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Diagnostic pitfalls of urogenital tuberculosis

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Abstract

OBJECTIVES To describe characteristics, details of diagnosis and outcomes of urogenital tuberculosis (UGTB) in a low-prevalence country.

METHODS We conducted a retrospective observational study of 37 consecutive patients diagnosed with UGTB between 1st January 2014 and 31st October 2019 in an East London hospital.

RESULTS 68% (25/37) of patients were male and the median age was 42 years (IQR 34–55). 89% (33/37) of patients were born outside the United Kingdom with 65% (24/37) born in the South Asian region. Renal (32.4%), epididymal (24.3%) and endometrial TB (21.6%) were the most prevalent forms of UGTB. Only 13.5% of UGTB patients had concurrent pulmonary TB. The median length of time from symptom onset to treatment was 163 days, while endometrial TB had an average delay to diagnosis of 564 days. Approximately half of patients with UGTB were culture positive (51.4%). However, 70% of early morning urines (EMUs) sent in urinary TB were culture positive. 11 patients (30.6%) underwent two or more invasive procedures, such as biopsy to obtain specimen samples. The mean treatment length for all UGTB cases was 7.3 months (SD 3.1). Notably, 25% of patients with endometrial TB required surgery despite antituberculous treatment.

CONCLUSIONS UGTB is challenging to diagnose as early disease is often asymptomatic. Clinicians faced with non-specific symptoms, or features suggestive of urogenital malignancy amongst patients from TB-endemic areas, should maintain a high suspicion of UGTB.

keywords urogenital tuberculosis, extra-pulmonary tuberculosis, tuberculosis diagnostics, tuberculosis treatment

Sustainable Development Goal: Good Health and Well-Being

Introduction

Tuberculosis (TB) is one of the top ten causes of death globally [1] and is a major public health concern causing significant physical and psychosocial morbidity. In 2019, it was estimated that there were 10 million new cases of TB and 1.4 million deaths globally attributable to TB [1]. 16% of worldwide TB cases in 2017 were extra-pulmonary (EPTB) and affected body sites other than the lungs [2]. EPTB is more common in the United Kingdom (UK) than EPTB globally, comprising approximately 58% of UK TB cases [2]. Urogenital TB (UGTB) can affect any part of the urogenital tract including the kidneys, ureter, bladder, prostate, urethra, penis, scrotum, testicles, epididymis, vas deferens, ovaries, fallopian tubes, uterus, cervix and vulva [3]. Urogenital TB can be broadly classified into three clinical categories; urinary TB, male genital TB (MGTB) and female genital TB (FGTB). Correct classification is important to choose the optimal therapeutic option [4].

Globally, UGTB is the second most common form of EPTB after lymph node TB [5] and represents approximately 27% of EPTB [6]. This can result from primary spread to the urogenital region but more commonly occurs in the context of disseminated disease [6]. It has been estimated that 2–20% of patients with pulmonary TB have concurrent UGTB [3] and 25–62% of patients with miliary TB develop haematogenous spread to the urogenital tract [5].

Patients with UGTB can be asymptomatic, but often present with non-specific symptoms of insidious onset [7, 8]. It is, therefore, under-recognised and under-diagnosed by clinicians leading to delayed referrals to TB services for management [9]. This invariably leads to disease progression and can result in longer TB treatment courses.

The diagnosis of UGTB relies either on culture or DNA identification of *Mycobacterium tuberculosis (M. TB)* from the urogenital site. Apart from urine analysis, diagnostic samples from the urogenital region can be difficult to obtain and may require invasive sampling [3]. The yield from culture and molecular tests is variable depending on the urogenital site. In women with UGTB, the yield from culture can be as low as 10.6% if the disease is subclinical and microbiological confirmation of TB is particularly difficult in FGTB [9]. Conversely, bladder TB has been shown to have a better molecular and microbiological sensitivity of diagnostic tests [10].

