Diagnosis and Management of Tuberculosis

Chapter 2

Genitourinary Tuberculosis - An Overview

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1. Abstract

Genitourinary tuberculosis (GUTB) is a condition that commonly affects humankind, many decades after the onest and treatment of primary tuberculosis. While most countries have achieved a control over spread of the disease, GUTB still poses a diagnostic challenge to most clinicians. The variety of symptoms with which this condition presents with, makes it even more difficult for the treating urologists.

In the pre-COVID-19 pandemic period, many countries had observed a decline in the overall numbers of cases of tuberculosis. After the onset of the COVID-19 pandemic, a sharp decline in the number of notifications is observed, owing largely to the lack of monitoring and follow-up by health care professionals.

Asian countries, especially India reports a maximum number oi tuberculosis cases. As GUTB is one of the most common forms of extra pulmonary tuberculosis, it is imperative for physicians in this part of the world to have a better understanding of the likely presentations of GUTB, the pathophysiology, pathological aspects, medical and surgical management.

This chapter gives a broader overview of magnitude of the problem, its pathogenesis, pathophysiological aspects, medical and surgical management of different forms of GUTB. We also discuss the role of revised national control

programme that effectively controlled the spread of this disease through the DOTS and DOTS-PLUS programmes.

GUTB is a Great Mimicker, presenting in various forms. It can present as a lower tract storage symptom or obstruction to urinary tract or a non-functioning kidney. A high index of clinical suspicion is the basic pre-requisite for an early, effective and appropriate management of such cases.

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1. Introduction

Tuberculosis (TB) is seen almost in every country of the world. World Health Organization (WHO) is committed to treating up to 40 million people including 3.5 million paediatric population and 1.5 million drug-resistant cases [1]. TB is still the leading cause of death, with about 1.5 million deaths reported in 2018, surpassing even the mortality rates of HIV [2]. India ranks first amongst the countries that are affected the most by TB [3].

Before the COVID-19 pandemic wreaked havoc across the globe, many countries started showing a decline in the overall numbers. In the last 5 years from 2015, there was a 9% overall reduction in incidence and 14% reduction in mortality in TB patients [4]. However, after the pandemic, a sharp decline by 25 to 30% in the number of notifications of TB was observed, which is feared to increase TB related morbidity and mortality in the subsequent years [5]. A constant monitoring, equitable access to prompt diagnosis, prevention of the disease and appropriate treatment are the basic pre-requisites for effective control of this dreaded disease.

TB is a multi-system disease, affecting various organs in the body either synchronous or metachronous. Genito Urinary Tuberculosis (GUTB) is one of the chronic infectious diseases that affect the urinary tract or genitalia. Though various species affect humans, Mycobacterium tuberculosis (MTB) is the commonest species known to cause the disease [6]. In 1882, Robert Koch discovered that MTB is the causative organism responsible for this disease [7]. Hans Wildbolz, in 1937, coined the term GUTB [8].

GUTB gains importance from the fact that it is the most common form of extra-pulmonary TB (EPTB), second only to lymph node involvement [9]. It constitutes up to 20% of EPTB and usually follows 10 to 20 years after treatment of pulmonary tuberculosis (PTB). The delay in the onset of GUTB after PTB is due to the reactivation of quiescent MTB after a longer period of dormancy [10]. Hence a prolonged period of surveillance is needed in those who are being treated for PTB in the past.

2. Historical Aspects

Tuberculosis is a disease that affected humans from time immemorial. The earliest evidence of

TB in humans was observed in the skeletons with Gibbus deformity, suggestive of Pott's spine, as early as 8000 BC [11]. Evidence of scarring of the lungs, similar to pulmonary fibrosis that we get in PTB was reported as early as 2000 BC in India. Evidence of Acid Fast Bacilli was seen in the psoas abscess of mummified bodies. Due to multi-varied presentation, tuberculosis was not given a proper name until 1834, when Johann Lucas Schonlein coined the term tuberculosis and grouped all these lesions that characteristically presented with tubercles [12].

The earliest reports of GUTB involving the kidneys and urinary tract were published by G L Bayle as early as 1810. The clinical importance and significance of storage symptoms related to GUTB were emphasized by Howship [13]. After Porter made his earliest note on GUTB in 1894 and Wildbolz coined it as GUTB, the term GUTB has undergone so many changes and modifications. Singh et al observed that the terminology is better described as 'Urogenital' rather than 'Genito-urinary', as the disease most often affects the kidneys primarily [14]. Kulchavenya observed that only about 50% of patients with renal involvement exhibited genital lesions. On the other hand, in up to nearly 80% of those with genital involvement, a renal lesion was found associated [15,16].

Despite innumerable book chapters and peer-reviewed publications on this entity, GUTB continues to surprise us with a myriad of presentations. The symptoms are varied and may be non-specific too. Rarely, the whole kidney becomes non-functional, without any specific bothersome presenting symptom. Hence GUTB is also known as a 'Great Mimicker'. In this chapter, let us try to consolidate various aspects of GUTB and arrive at a meaningful consensus to clear the quandary around this quagmire.

3. Magnitude of the Problem

Tuberculosis is a pandemic disease. The World Health Organization (WHO) 2020 report estimated a whopping 1.8 billion population being affected by Mycobacterium tuberculosis in 2020 [17]. The year 2019 witnessed a 1.4 million death all over the world. The year 2020 witnessed yet another global pandemic (COVID-19) that confined most of us to stay indoors. Physicians, Para medical and supplementary health workers were badly affected by this pandemic, as a result of which the quarterly notification that happens for other diseases too took a massive hit.

WHO 2020 reports suggested that more than 25% of TB cases were reported from India. Shrinivasan et al, in their study on the impact of COVID-19 pandemic on tuberculosis, observed that there was a 50% reduction in the number of reported cases in the three-month period from Feb 2020 to April 2020 [18]. A synchronous involvement of ureters and bladder along with kidneys is seen in one-fourth of all patients with GUTB [19,20]. As GUTB constitutes the second most common form of EPTB, it is imperative that this entity should not be taken lightly.

The presence of co-existing morbidities and immuno compromised conditions including diabetes mellitus, chronic kidney disease, maintenance hemodialysis, immune-suppressive agent usage and malignancies are seen to coexist with GUTB in as high as 46% [21]. Min et al, in one of the largest studies on nearly 60,000 patients receiving hemodialysis, observed an increase in incidence of new-onset tuberculosis patients. The increase in tuberculosis in patients with chronic kidney disease would lead on to an increase in GUTB cases as well, over time [22].

Patients after undergoing allograft renal transplantation, especially as they would also be on immune suppressive agents, are more susceptible to reactivation of latent tuberculous infections (LTBI). Krishnamoorthy et al, in their study on LTBI observed that TB is one of the most important problem that causes disease related morbidity and mortality in renal allograft recipients [23]. Eastwood reports an increased incidence of bladder tuberculosis in patients treated with Bacillus-Calmette-Guerin (BCG) for non muscle invasive bladder cancer [24].

4. Pathogenesis

Lungs are the principal focus of infection in most cases of GUTB. After gaining access to the human body by inhalational route, the Mycobacteriae are largely stored in the macrophages and remain dormant for many years [25, 26].

4.1. TB of urinary tract (Kidney, ureter, bladder)

Various theories were proposed for the way the urinary tract gets infected following a lung infection.

Fig 1 summarizes the various theories proposed for the development of GUTB.

