Tuberculosis of the urinary tract and male genitalia – a diagnostic challenge for the family practitioner

Abstract

Tuberculosis (TB) of the urinary tract and male genital system can be very difficult to diagnose unless a high index of suspicion is maintained. The most common presenting features of urogenital tuberculosis (UGTB) are lower urinary tract symptoms (LUTS), haematuria, recurrent urinary tract infection (UTI) by Gram-negative organisms, flank pain, and scrotal swelling. The classically described sterile pyuria should arouse suspicion of UGTB, but in about a third of patients a Gram-negative organism is cultured from the urine, so recurrent bacterial UTI should always be further investigated.

Intravenous pyelography (IVP) remains the best imaging study available to screen for UGTB, but ultrasound and computerised tomography (CT) imaging can also be useful. The diagnosis of UGTB is most often confirmed with urine culture: at least 3–5 early morning urine specimens must be submitted and the results may take 4–6 weeks. Histological diagnosis on bladder or testicular biopsies can be made if granulomatous inflammation and Ziehl-Neelsen (ZN) positive organisms are seen. HIV-positive individuals are at greater risk of acquiring TB, and patients with confirmed or suspected UGTB should always be tested for HIV infection. Medical treatment of UGTB requires combination anti-TB drug therapy for at least six months. Patients should be followed up closely with monthly imaging because upper tract obstruction may develop due to fibrosis while on therapy. Surgery for UGTB can be extirpative (e.g. nephrectomy) or reconstructive (e.g. enterocystoplasty, to enlarge a fibrotic bladder). The outcome of UGTB is good if the diagnosis is made early, but delayed diagnosis may lead to loss of renal function.

Introduction

The Mycobacterium tuberculosis (MTb) bacillus has, since ancient times, been both a “great imitator” and a “mass murderer”. It has been found in animal remains dating back 17 000 years, as well as in Egyptian mummies dated to 3 000 BC.1,2 It is an adversary with many aliases (Table I). In 1882, the microbiologist Robert Koch unmasked the nameless foe and discovered the bacillus that causes tuberculosis (TB). For this achievement he received the Nobel Prize in 1905.

Comprehensive reviews of TB affecting the female genital tract were recently published in this journal and elsewhere.3,4 The most common gynaecological presentation of TB is infertility, but women with TB peritonitis may present with abdominal pain and distension due to ascites, resembling the presentation of advanced ovarian carcinoma.3 The aim of this paper is to review the urological aspects of TB affecting the urinary tract in both sexes, and the genital organs in men.

Epidemiology

In 2006, 9.2 million new cases of TB were reported worldwide, with an estimated 7.7% occurring in human immunodeficiency virus (HIV) infected individuals. India, China, Indonesia, South Africa and Nigeria rank first to fifth in terms of incident cases – they are the top five among the so-called high burden countries (HBCs). Twelve of the top 15 HBCs are in Africa.5 TB is most commonly found among those living in developing countries, where poor socio-economic circumstances provide the ideal setting for the spread of the disease.

The urogenital system is a common site of extrapulmonary TB in adults, but the true incidence of urogenital TB (UGTB) is less clear.6–9 Estimates regarding the incidence of UGTB as a manifestation of non-pulmonary TB vary from 4% to 73%.9–11 Extrapulmonary TB is not rare in children, but UGTB is.12,13 Common sites of extrapulmonary TB in children include the lymph nodes, meninges, gastrointestinal tract, bones and joint spaces.14

Table I: Historical names for tuberculosis

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
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<tbody>
<tr>
<td>consumption</td>
<td>phthisis in Greek – to Hippocrates (460–357 BC) it seemed to consume people from within</td>
</tr>
<tr>
<td>scrofula</td>
<td>(“the King’s evil”) – enlarged, sometimes ulcerating lymph nodes in the neck, once thought amenable to cure by the physical touch of the king of England or France</td>
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<tr>
<td>white plague</td>
<td>paleness of infected individuals, relentlessly wasting away</td>
</tr>
<tr>
<td>tabes mesenterica</td>
<td>abdominal tuberculosis</td>
</tr>
<tr>
<td>lupus vulgaris</td>
<td>cutaneous tuberculosis</td>
</tr>
<tr>
<td>Pott’s disease</td>
<td>thoracic kyphosis caused by tuberculous osteitis, causing vertebral body collapse</td>
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</tbody>
</table>
**Pathobiology**

