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Original Research Article

EFFECTS OF TUBERCULOSIS ON GENITOURINARY SYSTEM

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Abstract

Background: Genitourinary Tuberculosis (GUTB) is a common site of extrapulmonary tuberculosis. The disease involves the kidneys, ureters, bladder, or genital organs. Clinical symptoms develop 10 – 15 years after primary infection. Only one-quarter of patients with GUTB have a known history of TB and about half of these patients have chest radiography findings. The current study aimed to determine the effects of GUTB.

Methods: The included patients were successive cases with a diagnosis of genitourinary tuberculosis. A total of 62 cases were reported with the diagnosis of genitourinary tuberculosis. PCR for MTb was done in 37 cases. Radiological evaluation included chest X-ray, KUB in all cases, and intravenous urogram when serum creatinine was normal. FNAC was performed in cases with serosal masses. All patients received antitubercular drug therapy with 4 drugs (Rifampicin, Ethambutol, Isoniazid, and Pyrazinamide) for 2 months followed by 2 drugs (Rifampicin and Isoniazid) for 7 months.

Results: Positive AFB staining and positive MTb culture in urine were seen in 31.37% and 41.17% of cases, respectively, confirming the presence of Mycobacterium tuberculosis in some GUTB patients. Positive PCR for MTb in urine is present in 67.56% of cases (in a subset of 37 patients). MTb culture in pus is only observed in 4 out of 7 cases, suggesting its less frequent occurrence compared to other positive findings. Sterile urine is found in 78.95% of cases, and Radiological abnormalities (IVU/NCCT/MUCG) suggestive of GUTB was found in 46/57 (80.7%) cases. Bladder biopsy was positive in 12/25(48%) cases done. A comparison of urinary PCR with urine for AFB staining urine for MTb culture and bladder biopsy was done.

Conclusion: The urinary (PCR) stands out as the most sensitive indicator among all microbiological tests. When coupled with radiological abnormalities, it significantly expedites the diagnosis of genitourinary tuberculosis. Optimal treatment involves a combination of multidrug chemotherapy and judicious surgery, as necessary. It is highly advisable to make every effort to reconstruct the urinary tract due to the rewarding outcomes associated with this approach. However, in cases where tissue is infected and irreparably damaged, the most effective course of action is ablating the affected tissue.

Keywords: Genitourinary Tuberculosis (GUTB), Mycobacterium Tuberculosis, Polymerase Chain Reaction (PCR)

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Introduction

Tuberculosis (TB) is the leading global cause of mortality from infectious diseases, [1] accounting for nine million new cases and two million deaths annually, with approximately 95% occurring in developing countries. [1, 2] Despite modern diagnostic tools and treatments, India sees over 1000 daily TB-related deaths. [3] The resurgence of TB is observed globally, attributed to factors such as increased migration, the HIV pandemic [4], and the emergence of drug-resistant Mycobacterium tuberculosis strains. [1, 5, 6] A rise in extra-pulmonary TB is noted alongside a significant decline in pulmonary tuberculosis cases. [7] The genitourinary tract is a primary target for hematogenous infections and the most common site of extra-pulmonary TB, constituting 14-41% of such cases. [8-10] Genitourinary tuberculosis (GUTB), first termed by Wildbolz in 1937, [11] is a global ailment with more destructive effects in developing nations, predominantly affecting the kidneys. Increased extra-pulmonary TB incidence is observed in individuals with acquired immunodeficiency syndrome (AIDS). Globally, 15% of TB patients are co-infected with HIV, rising to 75% in HIV-endemic areas, emphasizing the importance of testing HIV-positive patients for TB and vice versa. With improving AIDS patient survival rates, an escalation in urinary tract TB incidence is anticipated. [12]