Elimination theory	– Cohnheim
Direct hematogenous theory	– Ekehorn
Metastatic theory	– Medlar
Bacteremia theory	– Rosenberger
Unified theory	– Wildbolz

Figure 1: various theories of pathogenesis of GUTB.

a) Elimination theory

Cohnheim in 1879, proposed the ‘Elimination theory’. According to this theory, tubercle bacilli, after gaining access to blood circulation, were eliminated in the urine. After entering the kidney, they lodge themselves in the renal parenchyma and remain dormant for many years, before manifesting.

b) Direct hematogenous Spread theory

Three decades after Cohnheim's theory, Ekehorn, in 1908, proposed his 'Direct Hematogenous theory'. According to his theory, the tubercle bacilli migrated to the kidneys through renal capillaries in the form of an embolus. After lodging in the kidney, they form a tubercular focus. According to Ekehorn, the rest of the urinary tract was secondarily infected with the spread happening via the transport of urine. He also observed the large colonies of bacilli in urine reflect the source of origin of the infection to the kidneys, especially because so much of the infection does not arise from the ureters or urinary bladder [27].

c) Bacteremia theory

In the early 1900s, Dr R C Rosenberger had suggested that tuberculosis principally spread through bacteraemia and that a secondary localization of tubercle bacilli at various organs resulted in the development of lesions in those organs. However, in 1910, McFarland disputed this theory, stating that the laboratory distilled water was contaminated with acid-fast bacillus, as a result of which the blood showed false evidence of septicaemia [28].

d) Metastatic theory

The pathogenesis of GUTB was ambiguous until 1926, when Medlar, (through his experimental study on 30 patients who died from pulmonary tuberculosis), called the whole process of infection of the urinary tract, 'metastatic' because the kidneys were infected through the bloodstream [29]. Medlar and his associates studied 100,000 serial sections of the kidneys of these 30 patients. Multiple sections from the scars gave a higher yield of tubercle bacilli. In their study, they concluded that renal TB was seen in more than 70% of patients with pulmonary TB and also that bilateral renal infection was the rule in every case of pulmonary TB. According to Scholl, Medlar concluded that patients dying of pulmonary TB often had involvement of the kidneys too [30].

e) Wildbolz Unified Theory

EarlIer, TB affecting kidneys, ureters and bladder were called Renal TB and those involving prostate, epididymis, testicles and Fallopian tubes were called Genital TB. Wildbolz in 1937 emphasized that renal and epididymal lesions were not two distinct entities, but were local presentations of the same source of primary infection. He combined both the varieties and coined the term Genito-urinary Tuberculosis [31].

4.2) TB of Male genitalia

Tuberculosis of male genitalia (MGT) is more often reported these days. Genital involvement more often is seen secondary to lung involvement [32]. Rajpal and his associates

concluded that MCT is associated with renal TB in two-thirds and with pulmonary TB in one-third of the cases [33].

a) Epididymis

The epididymis is the most common genital organ affected by TB in males [34]. The high vascularity of globus minor makes it more prone for tubercle bacilli to lodge and multiply at this site. The epididymis can also get involved by direct contiguous spread from the testicles. Urinary TB can also cause epididymal involvement in a retrograde manner through ductus deferens. A lymphatic spread of Tb infections to the epididymis has also been reported, though only in a minority of cases [35]. However, metastatic spread through the bloodstream appears to be the most common route of spread of infection.

b) Testis

Tuberculous orchitis, though rare, is not uncommon [36]. The usual presentation would be secondary to epididymal involvement. Isolated TB orchitis is an entity where the infection could reach the testicle by direct hematogenous spread. In most occasions, this disease closely mimics testicular malignancy [37,38]. Testicular cancer should be suspected in those patients who fail to show resolution after 3 weeks of anti-tubercular treatment [39].

c) Prostate

After epididymis, the prostate is the second most commonly involved organ in genital tuberculosis [40]. Because of its asymptomatic nature, most cases are detected at autopsy. Prostate gets involved by direct, lymphatic or hematogenous routes. Once infected, it results in caseation, necrosis, cavity formation [41]. Chan et al report an increased incidence of such cavities in patients infected with the Human Immunodeficiency virus [42]. Recto-urethral fistulae after TB prostate is not so uncommon. Most of them heal spontaneously within 6 weeks of conservative management [43].

d) Penis

Penile involvement by TB is a very rare disease, accounting for less than 1% of all cases of GUTB [44]. Patients with penile involvement characteristically present with proliferative mass, closely mimicking malignancy [45,46]. These tuberculids may remain asymptomatic or can manifest as papules and pustules over the glans penis, which slowly ulcerates and becomes proliferative. These lesions, if diagnosed pre-operatively, may obviate the need for a partial or total amputation of the penis. Such lesions dramatically melt and disappear with anti-tubercular treatment [47].

4.3 TB of Female genitalia (FGT)

The real incidence of FGT is often difficult to estimate as a large number of women either remain asymptomatic or present with non-specific symptoms [48]. The highest number of FGT is reported from South Africa and India [49, 50]. Though ascending infections from urinary tracts and hematogenous route are likely to produce FGT, recent studies have shown a strong correlation to sexual transmission [51]. The overall incidence in decreasing order of frequency is Fallopian tubes (95 to 100%, Endometrium of the uterus (50 to 60%), followed by ovaries, cervix and uterine myometrium [52]. Hysterosalpingogram and laparoscopy usually clinch the diagnosis [53,54]. Most patients usually respond to anti-tubercular therapy. The fallopian tubal block may need recanalisation. Total hysterectomy with bilateral salphingo-oophorectomy is rarely needed in intractable cases [55,56].

5. Pathological Aspects

Lesions of the kidney, either alone or in combination with ureters and bladder constitute up to 70% of cases of GUTB [57]. The pathology of GUTB almost centres on the events that take place in the kidney.

a) Kidney

Unlike most urinary tract infections, TB of the urinary tract takes a descending route and reaches the kidney through hematogenous spread [58]. Spontaneous healing of most cortical lesions is witnessed, without the need for any medical or surgical intervention [59]. Kidneys are affected by TB by two mechanisms. One is by direct hematogenous spread, causing multiple tiny whitish nodules of size around 1 to 2 mm each, scattered all around the renal parenchyma, called military TB [60]. The other is by localized ascending infection, causing cessation, necrosis, cavitations and cortical granulomas of the renal cortex or medullary lesions. Fig 2 illustrates the calcifications in the renal cortex before (blue arrows) and after excision of the calcified mass.

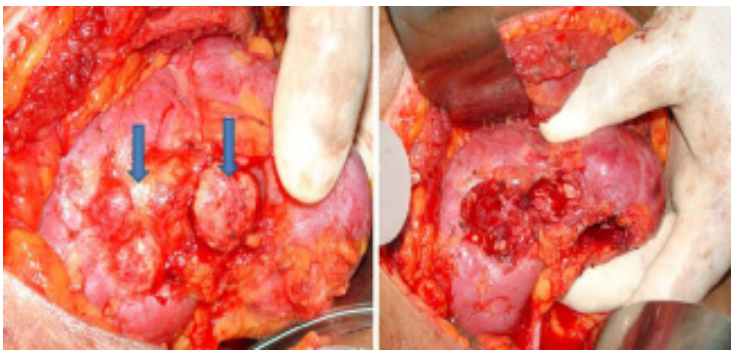

Figure 2: Calcified mass in the renal cortex, before (2a) and after (2b) excision of the mass lesion.