Diagnostic challenges of UGTB make estimation of prevalence challenging [11] and therefore it is difficult to determine which populations are most at risk of developing UGTB. Moreover, UGTB can lead to chronic sequelae of disease resulting in significant chronic pain disorders, functional abnormalities and infertility [11].

East London has a diverse population, including a large number of migrants from predominantly South Asian and Sub-Saharan African countries with high TB rates. For example, the borough of Newham had the highest TB incidence in the United Kingdom (103.9 per 100 000 population) in 2013 [12]. Here, we describe characteristics, details of presentation, diagnosis and outcomes of UGTB in a low prevalence country.

Methods

All cases of active TB diagnosed at our institution between 1st January 2014 and 31st October 2019 were identified from the London TB register. All consecutive patients who were diagnosed with UGTB were included from this cohort if they were older than 16 years and had no missing data. Data for patients with UGTB were obtained through electronic patient records. Information about site of disease, clinical presentation and the presence of comorbidities such as HIV co-infection was obtained. Data on microbiological and histopathological findings were collected. To evaluate diagnostic delay amongst these patients, information on time from symptom onset to presentation, time from presentation to diagnosis, and time from symptoms to initiation of treatment were recorded. Data on anti-tuberculous treatment (ATT) as well as treatment outcomes including death and relapse were captured. Demographic data of cases with UGTB were analysed and compared with that of non-UGTB cases. The chi-squared test was performed for categorical variables (Migrant status, gender, ethnicity and region of birth) and a Wilcoxon rank-sum test was used to compare age between the two groups. Statistical analysis was performed using STATA IC version 16. Alpha level was 0.05 for all statistical tests.

Results

Demographic results

There were 2181 patients treated for TB at Barts Health NHS trust between 2014 and 2019. Of these, 37 (1.7%) patients were treated for UGTB.

Cases with UGTB had a median age of 42 years (IQR 34–55). This was older than cases with non-UGTB, whose median age was 36 years (IQR 28–49) ($P = 0.03$). The proportion of cases who were born outside of the United Kingdom was similar between the two groups (89.2% vs. 81.1%; $P = 0.44$) and a significantly higher percentage of cases with UGTB had migrated from South Asia compared to non-UGTB cases (64.9% vs. 37.1%; $P = 0.03$) (Table 1). There was a higher proportion of male than female cases (67.6% vs. 32.4%) in the urogenital cohort and the median time between entry to the United Kingdom and diagnosis with UGTB was 10 years (IQR 4–22).

Urogenital TB sites and clinical features

Urinary TB was the commonest type of UGTB with the most prevalent site being the kidneys (32.4%). This was followed by MGTB with the majority of men presenting with epididymal TB (24.3%). FGTB was less common than the other types of UGTB with 21.6% of cases presenting with endometrial TB. Other urogenital sites of TB are displayed in Table 2. Fourteen patients (37.8%) had TB at another extra-pulmonary site concurrently, whilst five of the 14 patients (13.5%) had pulmonary TB in addition. No patients in the cohort tested positive for HIV. Two patients who developed renal TB and one patient with bladder TB were on immunosuppressive therapy after either renal or bone marrow transplants, two of whom had multi-site TB.

The majority of patients with urinary TB were asymptomatic but few presented with flank pain (3/16, 18.8%), urinary frequency (2/16, 12.5%), haematuria (1/16, 6.3%) and nocturia (2/15, 13%). Notably, half of urinary TB patients had renal impairment on initial presentation (8/16). Testicular swelling was common amongst MGTB patients (11/13, 84.6%), however, testicular pain was less common (3/13, 23.1%). All patients with prostate TB had lower urinary tract symptoms including urinary frequency and urgency, dysuria, nocturia and one patient described pain on ejaculation.