MTb is transmitted by inhalation of infective droplets coughed or sneezed into the air by a patient with pulmonary TB (PTB). In a host with a normal immune system, primary TB infection stimulates a T-cell-mediated immune response that induces hypersensitivity to the organism. The inhaled bacilli are transported to hilar lymph nodes, where caseous necrosis eventually aids in containing the infection in 90% to 95% of cases. The end result is a calcified scar in the lung parenchyma and in the hilar lymph nodes, together referred to as the Ghon-complex.

Patients with latent PTB are asymptomatic. TB bacilli in this dormant state can be reactivated, or re-infection may occur, leading to secondary TB with granulomas not only in the lungs, but also in distant organs, including the urogenital organs. HIV infection impairs the cellular immune response and renders the host much more susceptible to primary TB infection, as well as reactivation and dissemination of TB bacilli. Autopsy studies indicate that up to 49% of HIV-positive patients harbour TB in their kidneys.

**Kidney**

The kidney is the urogenital organ most commonly affected by TB, usually through haematogenous spread from a focus of infection in the lung. The renal medulla is the preferred site of involvement. Granulomas and caseous necrosis develop and may lead to papillary necrosis due to blood vessel damage and subsequent vascular insufficiency of the renal medulla. Other renal lesions are cavity formation, scarring of the renal pelvis, calcifications and stones. Spread of caseation to the renal pelvis can produce a pyonephrosis-like situation known as “putty” kidney. Nephrocutaneous fistulas may occur.

**Ureter**

Transluminal spread of infection from the kidney is the usual mechanism of ureteric involvement. TB ureteritis causes mucosal and mural granulomatous lesions, which may lead to strictures and obstruction, usually involving the distal third of the ureter. Dilatation of the ureter may be due to obstruction at the ureterovesical junction or vesicoureteral reflux. Advanced characterised by medial displacement and straightening of the ureter, calcification and thickening of the ureteric wall – the so-called “pipe-stem ureter”.

**Bladder**

Up to 75% of bladder involvement is secondary to renal infection, but it may also occur secondary to spread from the epididymis. Infection usually starts around a ureteric orifice, which appears inflamed and oedematous. If left untreated, inflammation will progress to granulations and later ulcers, eventually ending with bladder wall fibrosis. The ureteric orifice may assume a ‘golf-hole’ appearance.

**Prostate**

TB prostatitis can result from TB cystitis, mililiary TB or intravesical installations of Bacille Calmette-Guerin (BCG) for bladder cancer. Approximately 11% of patients with UGTB have involvement of the prostate. The serum prostate specific antigen (PSA) level may be increased and nodules or hard areas may be palpable on digital rectal examination, simulating prostate cancer. Other causes of granulomatous prostatitis are non-specific (usually after transurethral prostatectomy), malakoplakia, or infection with Treponema pallidum, viruses or fungi.

**Urethra**

TB of the urethra is extremely rare, but may occur in both men and women. It may take the form of a mass lesion or nodule or a urethral stricture.

**Epididymis and testis**

When TB involves the male genitalia, the epididymis is commonly affected. Haematogenous spread (specifically to the cauda epididymidis) is the most likely mechanism, and is attributed to its high vascularity. Retrograde spread from the urinary tract is another possibility – TB epididymitis has been described following intravesical BCG installations. Rarely, TB epididymitis may show calcifications. When TB involves the male genitalia, the epididymis is commonly affected. Haematogenous spread (specifically to the cauda epididymidis) is the most likely mechanism, and is attributed to its high vascularity. Retrograde spread from the urinary tract is another possibility – TB epididymitis has been described following intravesical BCG installations. Rarely, TB epididymitis may show calcifications. In advanced disease the entire testis and epididymis may be replaced by a cold abscess, with sinuses to the scrotal skin being relatively common (up to 20%) (Figure 2).

**Penis**

TB of the penis is rare. It may produce an ulcerating lesion similar to penile carcinoma (Figure 3). Penile TB may occur secondary to PTB, but it may also be a primary infection resulting from direct contact, including sexual transmission. The ulcerative lesion may progress with invasion into the corpora cavernosa and corpus spongiosum, or form an abscess. Cutaneous TB can also affect the penile skin, presenting as small indurated lesions called tuberculids.