Genitourinary tuberculosis (GUTB) typically impacts adults between the second and fourth decades, being considered rare in children and those in their fifth and sixth decades. [13] The average age of onset is 40.7 years, with a latent period of 5-40 years between pulmonary infection and renal disease manifestation. [8] Renal involvement is uncommon before the age of 20. The youngest reported case was a 2-year-old, but in India, children with urinary tract tuberculosis (UTB) are not uncommon. Symptoms of UTB have an insidious onset, lack specificity, and present with atypical features, contributing to diagnostic challenges and delays. Common local symptoms include frequent voiding, dysuria, pyuria, and abdominal or flank pain. Systemic symptoms such as fever, weight loss, and anorexia are less frequent. Hematuria and culture-negative pyuria are common findings. Laboratory analysis for acid-fast bacilli (AFB) in urine sediment is positive in 80-90% of cases. A negative chest radiograph and tuberculin test do not exclude the diagnosis of extra-pulmonary TB, and less than 50% of UTB cases show active TB or an abnormal chest radiograph. Imaging is crucial for diagnosis and follow-up, as it provides insights into the site and extent of the disease. Only 36.5% of UTB patients have a prior TB diagnosis or abnormal imaging studies, and evidence of active TB or an abnormal chest radiograph is present in less than 50% of cases. Additionally, 20-30% of UTB patients have a history of pulmonary TB, while 25-50% show radiographic evidence of prior subclinical pulmonary TB. The present study aimed to analyze various clinical presentations and treatment options in the management of patients with genitourinary tuberculosis.

Material and Methods

This cross-sectional study was done in the Departments of Urology/General Medicine, Deccan College of Medical Sciences(DCMS) & Owaisi Group of Hospitals [Owaisi Hospital and Research Centre(OHRC)/Princess Esra Hospital (PEH)] Hyderabad. Institutional Ethical approval was obtained for the study after following the due process for human research based on the Helsinki Declaration. Written permission was obtained from all the participants of the study after explaining the nature of the study in the vernacular language. The study tried to evaluate the role of urinary PCR in the detection of mycobacterium tuberculosis in patients with clinical suspicion of genitourinary tuberculosis and to compare its sensitivity with urine AFB smear urine for MB culture and bladder biopsy. The included patients were successive

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cases with a diagnosis of genitourinary tuberculosis who underwent treatment at our hospital. A total of 62 cases were reported with the diagnosis of genitourinary tuberculosis. Five patients were lost in follow-up after initial visits therefore, these patients were excluded from the study. The data was obtained from the remaining 57 patients available for the synthesis of results.
Management protocol: All the patients were evaluated with detailed clinical history and physical examination followed by a complete hemogram, Renal function tests, and Liver function tests. Urine examinations including bacterial culture were performed. Urine for AFB staining and mycobacterial cultures was obtained on the first-morning sample on 3 consecutive days. The first-morning sample of 37 cases was sent for PCR for detection of mycobacterium tuberculosis.

Technique for urinary PCR for MTb: In the lab, all the samples were processed in a class II biosafety cabinet. The first-morning sample of voided urine was collected. The samples were decontaminated, concentrated, and centrifuged at 3000 RPM for 30 minutes. The pellets were suspended in 20 mM Tris (pH 8.3). Two technicians worked independently in different areas of the laboratory without knowing the other's results. DNA extraction and PCR for amplification of the MPB-64 gene of the MTb complies were carried out according to the established protocol. DNA was extracted with proteinase K(1 mg/ml) and 0.5% Tween 20, followed by phenol/chloroform extraction and ethanol precipitation. The sequence of primers and probe were as follows;

Primer 1: 460-479 5'-TCCGCTGCCAGTCGTCTTCC-3'
Primer 2: 700-681 5'-ATCCTCGCGAGTCTACCA-3'
Probe: 601-617: 5'-CTTCAACCCGAGGGAGT-3'