The cortical granulomas stay dormant for many years and remain asymptomatic for as long as 10 to 15 years. These granulomas may coalesce, form cavitations and eventually ulcerate and erode into the papillae to finally communicate with the pelvicalyceal system, giving the characteristic ‘moth-eaten appearance’ in excretory urography. Slowly, over some

time, the whole of the kidney is affected, resulting in a malfunctioned, calcified kidney, known as ‘Putty Kidney’ or ‘Chalk kidney’.

Fig 3 illustrates the outline of various stages of renal TB

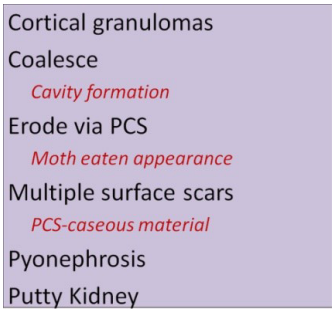

Figure 3: Various stages of renal tuberculosis.

The individual calyces may show areas of diffuse small to medium-sized calcifications or larger calcified abscess cavities, distorting and deforming the calyces [61], Bloom and associates, in 1970, proposed that tubercle bacilli were not grown in caseous lesions of non-functioning kidneys [62]. However, these calcifications gain clinical importance a decade later, as these calcified matrices have been identified to harbour dormant bacilli within them, which have the potential to flare up on a later date. Fig 4 shows the caseous matrix-like material within the pelvicalyceal system and the renal parenchyma.

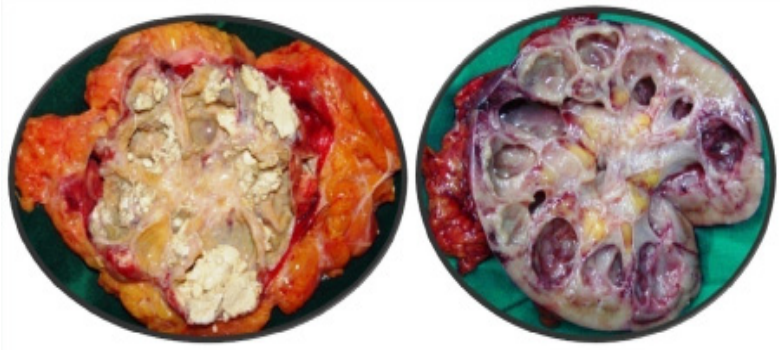

Figure 4: Caseous matrix in renal tuberculosis.

Wong and Lau, in their study in 1980 concluded that larger calcifications harboured the bacilli within their calcifications [63]. The tubercle bacilli usually lodge in the juxta-glomerular capillaries. Macrophages surround these bacilli and form caseating granulomas. The presence of epitheloid granulomas with Langhans giant cells is pathognomonic of renal tuberculosis [64].

The factors that decide the severity of illness include the dose of infecting organism, the virulence of the tubercle bacilli and host resistance. The outcome of mycobacterial infection in an immune-competent person who does not have prior exposure to the tubercle bacilli depends on the T-cell mediated immunity of the host. If the dose is less and virulence is low or if the resistance is high, the tubercles are replaced by fibrosis and healing takes place. If not, bacilli continue to multiply and produce calcification and caseation necrosis. Fig 5 illustrates the pathology of renal tuberculosis.

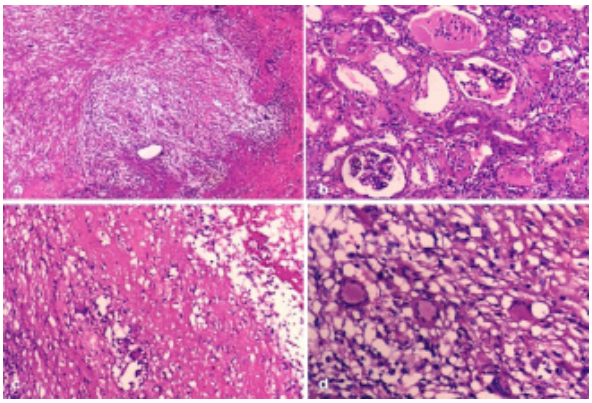

Figure 5: Microphotograph of Hematoxylin & Eosin staining of renal tuberculosis (Low power).

A calcified lesion is one of the hallmark findings of GUTB. The process of healing is followed by fibrosis and deposition of calcium salts, resulting in a calcified lesion. These lesions increase in size over time, resulting in erosion into the calyces leading to ulcero-cavernous lesions. Fig 6 illustrates the H&E staining of renal tuberculosis in high power view.

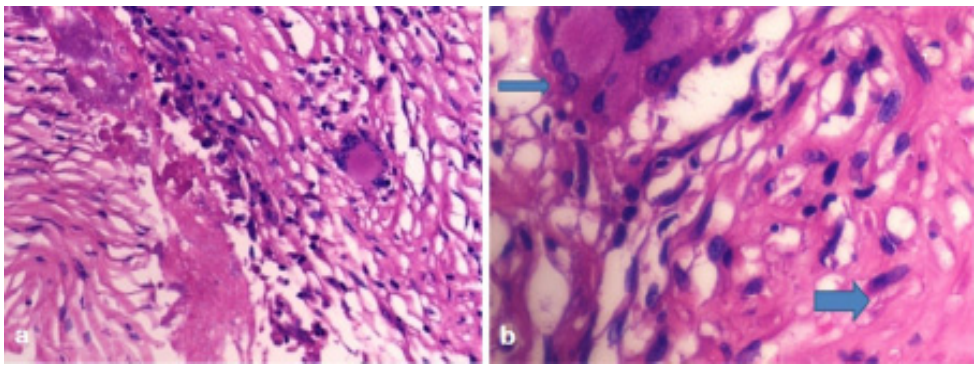

Figure 6: Microphotograph of Hematoxylin & Eosin staining of renal tuberculosis (High power).

As healing occurs with fibrosis, fibrous tissue may cause narrowing of the infundibulum, leading to dilatation of individual calyces or ureteropelvic junction narrowing. Once calyceal infundibular stenosis occurs, the vascularity to that portion of the kidney gets jeopardised. As most of these arteries are segmental, a lack of vascularity results in necrosis and abscess formation.

b) Ureter

The involvement of ureters is almost always secondary to renal involvement. Tubercular ureteritis more often involves the lower third of the ureter, especially the vesicoureteric junction [65]. Ureteric involvement is more dangerous than renal involvement, especially because ureteric obstruction can cause global hydroureteronephrosis and rapidly cause renal parenchymal destruction. Moreover, the extension of the fibrous and inflammatory process with a thickened wall of the ureter may present with a beaded appearance [66]. Ureteropelvic junction is the next common site affected, followed least commonly by the middle ureter.

Histopathology of the ureter shows a thick-walled inflamed ureter with chronic

lymphocytic infiltration. Epitheloid granulomas and Langhans giant cells confirm the diagnosis. Rarely, ureteral TB can mimic a tumour in the ureter [67].

c) Urinary Bladder

The urinary bladder is one of the common organs to be affected in GUTB. About 45.6% of those with GUTB develop bladder involvement [68].

