Genitourinary Tuberculosis

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Genitourinary tuberculosis (GUTB) represents a disease often underestimated by urological specialists, particularly in settings such as the European one, where the pathology is less frequent. Similar to other uncommon diseases at these latitudes, GUTB is a neglected clinical problem. Its symptoms might be mistaken for other urological diseases, and therefore its diagnosis might be delayed.

Keywords: GUTB ; genitourinary tuberculosis

1. Introduction

Tuberculosis (TB) remains one of the most serious public health problems in the world, representing one of the ten major causes of death [1]. In 2019, the WHO reported around 1.4 million TB deaths and over 10 million new infections [1]. Developing countries are those most seriously affected by the disease Mycobacterium tuberculosis (MTB) [2][3][4], but 6% of the global incidence of TB affects Europe, with increasing rates of drug-resistant TB (DR-TB) [3]. Overall, about 500,000 TB patients are coinfected with human immunodeficiency virus (HIV) and another 500,000 develop drug-resistant DR-TB [3].

TB can affect any organ, though the most prevalent and contagious is the pulmonary form (PTB). However, up to 45% of patients may have extrapulmonary involvement (EPTB) [2]. The urogenital tract is one of the most common sites of EPTB, with the urinary tract (kidney, ureter, bladder, urethra) more commonly affected than the genital organs [2][3][4].

Genitourinary tuberculosis (GUTB) represents a disease often underestimated by urological specialists, particularly in settings such as the European one, where the pathology is less frequent [5][6]. Similar to other uncommon diseases at these latitudes, GUTB is a neglected clinical problem. Its symptoms might be mistaken for other urological diseases, and therefore its diagnosis might be delayed. This might lead to irreversible organ damage, with both a worse prognosis for the patients and higher costs for the healthcare system. Furthermore, recently published experiences suggest that the COVID-19 pandemic has had an impact on TB patient care in terms of higher diagnostic delay, reduction in hospitalization, and a greater severity of clinical presentations [7].

2. Epidemiology

GUTB represents up to a quarter of worldwide EPTB cases. The frequency of GUTB depends significantly on geographical and development elements, with more than 90% of GUTB cases occurring in developing countries [8]. In these regions, GUTB is considered the second cause of EPTB, and only about one-third of EPTB patients have a previous diagnosis of TB. HIV is often a concomitant disease in patients with GUTB, especially male patients, who are affected at a rate twice that of than women [8]. In 2019, about 50,000 cases of TB were reported in Europe, resulting in a notification rate of 9.6 per 100,000 population in the EU [9]. Regarding age, the median age of patients affected by GUTB is around 40 years. However, even if it is a typical disease of the adult population, due to its long latency period, it has also been reported in pediatric ages [10].

3. Aetiology and Risk Factors

GUTB is caused by mycobacteria, of which the most frequently isolated species in humans is MTB *hominis* complex (responsible for about 90% of cases); *Mycobacterium tuberculosis*, *bovis* and *africanum* (especially in West Africa) are the most frequently isolated bacteria. GUTB is almost always secondary due to the hematogenous spread of chronic latent pulmonary TB (LTBI); therefore, primary and LTBI represent its most important risk factors [11][12][13]. Diabetes, old age, low body mass index, oncological comorbidities, immune suppression and renal failure may increase the risk of reactivation of dormant bacilli. This risk of reactivation is estimated to be up to 15% during one's lifetime [14]. Finally,

geographical and social conditions can be considered risk factors. GUTB is more frequent in developing countries and in communities where living conditions of high population concentration and poor hygiene are present.

4. Physiopathology

TB infection starts from inhalation of cough-generated aerosols containing mycobacterium tuberculosis. When *M. tuberculosis* bacteria enter the alveolar space, they are phagocytosed by alveolar macrophages [15]. In some patients, mycobacteria are totally destroyed by the innate immune system, while in others, they start to replicate into alveolar macrophages [15]. The mycobacteria could spread in other organs or could remain latent in lungs or lymph nodes. GUTB can result from a primary pulmonary infection or from reactivation of an old infection, even after decades [16][17][18]. The principal means by which GUTB develops is via hematogenous spread, reaching multiple organs. The kidney, epididymis and prostate may be sites of infection and disease. Penile TB can also be acquired during sexual contact with infected partners [19]. The upper urinary tract and bladder can be damaged by mycobacteria whenever the disease spreads with the urine, secondary to kidney infection. Prostatic TB has been described also as an adverse event after Bacillus Calmette-Guerin (BCG) intravesical instillation therapy, but it is not covered in this review [20]. In sexually active men, epididymal TB is the most common form of GUTB.