The amplification reaction was performed in a 50-p, L volume reaction mix of 10mM Tris HCT (pH 8.3), 50mM Nack, 1.5mM $MgCl_2$, gelatin 0.01% (Wt/Vol), 200µM each of the four dNTPs (Boehringer Mannheim, Germany). 0.4 gm each of inners I and 2, 1.25 of Taq polymerase (Boehringer Mannheim, Germany), and 10 µm of extracted DNA from the sample (0.5 to 1.0 µg) and at 94℃ for 2 minutes, annealing at 58℃ to 63 ℃ for 2 minutes and extension at 72 ℃ for 2 minutes for 40 cycles. PCR had adequate positive and negative controls. The amplified product was analyzed on 2% agarose gel containing 0.5µg/ml ethidium bromide for a 241-bp band. Results were confirmed by Southern blotting and hybridization with a 32p3' end-labeled oligonucleotide probe. In PCR assay a sample was considered positive for MTh based on the visualization of 241-bp fragment agarose gel after staining with ethidium bromide and negative if the 241-bp fragment was absent.

Radiological evaluation included chest X-ray, KUB in all cases, and intravenous urogram when serum creatinine was normal. A micturating cystourethrogram, nephrogram, and retrograde pyelogram ultrasound study of the abdomen, computerized tomography, and MRI were obtained as and when necessary. Cystoscopy and bladder biopsy were done whenever indicated. FNAC was performed in cases with serosal masses. Renal nuclear scans were done selectively to ascertain renal function in compromised kidneys. All patients received antitubercular drug therapy with 4 drugs (Rifampicin, Ethambutol, Isoniazid, and Pyrazinamide) for 2 months followed by 2 drugs (Rifampicin and Isoniazid) for 7 months. Temporary urinary diversion in the form of DJ stenting or PCN was performed in cases of obstruction. The operative procedure was selected depending on the organ involved, the extent of the disease, the functional status of the involved organs, and overall renal function. The tissue/organs removed were sent for histopathological examination.

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Statistical analysis: All the available data was refined and uploaded to MS Excel Spreadsheet and analyzed by SPSS version 21 in Windows format. Continuous variables were represented as mean, standard deviation, and percentages. Categorical variables were calculated using the chi-square test and p-values of (<0.05) were considered as significant.

Results

A total of 62 cases were recorded in 5 years period. Among the cases, 5 cases were lost during follow-up after initial visits. They were excluded from the study. A total of 57 cases were included in the study out of which 39(68.4%) were males and 18(31.5%). The male-to-female ratio was approximately 2:1.

Table 1: Depicting the age-wise distribution of cases GUTB included in the study.

Age group (years)	*Frequency*	*Percentage*
20 – 29	13	22.8
30 – 39	25	43.86
40 – 49	15	26.32
50 – 59	3	5.26
60 – 69	1	1.75
Total	57	100.0

Table 1 shows the distribution of GUTB cases that the majority of GUTB cases (43.86%) are concentrated in the 30–39-year age group. This indicates a potential peak in GUTB occurrence during this age period. The second-highest frequency (22.8%) is observed in the 20-29 age group, further supporting the prevalence of GUTB cases among younger individuals. The frequency of GUTB cases progressively decreases with increasing age, with only 5.26% and 1.75% of cases occurring in the 50-59 and 60-69 age groups, respectively. This suggests a possible decline in GUTB occurrence among older individuals.

Table 2: Showing the symptoms reported by the 57 cases in the study.

Symptoms of GUTB	Frequency	Percentage
Increased frequency of urination/ urgency	41	71.92
Flank pain	19	33.33
Hematuria	22	38.59
Constitutional Symptoms	18	31.57
Recurrent UTI	12	21.05
Scrotal masses	3	5.26
Penile ulcer	1	1.75

Table 2 presents the symptoms reported by 57 GUTB patients in the study. Increased frequency of urination/urgency is the dominant symptom, present in 71.92% of patients, highlighting its significance as a potential indicator of GUTB. Flank pain (33.33%), hematuria (38.59%), and constitutional symptoms (31.57%) are also prevalent, suggesting their importance in the diagnostic process. Recurrent UTI (21.05%) is evident in a notable portion of cases, indicating a potential link between these conditions. Scrotal masses (5.26%) and penile ulcers (1.75%) are less frequent, suggesting their occurrence in a smaller subset of patients. The note about the co-occurrence of symptoms highlights the complexity of GUTB presentation. Analyzing the patterns and combinations of symptoms could provide valuable insights into the disease process.

