

Diagnosis of Genitourinary Tuberculosis

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Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB) is a major health problem that causes significant morbidity and mortality in the world [1]. The first evidence of TB in men and animals is provided by bone findings- mainly fragments of the vertebra showing the gibbus deformity of Pott disease [2]. The oldest examples of spinal TB was about date of 8000 BC. Because of the symptom varieties, TB was not defined as a unified disease until 1820s and was not named as tuberculosis until 1834 by Johann Lucas Schönlein of Wurzburg. He described the term of tuberculosis to define the affliction with tubercles.

In 2012, aproximately 8.6 milion people developed TB enfection and 1.3 milion died from the disease [3]. Extrapulmonary TB accounts 20% of the reported cases and genitourinary TB(kidney,prostate and testis) was described by G.L. Bayle in 1810 [2,4]. The tubercle bacillus was isolated by Robert Koch in 1882 and this pathogen (acid fast aerobic bacillus) was identified in urine and sputum in 1883. In 1937, Hans Wildbolz used the term ‘genitourinary tuberculosis’ firstly. Genitourinary tuberculosis is one of the most common late manifestation of symptomatic

or asymptomatic pulmonary tuberculosis [5,6]. Genitourinary tuberculosis means that the inflammation of urogenital system organs in any combination caused by MTB or *Mycobacterium bovis* [7]. Genitourinary tuberculosis are divided into four groups; urinary tuberculosis, male and female genital tuberculosis and generalized urogenital tuberculosis.

Genitourinary tuberculosis is almost a result of haematogenous spread of MTB from pulmonary to reach the abdominal infection [8]. There are three principal routes used by bacillus to reach the genital tract; haematogenous route, descending direct spread and lymphatic spread [9,10]. Urogenital TB affects all age groups but men of 40-50 years age are affected predominantly. The diagnosis is often delayed due to the evaluation insidious with few and nonspecific symptoms with a lack of awareness of clinicians in developing countries [11,12]. In men the genital organs commonly affected are as follows; epididymis, prostate and testis [2]. The sites most commonly involved in females are fallopian tube, endometrium, ovary, cervix, myometrium and vulva/vagina.

CLINICAL SYMPTOMS

The patients with urinary TB present with malaise, lower urinary tract symptoms, gross hematuria, fever, weight loss, pyuria and microscopic hematuria [4]. The most common symptoms were flank pain, nocturia, frequent voiding and dysuria in a series of 105 patients with urogenital tuberculosis [13]. In another study by Figueireda et al. [14], storing symptoms (urinary frequency, urgency, urgency incontinence, nocturia), dysuria and hematuria were affected 50.5%, 37.9% and 35.6% of the patients, respectively. Clinical presentation of genital tuberculosis are primary infertility, secondary infertility, ectopic pregnancies, orchitis and ulcerations of the genitalia [2,8].

KIDNEY TUBERCULOSIS

There are four stage of nephrotuberculosis [7]. Chronic renal failure, fistula and high blood pressure are the complications of nephrotuberculosis.

- Stage 1 (Nondestructive): Low level of leukocyturia is usually seen in adult and most of the patients have no complaints.
- Stage 2 (Small destructive): The disease can be unilateral or bilateral, solitary or multiple lesions.
- Stage 3 (Destructive): Subcortical cavern is usually seen and the diagnosis is made after the operation.
- Stage 4 (Widespread destructive): The fistule formation is a result of pyonephrosis. Autoamputation of the kidney usually occurs and nephroureterectomy is indicated.

TUBERCULOSIS OF THE URETER

Ureteric involvement of tuberculosis is secondary to renal involvement and the vesicoureteric junction is the most common seen location [15]. Tuberculosis of the ureter usually develops in the intramural part of the ureteric wall and is characterized by ureteral thickening with post contrast ureteric wall enhancement on contrast-enhanced computed tomography imaging. Ureteral stricture and the obstructive uropathy is the result of tuberculosis of the ureter. Secondary sepsis, bleeding, pain, uncontrable hypertension and continued positive urinary cultures may be the clinical symptoms of the patients with ureteral tuberculosis [4].

BLADDER TUBERCULOSIS

There are five forms of bladder tuberculosis [7].

- Stage 1: Tubercle infiltrative
- Stage 2: Erosive ulcerous
- Stage 3: Spastic cystitis
- Stage 4: Real microcystitis up to full obliteration
- Iatrogenic form: After BCG therapy for bladder cancer

The presentation of the patients may be unusual and misleading [16]. However gross hematuria and dysuria are the main symptoms, Spontan bladder perforation and oncology cases were reported in the literature for bladder tuberculosis [17,18]

PROSTATE TUBERCULOSIS

The patients are usually asymptomatic and diagnosed by transurethral resection [19]. Frequency and nocturia are the most commonly seen symptoms of prostate tuberculosis. Dysuria, hematuria, hematospermia, fistula formation on the perineum and scrotuma may also be seen in the patients with prostate tuberculosis. Chronic pelvic pain, decreased sexual function and infertility are the other clinical symptoms [7].