Amongst women with FGTB, the predominant symptom was abdominal or pelvic pain (4/9, 44.4%). Other

Table 1 Demographic data of cases with urogenital TB (n = 37) compared to non-urogenital TB (n = 2143)

Demographics		UGTB	Non-UGTB	*P*-value
Age (years), median (IQR)		41 (31.5–50.5)	36 (28–49)	0.03
Male, *n* (%)		25 (67.6)	1348 (62.9)	0.56
Migration status, *n* (%)	Born in UK	4 (10.8)	394 (18.4)	0.44
	Born outside of UK	33 (89.2)	1737 (81.1)	
	Unknown	0 (0.0)	10 (0.5)	
Ethnicity	Bangladeshi, *n* (%)	11 (29.7)	424 (19.8)	0.44
	Indian, *n* (%)	11 (29.7)	453 (21.1)	
	Black-African, *n* (%)	5 (13.5)	316 (14.8)	
	White, *n* (%)	4 (10.8)	235 (11.0)	
	Other, *n* (%)	2 (5.4)	260 (12.1)	
	Pakistani, *n* (%)	2 (5.4)	332 (15.5)	
	Black-Caribbean, *n* (%)	1 (2.7)	74 (3.5)	
	Chinese, *n* (%)	1 (2.7)	18 (0.8)	
	Unknown, *n (%)*	0 (0.0)	5 (0.2)	
Region of birth	South Asian region, *n (%)*	24 (64.9)	794 (37.1)	0.03
	European region, *n (%)*	5 (13.5)	632 (29.5)	
	African region, *n (%)*	5 (13.5)	304 (14.2)	
	Eastern Mediterranean region, *n (%)*	2 (5.4)	298 (13.9)	
	Region of the Americas, *n (%)*	1 (2.7)	38 (1.8)	
	Western Pacific region, *n (%)*	0 (0.0)	55 (2.6)	
	Unknown, *n (%)*	0 (0.0)	22 (1.0)	

Table 2 Sites of disease and organs affected in urogenital TB cases (N = 37)

Urogenital TB type	Organ affected	No of patients, *N* (%)
Urinary TB	Kidney	12 (32.4)
	Bladder	3 (8.1)
Male genital TB	Epididymis	9 (24.3)
	Prostate	3 (8.1)
Concomitant urinary and male genital TB	Kidney & Epididymis	1 (2.7)
Female genital TB	Endometrium	8 (21.6)
	Ovaries	1 (2.7)

symptoms described in endometrial TB included infertility (2/8, 25%), amenorrhea (2/8, 25%), intermenstrual bleeding (1/8, 12.5%), post-menopausal bleeding (2/8, 25%), menorrhagia (1/8, 12.5%) and deep dyspareunia (1/8, 12.5%).

Night sweats were the most common non-specific symptom across the cohort (9/37, 24.32%), whilst seven (18.92%) had fevers and five (13.51%) experienced weight loss.

Diagnosis

In 35 patients, the median length of time from symptom onset to treatment was 163 days (IQR 73–243) with a maximum time to diagnosis of 1746 days (4.8 years). This information was missing in two patients. Patients with urinary TB had a median time from symptom onset to the treatment of 163 days (IQR 75–184). MGTB had a shorter median time of 105 days (59–219.5) with patients with epididymal TB taking 126 days (IQR 56–208) to start treatment. FGTB had the longest delay from symptom onset to treatment with a median of 347 days (IQR 76–897) with patients with endometrial TB taking 563.5 days on average to start on treatment (IQR 84–1329.5). Diagnosis of UGTB in our patient cohort relied on a combination of radiological investigations followed by more invasive diagnostic sampling from the affected site. Thirty-six of 37 patients with UGTB were included in the analysis as one patient transferred out. The majority of patients (19/36, 52.8%) had at least two radiological tests prior to diagnosis. The most common radiological investigations used to diagnose urinary TB included CT of the abdomen and pelvis and ultrasound of the renal tract. Eight of 16 patients had abnormal findings on imaging including renal scarring, echogenic kidneys, urothelial thickening, enlarged lymph nodes and fluid collections/abscesses on the native kidney or graft bed. Ultrasound of the testes was performed on all patients with epididymal TB with abnormalities detected in seven of the nine patients. Abnormal findings included orchitis, epididymo-orchitis, scrotal masses and abscesses. Prostate lesions were detected on

