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Genitourinary Tuberculosis: Diagnostic challenges and therapy

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Abstract: Urinary tract infections are among the commonest bacterial infections. Genitourinary tuberculosis must be suspected in patients with long-standing urinary symptoms and sterile pyuria. There are myriad presentations of this disease and there is intermittent shedding of tubercle bacilli in the urine in small numbers. Diagnosis by staining for acid-fast bacilli and mycobacterial culture may not always be rewarding. The use of molecular assays, computed tomography and magnetic resonance imaging may aid in the diagnosis. Treatment with antituberculous drugs is usually effective; however, some patients may require surgery.

Introduction

Urinary tract infections (UTI) are *among* the commonest bacterial infections encountered worldwide. Approximately 10% of humans have UTI at some time during their lives.[1] UTI is an inflammatory response of the urothelium to bacterial invasion, which is usually associated with bacteriuria (bacteria in the urine) and pyuria (presence of eight or more leucocytes cmm on microscopic examination of uncentrifuged urine). Depending upon the anatomical location of the infection, these can be either an upper UTI (ureter and kidney) or lower UTI (bladder, urethra, prostate and epididymis). UTI can also be classified as uncomplicated or complicated. Uncomplicated infections occur in healthy females and occasionally in infants and young males without any structural or neurological dysfunction. They readily respond to antibiotics to which the aetiological agent is susceptible. Complicated infections occur in both the sexes, who may have certain risk factors including underlying disease (diabetes, sickle cell anaemia), stones in the kidney structural or functional abnormalities of the urinary tract and indwelling urinary catheters. Complicated infections are more difficult to treat and have a greater morbidity and mortality than uncomplicated ones.

Types of urinary tract infections

There are four major types of UTI: urethritis, cystitis, acute urethral syndrome and pyelonephritis.

Urethritis : The symptoms include dysuria and frequency. Common causative organisms include *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Trichomonas vaginalis*.

Cystitis : Patients with cystitis present with dysuria, frequency, urgency and suprapubic pain. There may be tenderness over the bladder area due to mucosal inflammation of the bladder. Systemic signs are usually not present.

Acute urethral syndrome : Patients with this syndrome are young, sexually active women, who experience dysuria, frequency and urgency, but yield fewer than 10^5 colony forming units/ml in their urine. Most of these patients have pyuria.

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Pyelonephritis : Infection of the kidney parenchyma, pelvis, calyces, usually caused by bacterial infection, is called pyelonephritis. The clinical presentation includes fever, flank pain, frequency, urgency and dysuria. Systemic signs of vomiting, diarrhoea, chills, tachycardia and abdominal pain may be present. Forty per cent of these patients will be bacteraemic.

Patients with vague, long-standing urinary symptoms and sterile pyuria for which there is no obvious cause should be suspected to have genitourinary tuberculosis (GUTB).

GENITOURINARY TUBERCULOSIS

Tuberculosis (TB) has been observed in humans for more than 7000 years and continues to remain one of the world's most deadly infectious diseases. The World Health Organization (WHO) has declared TB to be a global emergency with approximately 3 million people dying each year, the majority of whom live in the developing countries.[2] In the western world, GUTB develops in 8%-10% of patients with pulmonary TB, compared with 15%-20% in developing countries.[3] GUTB is estimated to comprise almost 30% of non pulmonary TB.[4] The incidence of female genital TB is almost 10.3% in India.[5]

PATHOGENESIS

During the initial primary pulmonary infection, the microorganism *Mycobacterium tuberculosis* multiplies and evokes an inflammatory reaction. Progressive renal TB results from haematogenous seeding of the renal cortex to form small caseous foci that spread to the medulla, and a progressive caseous ulcerative lesion develops. Involvement of the adjacent renal papillae follows and spread to the lower urinary tract ensues.[6] The healing process results in fibrous tissue and deposition of calcium salts. The fibrous tissue involving the drainage system may cause strictures in the calyceal system or at the *pelviureteral* junction (PUJ) or ureter. Bladder

involvement is usually secondary to renal TB. Infection starts around one or another ureteral orifice with inflammation. The inflammation is replaced by fibrosis that starts around the orifice, which contracts and can produce a stricture or become withdrawn and rigid, assuming a golf hole appearance. TB of the testis, epididymis, penis, scrotum and prostate is almost always secondary to infection of the kidney.

