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Leading Article

Genitourinary tuberculosis

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Introduction

Although tuberculosis (TB) was known to have existed for more than 7000 years, the term genitourinary tuberculosis (GUTB) was coined only in 1937. It is credited to Wildbolz who showed that renal and epididymal TB were local manifestations of the same blood-borne infection (1).

About 8 million new cases of TB occur each year and about two million die of the disease annually (2). Hence control of TB is included in the millennium development goals to draw attention of the public as well as the authorities to this worldwide scourge. Accordingly the governments should take steps to halt and reverse the incidence of TB by 2015. The long-term goal of the Sri Lankan government and the National Programme for Tuberculosis Control and Chest Diseases (NPTCCD) is to eliminate TB, defined as less than one case per million population by 2050. In Sri Lanka 7000 new TB cases were reported in 2008 with 392 fatalities (3).

Though more than 90% of the cases and deaths due to TB occur in the developing world the incidence is rising in the developed world due to the emergence of HIV infection and increased number of transplants (4). This has drawn attention of the rich countries for funding of research and preventive measures related to the TB pandemic. The whole consignment of anti TB drugs necessary for Sri Lanka is given as a grant by the Global Drug Facility (GDF).

GUTB is the second most common form of extra-pulmonary TB in most countries. But according to the figures of the NPTCCD, the reported rate of GUTB is very low in Sri Lanka. In 2007 there have been 1966 cases of extra-pulmonary TB reported in Sri Lanka. But only 4 cases of GUTB were recorded by the NPTCCD. This may be due to deficiencies in reporting and documentation. Properly instituted chemotherapy is the best way to break the transmission of TB. Therefore the best way to prevent TB is to detect and treat cases effectively. To achieve this, directly observed treatment (DOTS) is practiced in Sri Lanka. This minimises the default rates of TB therapy. Multi-drug resistance is caused by poorly managed TB treatment and DOTS may help to effectively control this emerging menace.

Historical background

Tuberculosis has been known for many centuries. In 375 BC, Hippocrates described 'pthisis', a lingering disease with emaciation and diarrhoea (5). In 1761, Morgagni described a 15-year old boy with renal and retroperitoneal disease that was allegedly caused by TB. In 1882, Robert Koch isolated the tubercle bacillus. In 1883, Babes and Rosentein identified *Mycobacterium* in urine. Surgical treatment for GUTB was introduced in the latter part of nineteenth century. In 1870 Bryant performed the first nephrectomy for a pyelonephritic kidney. Initial high mortality following nephrectomy was reduced to about 10% around 1910. The occurrences of fistulae from the residual ureteric stumps lead to the first nephroureterectomy in 1895 by Howard Kelly.

Before the era of antimicrobials medical treatment of TB consisted of a long term stay (about one year) in a sanitarium with strict bed rest with passive exercises, controlled sunlight, well balanced diet and body massage (6). The antimicrobials for TB were introduced in the second half of the twentieth century. Introduction of rifampicin in 1966 was a turning point in the history of anti TB treatment.

Pathology

Almost all infections due to *Mycobacterium tuberculosis* are acquired by inhalation of the organism. The probability that a person will become infected depends on the duration of exposure to the index case, the size of the bacillary inoculation inhaled, the infectivity of the mycobacterial strain and the immunity of the host. The chance of a competent host developing active TB after *M. tuberculosis* infection is 5% to 10% over the person's lifetime (7). Up to 50% of the active disease occurs within 2 years of infection.

Like other forms of TB, GUTB is also caused by the members of *Mycobacterium tuberculosis* complex. The development of the disease and its progression depends on the interaction between the pathogen and the immune response of the host. Although the organism evokes both a humoral and a cellular immune response, cellular response determines the outcome of an infection.

GUTB results from blood stream spread of *M. tuberculosis* from the lungs. This happens about 10-15 years after the initial pulmonary inoculation. Therefore GUTB is rare in children (8). GUTB is rare among people under the age of twenty five, and these patients are more likely to have a family history positive for TB (9). Generally the bacillus infects one kidney and the disease progresses slowly. There is slow destruction of renal parenchyma with cavitation, abscess formation, fibrosis and calcification. Fibrosis leads to calyceal deformities, obstruction and tissue loss. Rarely, it produces a diffuse glomerulonephritis with acute renal functional impairment. Generally the symptoms of renal involvement are minimal. If not identified and treated the disease spreads down along the ureter into the bladder. The ureteric involvement and fibrosis leads to ureteric stenosis and stricture formation particularly at the vesico-ureteric junction and pelvi-ureteric junction. Once the bacilli enter the bladder the inflammatory process starts and leads to storage (irritative), urinary symptoms (e.g. frequency, nocturia, urgency), lumbar pain and haematuria. If it is still not treated, the bacilli ascends the contralateral ureter up to the other kidney.