MRI of the prostate in two patients with prostate TB. The third underwent an ultrasound demonstrating an enlarged prostate and calcific concretions. Amongst the FGTB patients, all women underwent a pelvic or transvaginal ultrasound. Of the eight women with endometrial TB, three were found to have a thickened endometrium, endometrial cysts were seen in two, one had a bulky uterus and another a heterogenous-appearing endometrium. Only one patient had no abnormal findings. Five patients underwent an MRI of the pelvis to further characterise the abnormalities seen on ultrasound. The one patient with ovarian TB had bilateral ovarian cysts seen on ultrasound and septated cysts visualised on MRI of the pelvis.

Twenty-eight of 37 patients underwent a biopsy of the urogenital site (65.1%); six underwent endobronchial ultrasound (EBUS) and lymph node biopsy (13.9%). Four of 37 patients underwent aspiration of fluid from the urogenital site or its surroundings (9.3%), two underwent excision of the site (4.7%), two underwent fine-needle aspiration of the site (4.7%) and one had a lymph node biopsy (2.3%). Eight patients (22.2%) underwent two invasive procedures before the diagnosis was made and three patients (8.3%) underwent at least three invasive procedures. 70% of UGTB patients (26/37) had granulomatous changes on histology samples from the urogenital site.

Ziehl-Neelsen (ZN) staining was performed on clinical specimens other than sputum in 32 out of 37 cases (86.5%) and four of these (12.5%) were smear-positive. *M.TB* was cultured in 51.4% of all patients (19/37). Out of 10 patients with epididymal TB, six (60%) were culture-positive; four of 8 patients (50%) patients with endometrial TB were culture-positive; five of 12 (41.6%) patients with renal TB were culture-positive. One of three patients with prostate TB was culture-positive and all three cases (100%) with bladder TB were culture-positive. Ten of 16 patients (62.5%) with renal or bladder TB had early morning urine tests sent for acid-fast bacilli (AFB) culture. Of those, 70% (7/10) were culture-positive. Of the positive TB cultures, 17 patients (89.5%) had fully sensitive TB and one patient had Isoniazid monoresistance and one patient had polyresistant TB. Two patients were culture-positive, but drug susceptibility testing failed. No patients within this cohort underwent TB PCR.

Management

Treatment duration was documented for 33 patients; two are still on treatment and one was lost to follow-up and were, therefore, excluded. Only four patients (11.43%) were admitted to hospital for initiation of treatment. Standard ATT (2 months of rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) followed by 4 months of RH was given to 51.6% of patients (16/31). Five patients with renal or bladder TB and renal impairment were started on RHZ and moxifloxacin (M). The mean treatment duration overall for UGTB was 7.3 months (SD 3.1). The maximum duration of ATT was 18 months in a case of widespread disseminated TB with concurrent renal TB. As the patient had been previously treated for disseminated TB and was responding poorly to initial treatment, s/he was switched to a multidrug-resistant (MDR) TB treatment regimen. The mean treatment duration of different urogenital TB sites is displayed in Table 3. Renal, epididymal and endometrial TB cases all had a longer treatment course than the standard 6 months ATT. Bladder and ovarian TB required at least 10 months ATT.

Nine of the 36 (25%) patients underwent surgical removal of the UGTB site: five of 9 (55.5%) of epididymal TB cases; two of 8 (25%) of endometrial TB cases; one of 12 (8.3%) of renal TB cases and one ovarian TB case. Five cases were lost to follow-up. There were no documented deaths at one year of follow-up.