Almost all lesions of the urinary bladder occur secondary to renal involvement. Bladder lesions characteristically involve the peri-ureteric regions. Bladder involvement by tuberculosis involves two phases: Acute and Chronic phase. In the acute phase, the bladder is inflamed, edematous and red, giving an angry-looking appearance. There will be abundant tubercles studded all over the bladder, giving the patient intense storage symptoms. The chronic phase shows bullous lesions over the bladder mucosa, with a reduced capacity. Bladder musculature will be thickened and show multiple tuberculomata. The ureteric orifice may be indrawn, rigid, circular and appear like a golf hole orifice, because of circumferential submucosal fibrosis. Moreover, the presence of a golf hole type of orifice does not always mean a refluxing orifice, as in urinary tuberculosis, such pattern of orifices may be associated with concomitant ureteric orifice obstruction too. The healed mucosal lesions characteristically present with a Stellate appearance, caused by bands of fibrous tissue, meeting at a central point.

d) Testis and Epididymis

Tuberculosis of testicles is almost always secondary to TB of Epididymis. Isolated tuberculous orchitis, with non-involvement of the epididymis, is rare. Very rarely, TB of testicles can closely mimic malignancy [69,70]. Isolated Epididymal tuberculosis is defined as one without the involvement of kidney. Such lesions are more commonly encountered in patients with HIV [71]. Fig 7 illustrates epididymal tuberculosis, closely mimicking a testicular mass.

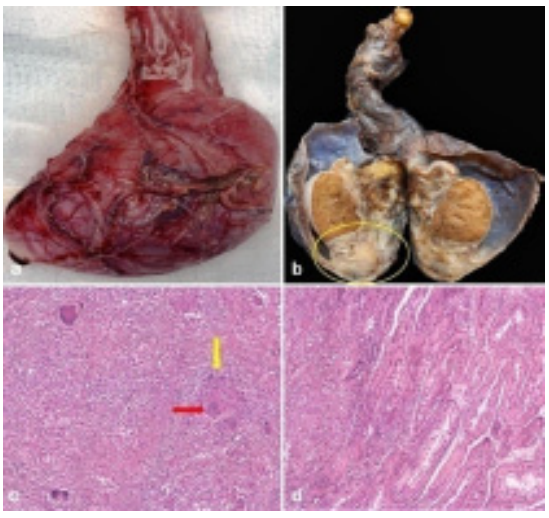

Figure 7: Illustration of isolated tuberculous epididymitis.

e) Penis

Tuberculosis of the penis is an extremely rare condition. It characteristically affects the preputial skin, glans penis or the corpora cavernosa. Most cases present as ulcero-proliferative lesions or rarely nodular or papulo-necrotic tuberculides [72,73]. On many occasions, demonstration of Acid Fast Bacilli may not be possible in the biopsied specimen. Diagnosis in many instances is based on corroborative findings including Langhans giant cells and epithelioid granulomas [74]. This condition melts and disappears with medical treatment, largely obviating the need for amputation of the penis, if picked up early.

f) Urethra

TB of the urethra is extremely rare. Very few cases are reported in the literature. Primary urethral TB is very rarely reported and usually mistaken for urethral caruncle. Iqbal Singh reported a similar case in a middle-aged lady, who presented with intense storage symptoms. Excision of the caruncle showed a chronic granulomatous lesion, suggestive of TB [75]. Even though urinary or genital tuberculosis is not so uncommon, it is still unclear as to why, despite constant exposure to infected urine, urethral TB is not so commonly encountered in clinical practice. However, the presentations may be acute or chronic. In the acute phase, patients may present with painful urethral discharge. Chronic cases may present with urethral stricture and obstruction to urinary flow.

6. Clinical Presentation

GUTB, a great mimicker, can have a myriad of presentations. Usually, the mode of presentation correlates well with the organ affected. The kidneys, bladder, Fallopian tubes and the scrotum are the most commonly involved organs in descending order of frequency [76]. The most common presentations include intense storage symptoms like dysuria, frequency, urgency and suprapubic pain. A recurrent urinary tract infection with sterile acid pyuria may sometimes be the sole presentation [77]. The rarer presentations include loin pain (hydronephrosis), infertility or renal failure [78,79]. The other constitutional symptoms include evening rise of temperature, loss of appetite, loss of weight and non-specific abdominal pain.

The evening rise of temperature is one of the classic presentations of GUTB. The normal diurnal rhythm is under the influence of serum cortisol. During any day, under normal circumstances, the body temperature is lowest in the early mornings at around 3 AM and is highest at 3 PM. Cortisol, a stress hormone, directly acts on the temperature-regulating centre in the brain and controls the temperature [80]. The diurnal rhythm of cortisol, the variations in body temperature and the failure to notice a rise in temperature due to day time activities are all considered various reasons that may be considered for the evening rise in temperature. Fig 8 illustrates the variations in body temperature and in serum cortisol levels during day and night time.

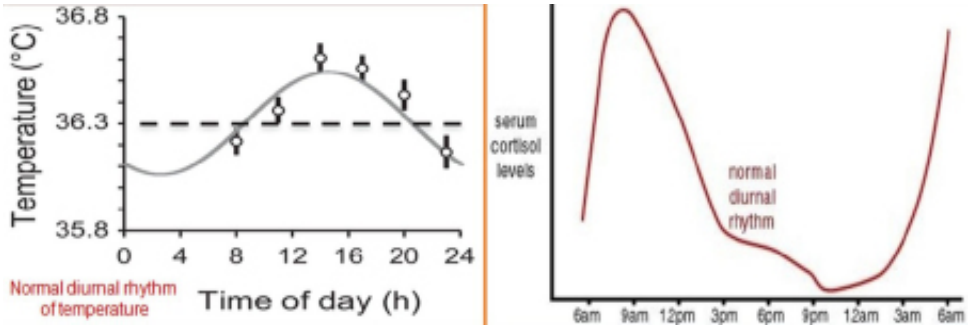

Figure 8: Diurnal variations in body temperature and serum cortisol.

Loss of appetite and loss of weight are the other symptoms that almost always point towards TB, especially in the developing world. Patients with tuberculosis express elevated leptin levels that in turn lead to anorexia and loss of weight. Fig 9 illustrates the mechanism by which TB results in anorexia.

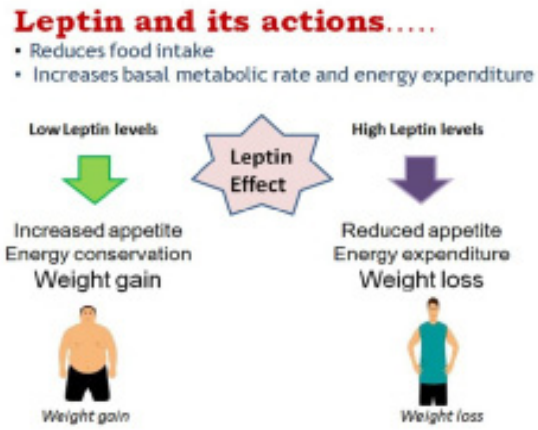

Figure 9: Effect of Leptin on body weight.

Patients with urinary bladder involvement are seen in one-third of those with renal involvement [81]. Patients with acutely inflamed bladder will have intense storage urinary symptoms. The frequency of urination is observed both during day and night, disturbing their sleep. A chronically inflamed bladder will have poor compliance and grossly reduced capacity. Such gross reduction in bladder capacity (thimble bladder) can result in a decreased functional bladder capacity and urinary incontinence.

7. Diagnosis

The various diagnostic methods for making a diagnosis of GUTB include microbiological and histopathological tests, radiometric assays, radiological methods and polymerase chain reactions [82]. Demonstration of acid-fast bacilli in urine or tissues may not be possible on most occasions, where the decision to treat patients with anti-tubercular drugs is solely based on radiological methods.

The authors, in one of their earlier publications, had observed that one-third of their patients were treated based on radiological diagnosis [83]. Fig 10 summarizes the diagnostic methods (used by the authors in their earlier study on GUTB) to make a diagnosis of GUTB.