Epididymal tuberculosis is almost a separate entity and the organisms reach the epididymis via the blood stream. Therefore most instances epididymal TB is an isolated finding without urinary tract involvement. Few cases of epididymal TB have been reported where the infection occurred by direct retrograde spread of the organism or via lymphatics from the urinary tract. But these modes of spread are rare. Though epididymal TB is common, testicular involvement is rare. Most patients with epididymal TB have a normal testis. Therefore even after the vasal involvement and blockage causing subfertility, sperms can be retrieved from the testis for purpose of artificial insemination (10). Since the obstruction is close to the epididymis, reconstruction is difficult and results are poor. In India about 2% of subfertile men have vasal obstruction due to TB (11).

Tuberculous involvement of the prostate is rare in Sri Lanka. Only one contemporary urological surgeon in Sri Lanka has come across a single case where prostatic chips after TURP became positive for TB (12). Spread of the organism to the prostate is also via the blood stream in most patients (13). Direct spread from the urinary tract is possible but rare. The transmission of genital TB from male to female is very rare. Occasional reports of pelvic tuberculosis in the sexual partner of patients with epididymal TB suggest the possibility of female to male sexual transmission (14). TB of the penis is extremely rare. Primary TB of the penis occurs after coital contact with organisms already present in the female genital tract or by contamination from infected clothing (15). Blood stream spread also has been reported.

Clinical features

The symptoms of GUTB are non-specific. Hence a clinical diagnosis is almost impossible. Any symptom related to urinary tract can be due to GUTB! Tuberculous infection in the past as primary pulmonary TB or extra-pulmonary TB gives an important clue. Storage symptoms not responding to antibacterial treatment associated with haematuria, occurring from time to time is a common presentation of GUTB.

Tuberculous involvement of the epididymis presents as a solid mass in the scrotum. The commonest lump related to the epididymis in clinical practice is the epididymal cyst which is soft, fluctuant and transilluminant. It can be differentiated from a solid mass of TB easily by clinical means. In most cases the testis can be felt separately and is normal. If longstanding, tuberculous epididymitis may rarely progress to sinus formation.

Constitutional symptoms like night sweats, evening pyrexia and malaise are rare in GUTB. The commonest age group where GUTB is seen is 20-55 years. In this age group presence of vague, longstanding urinary symptoms for which there is no obvious cause should raise the suspicion of GUTB. It is important to realise that GUTB is not a disease of the very old, frail people who are cachectic and severely ill.

Persistent pyuria is characteristic of GUTB. But GUTB is not the commonest cause of sterile pyuria. Partially treated urinary tract infections with or without bladder outlet obstruction and urolithiasis are the common causes of sterile pyuria. However, once bladder outlet obstruction leading to recurrent urine infections and urolithiasis are excluded, one has to think of GUTB if the pyuria continues. At the same time it is important to remember that up to 20% of patients with GUTB may not have any leucocytes in the urine.

It is important to remember that GUTB is non-infective if there is no concomitant lung infection.

Investigations

Microbiology and laboratory diagnosis

A microbiologic diagnosis of TB is made by isolation of the organism from urine or biopsy material on conventional solid media. Detection of acid-fast bacilli from urine samples by Ziehl-Neelsen stain is not reliable to make a definitive diagnosis due to the possible presence of *M. smegmatis* which are acid-fast bacilli too. However, it helps to screen suspected cases. At least three (some even suggest five) early morning samples (the whole urine sample voided first in the morning) should be sent for examination. For the acid-fast bacilli to be positive at least 10,000 bacilli/ ml should be present in urine. Since GUTB is a pauci-bacillary disease, false negatives with urine microscopy are common.