TUBERCULOSIS EPIDIDYMOORCHITIS

Painful, inflamed scrotal swelling is the usual presentation of the patients [19]. Discharging sinus may be found posteriorly; fistulous forms were seen in 12.4% of the patients. Infertility may be result of bilateral vasal obstruction [2]. Although nodular beading of the vas is a characteristic physical finding, orchitis and scrotal swelling can be difficult to differentiate from other testicular mass lesions.

TUBERCULOSIS OF THE PENIS

Tuberculosis of penis is may be primary or secondary to an active focus at other sites in the body [20]. The patients can present with small ulcer on glans penis or corona, multiple ulcers or

nodule on penis, swelling of the penis, erectile dysfunction, discharge from ulcer on penis and a mass on glans penis or prepuce [21]. Sexual coitus with the infected females, direct infection through penile wound during ritual circumcision and after BCG therapy play important role for occurring the penile tuberculosis [7].

FEMALE GENITAL TUBERCULOSIS

The bacillus reach the genital tract by three routes as hematogenous route, direct spread and lymphatic spread [2]. Primary infection of the genitalia is rarely seen as a result of direct inoculation during sexual intercourse with patients infected genitourinary tuberculosis. The low percentage of (3.9%) male patients with genitourinary tuberculosis harbor bacili in semen. Involving of uterus and fallopian tubes with tuberculosis causes strictures. Primary infertility, secondary infertility and ectopic pregnancies are the clinical presentations of these patients [8].

RADIOLOGIC IMAGING

The plain radiography may show the extra pulmonary manifestations such as calcification of lymph nodes, adrenals, prostate, seminal vesicles, or vas deferens; psoas abscesses; calcified granulomas in the liver or spleen; as well as spinal abnormalities [22,23]. Radiographic identification of calcification may be the first sign that TB is present and a lobar pattern of calcification, with calcific rims outlining the periphery of distorted renal lobes, is the pathognomonic finding of kidney TB [24]. The intravenous urogram (IVU) is the gold standard imaging modality in the early kidney TB. In a study by Navarro Vilasaró et al, including 45 patients, the IVU had a positive diagnosis rate of 88% in urinary TB [25]. The earliest urographic changes are subtle initial signs such as minimal calyceal dilatation that occurs in the minor calyces [26] and mild loss of calyceal sharpness due to mucosal edema [27]. However calyceal erosion has been described as the first IVU sign in renal TB, some authors think that early the first sign is papillary necrosis. The late radiological manifestations of kidney TB are extensive cavitation, fibrotic strictures, cortical scars, mass lesions, calcification, autonephrectomy, perinephric abscess, and fistula formation.

Sonographic findings in renal TB include parenchymal masses, cavities, urothelial thickening, and calcifications. In sonographic evaluation; there are two patterns of TB [28].

Infiltrative pattern is more commonly seen with increased echogenicity due to calcifications, infected debris, abscesses and ***hydronephrosis or pyonephrosis*** with dilated calyces and a small renal pelvis [29,30]. But most of the patients have the sonographic findings with the combination of both processes. The focal renal lesion (parenchymal granuloma) is the most frequently sonographic abnormality in kidney TB.

Computed tomography (CT) is useful radiological technique both in the kidney TB diagnosis and assessing the severity of renal function and involvement of other organs [31]. Detecting small urothelial lesions; computed tomography shows more details of pathologic anatomy and is superior to retrograde pyelography, intravenous urography and ultrasonography [32] CT is the best radiological imaging for demonstrating the extent, nature and distribution of calcification

within the abnormal kidney [33]. Early changes in renal TB are small granulomas (≤ 3 mm) and papillary necrosis [32]. The granulomas may be seen as a solid mass with little or minimal enhancement after contrast administration and mimic renal neoplasms, which may lead to unnecessary surgery; these are therefore called as ‘pseudo-tumor’[34,35]. The lobar pattern of calcification and caseation are pathognomonic for TB and the calcification is well appreciated on axial CT images, especially when occupies just a lobe or two, or even a part of the same lobe [32]. The lobar pattern of caseation that arises from the assimilation of the calyces into the caseous parenchyma of each destroyed lobe, is virtually diagnostic of renal TB. Renal abscess, cavitation within the renal parenchyma, cortical thinning, fine calcifications are the CT findings in the evaluation of kidney TB. Involvement of collecting system leads to ulceration, wall thickening and fibrosis with stricture formation [36]. CT has advantages for evaluation of retroperitoneal extension of disease, psoas muscle affection, perirenal and pararenal spaces. Fistulas of kidney TB is commonly associated with colon, duodenum and stomach [37].

