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Genitourinary tuberculosis: A profile of 55 in-patients

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Abstract

Objective: To outline the pattern and trends in major cases of genito-urinary tuberculosis (GUTB) which require hospital treatment.
Method: We retrospectively reviewed 55 patients with proven GUTB who were treated as in-patients in a major referral hospital in Pakistan.
Results: The male/female ratio was 3:1. Prevailing symptoms were lower urinary tract symptoms, flank pain, gross hematuria and fever. A urine culture was positive for tuberculosis (TB) in 57%, bladder biopsies in 54%. For renal TB, intravenous urogram (IVU) and ultrasound were suggestive in about 50% of cases. Ultrasound was very helpful in the diagnosis of testicular TB. Patients underwent surgery in 36% of cases. In contrast to the general trend reported worldwide, surgery was mainly ablative rather than re-constructive. Patient compliance in clinical follow-up and drug therapy was poor.
Conclusion: Surgery for GUTB in Pakistan is still mainly ablative, probably due to a high number of complicated and progressed cases, To date, therapy of GUTB is mainly based on anti-tuberculosis chemotherapy (AU). However, huge efforts will be required to improve patient compliance without which every therapeutic approach will remain futile JPMA 50:265, 2000).

Introduction

Tuberculosis (TB) still causes a great deal of ill health in the population of most low income countries. In Pakistan, there are 300,000 new cases every year as per WHO estimation. Three quarters of patients are concentrated in the productive age group of between 15 and 59 years which means an enormous social and economic burden[1]. Thirty-three percent of all TB cases are extrapulmonary (EPTB). Although patients with EPTB hardly ever spread the disease[1], this form of the disease is a major health problem due to its destructive nature[2]. Genitourinary tuberculosis (GUTB) is the most frequent type of extrapulmonary TB in 40.9 to 54%[3,4], After the introduction of anti-tuberculosis chemotherapy (ATT), the incidence of GUTB has remained stable for some time3 and is now on the rise again in most countries, partly due to the development of drug-resistance and to its frequent association with AIDS[5]. Diagnosis has become more sophisticated using serological tests and polymerase chain reaction (PCR)[6]. The incidence of GUTB is now estimated at 3 new cases per million population per year (WHO, 1981).
Yet, to our knowledge there are only a few studies dealing with GUTB. One series reports of more than 1000 cases, however during a period of 34 years which includes entirely different and incomparable treatment approaches[7]. There are two more reports of series of8l 4 and 12 3 cases, respectively. These studies have been conducted in Europe. There are few studies comprising a representative study population from so called low income countries [8,9]. Therefore, we have reviewed 55 of our cases and like to share our findings here.

Material and Methods

In a retrospective study, we reviewed the medical records of 189 patients who had been treated as in-patients for genitourinary tuberculosis (GUTB) at the Aga Khan University Hospital from 1985 to 1997. Since only in-patients are coded for diagnosis in our hospital to date, we had to limit our analysis to in-patients. Also, only such patients were included who had a GUTB proven either by at least one urine culture positive for Mycobacterium tuberculosis, or a histopathological confirmation of caseating necrotic lesions in a biopsy or surgery specimen. The medical records of 55 such qualified patients were analysed with regard to age, sex, concomitant diseases, medical history, symptoms, diagnosis, treatment and follow-up. The remaining 134 patients had been treated on strong clinical suspicion alone and were, therefore, excluded from the study. Our results were then compared with those of other series reported in the international literature.

Treatment of GUTB patients in our institution followed WHO categorisation guidelines (WHO, 1996), rcommending for most patients a 4-drug regimen (isoniazid, ethambutol, rifampicin and pyrazinamide or, alternatively, in few selected cases streptomycin) for an initial phase of 2 months and a 2-drug regimen (usually comprising isoniazid and rifampicin) for a further 6 months. If indicated, patients were tested for multi-drug-resistance. A databank was set up by means of Microsoft Excel® software.