In women with genital TB, the fallopian tube is involved in more than 90% of cases. Endometrial involvement is secondary to tubal involvement.[7] The ovaries, cervix, vulva and vagina may also be involved.

CLINICAL FEATURES

The predisposing factors GUTB include immune suppression, exposure to an active case of TB, diabetes mellitus, chronic renal failure, malignancy and organ transplantation. Males are more often affected than females (male to female ratio 2:1). The manifestations of GUTB can be variable (Table 1).[8]

Table 1. Clinical manifestations of GUTB.

Organs involved	Clinical manifestations
Kidney	Frequency, pyuria, haematuria, colic, renal failure, flank pain
Ureters	Ureteral colic
Urinary bladder	Pyuria, frequency, dysuria, urgency, suprapubic pain
Prostate and urethra	Urethritis, prostatitis
Male and female reproductive system	Infertility
Penis	Penile ulcers
Scrotum	Scrotal mass
Female genital tract	Menstrual disturbances: menorrhagia or secondary amenorrhoea, pelvic pain, vaginal discharge and abdominal masses

DIAGNOSIS

Microscopic examination of the urine usually reveals pyuria and red blood cells. Sterile pyuria is the classic urinary finding. Secondary bacterial infection is seen in 20% of cases and may lead to misdiagnosis.

Mycobacteria are shed intermittently in the urine and are present in small numbers. Hence, it is essential to evaluate 3-5 early whole morning urine samples. After thorough cleaning of the genitalia, the first early morning whole sample of the urine should be collected in sterile containers. Each specimen of urine should be inoculated as soon as possible after collection, because the longer the urine remains in contact with organisms, the less likely they are to remain viable.[9] Urine samples from each kidney can be separately collected by ureteric catheterization, which helps localize the infection. A minimum of 50 to 100 ml of whole morning urine is centrifuged (4000 *g* for 30 min), and the deposit is used for staining and culture. A prostatic massage may increase the yield of acid fast bacilli (AFB) in the seminal fluid. Uterine curettage, cervical biopsy or laparoscopic biopsy is used for the diagnosis of female genital TB. Endometrial curetting is performed shortly before menstruation.

The two commonly used stains are the Ziehl-Neelsen and Auramine-Rhodamine stains, the latter being a more sensitive[10] and valuable technique (Table 2).

Table 2. Comparison of Zich-Neelsen stain and direct fluorescence[11]

Sample	Positivity (%)	Direct fluorescence positivity (%)
Respiratory samples	60	74
Pus, tissue	43	87
Urine	40	48
Overall positivity	50	70

CULTURE

Culture still remains the 'gold standard' for the diagnosis of mycobacterial infections. This is more sensitive than staining techniques, and allows for exact identification of the mycobacterial species and its sensitivity pattern. The urine sediment obtained after centrifugation is first decontaminated with 4% sodium hydroxide and then inoculated on the desired culture media (Table 3). For maximal recovery, one liquid and one solid media are recommended. Conventional culture techniques take 4-6 weeks for growth while the automated methods take 10-14 days. In general, the rates of recovery of mycobacteria do not differ considerably among the different automated systems and are higher for solid media.[12]

Table 3. Conventional and automated culture methods

Conventional Methods		
Egg-based solid media	Lowenstein Jensen medium	
Agar-based media	Middlebrook 7H10, 7H11 medium	
Broth media	Middlebrook 7H9, Dubos Tween albumin broth	
Automated/semiautomated		
Biphasic medium	Septichek system	Becton-Dickinson
Radiometric	BACTEC 460 system	Becton-Dickinson
Non-radiometric	MB/BacT system	BioMerieux
Fluorescence	MGIT, BACTEC 9000MB	Becton-Dickinson

Due to the paucibacillary nature of the disease, smears are often negative and cultures are positive in 10%-90% of the patients.[8] In a 10-year retrospective study by Mortier *et al.*[13], 7200 midstream morning urine specimens obtained from 2814 patients with a presumptive diagnosis of tuberculosis were inoculated onto Lowenstein-Jensen medium. Only 33 patients (1.2%) yielded positive cultures for *M. tuberculosis*. Of these 33

patients, 22 presented with pulmonary tuberculosis and 7 patients had tuberculosis limited to the genitourinary tract as diagnosed by clinical signs and symptoms.

