significantly higher recurrence and progression rates compared to stage-matched pure UC. They recommend radical cystectomy in recurrent cases.

Trophoblastic Differentiation

Trophoblastic differentiation is a rarer subtype of UC with divergent differentiation. It is defined by the presence of syncytiotrophoblasts, which make human chorionic gonadotrophin (hCG).[4] The syncytiotrophoblasts often have multiple,

large nuclei and an eosinophilic cytoplasm with cytoplasmic lacunae. Immunohistochemical markers for trophoblastic differentiation include the β-subunit of hCG, placental alkaline phosphatase, human placental lactogen, α-inhibin, epithelial membrane antigen, and various CK (1–8, 10, 14–16, 19).[27] The molecular subtype of trophoblastic differentiated UC is unknown.[6]

Due to its rarity, there is little information regarding prognosis for trophoblastic differentiation. Elevated hCG levels may be associated with poor response to radiation therapy and increased rate of disease progression. Survival time is <1 year in most cases.[27]

NESTED UROTHELIAL CARCINOMA AND VARIANTS

Nested UC has been reported in patients aged 42–90 years, but has a propensity for men >60 years-old.[28] The 2016 WHO classifications characterise nested UC as cytologically bland tumour cells which infiltrate as disorderly, discrete, or confluent nests or tubules.[4] The nests are closely packed and have an irregular shape and distribution.[23] The key to identifying nested UC is understanding its infiltrative nature and recognising the irregular epithelial-stromal interface that indicates invasion.[3] Deeper portions of a tumour tend to have more advanced cellular atypia.[23] The 2016 WHO classifications go on to describe a 'large variant' of nested UC, which is not mentioned in the 2004 WHO classifications.[4] Compared to typical nested UC, the large variant has bigger cell nests and more fibrous stromal tissue between nests.[27] Immunohistochemical stains for nested UC include CK7 (100%), p63 (100%), HMCK (100%), S100P (90%), GATA (70%), thrombomodulin (55%), uroplakin III (40%), and CK20 (30%).[11] The molecular subtype of nested UC can be either luminal or basal.[6]

Nested UC tends to present with advanced tumour stage and lymph node invasion.[23,24] Compared to conventional UC, nested UC is associated with a higher incidence of metastatic disease, muscle invasion at TURBT, and extravesical disease at cystectomy.[29] At similar stages, there is similar survival to conventional UC. Linder et al.[30] identified 52 nested UC patients treated with radical cystectomy and found no increased rate of disease recurrence or adverse survival compared to patients with stage-matched conventional UC. Mally et al.[31] identified 30 non-muscle invasive nested UC patients treated with TURBT and found that nested UC metastasises to lymph nodes earlier and presents with a higher rate of upstaging when compared to non-muscle invasive conventional UC patients. However, no significant difference in metastasis-free survival or cancer-specific survival was found. Based on this limited data, early radical cystectomy may be beneficial in patients presenting with non-muscle invasive nested UC.

MICROPAPILLARY UROTHELIAL CARCINOMA AND VARIANTS

Micropapillary UC is an aggressive variant of UC with an estimated prevalence of 0.7–8.0%.[24] The mean age of presentation is 66 years.[27] According to the 2016 WHO classifications, micropapillary UC is morphologically characterised by small nests and aggregates of tumour cells within lacunae.[4] Surface tumours are characterised by filiform processes and papillary tufts, and they may also contain fibrovascular cores. Invasive tumours are often seen in tissue retraction spaces and contain small, tight nests of cells.[27] Tumours that only have micropapillary UC morphology in the surface component are not associated with worse outcomes compared to conventional UC. Accordingly, classification of micropapillary UC requires the invasive component of the tumour to show micropapillary morphology.[6] Immunohistochemical stains for micropapillary UC include epithelial membrane antigen, CK20, Leu-M1, CK7 (100%), S100P (96%), HMCK (96%), GATA3 (86%), CK2 (73%), p63 (54%), uroplakin III (38%), and thrombomodulin (38%).[11,27] The molecular subtype of micropapillary UC is luminal in >50% of cases.[6]

The prognosis for micropapillary UC is poor; 20% of patients present with metastases at time of diagnosis.[27] Some suggest that patient prognosis is linked to the proportion of micropapillary UC within a tumour, but this concept remains controversial.[6,22,23,27] When standard clinicopathologic predictors are controlled for, there is no significant difference in long-term outcomes following radical cystectomy in micropapillary UC patients compared to conventional UC patients.[32] Treatment of

micropapillary UC with bacillus Calmette–Guérin therapy is prone to failure, with many patients going on to develop metastases and few surviving longer than 10 years.[33] A 2019 meta-analysis reviewed treatment outcomes in 3,154 patients with tumour Stage 1 (T1) micropapillary UC and found that while the 5-year cancer-specific survival for TURBT or bacillus Calmette–Guérin therapy was only 60–85%, it was 81–100% for early radical cystectomy.[34] Early cystectomy is generally preferred in this subset of patients.