Results

The mean age of the 55 patients included in this study was 39.9±17.1 years (7-81 years). There were 41 (74%) males. Fifty-one (93%) patients were in category 1 (active pulmonary TB or extra-pulmonary TB with serious illness), 3 (5.4%) in category II (re-treatments) and 1(1.8%) in category Ill (extra-pulmonary TB without serious illness and children under 15 years of age). The prevailing symptoms were of the lower urinary tract, flank pain and fever (Table 1).

Table 1. Presenting symptoms (n = 55).

Lassitude	5	13%	Dysuria	27	49%
Fever	20	36%	Frequency	22	40%
Weight loss	7	13%	Urgency	8	15%
Testicular swelling	7	13%	Flank pain	20	36%
Renal colic	1	1.8%	Suprapubic pain	5	9%
			Gross hematuria	17	31%

None had a history of previous pulmonary tuberculosis (PTB). However, 6 patients (11%) had a history of extrapulmonary tuberculosis (EPTB) which dated back 4 years on average. Five had had GUTB and one a pleural affection. The chest X-ray suggested previous PTB in 14% of our cases. Concomitantly, there was diabetes mellitus in 33% of our patients, but no malignancy, or long-term cortisone therapy and no AIDS.

As to laboratory findings, 36% of patients had microhematuria in their urine, 56% had a

leucocyturia and 19% had a sterile pyuria. In 44 patients, one or more urine cultures were taken. They were positive for Mycobacterium tuberculosis in 25 (57%). A concomitant urinary tract infection with organisms other than mycobacteria was present in 9 patients (20%). Ziehl-Neelsen stained urine smear was positive for Mycobacterium tuberculosis in only one case. In two patients, mycobacteria could be cultured in abscess fluid (Table 2).

Table 2. Laboratory findings.

	Urine report (n = 55)			Urine Culture (n = 44)	
Red blood cells+	20	36%	M. tubercul+	25	57%
White blood cells+	31	56%	Other Infect.	9	20%
Sterile pyuria	6	19%			
	Urine smear (n = 39)		Abscess culture (n = 2)		
M. tubercul+	1	2.5%	M. tubercul+	2	100%

Of a total of 26 bladder biopsies, 14 (54%) showed evidence of tuberculosis. The results of diagnostic imaging and cystoscopies have been listed in Table 3.

Table 3. Diagnostic imaging and endoscopy (findings suggestive for TB).

	IVU (n = 31)	US (n = 22)	CSY (n = 18)	RUG (n = 3)	UCG (n = 1)
Kidney	17 (55%)	11 (55%)			
Ureter	9 (29%)	2 (9%)		2 (66.6%)	
Bladder	2 (6.5%)	1 (4.5%)	12 (66.6%)		
Testes (n = 5)		5 (100%)			
Urethra					1 (100%)