IDENTIFICATION

It is important to differentiate organisms belonging to the *M. tuberculosis* complex from non-tuberculous mycobacteria, since the treatment modalities differ between these two groups. Species identification is done by conventional biochemical tests.[14] The NAP (p-nitro–α-acetylamino–b-hydroxy propiophenone) test, high-performance liquid chromatography, gas liquid chromatography and nucleic acid probes (Accuprobe- Genprobe) can be used to identify isolates from culture.

MOLECULAR METHODS

Nucleic acid assays (NAA) include the *Mycobacterium tuberculosis* direct (MTD) test, AMPLICOR MTB assay, nucleic acid sequence based assay (NASBA), transcription-mediated assay (TMA), strand displacement assay (SDA), and the ligase chain reaction (LCR). However, two NAA tests, the MTD (Genprobe BioMerieux) and AMPLICOR (Roche), have been cleared by the US Food and Drug Administration (FDA) for direct use in smear positive respiratory samples. Genprobe has also been approved for smear negative samples. NASBA and TMA detect rRNA in the samples, which is more abundant than DNA; this also gives added information about the viability of the organism. The inability of polymerase chain reaction (PCR) to differentiate between live and dead organisms renders it inappropriate for monitoring patients while on therapy. Moussa *et. al*.[15] found PCR to be a highly sensitive (95%) and specific (98%) tool for the rapid diagnosis of GUTB. Fontana *et al*[16] performed the MTD on 95 patients, comprising 35 subjects with a high index of suspicion for GUTB and 60 subjects with evidence of non-mycobacterial disease. Assuming culture as the reference standard, the sensitivity, specificity, positive and negative predictive value of MTD were 100%, 91.93%, 86.84% and 100%, respectively.

SEROLOGY

In India, a positive tuberculin test is of not much value in our environment where nearly half the population has been exposed to TB and neonatal BCG is actively promoted. The results of seroassays must not be taken as the sole evidence of presence or absence of tubercular disease. There is no single seroassay having a reasonable amount of sensitivity and specificity.[10]

ANTIMICROBIAL SUSCEPTIBILITY

The Centers for Disease Control (CDC) recommends that all initial isolates from patients should be subjected to drug susceptibility testing, which should be repeated if the patient remains cultures positive after 3 months of receiving adequate therapy or if the patient does not respond to therapy.[17] Conventional susceptibility test methods include the resistance ratio and the proportion method, the results of which are obtained after 3 weeks. The rapid testing systems include the radiometric BACTEC 460 system, MGIT, MB/BacT, 3D system and the ESP culture system. These systems allow the sensitivity results to be available within 15 days. Various molecular techniques for detection of the *kat G* and *rpo B* gene are also used to predict resistance.

HISTOPATHOLOGY

Histopathological examination of the tissue obtained by biopsy may show the typical granuloma formation along with Langhans giant cells (Fig. 1). Diagnostic cystoscopy does not have much role in GUTB and biopsies of the bladder do not reveal tuberculosis in most of the cases unless the disease is far advanced.

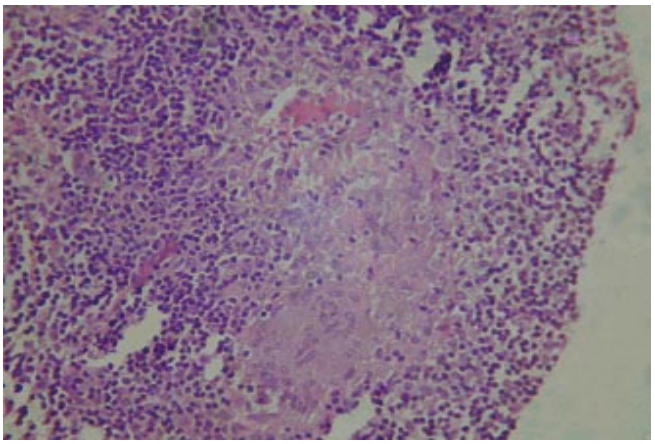

Fig.1. Photomicrograph (100X) of the endometrium showing typical granuloma formation

RADIOGRAPHY

The earliest radiographic findings of GUTB may demonstrate changes in the minor renal calyces with loss of sharpness and blunting.[8] Renal calcification may develop in 7%-14% of patients.