Culture of *M. tuberculosis* from urine or biopsied tissues is the gold standard in diagnosis of GUTB. The traditional methods take 6 weeks to yield results (Lowenstein-Jensen or Dubos media). However, there are newer automated techniques which are capable of giving the results within hours (BD ProbeTec ET System) (16). These are expensive and use specialised techniques (e.g. radiometry) to identify tiny colonies which cannot be seen by the naked eye. Quinolones (e.g. ciprofloxacin) can destroy the *M. tuberculosis* and should be avoided during the period when urine samples are collected for diagnostic purposes.

Nucleic acid replication techniques such as polymerase chain reaction (PCR) are used commonly to detect *M tuberculosis* in urine. Few studies done specifically to evaluate the success of PCR in detecting mycobacterial DNA in urine have shown satisfactory sensitivity and specificity (17, 18). Though the reported sensitivity and specificity rates of around 60% are good enough when compared with other tests to diagnose GUTB, clinicians who have to take decisions on individual patients may not be happy with these rates.

Utilisation of serum interferon (IFN) assays provides immunological evidence for tuberculosis exposure. This is useful in immunocompromised patients (e.g. end-stage renal disease, post-transplant patients) where tuberculin skin test is not useful (19). Positive IFN-gamma assay results (QuantiFERON TB Gold test and ELISPOT) may help the diagnosis of GUTB in such patients.

One drawback of laboratory investigations for the diagnosis of GUTB is the difficulty for the laboratory staff to get adequate experience necessary to gain expertise and for quality maintenance. This is due to the small number of samples received by a single laboratory during a given period of time since GUTB is not a very common disease. This is true for laboratories both in the government and private sector but more so with the private sector labs and with newer and expensive techniques.

Tuberculin test

The tuberculin test (Mantoux test) is done by intra-dermal injection of a purified protein derivative of tuberculin. A strongly positive (more than 20 mm) test is very useful in the diagnosis of GUTB. If the Mantoux test is over 15 mm, one has to pursue for TB relentlessly. However, a normal tuberculin test should not exclude a diagnosis of GUTB, especially epididymal TB. Mantoux test is negative in most patients with epididymal TB.

Radiology

Plain X-ray KUB is useful in patients with calcifications. Any unusual pattern of calcification should raise the suspicion of GUTB. Calcification of the renal paren-chyma develops in about 25% of patients with renal tuberculosis. Calcification due to tuberculosis is ill-defined, diffuse and does not fit into any pattern (20). Calcification does not mean inactive infection and need proper evaluation and treatment.

In spite of newer radiological investigations like ultrasound, CT scan and MRI, IVU continue to be the key investigation in the diagnosis of GUTB. Approximately 90% of patients with urinary tract TB cause abnormalities in the IVU. Renal lesions may appear as distortion of a calyx, as a calyx that is fibrosed and completely occluded (lost calyx), as multiple calyceal deformities or as severe calyceal or paren-chymal destruction and non-visualised kidneys. The IVU will demonstrate ureteric strictures when present. The cystogram is important in defining the changes in the bladder such as small capacity, irregular outline or vesicoureteric reflux.

Ultrasonography may detect changes associated with parenchymal involvement (e.g. calyceal dilation, cavities) but its main role is in percutaneous nephro-stomy in obstructed kidneys due to ureteric stenosis. CT is helpful in identifying small intrarenal lesions (scarring, masses and cavities) and autonephrectomy. Retrograde uretero-pyelography is useful to delineate the site and length of a ureteric stricture. Ureteral cathetrisation can be used to collect urine samples for culture from each kidney and the yield rates may be higher than ordinary voided samples.

Cystoscopy

Cystoscopy will show extensive inflammatory changes in the bladder in the presence of tuberculous cystitis.

Late cases show the classical 'golf hole' ureteric orifice due to scarring and contraction. However, bladder biopsy is to be avoided in the presence of tuberculous cystitis (21). The possibility of spreading the organisms to vertebrae via the venous plexus is given as the reason for this. This may cause tuberculous meningitis and spinal TB. This phenomenon has been described many decades ago and its relevance today is not very clear due to paucity of data refuting or supporting it.

Biopsy and histopathology

Biopsy specimens or resected ureteric strictures sent for histopathology show caseating garnulomas with Langhan's giant cells in TB. This will confirm the diagnosis in cases where the microbiology has failed. Recently several case reports have appeared where patients from south Asian and middle eastern countries presenting with renal impairment and a clinical picture of acute glomerulonephritis were found to have renal TB on their renal biopsy specimens (22). Most of them have responded well to anti TB drugs and the renal functions returned to normal.

