REVIEWS

Why do we miss isolated male genital tuberculosis diagnosis?

Running title: Genital tuberculosis diagnosis

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SUMMARY

Tuberculosis remains a worldwide health problem. It can affect the entire genitourinary tract. Tuberculosis of male genital tract still presents a diagnostic dilemma because of its varied presentations and the unavailability of sensitive and specific investigations.

"Urogenital tuberculosis" is the most common term used in the literature. Male genital tuberculosis (MGTB) is usually reviewed together with urinary tract tuberculosis because often both sites are involved simultaneously; however, this is not always the case and current terminology may need to be modified. Until now, little importance has been given to isolated MGTB diagnosis. The current methods used for diagnosis are not adequate and the optimal strategy warrants further studies with a special attention on the evaluation of sperm investigations.

In this review, we aim to establish a summary on the type of tuberculosis affecting only the male genital tract. We recommend that the diagnosis of MGTB should be made taking into

consideration the epidemiological data, the clinical presentation, and performance of latest molecular or immunological tools from urine, sperm, blood, other fluids or tissue specimens.

Keywords: Isolated male genital tuberculosis; Extrapulmonary tuberculosis; Diagnosis; Urogenital tuberculosis; Terminology.

INTRODUCTION

More than a century following the isolation of the causative organism, tuberculosis (TB) remains a worldwide health problem. Approximately one third of the world population is infected [1]. TB can affect the entire genitourinary tract. It is one of the most common sites of extrapulmonary tuberculosis (ETB) and accounting for about 30-40% of all cases [2, 3].

In the majority of literature, male genital tuberculosis (MGTB) is reviewed together with "urinary tract tuberculosis" (UTTB) because often both sites are involved simultaneously; "Urogenital tuberculosis" (UGTB) is the most common term used in the literature. However, the term may cause confusion as the infection does not always occur simultaneously.

There are currently quite a lot of difficulties that clinicians encounter when facing a possible case of isolated MGTB because of its varied presentations and unavailability of sensitive and specific investigations. Thus, TB of male genital tract still presents a diagnostic dilemma.

The aim of this review is to highlight the pathophysiology, clinical features, diagnostic challenges of tuberculosis affecting only the male genital tract and to improve awareness of MGTB in the differential diagnosis. This review also shows the variability and nonexistence of uniform consensus for this presentation.

MATERIALS AND METHODS

An electronic search was carried out at PubMed, MEDLINE, Scopus, Embase, and Google scholar to realize this narrative review. The search was limited to literature and studies including isolated MGTB, published in English, and was not limited up to July 2022. Search terms included "*isolated male genital tuberculosis"*, either separately or in different association. For PubMed/Medline database, we used MeSH terms that resulted in a total of 138 titles, 40 within the last 10 years (since 2012); among the articles of the last 10 years, 29 (72.5%) were case reports.

Terminology

Porter was the first to mention the term "urogenital tuberculosis" in 1894 [4]. Then, in 1937, the term "genitourinary tuberculosis'' was proposed by Wildbolz [5]. Actually, we think that these terms are incorrect because they involve both "urinary tract tuberculosis" and "male genital tuberculosis". Moreover, clinical and laboratory features and treatment approaches of each of these forms are different. Also, they do not provide an information of the site of TB process.

Nevertheless, since this term is commonly used in the literature, we will also use it here.

Male genital TB was classified by Kulchavenya as follows [6]:

- Orchiepididymitis (unilateral or bilateral);
- TB of the penis (TBP);
- Prostate TB;
- TB of seminal vesicles;

– The vas deferens and Cowper's glands involvement may also occur [7].

Complications of MGTB include strictures, fistula, infertility and sexual dysfunction [6].

Epidemiology

TB is a major public health problem worldwide, The World Health Organization (WHO) estimates that nearly one third of the world's population is infected with *M. tuberculosis* [8]. In recent years, the number of people developing TB has been gradually declining. Approximately a total of 10 million people developed TB in 2019 [9].

MGTB cases occurs most frequently in young adult males aged between 30-50 years [9-11]. Delays can lead to infertility if misdiagnosed or not early treated, and it is considered as a severe form of ETB [8, 12, 13].

The first site most commonly affected is the epididymis, followed by the prostate, the seminal vesicles and the testicles [14].

Above half of patients with male genital TB also have pulmonary and/or kidney TB [12]. However, isolated MGTB cases are rare: about 5% of all the cases [12]. They mimic other urologic conditions and have variable clinical symptoms, thereby these cases are hard to diagnose and have been broadly underreported and mainly published as case reports or as retrospective clinical reviews [15-19].