Ultrasound is done in all cases. If ultrasound shows any back pressure effects, then an intravenous urography is done to further define the problem and document the renal function Computed tomography (CT) scan (Fig. 2) is markedly superior in demonstrating parenchymal abnormalities caused by renal infection and delineating the extent of disease.[18] CT Scan also gives the functional status of the affected kidney. Magnetic resonance imaging helps to differentiate macronodular tubercular lesions from other mass lesions.[19] Retrograde pyelography is only necessary to define the ureters and proximal dilatation, if that has not been demonstrated by intravenous pyelography (IVP) and is always done before the procedure of double J stenting. Sometimes a selective sampling of urine is required, and ureteric catheterization can be done. Angiography is useful when focal lesions mimic a primary renal

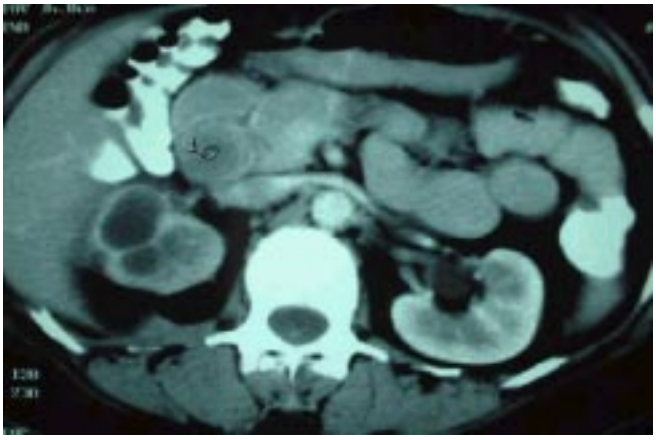

Fig.2. Contrast-enhanced computerized tomography (CECT) scan showing multiple abscesses caused by tuberculosis in the right kidney

mass or when partial nephrectomy is planned. Angiography also shows obliterated interlobar arteries and avascular lesions. Renal nuclear scan findings are nonspecific, but they can be used to assess the function of the kidney and monitor the effects of the therapy.

In a study of 35 patients with proven GUTB from India,[20] 94% had a positive PCR, 37% had a positive urine culture and 91% had abnormal radiographic findings. Bladder biopsies were positive in 46% of patients.

Management

The aims of management are to treat the active disease and preserve the maximal amount of renal tissue. Certain aspects of GUTB make it likely to respond well to anti-TB chemotherapy.[3] Fewer organisms are involved in the renal than in the pulmonary form of the disease. Isoniazid (INH) and rifampicin pass freely into the renal cavities in high concentrations and all these drugs reach adequate concentrations in the kidney, ureter, bladder and prostate. Two regimen plans can be used. The first regimen includes 2 months of daily INH, rifampicin, pyrazinamide and ethambutol (EHRZ), followed by twice a week INH and rifampicin for 4 months. The second regimen uses INH, rifampicin, ethambutol or pyrazinamide daily for 2-3 months followed by INH and rifampicin twice a week for 6-7 months.[21] Rifabutin can be substituted for rifampicin in human immunodeficiency virus (HIV)-positive patients. Follow up is done at 3, 6 and 12 months after finishing the course of chemotherapy. At each review, 3 consecutive early morning specimens of urine are examined.

The use of Corticosteroid is indicated in conjunction with antitubercular therapy to decrease fibrotic changes. Surgery continues to play an important but limited role in the management of GUTB.[22] Nephrectomy is indicated if the kidney is non-functioning, whether or not there is calcification. Reconstructive surgery is done in GUTB for ureteric strictures, most common at the ureterovesical junction, at the PUJ and rarely the middle third of the ureter. Double J stenting is required in cases of ureteric narrowing and it is often possible to avoid open surgery. Augmentation cystoplasty is required for small capacity bladders.

The treatment of female genital TB is EHRZ for 2 months followed by INH and rifampicin for 7 months.[23] The patients are examined monthly and after six months of therapy, endometrial curettage speimems are examined histopathologically and bacteriologically. If negative, the treatment is continued for another 3 months. Surgery is indicated when there is persistence or increase in the pelvic masses after a six-month course of antitubercular therapy.