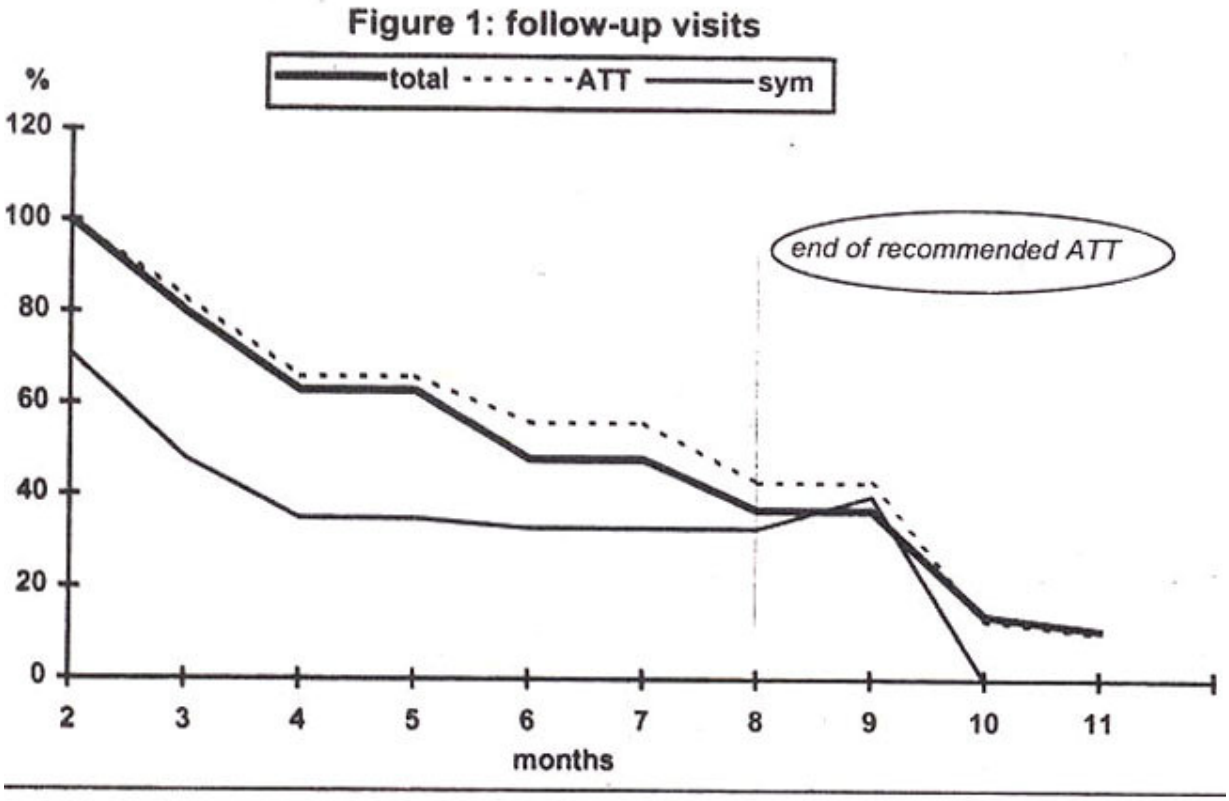
Legend: IVU = Intravenous Urogram; US = Ultrasound; CSY = Cystoscopy; RUG = Retrograde Ureterogram; UCG = Urethrocystogram.

Surgery was performed on 20 patients (36%). Most of the operations were ablative surgery, few re-constructive procedures (Table 4).

Table 4. Surgical procedures (n = 20).

Ablative procedures			Reconstructive procedures		
Nephrectomy	11	55%	Ureteral reconstruction	1	5%
Orchidectomy	4	20%	Auxilliary procedures		
Drainage of perinephritic abscess	1	5%	Double J*	4	20%
TUR bladder granuloma	1	5%			

Cystoscopies and bladder biopsies have not been listed under surgical procedures. Histopathology on surgical specimen showed evidence of tuberculosis in 8 out of 9 removed kidneys (89%) where these results were available and in 5 out of 5 removed testicles (100%). Anti-tuberculosis therapy (ATT) was recordedly started in 38 patients (69%). Sixteen patients (29%) were tested for multiple drug resistance. One patient developed a resistance against rifampicin (6.2%) and each two patients (12.5%) against isoniazid and strepromycin, respectively. Thirty-five patients (64%) were followed up after their initial visit. The average clinical follow-up in our out-patient clinic was 15.1 months (1-52 months). Patients had an average of 4.9 visits (1-21) during that time. Thirty-seven percent of patients visited our clinic after 8 months (which corresponds to the recommended duration of ATT) and 43% of patients recordedly completed the 8 months course of ATT. Symptoms ceased in half of the patients after 3 months and in >60% after 4 months. After 10 months, patients did no more complain about any previous presenting symptoms. The numbers of fo l towed-up patients, patients under ATT and patients with persistent symptoms associated with GUTB are depicted in Figure.