**Clinical presentation**

Concurrent active PTB at the time of diagnosis of UGTB is present in the minority of cases (9% to 33%). Nonetheless, a history of previous PTB is important – the latent period from primary infection to reactivation of the disease may be decades. Due to its non-specific symptoms, UGTB is notoriously difficult to diagnose, and therefore a high index of suspicion is necessary. The most common presenting features are lower urinary tract symptoms (LUTS) in 11% to 88% of cases and haematuria (usually microscopic) in 15% to 55%. Other symptoms include flank pain, constitutional symptoms, or recurrent urinary tract infection (UTI) by ordinary gram-
negative organisms. A flank mass or pseudotumor may be palpable in the case of a large renal abscess. Extensive TB of the bladder with fibrosis may present with severe frequency and urge incontinence due to a small capacity, contracted (“thimble”) bladder. Scrotal swelling (epididymo-orchitis) not responding to conventional antibiotics or associated with a draining scrotal sinus should arouse the suspicion of TB.

Patients with HIV infection, especially those with CD4+ T-cell counts < 50/μL, are at particular risk of developing PTB as well as UGTB. A high index of suspicion should be maintained in such cases.

Special investigations

Urinalysis is the least invasive method of diagnosing UGTB. The classically described “sterile pyuria” is neither sensitive nor specific enough for UGTB, but persisting sterile pyuria in an individual at risk (endemic area, immunocompromised patient) should increase the clinician’s index of suspicion. Urine Ziehl-Neelsen (ZN) staining for acid-fast bacilli (AFB) is often false negative. Urine culture for TB takes 6–8 weeks for a definitive result, and because the MTb organisms are excreted intermittently, a minimum of three (preferably five) consecutive early morning urine samples (EMUs) must be sent for culture.

Polymerase chain reaction (PCR): Nucleic acid amplification can be used to detect small numbers of MTb organisms in body fluids. Although sputum PCR has been studied extensively, fewer studies have specifically evaluated urine PCR for the diagnosis of UGTB. PCR appears to be more sensitive than urine culture (sensitivity is 37% to 79% for TB culture and 75% to 94% for PCR). Whereas a culture takes about six weeks for a final result, PCR provides confirmation within 24–48 hours. However, PCR is much more expensive than conventional urine culture, and it requires stringent laboratory technique to minimise false negative and false positive results. It is reasonable to consider performing PCR on the urine when the clinician strongly suspects UGTB despite negative microbiological and histopathological investigations. However, it should not be the sole modality for the diagnosis of UGTB.

Histology and cytology: Endoscopic bladder biopsies, transrectal ultrasound (TRUS)-guided prostate biopsies and open epididymal biopsies can be used to diagnose UGTB. The common histological features are granulomatous inflammation, caseating necrosis and the presence of ZN-positive organisms. Fine needle aspiration cytology has also been used with good results.

Imaging

Abdominal X-ray: The most common finding on plain radiographs is calcification of the renal parenchyma, visible in 25% to 50% of patients. The calcifications can be amorphous, granular, curvilinear, triangular, or ring-like in the case of papillary necrosis. Other organs that may show calcifications include the mesenteric lymph nodes, liver, spleen, adrenals, bladder, prostate, seminal vesicles and epididymis. Coexisting findings, such as vertebral body collapse, can sometimes be found (“Pott’s disease”).

Intravenous urography (IVU) may show “moth eaten” calyces, papillary necrosis, renal cavitation, infundibular stenosis, hydrenephrosis, or impaired or absent functioning of a kidney (Figures 4–6). Bilateral radiographic renal abnormalities are seen in 20% to 30% of cases.

The ureter may initially have a ragged and irregular urothelium. Stricture formation due to fibrosis occurs later, or the entire ureter may become shortened, straightened and medially displaced (“lead-pipe ureter”). Early lesions in the bladder resemble the filling defects of transitional cell carcinoma, and a small capacity bladder can be seen in advanced cases (Figure 7).

