Case report

Uncommon testicular localization of Disseminated TB: a case report from Mozambique
Evangelina Inacio Namburete¹, Francesco Di Gennaro*,² Cleide Jose Maria¹, Davide Fiore Bavaro², Gaetano Brindicci², Rossana Lattanzio², Damiano Pizzol³, Laura Monno² Annalisa Saracino²
¹Department of Medicine, Central Hospital of Beira, Mozambique
²Clinic of Infectious Diseases, University of Bari "Aldo Moro," Bari, Italy.
³Operational Research Unit, Doctors with Africa Cuamm, Maputo, Mozambique

Running title: Disseminated TB: a rare case report from Mozambique

SUMMARY
Tuberculosis (TB) of the testicle is a rarely reported and poorly described disease localization. There are no well-defined clinical features suggestive of testicular TB, which makes the diagnosis difficult to establish, especially in low-income settings like Mozambique, where TB is endemic and often associated with HIV-infection; both considered leading causes of death worldwide.

We reported the case of a 45-year-old male, HIV positive, naïve to antiretroviral treatment, admitted to the Department of Medicine of the Central Hospital of Beira to investigate chronic enlargement of the testicles.

Keywords: Tuberculosis, testicular TB, HIV, disseminated TB

Corresponding author: Francesco Di Gennaro
Clinic of Infectious Diseases, University of Bari "Aldo Moro," P.zza G Cesare 3 Bari, Italy
Email: cicciodigennaro @ yahoo.it; Number: +39 0805592471; Fax: +39 0805592890
INTRODUCTION

Tuberculosis (TB) and HIV are a public health challenge for Mozambique; moreover, TB-HIV co-infections are increasing in this country, so that in 2008 about 60% of TB patients resulted anti-HIV positive (WHO, 2017). In fact, Mozambique, holding the 19th position in the ranking of the 22 countries with the highest number of TB cases in the world, is also burdened with one of the highest HIV-infection prevalence, with an estimated 62,000 deaths per year (WHO, 2016; WHO, 2017; Di Gennaro et al., 2018).

TB and HIV are strictly correlated; in fact, HIV-1 infection greatly increases the risk of active TB, and TB, in turn, is an AIDS-defining illness (WHO, 2017). Pulmonary TB is the most common presentation of the disease, while extra-pulmonary TB (EPTB) accounts for about 10-15% of all cases (Krishnan et al., 2010; Webster et al., 2015). Among EPTB cases, lymph nodes are the most frequent localization of the disease. Conversely, genital tuberculosis is overall rare, and testicular localization is even more rare, accounting for less than 3% of all genital TB (Seo et al., 2013; Dong et al., 2015). Generally, testicular involvement occurs during disseminated TB, while testicular TB as sole localization is extremely rare (Mohammed et al., 2018; Das et al., 2016). Differential diagnosis should be established with other common testicular diseases such as cancer, testicular infarction or torsion (Khan et al., 2015), since the most common sign of testicular involvement in all these diseases is increase in testicular volume. Moreover, as in testicular infarction and cancer (Bhargava et al., 2009; Badmos et al., 2012), young adults between 20 and 40 years are the most affected. However, unlike other illnesses, testicular pain may be missing in testicular TB, while systemic symptoms related to tuberculosis are commonly present (weight loss, night sweats, serotina fever, etc.). Therefore, ultrasonography (US) is essential to confirm the clinical suspicion and should be followed by a fine-needle aspiration biopsy (FNAB) in ambiguous cases, especially in patients at higher risk for malignancies, like elderly patients (Paul et al., 2010; Bae et al., 2015, Bobbio et al., 2019). When testicular TB is diagnosed either correctly or early, the standard treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol is the gold standard therapy (Gaifer et al., 2017; Das et al., 2016).

Herein, we present an uncommon case of disseminated TB diagnosed thanks to the testicular involvement.

CASE REPORT
A 45-year-old male was admitted to the Medicine Department of the Central Hospital of Beira due to durable enlargement of the testis. The volume of the right testis had increased about two months before; after a few days, the patient noted that also the left testis was swollen. Although he was initially asymptomatic, he began to complain of increasing bilateral testicular pain associated with intermittent fever (T max 37.4°C), loss of weight, generalized weakness, anorexia, and nightmares. Apart from these symptoms, he did not complain about other diseases, like diabetes or chronic kidney impairment, and denied smoking or excessive alcohol consumption. However, the patient was aware of his HIV-positive status, although he had never accepted antiretroviral treatment.

Physical examination
At admission, he was clinically stable, alert, oriented and eupnoic; urgent vital medical support was not required. Nevertheless, his general condition was poor, dehydrated and cachectic. Body temperature was 37.4°C, heart rate was 92 beats per minute and respiratory rate was 18 acts per minute. Blood pressure was 120/70 mmHg and oxygen saturation rate in ambient air was 98%.

Clinical examination of the thorax showed no abnormalities, with no respiratory symptom, as did examination of the abdomen. Heart sounds were rhythmic without added pathologic noises. No enlarged lymph nodes were found. Both testicles were increased in volume; the skin of the right scrotal area was thickened, but local temperature and color were normal and without other signs of local illness.

Blood tests
Blood count showed medium-severe anemia (HGB-8.9 g/dl) and a slight leukocytosis (white blood cells were 13,300 cells/mm3) with increased absolute number of neutrophils (Neut-79.7%; 10600/μl). Erythrocyte sedimentation rate (ESR) was considerably high (85mm/h).