Legend:
total = number of patients followed-up
ATT = number of patients under ATT during follow-up
sym = number of patients with persistent symptoms related to GUTB

Urine cultures after the onset of ATT remained negative for M. tuberculosis in all cases. There were few positive bladder biopsies within the first 3 months of follow-up, however, none after that time.

Discussion

Tuberculosis (TB) in general and genitourinary tuberculosis (GUTB) in particular. can be defined as an infectious, systemic, chronic and granulomatous disease[1]. These characteristics imply a lot of well known clinical problems. But apart from clinical problems, TB has an enormous social and financial impact upon the population in Western, as well as in so called low income countries[1,2]. As all forms of TB, GUTB, too, affects mostly people in the productive age between 15 and 59 years [1,3,4,7,10,] This is also true for our patient population as shown by our mean age of 39.9±17.1 years. In a country like Pakistan, frequently many people within a family depend on one limited income. In case that the earner falls ill, there is no 'social net' to compensate for the loss of income, no health insurance to cover the costs of treatment and no government welfare office for those people to turn to. The clinical burden of GUTB may hence turn into a social catastrophe.
It seems, therefore, reasonable to re-evaluate the profile of GUTB as it presents today in a major

urology unit in Pakistan. Although it is recommended and commonly accepted that patients with the clinical picture of a likely TB who, in addition. did not clinically respond to two weeks of antibiotic therapy, are classified and treated as TB [1], we included in this study only in-patients with a microbiologially or histopathologically proven GUTB. There were 55 such patients out of 189 who had been diagnosed and treated as in-patients for GUTB on grounds of strong clinical suspicion. There was, however, a limitation in our choice of patients insofar as only in-patients are coded for diagnosis in this hospital, There is a number of patients with GUTB who had never been admitted and were, therefore, unidentifiable. Therefore, the number of 55 patients with proven GUTB does admittedly not reflect the true incidence of the disease in this country and in our hospital. However, it does reflect the picture of all the shades of the disease in a more progressed state. There is a male predominance in GUTB[4,7] which was also confirmed in our study with a male/female ratio of 3:1.

None of our patients reported a history of previous pulmonary TB (PTB) and chest X-rays were suggestive of previous PTB in 14%. This is in contrast to other studies which reported a history of PTB in 16 to 30% of cases[3,4,7] and TB positive chest X-rays in as much as 58%[4]. The lack of a history of previous PTB in our patients may be explained by the lack of screening and health care in our population, possibly resulting in a previous PTB going unnoticed and undiagnosed.

It is well known, that GUTB occurs more frequently in persons who display concomitant conditions such as malignancy, diabetes mellitus, long-term cortisone therapy, malnutrition [11,12] and more recently, AIDS5. Of those, only diabetes mellitus was associated with tuberculosis in our study population. Thirty-three percent of our patients had indeed, diabetes mellitus. This can be explained by the fact that there is a comparatively higher incidence of diabetes mellitus in Pakistan than in other countries[13] which may have genetical and nutritional reasons but certainly puts more people to the risk of concomitant infections such as tuberculosis.

In general, GUTB is characterised by the occurrence of local symptoms rather than constitutional ones[4]. Lower urinary tract symptoms have been reported as the most frequent symptoms in GUTB4 [4,10]. Also, due to the fact that renal TB accounts for 50% of cases of GUTB, flank pain is a frequent symptom in GUTB4. Gross hematuria in 10[14] to 36%[4] of cases frequently is the symptom that finally urges the patient to see a doctor. Our findings compare very well with these reports with one exception, however, fever occurred in 36% of our patients. This is most likely due to a high number of complicated and progressed cases displaying associated complications as we see them frequently. Again, this results from a lack of health education and infrastructure in this country which causes a delay in reporting to a primary health carer who then refers them to us as a complicated case.