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Laboratory findings: Raised ESR (erythrocyte sedimentation rate) is the most prevalent finding, with 82.45% of cases showing this abnormality. Pyuria is also common, occurring in 56.14% of cases, highlighting its role in the diagnosis of urinary tract infections associated with GUTB. Anemia and poor renal function are observed in a significant proportion of patients (45.61% and 29.82%, respectively), indicating potential disease-related complications. Positive Mantoux test (indicating past exposure to tuberculosis) is present in 36.84% of cases. Positive AFB staining in urine (detection of acid-fast bacilli) and positive MTb culture in urine are seen in 31.37% and 41.17% of cases, respectively, confirming the presence of Mycobacterium tuberculosis in some GUTB patients. Positive PCR for MTb in urine is present in 67.56% of cases (in a subset of 37 patients), demonstrating its potential as a diagnostic tool for detecting Mycobacterium tuberculosis in urine. Positive MTb culture in pus is only observed in 4 out of 7 cases, suggesting its less frequent occurrence compared to other positive findings. Sterile urine is found in 78.95% of cases, highlighting the importance of additional tests for diagnosing GUTB beyond urine culture alone.

Table 3: Showing Laboratory findings in cases of GUTB in cases of study

Lab findings	*Frequency*	*Total cases examined*	*Percentage*
Anemia (<10gm/dl)	26	57	45.61
Poor Renal function (Cr > 1.5mg/dl)	17	57	29.82
Leukocytosis (>11000 cells/mm^3)	11	57	19.29
Raised ESR	47	57	82.45
Positive Mantoux test	21	57	36.84
Pyuria (WBC >1.0/hpf)	32	57	56.14
Sterile urine	45	57	78.95
Positive AFB staining in urine	16	51	31.37
Positive MTb culture in urine	21	51	41.17
Positive MTb culture in Pus	4	7	57.14
Positive PCR for MTb in urine	25	37	67.56

PCR for the detection of mycobacteria was also done in pus samples which were aspirated while performing percutaneous Nephrostomy in cases of pyonephrosis and tissue from surgical specimens or bladder biopsies were sent for PCR to identify Mycobacterium tuberculosis. The results showed that urinary PCR was positive in 25/37(67.5%) cases, pus PCR was positive in 5/7(71.4%) cases and tissue PCR was positive in 10/12(83.33%) of cases.

Radiological abnormalities (IVU/NCCT/MUCG) suggestive of GUTB was found in 46/57 (80.7%) cases. Bladder biopsy was positive in 12/25(48%) cases done. A comparison of urinary PCR with urine for AFB staining urine for MTb culture and bladder biopsy was done.

Table 4: Comparison of urinary PCR with urine for AFB Smear, urine for MTB culture, and bladder biopsy.

PCR	Urine for AFB		Urine for MTb culture		Bladder biopsy	
	Positive	Negative	Positive	Negative	Positive	Negative
Positive	4	16	11	14	8	8
Negative	1	11	2	10	4	5

Organ involvement: Kidney was involved in 26(45.6%) cases and ureter in 24(42.1%) and bladder in 28(49.1%) cases. Radiological evidence suggestive of tuberculosis such as

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calcification, calyceal destruction, ureteral stricture, vesicoureteral reflux, and small capacity bladder was apparent in 80.7% of cases. Cystourethroscopy was performed in 37 cases and stricture urethra was seen in 2 cases. The bladder had evidence of chronic cystitis in the vast majority of cases. Bladder biopsy was diagnosed in 12(48%) of 25 biopsied cases. FNAC was suggestive of tuberculosis in 3 cases of epididymitis (Figure 1).