Pathogenesis

The TB disease most commonly affects the lungs through the inhalation of aerosols containing *M. tuberculosis* [2]. Bacillaemia can occur during primary pulmonary TB, miliary TB or in the reactivation of the latent TB infection. This leads to the development of the tubercle bacilli in any part of the genitourinary tract. The possible modes of genital tract involvement includes reactivation of the latent bacilli, descending infection from the urinary tract, blood-borne infection without urinary tract involvement, lymphatic spread, complication of intravesical bacille Calmette-Guérin (BCG) therapy for the treatment of transitional cell carcinoma of the bladder [3].

The first genital organ most commonly affected is the epididymis [20]. Epididymo-testicular TB usually results from a hematogenous, canalicular spread, lymphatic route, or descent from

the kidney [21]. Kim et al. showed that the disease primarily starts in the tail of the epididymis possibly due to the increased vascularity; usually the process is extended progressively until the whole epididymis became involved [22]. Although in the past, bilateral involvement was the rule, Gow et al. showed that this is no longer the case today and involves epididymis of one side [23]. Testicular involvement frequently results from contiguous spread through the epididymis [20]. Given the existence of a blood testes barrier, hematogenous spread is extremely rare [20]. However, hematogenous spread is more common than spread from urinary tract in prostate TB [3].

The seminal vesicles, vas deferens, and ejaculatory ducts become involved by retrograde ascent of *M. tuberculosis* bacilli via an infected prostate or a source elsewhere in the genitourinary tract [20]. Despite regular contact with infected urine, urethral TB is uncommon [12].

TBP may very rarely occur as a primary infection of the genitalia through sexual transmission with an infected partner and following ritual circumcision as a result of sucking the penis by tuberculous operators for hemostatic styptic measure [24, 25].

DIAGNOSTIC EVALUATION

History and clinical findings

M. tuberculosis can affect several sites within the male genital organs, especially the epididymis and prostate, and thereby causes infertility. It can occur at any age, nevertheless men in age group (30-50 yrs) are the most affected [17]. In most cases, MGTB is responsible for varied clinical symptoms because multiple genital organs can be involved [11, 18].

Constitutional symptoms, including anorexia, fever, night sweats and weight loss are uncommon [26].

However the disease can be also asymptomatic and many patients are incidentally diagnosed on histopathology or after presenting an infertility [11]. The risk of tuberculosis infection

should be screened for by history of personal TB or TB contact; recent immigration or travel to an endemic region; HIV positive status, even if a minor, has such history [12].

Different organs affected

1) Epididymal and testicular TB

Epididymo-testicular TB has a multitude of clinical presentations, often as acute or chronic, painful, or most commonly painless scrotal swellings; single, bipolar or multiple epididymal nodules; non-tender testicular mass, disappearance of the epididymo-testicular groove or can present late as an abscess or a fistulae discharging pus [11, 18, 27, 28].

Tuberculous orchitis with no epididymal involvement is very rare; this presentation can mimic a testicular tumor. Differentiating between the two disease is difficult [1].

Patients with isolated epididymo-testicular TB have no urinary tract symptoms [10]. These symptoms are seen only when there is a concomitant renal and/or prostatic involvement [10].

2) Prostate and seminal vesicle TB

Prostate is the second most commonly involved genital organ in MGTB [29]. The symptoms and signs of prostatic TB in its early stages are occult. Many cases remain undetected and are diagnosed during autopsy or as an incidental pathological finding when samples are sent after biopsy to rule out malignancy or after a transurethral resection [16, 29].

The usual presentation of prostate TB consists in frequency and nocturia; other symptoms such as dysuria, hematuria, perineal pain or hemospermia may be present [11]. Generally, there is no urgency [11]. Prostatic abscess is rare during genital TB but can occur among immunocompromised patients or neglected cases [30].

3) Penis TB

TBP is an extremely rare condition and represent less than 1% of UGTB [2, 25]. Skin of the penis, glans or cavernous bodies may be affected [24]. In the majority of cases penile lesions present as subcutaneous nodules, ulcers or cavernosal cold abscess which may gradually

progress, inguinal lymphadenopathy may be palpable [24]. TBP may be misdiagnosed for more common causes of ulcerative penile lesion [31]. It should be considered in the differential diagnoses of persistent genital ulcer after conventional treatment [31]. The presentation as an indurated mass on glans penis can mimic penile carcinoma [24].

Diagnosis

Early diagnosis of MGTB is critical as it can save the patient from infertility and avoid unnecessary invasive procedures, so the identification of patients who are at high risk is a crucial step [28]. However, the diagnosis of isolated cases of MGTB is a very difficult task, as the disease has no pathognomonic symptoms and most laboratory findings have been evaluated in patients with concomitant renal tuberculosis [11, 14]. As a result, diagnosis is rarely made prior to the development of serious urogenital lesions [16].