The diagnosis of GUTB is based on a combination of clinical signs and ideally on a positive Ziehl-Neelsen stained smear or urine culture, or a positive biopsy. Whereas there was only one positive urine smear, urinary culture showed evidence of GUTB in 57%. In two cases, the diagnosis was confirmed by culture of abscess fluid.

Bladder biopsies were confirmative for GUTB in 54%. In other series, urine cultures have been reported to be positive in 54 to 73% of GUTB cases[10,15] endoscopic biopsies in 15%[10]. Our findings confirm that the sensitivity for urine cultures lies somewhere around 50%. However, they suggest that also bladder biopsies have a similar sensitivity range and are, therefore, a useful diagnostic tool in the evaluation of GUTB.

Other urinary parameters such as microhernaturia or leucocyturia may support the diagnosis[4,10]. They occur quite frequently. However, the often cited classical sign of sterile pyuria was present in only 19% of our cases.

Diagnostic imaging and endoscopy can only give indirect clues for the diagnosis of GUTB. We cannot confirm the high incidence of kidney abnormalities in GUTB as shown by IVP of 95%[4] However, about half of our patients showed renal alterations in IVP and sonography. Ultrasound was also very accurate in the diagnosis of testicular TB. The visualisation of a tuberculous bladder gave the right clues in as much as 57% which, together with the number of positive bladder biopsies, makes it a valuable diagnostic tool for GUTB of the bladder.

As to the treatment, 35 patients (64%) were managed conservatively and 20 (36%) underwent surgical procedures. Since the arrival of ATT, there was a shift from ablative to reconstructive surgery for the treatment of GUTB[16]. Compared with the literature[7,17] we performed, however, clearly more ablative surgery (80% versus 48/58%) and few reconstructive procedures. This may be caused, as mentioned earlier, by the referral of complicated cases to us as a tertiary referral centre which necessitated radical surgery as ultimate means. Similarly, given the patient and health system structure in low income countries, we see quite a lot of progressed cases with extended tissue destruction which also necessitate ablative surgery rather than reconstruction.

The introduction of ATT has reduced the mortality of GUTB from formerly 58~85%[18] to less than 5%[19] However, there is no unanimosity with regard to ATT for GUTB. More than 15 possible drug combinations have been described[20] and recommendations for the duration of treatment vary from 4 to 12 months[4,7]. The effectiveness of ATT is also somewhat questionable, since in 52% of surgical specimens, a florid TB was found after previous ATT for 9 (!) months[17].

For our patients, we followed the WHO guidelines which to date recommend a 4-drug therapy for an initial phase of 2 months, followed by a 2-drug regimen for a further 6 months (WHO, 1996). Usually, rifampicin and isoniazid are give in both phases. However, especially in a infrastructurally and educationally weak country like ours, there is a huge problem with patient compliance. Long-term follow-up is only followed by a minority of patients and only 43% of patients under ATT completed the full 8 months course. Patient guidance, motivation and education clearly are areas of emphasis in the future.

This will also have an impact on the sharp rise of ATT-resistant TB following incomplete or incorrect drug regimens. There are to date no data available with regard to the multi-drug-resistance in our country, however, our findings may give valuable clues to that regard; drug resistance was found in 6.2% of patients for rifampicin and in 12.5% for either isoniazid and streptomycin. And this in spite of the fact that only 5.4% of our patients were re-¬treatment cases.

First steps have been taken in our institution to improve patient compliance and overall performance of everyone involved in tuberculosis treatment with the introduction of a TB surveillance program which is, however, still in its early stages.