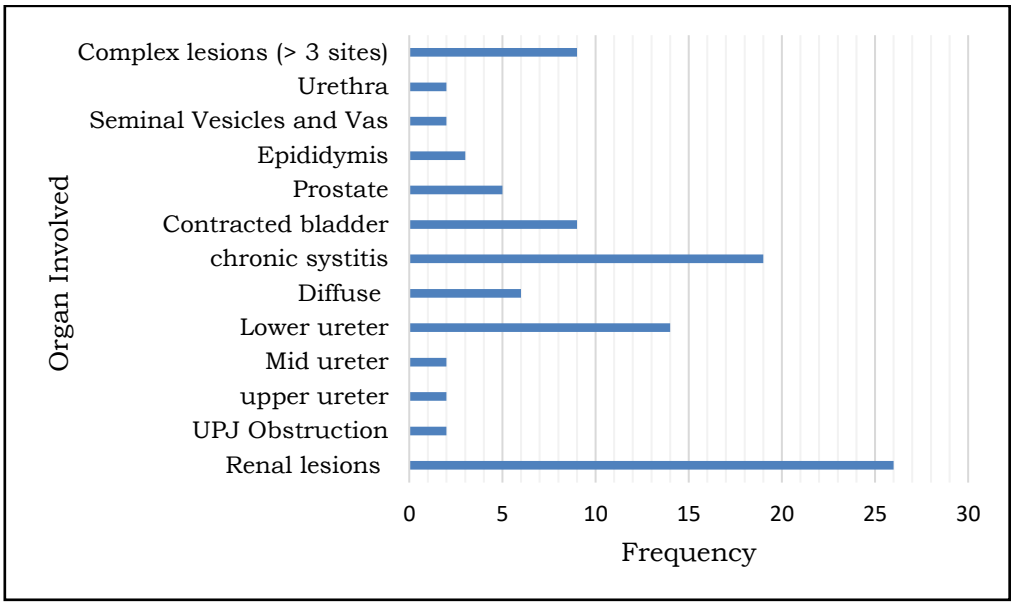

Figure 1: Showing the frequency of organ involvement in cases of GUTB

Nephrectomy/Nephroureterectomy is the most frequently performed surgery, with 26 cases. Sigmoid colocystoplasty is the second most frequent procedure, performed in 6 cases. Pyeloplasty (1 case), ureteroureterostomy (2 cases), ileal ureter (2 cases), Boaris flap (1 case), and ileocystoplasty (2 cases) are performed less frequently. Ileocystoplasty + Ileal ureter is performed in one case; the procedure was done for a complex case. Epididymectomy (3 cases) and visual internal urethrotomy (2 cases) are performed in a limited number of cases (Figure 2).