Our experience with GUTB

One hundred and eighty-two patients (92 men and 90 women; between 3 and 76 years of age) were diagnosed as cases of GUTB on the basis of clinical examination, laboratory and radiological findings at Sir Ganga Ram Hospital. Seventy-eight per cent of the patients were above 31 years of age. The presenting symptoms of these patients are shown in Fig. 3. The other features included suprapubic pain (3%), genital pain (1.6%), bilateral *epididymo-orchitis* (1%), haemospermia (2%), cough (2%), infertility (1%), backache (1%), alternate diarrhoea and constipation (1%), and constipation (1%).

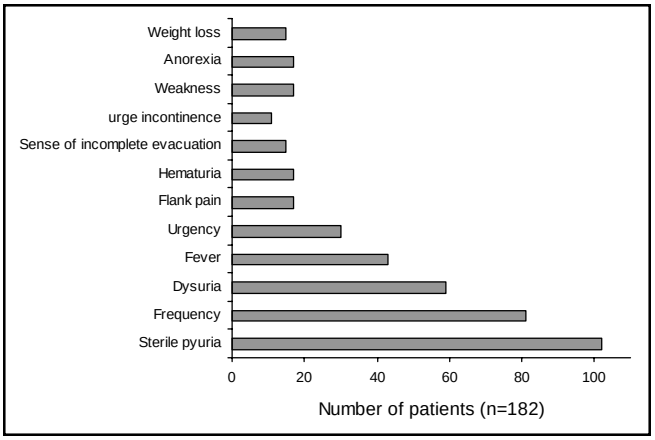

Fig. 3. Common presenting symptoms seen in patients with GUTB at Sir Ganga Ram Hospital.

Direct fluorescence staining was positive in 34 out of 40 patients; AFB culture in 7 out of 145. PCR of the urine for TB was positive in 142 patients out of 150 patients and NASBA was positive in 10 out of 15 patients. However, 'gold standard' by way of culture positivity was not achieved in all 182 cases diagnosed clinically as cases of GUTB. It appears that NAA may sooner or later replace culture as the 'gold standard' in the diagnosis of GUTB. The radiological findings observed in our patients are given in Table 4.

Table 4. Radiological findings of patients at SGRH

Diagnostic modality	Findings
Ultrasound (182)	31 hydronephrotic changes
Intravenous urography (IVU) (31)	14 ureteric narrowing
computed tomography (CT) scan	7 mass lesions
Associated stones	6

Figures in parenthesis indicate number of cases.

PITFALLS IN DIAGNOSIS

There is intermittent shedding of mycobacteria in the urine; hence 3-5 samples are required to be processed immediately after collection. The patient should not have received antibiotics 48 hours prior to sending the sample for culture. In GUTB, the number of organisms present in the urine may be too small to be detected by smear and culture. Some urine samples also have inhibitors which make interpretation of molecular assays difficult.[24] The currently available NAA should be used along with culture methods and each test should be interpreted along with the clinical and radiological findings of the patients, since culture positivity in GUTB remains poor.

All 182 patients were treated with a six-month course of short-term chemotherapy (2EHRZ + 4HR). Nephrectomy was done in 5 cases, double J stenting in 12 and augmentation cystoplasty in 3 cases. Twelve patients had received steroids in addition to ATT and had stenting done. There was recurrence of the disease in 1 patient only and complete clinical recovery in *the* rest of the 181 patients. Two patients did not complete the course of therapy; of these one required nephrectomy at a later date. There appears to be a good correlation between NAA positivity and clinical recovery.

Summary

Patients with long-standing urinary symptoms and sterile pyuria should be investigated for GUTB. The manifestations of GUTB can be variable and cause a variety of clinical patterns. Mycobacterial culture and staining, radiological investigations and molecular assays may all aid in the diagnosis. Short-course chemotherapy with EHRZ is effective. Some patients may need surgical intervention. Genital TB usually presents as infertility in females. GUTB is difficult to diagnose and all cases must be investigated thoroughly. The role of molecular assays cannot be overemphasized; however, these assays cannot be taken as the sole evidence of disease.

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