In conclusion, GUTB is still a prevalent problem with an enormous clinical and social impact. The latter is aggravated in low income countries due to the lack of compensatory mechanisms. The clinical picture compares with that reported in Western series. In summary, surgery for GUTB in Pakistan is still often ablative due to the high number of complicated and progressed cases. However, there are to date many centers in Pakistan using re¬constructive procedures such as bladder augmentation, cystoplasty, pyeloplasty and ureteroplasty in an effort to maintain the organs and to ensure a better quality of life for the patient. For diagnosis of bladder TB, we found cystoscopy and bladder biopsy a valuable tool. Therapy of GUTB is mainly based on ATT. However, huge efforts will be required in the future to markedly improve patient compliance without which even the best therapeutic approach will remain futile.

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References

1.National Guidelines for tuberculosis Control in Pakistan. Directorate of Tuberculosis Control. Federal Ministry of Health Pakistan. 1995.
2.Weir MR. The enigma of extrapulmonary tuberculosis. N. Y. State J. Med., 1989;89:251-52.
3.Petersen J, Mommsen S. Pallisgaard G. Male Genitourinary Tuberculosis. Scand. J. Urol. Nephrol., 1993;27:425-28.
4.Garcia-Rodriguez JA, Garcia Sanchez JE. Munoz Bellido JL, et al. Genitourinary Tuberculosis in Spain: Review of 8l Cases. CID, 1994:18:557-61.
5.Marqus LP, Rioja LS, Oliveira CA, et al. AIDS - associated renal tuberculosis. Nephron.. 1996;74:701-704.
6.Missirlu A, Gasman D, Vogt B, et al. Genitourinary tuberculosis: rapid diagnosis using the polymerase chain reaction. Europ. Urol., 1996;30:523-24.
7.Gow JG, Barbosa S. Gentiourinarv Tuberculosis. A study of 1117 cases over a penod of 34 years. Br. .1. Urol., 1984;56:449-55.
8.Rizvi A. Genitourinary tuberculosis. Europ. Urol. (update series), 1996;5:42 48.
9.Rizvi SAH, Naqvi SAA. Genitourinary tuberculosis. In: Whitfield tIN, et al (eds). A textbook of Genitourinary Stirgety, 2nd edition, Oxford, Blackwell Science, 1998;1:662-75.
10.E3ennani 5, Hafiani M, Debbagh A, et al. Urogenital Tuberculosis. Diagnostic aspects. J. Urol. Paris., 1995;101:187-90.
11.Alvarez S, McCabe WR. Extrapulmonary tuberculosis revisited: a review of experience at Boston City and oilier hospitals. Medicine. l984;63:25-55.
12.Cos LR, Cockett ATK. Genitourinary tuberculosis revisited. Urol., 1982;20:111-17.
13.Bhopal R, Unwin N, White M, wt al. Heterogeneity of coronary heart disease risk factors in Indian, Pakistani, Bangladeshi and European origin populations: cross sectional study. Br. Med. J., 1999;24:215-20.
14.l3ennedsen J. Tuberkulose-stadig at aktuelt problem. Editorial (in Danish). Ugeskr. Laeger. 1992;154:695.
15.Ferrie BG, Rundle JSH. Genitourinary Tuberculosis in Glasgow 1970-79: A review of 230 patients. Scott. Med. J., 1985:30:30-34.
16.Yaqoob M, Goldsmith I-U, Ahrnad R. Bovine Genitourinary Tuberculosis Revisited. Quart. J. Med., (New Series), 1990;74:l05-109.
17.Fischer M, Flamm J. The value of surgical therapy in the treatment ot' urogenital tuberculosis. Urologe. A., 1990;29:261-64.
18.Sporer A, Openheimer GD. Renal tuberculosis J. Mount Sinai Hospital, 1956;23:521-28.
19.Gow JG. Results of treatment in a large series of cases of genito-tirinary tuberculosis and the changing pattern of the disease, Br. J, Urol., 1970:42:647
20.Dolbcrg OT, Schlaeffer F, Greene VW, et al. Extrapulmonarv Tuberculosis in an Immigrant Society: Clinical and Demographic Aspects of 92 cases. RID, 199 1:13:177-79.