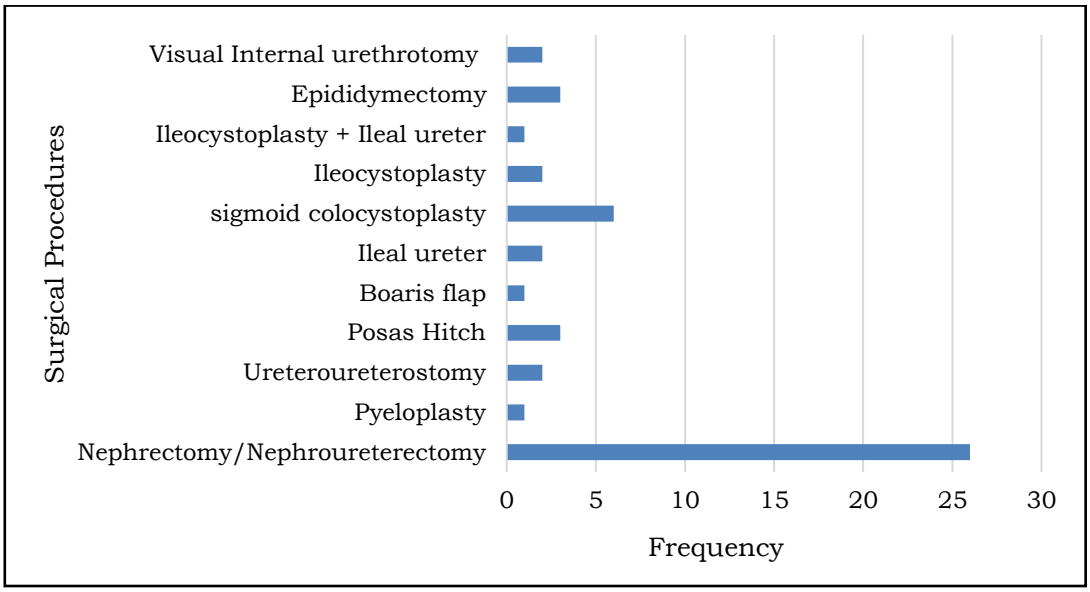

Figure 2: Details of surgery done in the cases of GUTB in this study

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Augmentation cystoplasty was performed in 9 patients and bladder capacity improved significantly in all patients. One patient underwent Ileocystoplasty along with ileal ureter replacement and his renal function has improved in the follow-up period. All the patients were followed up regularly at 2 weeks, 3 months, and 6 months after discharge and every 6 months thereafter. Follow-up ranged from 3 months to 5 years and one patient died of renal failure and sepsis following surgery for renal calculus. Renal functions improved in 22 patients stabilized in 12 patients and worsened in 6 patients.

Discussion

Tuberculosis can involve any organ system in the body and produce protean manifestation. Genitourinary tuberculosis (GUTB) is estimated to occur in 15% to 20% of cases of pulmonary tuberculosis with a prevalence of 400 per one lakh population. [14] The most common presenting symptoms in patients of GUTB are irritative voiding symptoms and hematuria in up to 50-60% of cases respectively. In our series irritative voiding symptoms were reported in 72% of cases, hematuria in 38.5% of cases, and constitutional symptoms in 31% of cases. In our patients, 21% had recurrent urinary tract infections. The incidence of renal failure in our series was 29.8% which is comparable to that of 24% reported in the literature.

Mycobacterium was grown in urine culture in 41.1% of our cases as compared with other similar studies where they reported growth in 50 – 90% of the samples. [14, 15] The lower detection rate in our cases was probably due to incomplete and intermittent treatment by primary care physicians for tuberculosis in the past. Radiological abnormalities in genitourinary tuberculosis are reported in 63% - 95% of cases. [16] In this study, we found evidence of abnormalities in 80.7% of cases. The common radiological abnormalities seen were calcification, cortical scarring, calyceal destruction, non-visualized kidney, ureteral stricture or irregularity, and contracted madder. This high percentage may be due to the late presentation of cases. We performed bladder biopsy in 25 cases to aid in the diagnosis and positive yield was obtained in 12(48%) cases. Wong et al., [17] achieved a tissue diagnosis in 18.5% of cases and reported no adverse effects of bladder biopsy. However, Gow et al. [18] suggested bladder biopsy should not be carried out unless a malignancy needs to be excluded. The high sensitivity of PCR is particularly in paucibacillary situations. PCR can provide much faster confirmation of the diagnosis (24-48 hrs) than MTb culture. [19] the limit of detectability of PCR may vary from about 10 microorganisms to as little as a single bacillus. Urinary PCR is specific for the MTb complex (MTb and M bovis) and has no crossover reaction with other mycobacterial species. In the 37 cases of proven GUTB where PCR was done it was found to be positive for 67.5% of cases which is lower compared with other studies where they reported a range of 85% to 95% [6, 20] In this study urinary PCR is falsely positive in 1 case (2.7%) and it may be caused by contamination due to the presence of amplicons or MTb complex bacilli or DNA. False negative results are found in 32.5% of the samples in our study in contrast 5 – 15% reported in the literature. [21] False negative findings may result from the presence of inhibitors, nonhomogeneous distribution of bacteria in the specimen so that the fraction tests do not contain mycobacteria or a low number of Mycobacteria in the specimen which decreases the probability of the presence of organisms in the fraction analyzed by PCR. In our study, the sensitivity of Urinary PCR is high (67.5%) when compared to the sensitivities of urine for AFB staining (31.3%) MTb culture (41.1%), and bladder biopsy (48%).