Discussion

This study reports that UGTB predominantly affects male patients in their 40s and ethnic minorities originating from high TB prevalence countries, which is comparable to other UGTB cohort studies [9, 10, 13, 14]. The region where the largest proportion of UGTB cases was born was South Asia. The ethnic minorities most affected by UGTB in East London were Indian and Bangladeshi. Notably, 40% of patients with UGTB had another site of non-UGTB indicating disseminated disease [6] and 13.5% of UGTB patients had concurrent pulmonary TB,

Table 3 Treatment duration for different urogenital tuberculosis (TB) sites

Urogenital TB site	patients with treatment duration	Duration of treatment in months, mean (SD)
Renal	11	7.6 (4.6)
Epididymal	7	6.4 (1.1)
Endometrial	8	6.5 (1.1)
Bladder	2	10.5 (2.1)
Prostate	1	6.0 (0.0)
Renal & Epididymal	1	9.0 (0.0)
Ovarian	1	10.0 (0.0)

which is similar to other extra-pulmonary TB studies [13]. Only a few patients presented with constitutional symptoms suggestive of TB, but many had no symptoms or non-specific symptoms not typical of TB.

The most common site of UGTB in our cohort was the kidneys, which is supported by other cross-sectional studies [5, 6]. A high proportion of our patients with renal TB presented with end-organ damage indicating a significant delay in diagnosis. The average time from symptoms to starting treatment for urinary TB was 163 days. This is almost double the time period expected for patients to be diagnosed with pulmonary TB [15]. In addition, our study found that three patients (25%) who developed renal TB were on immunosuppressant therapy, post-renal and bone marrow transplant. Increased rates of TB have been observed amongst transplant recipients and transplantation remains an important risk factor for the development of TB [16].

Early morning urine (EMU) is a useful non-invasive method to diagnose renal and/or urinary tract TB, but there is a large variability in its sensitivity ranging from 10.7% to 80% depending on the site and severity of disease [9]. In our study, 70% of EMUs that were sent in renal and bladder TB were culture positive for *M.TB*. Despite this, 75% of patients underwent a renal biopsy in renal TB and 66.7% had a bladder biopsy in bladder TB in order to make a definitive diagnosis. An earlier suspicion of TB prompting an EMU could avoid more invasive diagnostic tests and should, therefore, be used as a first-line test to diagnose renal and urinary tract TB. This is especially important in patients with sterile pyuria and risk factors for TB [17, 18]. Confirmation of *M.TB* through culture or PCR is essential due to contamination of urine samples by other non-pathogenic environmental mycobacteria [18]. PCR performed by the GeneXpert MTB/Rif or BDMax assays [19] can also be used to detect *M.TB* and has been demonstrated in some studies to have superior sensitivity in diagnosing urinary tract TB compared to culture and microscopy [20].

Endometrial TB occurred in 89.9% of FGTB in our cohort, which is higher than the estimated 50–80% from retrospective studies performed in high TB prevalence countries [8, 21]. Infertility has been the most commonly reported symptom in studies, ranging from 40–80% of endometrial TB cases [8]. Only a quarter of patients with endometrial TB in our cohort presented with infertility (25%). Other common symptoms in our cohort of endometrial TB cases included abdominal/pelvic pain (37.5%) and vaginal bleeding (37.5%), which have slightly different prevalence in previous studies (50–55% and 20–25%, respectively) [21]. Our findings of delayed diagnosis in endometrial TB are, however, supported by other studies [15]. The average delay to diagnosis for patients presenting with symptoms related to their endometrial TB was approximately 1.5 years and the maximum delay was over 4 and a half years. The significant delay between symptom onset and presentation to health care highlights the insidious nature of endometrial TB.