Diagnostic modality	%
Urine AFB	21
Urine AFB culture	5
Bladder biopsy	17
Histopathology	13
Serology	5
Scrotal sinus biopsy	5
Radiological diagnosis	33

Figure 10: Various methods of investigation used to diagnose GUTB.

a) Urine analysis

Urine microscopy and analysis is the commonest mandatory initial evaluation in any patient with storage urinary symptoms. Sterile acid pyuria is one of the hallmark findings suggestive of GUTB. Various other conditions like urine contamination recently treated urinary tract infections, interstitial nephritis, analgesic nephropathy, contrast injection, urothelial malignancy and renal calculi can also produce sterile pyuria.

b) Urine smear for AFB

Traditionally, demonstration of tubercle bacilli in urine has been the test of choice to make a diagnosis of GUTB. Given intermittent bacilluria and to increase the positive yield, three to five consecutive early morning urine specimens should ideally be examined [84]. The South Indian Consensus committee in 2015, had presented their guidelines for the diagnosis of GUTB. Figure 11 summarizes the criteria for interpretation of urine smear for AFB [85].

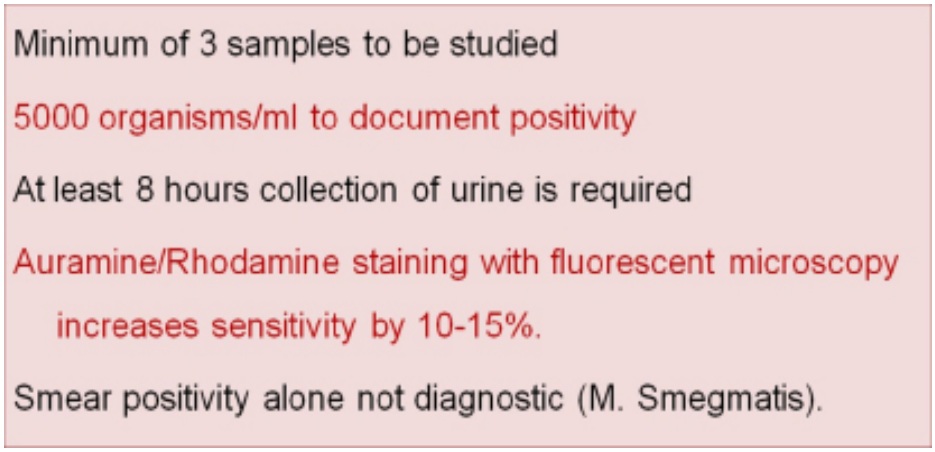

Figure 11: South Indian Consensus criteria for interpretation of urine smear for AFB.

The criteria laid down by the committee includes certain major and minor criteriae. The minimum required criteriae to diagnose GUTB include atleast one major or two minor criteriae. Fig 12 depicts the major and minor criteriae defined by the South Indian Consensus committee in 2015, for the diagnosis of GUTB.

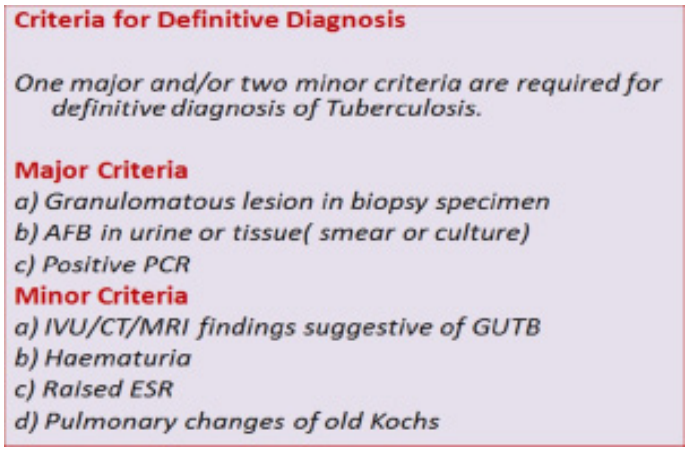

Figure 12: South Indian Consensus committee criteria to diagnose GUTB.

c) Urine AFB culture

Urine for AFB culture is conventionally done using Lowenstein Jensen (LJ) medium. Though LJ culture remains the keystone in the diagnosis of urinary tuberculosis, these traditional methods are slow and have low sensitivity, because of the low yield of tubercle bacilli in the urine. Various egg-based and agar-based culture media are used. Fig 13 gives a summary of the properties of the egg and agar-based culture media.

Conditions	Egg-based Media	Agar-based Media
Selective	Added malachite green	Added antibacterial and anti fungal
Rate of growth	Slower	Faster and able to support INH Resistant and fastidious strains
Contamination	Usually less,but if present, involves entire surface	More frequent, but can still isolate colonies
Area of inoculum	Relatively small	Large
Visual Examination	Difficult due to media opacity	Media is clear; allows easier colony quantification and morphology confirmation
CO_2	Not required	Required
DST	Not performed on LJ in United States	Preferred due to larger surface area and faster rate of growth
Shelf Life	Long(8–12 months)	Short(1–2 months)

Figure 13: Comparison of the different types of culture media.

d) Radiometric assay

Radiometric assay systems provide rapid results, with the result obtained in 2 to 3 weeks. They are highly sensitive and specific. BACTEC test, marketed by Becton Dickinson, USA, uses fatty acid substrates labelled with radioactive carbon. As mycobacteria metabolize the fatty acid substrate and release carbon, the radioactive carbon-di-oxide that is released acts as a marker of mycobacterial growth.

e) Polymerase chain reaction

Polymerase chain reaction (PCR) is a very useful investigation that gives the results in a few hours. The sequence of DNA fragment from very few mycobacteria can be amplified in vitro and the amount of amplified DNA can be identified and visualized [86]. The overall

specificity is 100%. The main limitation of this test is its false negativity. Patients with non-tuberculous mycobacterial infection can show false negativity. Multiple urine sampling and testing in centrifuged urine may decrease the extent of false negativity to a greater extent. Hemal et al reported that urine PCR was the most sensitive indicator and a rapid, sensitive and specific diagnostic tool [87].

8. Role of Imaging

a) Ultrasound abdomen

Ultrasound abdomen has these days become an extension of clinical examination. Most clinicians, especially obstetricians and urologists, do bedside screening ultrasound. The earliest ultrasound findings of renal tuberculosis include cortical granulomas. Smaller lesions, less than 15 mm, are either echogenic foci or have areas of hypoechogenicity within themselves. Ultrasound helps make a diagnosis of tuberculosis in up to 59% of cases [88]. Focal parenchyma calcifications are observed as strongly echogenic foci with characteristic post acoustic shadowing. Multiple infundibular narrowing may be diagnosed by individual dilated calyces, non-communicating with each other. In most instances of the non-functioning kidney, the renal parenchyma is normal in thickness. In such cases, the obliterative endarteritis causes de-functioning of the kidney, resulting in a non-functional status. The relative user-friendliness, convenience, cost-effectiveness, non-invasive advantage makes ultrasound, a popular initial investigation [89,90]. Becker, in his review on renal tuberculosis, concluded that ultrasound is best suitable to diagnose chronic changes in the kidney [91]. Fig 14 illustrates the sonographic appearance of a tuberculous kidney. Fig 14a shows dilated individual calyces non-communicating with each other or with the renal pelvis. Fig 14b depicts global hydronephrosis, with all the calyces dilated and communicating with the centrally located renal pelvis, suggestive of ureteropelvic junction stricture.