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Modern antitubercular chemotherapy remains the cornerstone of the management of genitourinary tuberculosis. Gow has recommended a short course of chemotherapy of 6 months as there were fewer bacilli in renal lesions than in pulmonary ones, high concentrations of rifampicin are achieved in urine and there is good penetration of streptomycin and isoniazid into cavities. While short-course chemotherapy is also recommended by WHO for uncomplicated extrapulmonary tuberculosis a large number of our patients have received intermittent incomplete antitubercular therapy before presenting to us. To ensure maximal chances of cure, we preferred to treat genitourinary tuberculosis as a complicated tuberculous infection with chemotherapy for at least 9 months. [22] The role of surgery is complementary to antitubercular chemotherapy. A minimum of 4 weeks of ATT is recommended before any surgical intervention. This period allows stabilization of the lesion and better planning of the conservative reconstructive surgery. In patients with compromised renal function due to obstruction, this period also aids recovery of renal function if adequate temporary urinary diversion is provided. We performed 26 nephrectomies including 12 nephroureterectomies for concomitant ureteral lesions. Of these patients, 2 had nephrocutaneous fistula. Involvement of the renal parenchyma is often irreversible even with adequate chemotherapy. However, not all patients with azotemia at the presentation have irreversible renal damage. [23] Tuberculosis may result in compromised renal function unilaterally or bilaterally due to obstruction at the ureteropelvic junction or due to ureteral or urethral strictures. These conditions are amenable to renal salvage if early intervention in the form of temporary diversion is instituted along with anti-tubercular therapy. Once the lesions are stabilized a decision regarding definitive management can be taken. Discrete lesions can be managed initially with minimally invasive endoscopic procedures. If they fail, open surgery may be offered according to the merits of the case. [24] Reconstructive surgery for genitourinary tuberculosis is required in cases with grossly distorted and dysfunctional anatomy that is unlikely to regress with chemotherapy alone. Earlier reconstructive surgery was performed in about 10% of cases of advanced genitourinary tuberculosis but has increased to 56% in recent times. In this study, we performed 46 surgical procedures, and out of these 38.2% were reconstructive. Various bowel segments have been used in the process of reconstruction. We have used the ileum and sigmoid colon and both segments produced equivalent results in terms of increase in functional capacity. Problems of dysuria and mucus discharge regressed specifically after a year and did not pose much of a problem thereafter.

Conclusion

The manifestations of genitourinary tuberculosis can be variable and cause a variety of clinical patterns that mimic other diseases. Most of these cases present with advanced disease and a high index of suspicion is necessary for the early diagnosis of genitourinary tuberculosis. PCR presents an advance in the diagnosis of GUTB. Urinary PCR is the most sensitive indicator of all microbiological tests and in combination with radiological abnormalities provides a much faster diagnosis of genitourinary tuberculosis. However, it is an elaborate test and requires meticulous care to avoid false positive and false negative results. Multidrug chemotherapy combined with judicious surgery as and when indicated is the ideal treatment. All attempts must be made to reconstruct the urinary tract as the results are gratifying. However, infected and destroyed tissue is best ablated.

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