Endometrial biopsies are the most common specimen used for diagnosis of endometrial TB [22] and all patients with endometrial TB underwent a biopsy of their endometrium in order to make the diagnosis. Endometrial TB is paucibacillary and only half of patients were diagnosed by culture of *M.TB* [8]. Imaging is also of limited use due to non-specific radiographic findings that are often difficult to differentiate from other conditions such as a malignancy or other infection in the endometrium [8]. Imaging is more useful in ovarian TB as tubo-ovarian masses are often seen on MRI pelvis [8] as demonstrated by one patient in our cohort who had ovarian TB.

Epididymal TB was found to be the second most common UGTB site and is usually one of the commonest sites of male UGTB, alongside the prostate [23, 24]. All patients with epididymal TB within our cohort presented with either scrotal or testicular swelling, which has also been reported by other studies [24]. Testicular pain or tenderness is not a frequent feature [24] and was only present in two patients within our cohort. Epididymal TB commonly causes an epididymo-orchitis with formation of a hydrocoele, abscess or calcification, which can usually be seen on ultrasound [9] and was the commonest diagnostic test used in our cohort. The median time from symptom onset to diagnosis was 18 weeks, which was less than almost all urological and FGTB. Diagnosis relied on sample from the site either by biopsy of the epididymis or testicle, aspiration of hydrocoele or scrotal abscess or in two cases, excision of the testicle. In the two cases that had an orchidectomy prior to diagnosis, this was performed as there was a concern of malignancy. In a larger cohort of patients with MGTB, it has been reported that one in five patients with epididymal TB was only diagnosed after orchidectomy [25]. An isolated tuberculous epididymo-orchitis without the presence of systemic TB features or evidence of TB at other sites can often be mistaken for testicular cancer [26]. This often causes delays in TB diagnosis and can result in unnecessary radical treatment such as orchidectomy [7, 25, 26].

Studies suggest that prostate TB accounts for 11% of UGTB [25], however, there were few prostatic TB cases within our population. Our cases were also diagnosed quickly as they presented with lower urinary tract symptoms prompting examination and early imaging of the

prostate. This is contrary to the literature, where prostate TB is largely asymptomatic and remains undetected until incidental finding on prostatic biopsy [13, 27]. Prostatic TB, similar to epididymal TB, is often assumed to be prostate cancer on initial presentation [27] prompting biopsy of the prostate [28]. This occurred in two out of three cases, while the other case had a positive EMU for TB culture immediately after presentation.

Diagnosis of TB relies on histology suggestive of TB or culture/molecular TB diagnosis from the UG site [3]. However, only half of patients with UGTB were culture positive (51.4%) [17]. Eleven patients (30.6%) underwent two or more invasive tests to obtain specimen samples. This was frequently due to a failure to send specimen samples for mycobacterial culture or TB PCR.

Management of UGTB is similar to that of pulmonary TB and a standard treatment course of 6 months is usually sufficient in drug-susceptible UGTB [23]. The mean treatment duration for all UGTB patients was 7.3 months (SD 3.1), suggesting that a longer treatment course was required. Although endometrial TB was treated on average for 6.5 months, two patients with endometrial TB required surgery after treatment. Over half of patients with epididymal TB underwent surgery prior to diagnosis [25].

Limitations of our study include its retrospective nature and a lack of HIV-positive cases within our cohort, who are at higher risk of developing EPTB [29]. Patients were usually discharged from TB services on completion of ATT and therefore information regarding long-term sequelae was not available.

Our results demonstrate that UGTB often goes undetected for long time periods in low prevalence settings. Poor recognition of high-risk groups, as well as non-specific clinical features of UGTB, means that patients not only experience delay to diagnosis but may be subjected to multiple invasive investigations.

Conclusions

UGTB can be challenging to diagnose, with patients frequently presenting with more advanced disease compared to pulmonary TB. Our study highlights that UGTB should be suspected in patients from high TB incidence countries presenting with urogenital signs and symptoms, ensuring that samples are sent for TB culture without delay. Early diagnosis can help prevent irreversible end-organ damage and the need for surgical intervention.

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