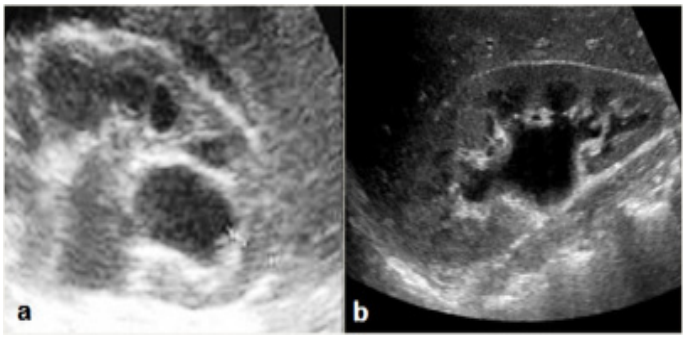

Figure 14: Sonographic appearance of Hydronephrotic tuberculous kidney.

Fig 15 illustrates the ultrasound findings in various stages of urinary tuberculosis. Cortical granulomas are picked up in the very early stage of the disease. End-stage disease characteristically presents with calcified or shrunken non-functioning kidney or a thimble bladder.

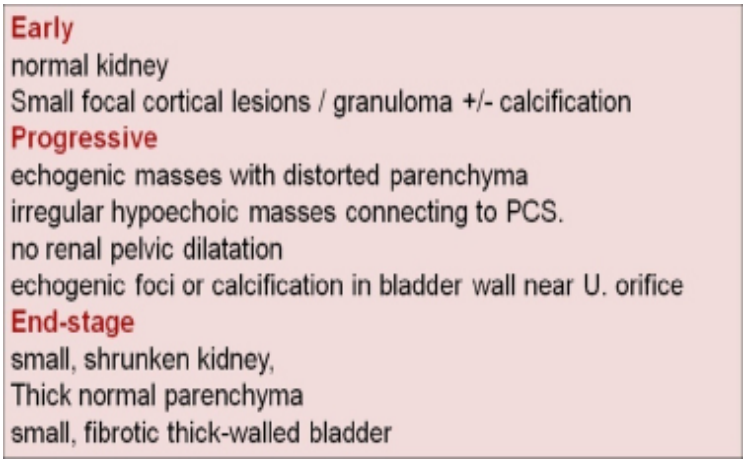

Figure 15: Sonographic appearance of various stages of tuberculosis.

b) Plain X-ray and Nephrotomogram

Plain X-ray abdomen gives information about the calcifications seen in renal parenchyma. The extent of parenchymal calcifications, the renal contour and the size of the kidneys are better delineated by a tomogram of the kidneys [92]. However, after the advent of Intravenous urography and Computed Tomography plain x-ray has become a redundant investigation.

c) Excretory urography (Intravenous urography)

Excretory urography (EU) is considered the hallmark radiological tool for making a diagnosis of GUTB. As a study that gives functional and anatomical details about the collecting system of the kidney, its utility in making a diagnosis is so immense. With the advent of Computed Tomography (CT) and its increasing usage these days, the role of the EU may have come down, but cannot be fully discarded. Fig 16 shows the EU images of a tuberculosis kidney with bilateral distal ureteric obstruction and small capacity urinary bladder.

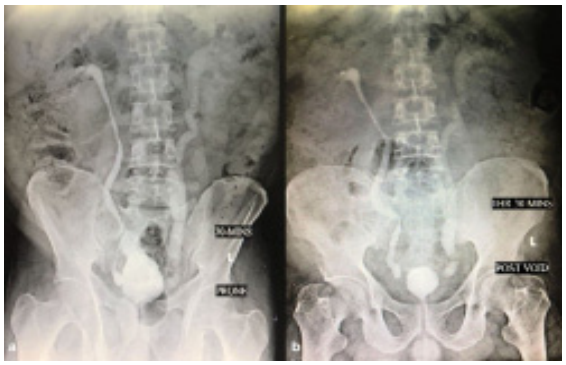

Figure 16: Excretory urography of a patient with renal tuberculosis.

The main advantage of EU is its cost-effectiveness and lesser radiation exposure. Moreover, EU plays a major role in the follow-up and monitoring of those patients who underwent reconstructive surgeries like uretero-calycostomy or ileal ureter replacement. Women of childbearing age would better tolerate EU than other forms of axial imaging. EU plays a significant role in delineating the ureteric pathologies. The extent of ureteral involvement, the

number of strictures, the degree of narrowing and reflux across the ureters can be diagnosed well in Excretory urography. The major limitation of EU is when the collecting system is non-visualized.

d) Computed Tomography

Computed Tomography (CT) has largely replaced EU, owing to its distinct advantages. This imaging is particularly useful in patients with pathology involving the renal parenchyma and in those with peri-nephric or peri-ureteric pathology. The extent of parenchymal scarring and parenchymal masses are better delineated by CT. Smaller lesions within the renal cortex and extra-urinary pathology are better demonstrated by CT scan [93]. The degree of enhancement of renal parenchyma after injection of intravenous contrast could give more information about the functional status of that kidney. It also helps in assessing the extent of involvement of adjacent organs [94]. The one area, where CT scores over EU is in patients with non-functioning kidney. In such instances, a CT scan gives information about the nephric and peri-nephric events with a higher degree of accuracy [95]. Fig 17 a,b,c,d illustrate the CT and intra-operative pictures of calcified mass in the renal parenchyma, before and after excision of the mass.

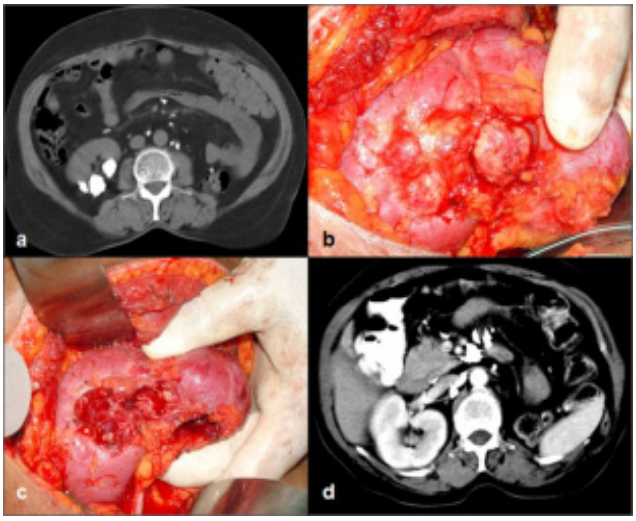

Figure 17: CT images before and after excision of calcified mass.

CT is an excellent alternative for a retrograde ureterogram, as in an inflamed or contracted urinary bladder, one may find it difficult to identify and cannulate the ureteric orifice. In few instances where there are proximal and distal ureteric obstructions, as contrast may not flow well across the site of proximal narrowing, EU may be non-informative, whereas CT scan provides complete details about the status of the distal ureter. Nowadays, incorporating multidetector technology in CT scan (MDCT) has replaced EU in all its indications. MDCT gives an improved assessment of renal lesions and that of the urinary tract using reformatted and reconstructed images such as maximum intensity projection (MIP) and multiplanar reconstruction (MPR) [96]. Low dose CT urogram MPR is becoming more popular in many centres, especially in the paediatric population [97].

e) Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) provides a good assessment of the renal morphology. MRI is especially useful in those patients in whom CT imaging is ambiguous or equivocal [98]. It is yet another tool that is very useful in imaging patients with GUTB. Though CT urogram with MPR is becoming the diagnostic procedure of choice, MRI is very useful in specific and selective cases. Pregnant women, women in the childbearing age group, children who cannot be exposed to high dose ionizing radiation, patients with contrast allergy, those with renal compromised status and those who need regular follow up imaging are ideal candidates for MRI [99, 100]. The main limitation of MRI is the non-demonstrability of parenchymal calcifications. MRI is also useful in diagnosing pelvic pathologies. Tuberculosis involving prostate, seminal vesicles and epididymis and ductus deferens are better demonstrated by MRI than CT [101].