Other available blood tests at the time of admission were: RBC-3100/μl; HCT-26.1%; MCV-74.2fl; MCH-25.7pg; MCHC-34.1g/dl; PLT-159000/μl; LYM-12.2%, 1600/μl; 1100 μl. HIV Determine and Unigold-Reagent; CD4+ 3.53%; 21 cells/μl. The Quantiferon-TB gold was unavailable at the Hospital of Beira.

Radiological features
The chest x-ray, prescribed after the HIV-positive result, showed a miliary-reticulo-nodular pattern involving both the pulmonary parenchyma and the periphery (Figure 1), although the patient denied any respiratory symptom. The scrotal ultrasound examination of both right and left testis (3.14-3.21cm and 3.29-3.51cm, respectively) showed a generally homogeneous echo-
texture. However, some abnormal echoic areas were present in the left testis. Therefore, a testicular fine needle aspiration biopsy was performed, and four smears (two each testis) were examined after May-Grunwald Giemsa coloration. A colliquate white nodule was observed, suggestive of granuloma with central necrosis. Ziehl-Neelsen staining and blood mixed particulate obtained by fine needle aspiration biopsy revealed acid-fast bacilli (AFB) (Figure 2).

After the diagnosis of testicular and pulmonary TB was confirmed, a standard anti-TB treatment regimen was prescribed: rifampicin; isoniazid, pyrazinamide and ethambutol RHZE (150mg/75mg/400mg/275mg), 4 tablets a day for 2 months, followed by rifampicin and isoniazid (RH) (150mg/75mg), 4 tablets a day for four months. Counseling to ensure good adherence to treatment was provided.

Antiretroviral treatment with Tenofovir (300 mg daily) plus Lamivudine (300 mg daily) plus Efavirenz (600 mg/die) started one month after the initiation of TB therapy.

The patient was referred to the out-patients Department of Urology and Infectious Diseases to continue the follow-up. Complete resolution of testicular swelling and pain, and of the X-Ray chest image was documented at the end of 6 months of treatment.

**DISCUSSION**

Genitourinary TB is an unusual presentation of TB, accounting for 8-15% of extra-pulmonary TB and affecting mainly males (male/female ratio 2:1) in the 30 to 50 age group (Hadadi et al, 2012; Das et al.,2016).

The mechanism of tubercular bacilli dissemination to the testis is unclear. Hematogenous and/or lymphatic diffusion is a possible but rare cause, while the retrograde diffusion from the urinary tract (including prostate, seminal vesicle, vas deferens and epididymis) is considered more frequent (Krishnan et al., 2010; Pasticci et al., 2012).

Testicular tuberculosis generally complicates a previous urinary tract and/or kidney tubercular infection; thus, it is often associated with urinary urgency or hematuria. Epididymo-orchitis, prostatitis, scrotal ulcer, and swelling (with or without discharge sinus) may be other manifestations associated (Fanosie et al., 2016; Gaifer et al., 2017).

In our case, the initial presentation was the swelling of the right scrotum with subsequent volume increase of the ipsilateral testis and the emergence of pain in both testicles. Notably, no respiratory or urinary tract symptoms were reported by the patient.
In this case, US was the main diagnostic tool to exclude other testicular diseases (cancer and torsion) and to detect signs of possible extra-pulmonary TB (Yadav et al., 2017; Paul et al., 2010).

It should be remarked that, in a low-income setting like Mozambique, Quantiferon Tb test as well as other radiological and microbiological diagnostic tools are frequently too expensive and/or unavailable, even though required because of the high incidence of HIV-infection and TB (Fanosie et al., 2016; Di Gennaro et al., 2018; Schiavone et al., 2016, Marotta et al., 2018).

Last but not least, performing FNAB was crucial to confirm TB diagnosis. To the best of our knowledge, there are no alternative algorithms for the diagnosis of testicular TB in low-income settings, where microbiological tools are unavailable (Yadav et al., 2017; Fumo et al., 2016; Bonura et al., 2012). Indeed, FNAB is the main diagnostic method in our experience, especially in this HIV-infected patient, and avoided more complex and invasive medical intervention, such as orchidectomy (Bhargava et al., 2009; Seo et al., 2013).

Notably, our patient presented many of the risk factors for EPTB reported in a recent metanalysis: HIV status, age, malnutrition, diabetes, African origin (Mohammed et al., 2018; Pizzol et al., 2017). Although it was not possible to perform the Genexpert test to confirm the rifampicin-sensibility, the six-month regimen of standard anti-TB chemotherapy effectively obtained a complete resolution of disseminated TB. Furthermore, other experiences in the literature have shown that the testicular localization of TB, generally rare, was more frequently observed in primary than in disseminated Tuberculosis, mimicking cancer metastasis (Dong et al., 2015; Paul et al., 2010).

This report presents not only a rare case of testicular TB successfully managed, useful for healthcare professionals in low-income countries facing similar situations, but also leads to some considerations. First, in HIV-positive patients, especially those naive to antiretroviral treatment, TB should be suspected in every case, even with uncommon localization (Norbis et al., 2012; Yadav et al., 2017).

Second, radiographic TB pulmonary screening should be prescribed for all HIV-positive patients, even without any known or objective evidence suggestive of active TB. This screening is crucial in low-resource settings, where other TB tests are usually unavailable (Khan et al., 2015; Tatar et al., 2009). Special attention should be paid to people with lower socioeconomic status due to their increased risk of disease and treatment failure (Di Gennaro et al., 2017).

Finally, we would like to underline how case reports might help as a form of experience-sharing platform, especially for healthcare professionals in low-income countries, thereby playing an important role in solving complex and uncommon clinical cases.
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Figure 1. Chest x-ray image showing reticulo-nodular infiltrates with miliary pattern in both lung parenchyma.
Figure 2. Panels A and B show granulomas with central necrosis.