Computerised tomography (CT) has replaced IVU as the imaging modality of choice in many institutions. It is more sensitive than IVU to demonstrate thickened urinary tract walls associated with UGTB. It also gives additional information on the extent of disease outside the urogenital tract. Contrast-enhanced CT of the prostate demonstrates hypo-attenuating lesions, which likely represent foci of caseous necrosis and inflammation.

Ultrasound is useful in evaluating the scrotal contents. Findings in TB epididymo-orchitis can include multiple small, hypoechoic nodules within the testis, an enlarged, heterogenous epididymis, or an irregular margin between the testis and epididymis. Blood flow to the epididymis is often increased, as measured with colour Doppler. On TRUS of the prostate, the most common finding is hypoechoic lesions with an irregular pattern in the peripheral zone. Ultrasound can also be used in guiding fine needle aspiration of renal and epididymal masses.
Treatment

Medical

Treatment with a combination of anti-TB drugs is the standard of care in the medical management of UGTB. The World Health Organization (WHO) recommends exactly the same treatment regimens for UGTB as for PTB (Table II).56

Generally, TB treatment is the same for HIV-positive as for HIV-negative patients, except that use of the drug thiacetazone is contraindicated, because it is associated with a high risk of severe, and sometimes fatal, skin reactions in HIV-infected individuals. Patients with renal failure can safely take isoniazid, rifampicin and pyrazinamide, but the dosages of streptomycin and ethambutol must be reduced due to renal excretion of these drugs.

Although the recommended standard treatment course for UGTB is six months, some authors advise a longer regimen with an extended continuation phase due to a reported relapse rate of up to 19%, even after 12 months of anti-TB treatment.34 When clinical and radiological suspicion is high, initiating full courses of drug treatment for suspected UGTB in the absence of microbiological or histological evidence is not an uncommon practice.50,57

Patients should be closely monitored after starting anti-TB treatment, as bladder and ureteric lesions heal with fibrosis, which may cause

Figure 6: IVP showing hydronephrosis due to ureteric TB

Figure 7: Cystogram showing a small, contracted bladder due to TB cystitis

Figure 8: Serial IVPs taken 4–6 months apart, in a patient with recurrent UTI, showing TB progressing to hydronephrosis and non-functioning of the left kidney because of delayed diagnosis.

### Table II: Medical treatment of UGTB

**New cases**
- An initial (intensive) phase lasting 2 months consisting of 4 drugs: isoniazid (INH) + rifampicin + pyrazinamide + ethambutol
- A continuation phase lasting 4–6 months consisting of 2 drugs: isoniazid + rifampicin

**Retreatment cases (relapse or treatment after default):**
- Add 1 month duration and 1 drug (streptomycin) to the initial phase
- Add 1 drug (ethambutol) to the continuation phase
progressive upper urinary tract obstruction (Figure 8). Renal ultrasound or excretory urography should be performed after four weeks of treatment, and upper tract dilatation should be managed with insertion of a percutaneous nephrostomy or double-J ureteric stent. Patients should be followed up monthly during treatment to ensure compliance with medication, and urine should be sent for TB cultures to detect resistant MTB organisms.

Drug-resistant UGTB appears to be rare, but there seems to be an increasing incidence in areas with a high HIV/AIDS prevalence. Multidrug-resistant TB (MDR-TB) refers to MTB isolates that are resistant to both isoniazid and rifampicin—the two most powerful anti-TB drugs. The incidence of MDR-TB is increasing: in 2006 there were an estimated 0.5 million cases. Extensive drug-resistant TB (XDR-TB) is defined as MDR-TB that is resistant to at least one of the injectable second-line drugs: kanamycin, capreomycin and amikacin.

Patients with proven or suspected MDR UGTB ideally need individualized treatment regimens that include drug susceptibility testing (DST). Drugs used in the management of MDR and XDR-TB include kanamycin, amikacin, capreomycin, streptomycin and the quinolones: moxifloxacin, levofloxacin and ofloxacin.

Surgical

Surgery is usually reserved for managing the complications of UGTB, and up to 50% of patients may require surgical intervention.

Upper tract obstruction (hydronephrosis) requires urgent drainage by means of a percutaneous nephrostomy or double-J ureteric stent. Patients should be followed up monthly during treatment to ensure compliance with medication, and urine should be sent for TB cultures to detect resistant MTB organisms.

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