Magnetic resonance urography (MRU) demonstrates the ureters’ calibrations and confirms the presence of stenosis [38]. This imaging is useful for the patients with moderate to severe dilate collecting systems and impaired renal function [39]. The TB granulomas are usually seen as variable sized solid mass [32]. Renal angiography shows normal vascular imaging in early stage of disease, zones of irregularity and complete occlusion can be seen in the patients with more advanced stage of disease. It is also helpful for embolization.

Transrectal ultrasonography may show hypoechoic lesions in the peripheral zone of the prostate [19]. Low density or cavitation lesions due to necrosis and caseation are the findings of contrast enhanced computed tomography.

DIAGNOSIS OF URINARY TUBERCULOSIS

The diagnosis of urinary tuberculosis needs the demonstration of *M.tuberculosis* in the urine [4]. Sterile pyuria, hematuria and dysuria are the main symptoms of the patients.

The renal tuberculosis diagnosis is based on clinical suspicion, microbiological confirmation and radiological localization [40]. Tuberkulin skin tests are positive in about 80% of the patients with renal TB. Three to six first morning midstream urine should be evaluated for acid-fast bacilli (AFB) to maximize the likelihood of positive results [4]. The sensitivity of acid fast staining with EZN technique is about 42.1-52.1%. Additionally, each urine specimen should be cultured on two slopes as Lowenstein-Jensen and pyruvate egg medium containing penicillin to identify *M.bovis* [40]. A false positive result on culture may be caused by the presence of *M.smegmatis* in the urine. Although AFB microscopy and Lowenstein-Jensen culture are the cornerstone of the diagnosis of TB, these methods are slow and their sensitivity is low because of the clinical samples that contain small number of organisms [41]. Radiometric BACTEC system has a specificity of 37.5% in the diagnosis of urinary tuberculosis. Nonradiometric method using advanced flurometric technology to detect O_2 consumption for to detect *Mycobacteria* is the mycobacterial growth indicator tube (MGIT) [42].

In recent years, Polymerase Chain Reaction (PCR) has become the ideal test for *M.tuberculosis* identification in urine [4]. The sensitivity of culture methods vary from 10-90%, PCR method has a sensitivity of 98.1%. PCR method gives result in less than one day, compared to average 24 days for Lowenstein-Jensen culture, 12 days for radiometric BACTEC techniques [41]. The limit of detectability of PCR is about 10 organisms to as little as 1 bacillus in the specimen [43]. Urinary PCR is specific for the MTb complex (MTb and *M. bovis*) and there is no crossover reaction in other mycobacteria forms. Endoscopy has limited role in the diagnosis of tuberculosis [41]. Although there is no pathognomonic lesion for tuberculosis, ulcerative lesions and 'golf-hole' ureteric orifice can suggest tuberculosis and in this situations a biopsy should be done.

The diagnosis of genital tuberculosis is difficult because absence of pathognomonic clinical signs [19]. Careful study of history is the first step of the diagnosis. The female patients have usually an indolent infection and clinical manifestation takes years after initial seeding [44]. The female patients with genital tuberculosis may present with infertility, pelvic pain, menstrual disorders and vaginal bleeding. The male patients with genital tuberculosis present with nonspecific symptoms and only 36% of the patients had positive culture [19]. Leucocyturia and hematuria are seen more than 50% of the patients. Three glass test can be helpful for the localization of the tuberculosis. Digital rectal examination with soft massage of the prostate should be done after urinalysis. Prostatic secretion or ejaculate have to be investigated for culture, microscopical examination and PCR. There is no gold standard test for diagnosing female genital tuberculosis [45]. Use of endometrial tissue and menstrual blood for culture and molecular tests have low sensitivity and there is no way to take fallopian tubes. Laparoscopy is an alternative method but this procedure is invasive, expensive and often nonspecific procedure which absolute diagnosis of female genital tuberculosis can not be made by laparoscopy. Ovarian tissue biopsy, endometrial aspirations, pelvic fluids and fluid from the pouch of Douglas may support the endometrial tissue biopsy for diagnosis of female genital tuberculosis.

In histological examination, granulomatous inflammation with central necrosis is the characteristic lesion of the tuberculosis [46]. Granuloma without necrosis is often seen and tuberculosis should be differentiated from other granulomatous diseases such as sarcoidosis.

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