LYMPHOEPITHELIOID-LIKE UROTHELIAL CARCINOMA AND VARIANTS

Lymphoepithelioid-like urothelial carcinoma (LELUC) of the bladder represents between 0.4–1.3% of all bladder cancers and has been reported in patients aged 44–90.[35,36] Histologically, LELUC has a mixed epithelial composition on a background of inflammatory infiltrate.[37] This infiltrate is normally lymphocyte-dominated but can also be composed of an assortment of neutrophils, eosinophils, lymphocytes, histiocytes, and plasma cells.[38] The mixed epithelial cells form syncytial-like sheets, have prominent nucleoli, and undergo brisk mitotic activity.[39] Despite LELUC having a similar appearance to nasopharyngeal carcinoma, it is not associated with Epstein–Barr virus (EBV) infection.[40] Various stains are used to demonstrate both the epithelial (CK7, CK20, AE1, AE3, EMA, CD46v6) and lymphocytic (CD20, CD21, CD45RO, CD68, CD79a, D33) tumour components.[41]

The scarcity of reported LELUC cases has caused difficulty in defining prognosis and optimum treatment.[35] Several studies have shown that tumours which consist predominantly or purely of LELUC carry a better prognosis than those with only a focal LELUC component. When focally present, the neoplasm behaves like conventional UC of similar grade and stage.[36,42] A pooled analysis of 56 patients concluded that predominant or pure LELUC is amenable to bladder-preserving treatments while focal disease requires radical cystectomy.[35] In the aforementioned study, patients with predominant or pure LELUC that received systemic chemotherapy following TURBT demonstrated a 100% disease-free survival at a median follow-up of 34 months, while patients who received TURBT without systemic chemotherapy had 53% disease-free survival at a median follow-up of 25 months. Platinum-based agents have shown encouraging outcomes; cisplatin was utilised as a primary chemotherapy for three patients with muscle-invasive bladder LELUC, and all three remained free of recurrence after 6 years follow-up.[35]

PLASMACYTOID UROTHELIAL CARCINOMA AND VARIANTS

Plasmacytoid UC tumours are uncommon, although the incidence of plasmacytoid differentiation in muscle-invasive bladder cancer was found to be 2.7%.[43] The age of reported cases ranges from 48–87 years.[27] Plasmacytoid differentiation consists of histologically dissociated cells with eccentrically placed or irregular nuclei, eosinophilic cytoplasms, and occasional eosinophilic perinuclear halos (reminiscent of plasma cells). On top of this plasma cell morphology, single cells with cytoplasmic vacuoles (with or without mucin) impart a signet ring appearance.[6] Loss of epithelial-cadherin, encoded by *CDH1,* has been described in a large cohort of plasmacytoid UC patients, and may account for the decohesion of cells.[6] This infiltration mechanism allows it to permeate the bladder in a linitis plastica-like manner, spreading along fascial planes into the peritoneum, and a 'coat sleeve pattern' along nerve bundles.[44] In tracking a carcinoma capable of such spread, it is important to note that antibodies for CK7 and CK20 confirm this cancer's epithelial origin, and a majority of cells label for CK AE1/AE3, EMA, GATA-3, CD15, p53, and p16.[3] Multitarget fluorescence *in situ* hybridisation has shown plasmacytoid UC tumours to be both aneuploid and polysomic, with deletions on chromosome *9p21* being common.[27]

Plasmacytoid UC has characteristic infiltration that causes it to present with higher tumour stage and greater metastases than conventional UC. It is more likely to be associated with positive surgical margins.[6] Its extensive bladder wall involvement and extension into perivesical soft tissue leads to increased rates of local recurrence, metastatic disease, and cancer-related deaths compared to conventional UC.[45] A diagnosis of plasmacytoid UC carries a poor prognosis; hence, correct diagnosis is essential. Immediate radical cystectomy is typically suggested.[33]

SARCOMATOID UROTHELIAL CARCINOMA AND VARIANTS

Sarcomatoid UC comprises 0.3–0.6% of all bladder cancers.[3,33] The mean age and range of patient ages is 60 and 50–77 years, respectively.[46] These tumours have carcinomatous and sarcomatous components when observed histologically and immunohistochemically.[3,6] Histologically, sarcomatoid UC displays anaplastic spindle cells densely compacted into bundles.[3] The immunoprofile of sarcomatoid UC includes staining for p63 (69%), HMCK (56%), CK7 (56%), GATA3 (30%), S100P (27%), CK20 (6%), PAX8, and CK AE1/AE3.[11,27] Molecular data shows that the carcinomatous and sarcomatous components are derived from the same malignant clone.[3]