All patients with genital TB need to be checked for pulmonary and urinary tract involvement [13]. Their involvement must be ruled out to retain this definite diagnosis of isolated MGTB [1]. The diagnosis is established by a combination of compatible clinical, microbiological and pathological results.

<u>Laboratory investigations</u>

1) The tuberculin skin test

The tuberculin skin test has been primarily employed for identifying latent TB infection and to support the diagnosis of active TB disease [32]. The purified protein derivative (Mantoux test) is positive in >90% of TB patients, but it has no significance in areas where there is a severe epidemic situation, and about all adults gets a positive skin tuberculin test [1].

2) Urine tests

Smear microscopy of urine refers to the microscopic examination for detecting acid-fast bacilli (AFB) performed by Ziehl-Neelsen staining, which is regarded as the first-line

test for UGTB [32, 33]. Ye et al. reported that smear microscopy possessed poor sensitivity value of 9.8%. It could be due to excretion of bacilli in low concentration within urine specimens [34]. Smear microscopy could not differentiate *M. tuberculosis* from non-tuberculous mycobacteria leading to false-positive results [19].

The gold standard method for a definitive MGTB diagnosis is the isolation of *M. tuberculosis* by culture [35]. However, results can take about 6 to 8 weeks, and due to the paucibacillary specimens in urine this frequently leads to poor sensitivity. Ye et al. demonstrated that culture possessed a poor sensitivity value of 13.8% even in UTTB [34]. False negative cultures may occur by using concomitant broad-spectrum antibiotics as a result of inhibiting mycobacterial growth [36]. Unfortunately, there has been no systematic study carried out for identifying AFB by microscopy and *M. tuberculosis* by culture in case of isolated MGTB [32].

Urine nucleic acid amplification tests (NAAT) are useful complementary tools for fast diagnosis, shortening the time to obtain the results [11]. They provide greater results even in low bacillary concentrations increasing the sensitivity, specificity and identifying mycobacterial DNA in 80.9% of suspected UGTB patients [35].

There is currently one NAAT-based platform, the GeneXpert® system, with minimal carry-over contamination and it provides results in less than two hours avoiding the delay of the start of therapy [2, 12, 32]. It also indicates resistance to rifampicin. However, to date NAAT tests studies has not taken into account isolated MGTB cases.

3) Prostatic secretions and ejaculates tests

In isolated MGTB cases, the infected genital tract may not be in direct contact with the urinary system thus only few bacilli are seen; therefore, the identification rates of these cases on urinary analysis can be lower than that for UTTB [12]. Consequently, the ejaculate and/or the fluid obtained using prostatic massage must be analyzed using microscopy, AFB culture, and NAAT [1, 2, 12, 32]. The sensitivity range for the gold standard test of UGTB, culture, is

between 10 to 80%. NAAT can identify mycobacterial DNA with a sensitivity of 80.3%. Optimal diagnosis methods for identifying TB in sperm are poorly evaluated and warrants further studies.

4) Blood tests

Immunological procedures such as the interferon-γ release assays *i.e*. Quantiferon Gold in-Tube and T-SPOT.TB are widely employed for the early detection of UGTB cases and other clinical forms of EPTB [37]. Currently, these tests are recommended by the WHO as a useful and reliable technique for the evaluation of TB infection in BCG-vaccinated individuals, especially in countries where BCG vaccination is administered after infancy or repeated vaccinations are given, but negative results do not rule out active TB disease [9].

Quantiferon-TB Gold in-Tube assay with the peripheral blood is reported to have a sensitivity of 52.6% in detecting UGTB [37]. The results of the urine AFB stain and culture were positive in 8.8-12.2 %, respectively and the results of PCR were positive in 15.8 % in the same study, hence Kim et al. often proposed realization of this test in addition to urine smear/culture [37].

5) Other body fluids

Bacilli should be also searched using in all body fluid specimens from different sites of infection, such as pus from prostatic or epididymal abscess and discharge from a draining scrotal perineal fistula or penile ulcer [12].

To date, current laboratory methods used for these studies are focused on UGTB cases, where only few isolated MGTB specimens were included. Further research should be carried out to investigate the possibility of using other novel modalities for a reliable and timely MGTB diagnosis.

<u>Imaging findings</u>

Imaging investigations in UGTB are used to better identify the site of lesions or tissue damage, to determine the extent of the infection, to monitor the efficacy of treatment, and to detect complications [28].

For approximately 10.4% of UGTB patients, in circumstances where laboratory investigations are normal, the diagnosis is presumptive and based on suggestive clinical, and radiological findings, without microbiological or histological confirmation [29]. Imaging findings can provide crucial supportive evidence and anti-tubercular treatment should be given [12].