9. Medical Treatment

a) Evolution of medical treatment

Tuberculosis is a disease that is known to affect humankind for many centuries. This is one of the oldest known diseases which is best understood and studied than any other disease in the world. The first-ever randomized controlled trial in the history of modern medicine was conducted for tuberculosis, where a gold compound, Sanocrysin, was used [102,103]. However, it's distressing to observe that TB continues to be a killer disease in many parts of the developing world, especially India [104].

The discovery of Streptomycin, as a possible cure for tuberculosis, changed the myths and fear about this dreaded disease. Until this discovery, as it was the only compound available for the treatment of TB, patients and treating physicians had no other option but to go for Sanocrysin. The toxicity of the gold compound greatly outweighed the benefits that it offered and hence was discarded even before the discovery of Streptomycin [105].

b) Revised National Tuberculosis Control Programme (RNTCP)

Ever since the National tuberculosis control programme was launched in the early 1960s in India, treatment of tuberculosis has undergone a paradigm shift. However, three decades later, in 1992, it was observed that only 30% of the patients were diagnosed and of them, only 30% were treated successfully [106]. The reasons postulated were multi-factorial. An absence of self-motivation to take the medicines regularly, lack of proper follow-up by the patients and defective supervision and monitoring by the health authorities were a few reasons identified for non-compliance with this programme. To set these defects right, a revised programme (RNTCP) was initiated in 1993 and scaled up further in 1998.

RNTCP initiated the short-course therapy that was given to each patient under direct supervision. This therapy was popularized as DOTS (Directly Observed Treatment, Short-course) [107]. The principal aim of DOTS treatment is to ensure that the drugs are delivered in person, free of cost and also to ensure that the patient has taken medicines on all days without fail. Sivaraj et al, in their comparative trial between with and without DOTS, observed that the TB cure rates without and with DOTS were 66% and 80% respectively [108]. Fig 18 illustrates how a DOTS program would work. DOTS not only ensure an issue of the medicines but also confirm that the patient consumes those medicines. DOTS plus program enhances the feasibility and effectiveness of multi-drug resistant TB treatment.

Figure 18: Phases of DOTS programme.

As per the classical RNTCP guidelines, four categories of treatments were suggested. Genitourinary TB comes under extra-pulmonary TB. All forms of EPTB are recommended to adopt Category I regime, which includes 4 drugs for 2 months and 2 drugs for the next 4 months. Fig 19 gives a detailed illustration of the various categories of the RNTCP regime.

Category	Type of Patient	Regimen	Duration in months
Category I	New Sputum Positive Seriously ill sputum negative, Seriously ill extra pulmonary,	2 (HRZE), 4 (HR)	6
Category II	Sputum Positive relapse Sputum Positive failure Sputum Positive treatment after default	2 (HRZES) 1 (HRZE 5 (HRE	8
Category III	Sputum Negative, extra pulmonary not Seriously ill	2 (HRZ) 4 (HR)	6
Category IV	MDR-TB case 6-9 (Km Ofx (Lvx) Eto Cs Z E), 18 (Ofx (Lvx)Eto Cs E)		24-27

Figure 19: Treatment categories for GUTB patients.

Corticosteroids are generally not indicated in the treatment of GUTB. Patients with severe acute cystitis and involvement of ureters or Fallopian tubes may benefit from corticosteroids. A high dose of prednisolone, up to 20 mg thrice a day may be needed to alleviate the symptoms and sequelae of treatment. As Rifampicin reduces the oral bioavailability of steroids, high

dosage may be needed.

10. Surgical Management

The surgical management of GUTB includes the following principles:

1. Drainage of the obstructed system in the form of internal (JJ stenting) or external (percutaneous nephrostomy) diversions.

2. Drainage of the parenchymal abscess or peri-nephric collections

3. Local treatment for the damaged portion of the kidney, including calycorrhaphy, cavernotomy, partial nephrectomy.

4. Removal of the non-functioning or badly infected kidney (nephrectomy), that may be done either by open, laparoscopic or robotic techniques.

5. Reconstructive procedures like uretero-calycostomy, ileal ureter replacement or ureteric reimplantations.

a) Internal diversion

JJ stenting is the commonest type of intervention performed in patients with renal TB. Hydronephrosis may occur due to infundibular narrowing, ureteropelvic junction obstruction or ureteric narrowing. With anti-tuberculous treatment, healing occurs with fibrosis, as a result of which obstruction further worsens. JJ stent placement across the site of narrowing not only helps in keeping the lumen patent, but also facilitates a passive dilatation of the urinary tract, by acting as a splint across the site of narrowing [109]. A periodic follow-up using Excretory urography would greatly aid in assessment of improvement or deterioration of the hydronephrosis. Worsening of obstruction after JJ stenting warrants a more active surgical intervention.

b) External diversion

Percutaneous nephrostomy (PCN) is the classical form of external diversion in GUTB patients. Though JJ stenting is widely done in such patients, such stenting may not be beneficial in patients with multiple infundibular narrowing. Such non-communicating calyces are best decompressed by PCN tube placement. Sometimes, it may be necessary to place multiple PCN tubes, in order to effectively decompress the entire kidney.

c) Percutaneous drainage

Sometimes, the pathology may extend into the renal parenchyma. Cavitations within the parenchyma with resultant abscesses may cause a gradual destruction of the renal cortex

and also cause a deterioration of renal function. In such instances, an external drainage of the collection through a PCN catheter (under ultrasound or CT guidance) may be very effective in restoration of the parenchymal function. Large parenchymal abscesses, sub capsular urinoma, perinephric abscess and psoas abscess are best treated by percutaneous drainage.

d) Partial nephrectomy

Parenchymal calcifications that are insidious in onset and slow growing need to be removed, as there is an inherent fear of gradually destroying the entire kidney [110]. Localized polar lesions with calcifications that are either growing or fail to respond even after 6 weeks of anti-tubercular therapy needs to be excised as well [111]. Fig 20 illustrates partial nephrectomy for an upper polar tuberculous cavitation. Fig 20 a and b illustrate the axial and coronal sections of CT scan showing an upper polar tuberculous cavitation. Fig 20 c,d,e and f show the intra-operative pictures of upper polar partial nephrectomy.

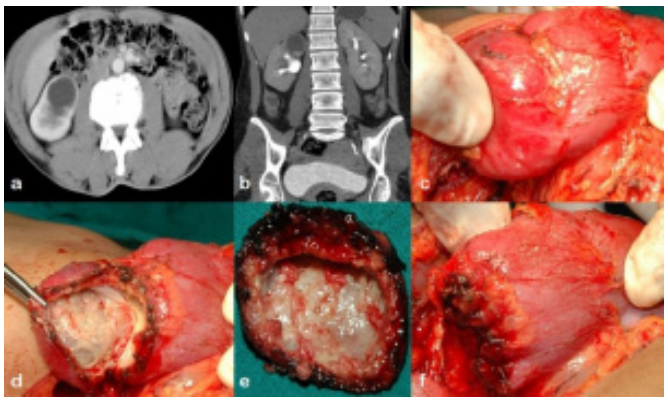

Figure 20: Partial nephrectomy for upper polar cavitation.