Sarcomatoid UC is highly malignant, has poor prognosis, and tends to metastasise widely.[3] A 2014 National Cancer Database study of 489 patients showed that sarcomatoid UC most commonly presents at clinical tumour Stage 2 (cT2) disease and has a median survival of 18.4 months.[47] *TERT C228T* mutations are present in 35% of sarcomatoid UC, and all patients with this mutation died of cancer within 2 years of surgery.[6] Even shorter overall survival may be associated with carcinomas that have myxoid or choroid features.[24] Early cystectomy is recommended for sarcomatoid UC due to higher cancer-specific mortality compared to patients with conventional UC.[33] High incidence of local and distant metastases necessitate the use of follow-up adjuvant chemotherapy and radiation in most patients.[48] Further multicentre research is necessary to establish adequate treatment recommendations.[48]

PLEOMORPHIC GIANT CELL UROTHELIAL CARCINOMA AND VARIANTS

Pleomorphic giant cell urothelial carcinoma (PGCUC) is a rare, aggressive form of bladder cancer that is similar in morphology to giant cell carcinoma of the lung. Its features were not delineated until 2009.[49] PGCUC is composed of giant, anaplastic, and bizarre multinucleated cells that oftentimes form nests, but can also arrange into cords which infiltrate the muscular wall of the bladder.[3] PGCUC occurs more frequently in older males and has been reported in patients aged 55–88 years.[27] Immunohistochemically, PGCUC stains positive for CK7, anti-CK (CAM 5.2), EMA, p63, and GATA3; the literature notes that this means immunohistochemistry plays a limited role in identification.[6]

PGCUC typically presents in combination with other types of UC. In a study of 13 patients with PGCUC, eight had high-grade UC, five had UC in situ, three had micropapillary UC, and one had plasmacytoid UC.[50] PGCUC tends to have lymph node metastases at time of presentation and overall prognosis is poor.[3] In a study of 10 patients by Samaratunga et al.,[50] five died within 1 year, one developed metastases at 17 months, three had recurrent high-grade disease within 3 years, and only one was alive and well at 46-month follow-up. A separate study reported on a group of eight patients with PGCUC; seven of the patients were either dead or alive with metastases at 2-year follow-up, and only one patient was alive and well.[49] Multiple studies suggest that PGCUC represents an extreme de-differentiation of conventional UC, which explains why prognosis is so poor.[49,50] Total excision is an adequate treatment choice.[51]

LIPID-RICH UROTHELIAL CARCINOMA AND VARIANTS

Lipid-rich UC is a rare tumour that has presented in patients aged 42–92 years, with the mean age being 70.[27] Histologically, lipid-rich UC is comprised of lipoblast-like cells with eccentrically placed nuclei and abundant vacuolated cytoplasms.[6] Immunohistochemical stains for lipid-rich UC include CK AE1/AE3 and CK7, and variably include CK20, CAM 5.2, EMA, thrombomodulin, and CK34βE12.[27] Molecular analysis has revealed a loss of heterozygosity patterns at polymorphic microsatellite marker sites *DS9S171*, *D9S177*, *IFNA*, and *TP53*; this suggests a common clonal origin between conventional UC and lipid-rich UC.[6,27,52]

Most cases of lipid-rich UC present at an advanced stage and it may be associated with worse outcomes.[6] In the largest study to date, Lopez-Beltran et al.[6] reported on 27 cases;[52] 40% of patients had lymph node metastases at time of presentation. At 58-month follow-up, 16 patients had died of disease, three died of other causes, and eight patients were alive with the disease. As

there is a limited number of published cases of lipid-rich UC, therapeutic strategies to treating this cancer are unclear.[24]

CONCLUSION

There are many histological variants of UC. Correct identification, while difficult, allows physicians to more accurately inform patients of their prognoses. Lymphoepithelioid-like UC is the only variant that holds a more benign prognosis than conventional UC. Squamous differentiated, glandular differentiated, trophoblastic differentiated, nested, micropapillary, plasmacytoid, and sarcomatoid UC all present at more advanced disease states than conventional UC, resulting in worse patient outcomes. Pleomorphic giant cell UC and lipid-rich UC are rarer disorders but the limited data available indicates high patient mortality. Early identification of the more malignant variants of UC is important as it aids the physician in clinical decision-making and can lead to better patient outcomes.

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