5. Clinical Presentation

When *M. tuberculosis* reach the kidneys, cortical renal lesions are formed, which result in scarring. Subsequently, after a latent period, reactivation occurs, and the infection generally progresses from a single focus. Often, renal TB is asymptomatic, even though it heavily damages the kidney. Papillary necrosis, calcifications, caseous lesions and parenchymal destruction can be associated with GUTB. Furthermore, if both kidneys are affected, renal failure can occur [21][22]. These papillary lesions caseate and cavitate, forming ulcerocavernous lesions as they erode into the pelvicalyceal system. The ureter, bladder and genital organs are involved by a contiguous spread from the collecting system [23]. Multiple strictures and stenosis generally develop in ureters, with prevalence at the vesicoureteral and uretero-renal junctions [24]. Bladder TB often starts as an acute inflammation process from ureteral meatus with hyperemia and ulceration. Without any treatment, it will result in bladder wall fibrosis and a contracted bladder. Symptoms generally start when the bladder becomes involved. Hematuria, increased urinary frequency and difficulty voiding, as well as abdominal, lumbar and suprapubic pain are the most frequent symptoms. Men may present with penile ulceration and a scrotal/epididymal mass. Women may show menstrual irregularity and pelvic pain [2][4].

6. Diagnosis and Differential Diagnosis

The diagnosis of GUTB is challenging, since it lacks specific symptoms or signs. Non-specific lower urinary tract symptoms, abnormalities in semen or urine analysis and “sterile” pyuria and/or hematuria could be the first findings of GUTB. A past medical history of TB plays a crucial role in the diagnostic work-up of GUTB, which may have a latency from the pulmonary manifestation of more than 30 years in some cases [25].

6.1. Smear Microscopy

The diagnosis is established by the isolation of acid-fast bacilli (AFB) in urine samples, semen, tissue specimens, pus, or discharged or prostatic massage fluid, through microscopic examination using Ziehl–Neelsen (ZN) or auramine staining. AFB smear microscopy of the urine is a rapid test, with 97% specificity but only approximately 20% sensitivity [26].

6.2. Urine Culture

At least three early-morning urine samples, delivering first-void midstream, on consecutive days, are recommended for AFB culture. In general, the culture-based method for urine or tissue biopsy specimens is the gold standard, with a sensitivity of 80–90% and a specificity of roughly 100%. Moreover, it could concurrently provide data on TB drug susceptibility [26]. The disadvantage of culture-based methods is the time needed for the results. The liquid culture system, which is recommended as the diagnostic gold standard by the WHO, takes at least 9–10 days for positive results and 6 weeks to be considered negative.

6.3. Nucleic Acid Amplification Tests

In recent years, nucleic acid amplification tests (NAATs) have been introduced in the diagnostic pathway of TB, to overcome the limits of early and rapid diagnosis and of drug susceptibility testing. Currently, NAATs such as RT-PCR (Gene Xpert MTB/RIF by WHO in 2010 or GeneXpert MTB/RIF ultra by WHO in 2017) are recommended for the detection

of pulmonary TB as, according to the latest WHO policy updates of 2013, these technologies cannot be routinely applied on urine samples. They are promising technologies for detecting *Mycobacterium* DNA (Mbt DNA) in urine samples requiring further validations [27][28].

6.4. Whole-Genome Sequencing (WGS)

WGS can provide the complete genome of *M.* spp. in a sample, giving information such as drug-resistance and the transmission patterns. WGS can be very useful in providing particular information to build more effective and safer anti-TB regimens [29].

6.5. Histological Examination

The histopathological examination of tissue specimens collected from biopsies or fine-needle aspirates is helpful to detect granulomas and to identify mycobacteria. In some cases, the pathological report is the only chance to yield diagnosis, as in case of TB involving epididymis [30]. Differential diagnosis of granulomas includes a wide range of infectious diseases and non-infectious diseases [31].

6.6. Imaging

The positivity of laboratory assays does not reveal the site of GUTB nor the impact on the genitourinary system. Thus, radiological imaging plays a fundamental role in localizing the foci of the disease and the extent of the damage. The classical radiological findings are historically based on conventional radiography and intravenous urography (IVU). Currently, computed tomography (CT), Magnetic Resonance Imaging (MRI) and ultrasonography (US) are more frequently performed to yield a diagnosis. Moreover, imaging technologies could be applied for targeting biopsies. Overall, imaging techniques are up to 91.4% sensitive for GUTB [32].

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