Erythrocyte sedimentation rate

Traditionally ESR is considered a useful test in helping the diagnosis of TB. In GUTB majority of patients will have a ESR less than 50 mm. This is especially true in epididymal TB.

Treatment

Pharmacological treatment

Since GUTB is a pauci-bacillary form of TB, a six-months course of anti tuberculous drugs is adequate. In Sri Lanka now the drugs are given under direct supervision by health staff (DOTS) except in certain areas of the Northern province. Isoniazid (INAH), rifampicin, ehambutol and pyrazinamide are given for the initial two months (intensive phase). Isoniazid and rifampicin are given for the next 4 months (continuation phase). Now drugs are given in combination forms and this has improved the compliance. In complicated cases (e.g. recurrence of TB, HIV infection, immuno-suppression) longer courses (9-12 months) are recommended. Some believe drug regimens without streptomycin have lead to more renal scarring in patients who complete the anti TB treatment (23). However, there is no substantial data to prove this.

Steroids (along with ureteric stenting) have been tried in patients with ureteric stenosis to minimise late scarring and stricture formation until the effects of chemotherapy becomes established (24, 25). But the results have been disappointing. Almost all patients with ureteric stenosis and dilatation of the proximal urinary tract require reconstructive surgery later. If steroids are used, it is important to remember the necessity to adjust the doses in the presence of rifampicin which induces enzymes that metabolise steroids.

A serious problem at present is the occurrence of drug resistance in patients with TB. Multi-drug resistance (MDR) TB is defined as resistance to rifampicin and isoniazid with or without resistance to other drugs. Such patients require second line drugs which are less effective and more toxic. MDR is a growing problem of serious concern and at present those who contract MDRTB are destined to die of the disease. In 2007 Sri Lanka had 8 cases of MDRTB. Fortunately only one case of MDRTB was reported from Sri Lanka in 2009.

Hepatotoxicity is a major concern with anti-TB drugs. All patients should be observed for occurrence of jaundice. If jaundice occurs, expert help should be sought. It occurs in about 10-20% of patients and can be fatal.

Special considerations apply to the treatment of TB in patients with renal impairment. Rifampicin, isoniazid and pyrazinamide can be given in normal dosage. These are eliminated in the bile or broken down to metabolites that are not excreted by the kidney. Dose adjustment (according to the GFR) is required in the use of ethambutol. It is widely excreted by the kidneys. Ethambutol causes optic neuritis which may be irreversible. Encephalopathy is an uncommon complication of isoniazid and can be prevented by pyridoxine 50 mg per day.

Surgical treatment

Although chemotherapy is the mainstay of treatment, about 50% of patients with GUTB will require some form of surgical intervention at some stage of the disease. Half of them would require ablative surgery while the other half would require reconstructive surgery. Ablative surgery may be necessary in the initial management of GUTB to control sepsis or to treat abscesses. Nephrectomy is indicated if there is uncontrollable urinary tract sepsis, expanding calcification and hypertension attributed to the diseased kidney. Almost all these are non-functioning kidneys.

Main forms of reconstructive surgery are ureteric reimplantation (after excision of stricture) and bladder augmentation (for a small fibrotic bladder). Both ablative and reconstructive surgical procedures are recommended to be done after about 4 weeks of drug treatment within the intensive phase. Early ureteric stenting or percutaneous nephrostomy may be indicated if the kidney is obstructed and patient has not yet completed 4 weeks of treatment.

The ureteric strictures are commonly situated in the lower end at the uretero-vesical junction. It can occur in the upper end or in the mid ureter less commonly. Pelvi-ureteric junction obstruction can be treated with usual techniques of pyeloplasty (e.g. Anderson-Hynes or Culp). Lower end strictures require reimplantation, while the mid-ureteric strictures can be reconstructed by direct end to end anastomosis if the stricture is short. Otherwise it may be necessary to raise a Boari flap. Endoscopic dilatation of strictures has very low success rates and may jeopardise the kidney function. All TB strictures require reconstructive surgery.

Follow up

M. tuberculosis is an organism with very destructive capabilities. Its destructive nature is slow but long-standing. Even after making the urine free of organisms, tissue fibrosis and scarring may progress. Hence these patients with GUTB should be followed up carefully to identify the complications secondary to persisting tissue fibrosis.

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