However, the number of partial nephrectomise for tuberculous kidneys continues to decline over the past few decades. Hanley in 1970 observed that if the obstructing infundibulum is opened out, the infective material from the calyx is drained and if appropriate anti-tubercular drugs in proper dosage are administered, the number of cases needing ablative procedures may be significantly reduced [112].

e) Holmium Laser infundibulotomy

As tuberculous lesions commonly affect the renal poles, extensive cavitations are seen more commonly in the poles. The diagnostic difficulties due to non-opacification of those individual calyces makes it even more difficult to make a diagnosis in such instances. Moreover, due to endarteritis obliterans, the anti tubercular drugs may not that easily reach the affected site too, resulting in persistence of lesion even after the course of therapy is completed. Earlier, an open cavernotomy was done to relieve the obstruction. Holmium Laser using a flexible ureteroscope may be useful in performing infundibultomy endourologically.

f) Nephrectomy

Removal of the kidney, though gives a permanent relief from symptoms, may not be an easy decision to take. As calcifications are seen in up to 50% of patients with renal tuberculosis, parenchymal dysfunction too are seen in those individuals with such extensive calcifications. Extension of the lesion on to the collecting system and the renal pelvis further delays healing by causing obstruction to effective drainage of urine.

g) Reconstructive procedures

GUTB is a silent pathology, that is insidious in onset and slowly grows and destroys the whole kidney over time. The destruction is greatly enhanced by stricture formation with resultant obstruction to drainage of urine and parenchymal lesions including scars and cavitations [113]. A prompt diagnosis at an earlier stage is the basic pre-requisite for planning a reconstructive procedure.

Reconstructive procedures like ureteric reimplantation or augmentation cystoplasty are still very popular amongst the urologists. Patients with ureteropelvic junction obstruction may have a cicatrized intrarenal pelvis, in which case offering pyeloplasty may be difficult. Moreover, the peri-pelvic pannus makes it even more difficult to get the proper plane of dissection. In such instances, if the lower pole parenchyma is thinned out, a lower polar uretero-calycostomy may prove an excellent option for effective drainage of urine. With increased expertise, most of the procedures are done by laparoscopy or robotic methods [114-116]. Fig 21 illustrates the patient with ureteropelvic junction stricture, who had two PCN tubes placed (Fig 21a). Antegrade nephrostogram revealed an abrupt cut-off at the renal pelvis with contrast not entering the upper ureter. The renal pelvis was cicatrized and intra-renal (Fig 21b). Fig 21c represents ureterocalycostomy in progress. Fig 21d is the post operative excretory urography image after ureterocalycostomy.

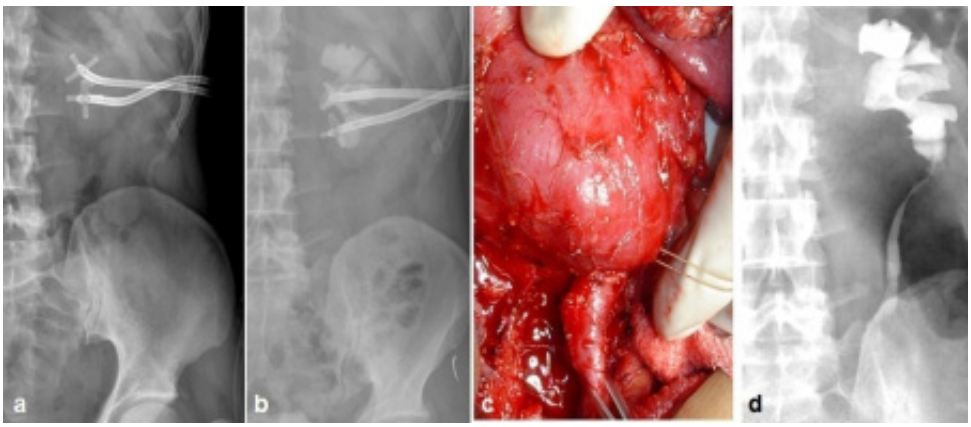

Figure 21: Renal tuberculosis with ureterocalycostomy being done.

Patients with contracted thimble bladder benefit well with augmentation cystoplasty. Patients with small contracted bladder with a functional bladder capacity of less than 100 ml of urine are ideal candidates for augmentation [117]. If the bladder is very much diseased and if

the thimble bladder capacity is very less, an excision of the bladder and orthotopic neobladder reconstruction is a feasible option [118].

11. Tb in Renal Failure

Patients with chronic kidney disease (CKD) are more prone to tuberculous infections. Patients with CKD have defective T-cell mediated immunity, as a result of which the host resistance to such infections is grossly reduced, predisposing to new-onset tuberculosis or reactivation of dormant tubercle bacilli. Malhotra reports an overall 6 to 16 times more propensity for tuberculosis in patients on hemodialysis than the general population [119]. Cheng reported up to 52.5 fold increased risk of tuberculosis in those with dialysis-dependent CKD [120,121]. As many patients head for transplantation in future, the chances of carrying the dormant tubercle bacilli from the donor kidney to the recipient for reactivation on a later date is much higher. Latent tubercular infection (LTBI) is a well-known entity,

On the other hand, renal tuberculosis can by itself lead to renal failure. Such renal diseases can be of insidious onset, resulting in progressive calcification and ultimate destruction of the renal parenchyma, leading to an extensive nephron loss. Renal TB can result in chronic kidney disease by various mechanisms: Firstly, obliterative endarteritis that sets in patients with Renal TB will result in extensive dystrophic calcification. Secondary amyloidosis may set in, which may lead to progressive renal parenchyma destruction, eventually leading to renal failure. Secondly, infundibular narrowing may cause hydrocalyx and tubercular ureteritis may result in gross hydronephrosis, resulting in post-obstructive atrophy [122]. Thirdly, the interstitial nephritis that develops as a result of tuberculous infection could damage and destroy the renal parenchyma, resulting in renal failure [123].

In their analysis of 241 patients, Gupta et al reported an incidence of renal failure in 22.4% of their cases [124]. However, Krishnamoorthy et al reported the overall incidence to be around 24% [125]. Patients with CKD also have elevated serum calcium levels, secondary to excess ectopic production of calcitriol by the granulation tissue [126]. Successful management of TB resulted in an adequate normalization of serum calcium levels [127].

Patients with ureteric stricture causing obstructive uropathy may benefit from JJ stenting. On the other hand, those with renal failure associated with multiple infundibular narrowing may not respond well to internal diversion. Such patients may benefit from percutaneous nephrostomy. Patients with ureteral tuberculosis who needed ileal ureter or those with thimble bladder who underwent augmentation cystoplasty may also develop renal failure over time.

To summarise, patients with obstructive uropathy with the dilated pelvicalyceal system are best managed by initial external diversion, followed by definitive treatment once a nadir level of creatinine is reached.

12. Summary

GUTB is one of the most common extra-pulmonary forms of tuberculosis. As the overall TB burden is so high in the developing world (especially India), the EPTB burden, though not so high, would cause a significant impact in the quality of life and the economy of any country. The introduction of pro-active initiatives by various governments like DOTS and DOTS-PLUS programmes have largely helped eradicate the disease in many countries, though India still records the highest number of infected cases and disease-specific mortality. The advent of short course therapy not only increased the patient compliance, but also facilitated an easy monitoring of proper intake of medicines by the patients. As TB is a great mimicker, a high index of clinical suspicion is mandatory amongst the treating primary care physicians, in order to diagnose the disease when it is fully curable. Since TB is a global disease, the aim of any government should be not only to cure the disease, but also to limit the morbidity, contain spread of the disease and ultimately eliminate the disease from their community.

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