In all patients with genital inflammation, an ultrasound of the urinary tract should be done [1]. Imaging appearance of epididymal or testicular TB are non-specific and can mimic other scrotal diseases [1]. Color Doppler ultrasound is the first choice for imaging analysis. It may show diffuse hypoechogenicity in the epididymis with a heterogeneous echotexture [20]. In cases of involvement of the testicle, it presents several different patterns, miliary type and nodular type [20]. The most typical manifestation is a diffusely enlarged and heterogeneously hypoechoic testis [20]. A homogenous echo pattern is less frequently encountered [20]. Some situations appear as a single or several hypoechoic intratesticular nodules [20]. Creating a 'miliary' pattern by conglomerate of granulomas or micro-granulomas [20]. It might be hard to differentiate between testicular tuberculoma from tumor [11].

Common findings in prostate TB on transrectal ultrasonography (TRUS) are irregular prostate or prostate enlargement with well-defined hypoechoic peripheral lesions [20, 28]. The color Doppler flow can be increased [20]. These lesions may develop into abscesses and TRUS-guided needle drainage may be used [20].

Retrograde urethrography is important for the diagnosis of cavernous prostate tuberculosis [13]. TB of the prostate or seminal vesicles can be observed on a contrast-enhanced CT scan as low-density or cavitation lesions due to destruction and caseation with or without calcification [13]. In the absence of calcification and in diffuse form of prostate TB, the main

differential is pyogenic prostatic abscesses [13, 20]. Magnetic resonance imaging (MRI) is particularly useful when malignancy is suspected, watermelon skin sign suggest TB [11]. When abscesses are present in the prostate, peripheral enhancement may be seen [11, 28].

The most common appearance of tuberculosis involving the seminal vesicles on TRUS and MRI is granulomatous inflammation, which could progress to thickness or abscesses [20].

Chest radiographs may reveal abnormalities consistent with prior pulmonary TB, which may be suggestive of TB or can be used to exclude active concomitant pulmonary TB [9, 28].

Histological/cytological examination

In the absence of microbiologic evidence, tissue biopsy may be required in cases with isolated genital TB without urinary involvement [13]. Histopathological examination of specimens from biopsies and fine-needle aspiration cytology (FNAC) can identify epithelioid granuloma or caseous necrosis and can be considered diagnostic for TB [12, 13]. However, UGTB and other granulomatous diseases cannot be differentiated by histology, only the presence of mycobacteria on a smear or culture or tissue PCR can provide a definitive proof [12, 32].

Diagnosing prostate TB can be challenging, Lee et al. have found that transrectal prostate biopsy may be a useful diagnostic tool specifically to exclude an underlying adenocarcinoma [38]. Histology and bacteriology should be performed on prostate biopsy specimens at the very least by PCR [35, 38].

In such cases of genital tuberculosis with isolated epididymo-testicular lesions and high suspicion of malignancy, diagnosis is generally made on histopathology after inguinal exploration, FNAC being contraindicated [13, 39]. Nonetheless, when there is low suspicion of testicular tumor, in comparison to open surgical surgery, FNAC showed a higher sensitivity (87%) and specificity (93%) [40]. Furthermore, it has displaced investigations leading to unnecessary epididymectomy or orchiectomy in some cases [12, 41].

Such biopsies must be performed with caution, regarding the possibility of major consequences due to fulminant generalization of TB in untreated patients with active UGTB [13].

CONCLUSIONS

The isolated male genital tuberculosis is a serious and insidious disease. It can be challenging to diagnose since there are no pathognomonic signs, leading to a diagnostic delay with possible destruction of the genital organs.

Although UGTB has been long recognized by urologists and infectious disease specialists, MGTB is still largely unknown. Most researchers have only described UGTB as a whole. It is important to adopt a new classification while changing the current terminology, grouping them separately such as following “urogenital TB”, “urinary tract TB”, “male genital TB and female genital TB”.

In response to the question posed in the article's title and given the lack of publications of isolated cases of MGTB, we recommend carrying out further studies on case series with a special attention on the evaluation of sperm and prostatic secretions investigations for TB.

While awaiting the establishment of clear recommendations, we recommend that the diagnosis of MGTB should be made taking all these into consideration the epidemiological data, careful study of the history and clinical presentation and performance of latest molecular or immunological tools from urine, sperm, blood, other fluids or tissue specimens.

CONFLICT OF INTEREST

Authors have no conflicts of interest to declare.

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AUTHORS’ CONTRIBUTIONS

YR collaborated in the original idea, concept, design, and writing and drafting the article. YK and AK contributed to all stages of the process and mainly participated in drafting the article, writing, and editing the final version to be published. All the authors read and approved the final version of the manuscript.

AVAILABILITY OF DATA AND MATERIAL

All articles used in the current review available from the corresponding author on reasonable request.

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