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Tuberculosis Infection in the 21st Century: Can We Win?

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Abstract

Tuberculosis continues to be a leading cause of morbidity and mortality in the 21st century. The rise of multi-resistant strains of *Mycobacterium tuberculosis* associated with an increase of disseminated tuberculosis due to the higher numbers of Human Immunodeficiency Virus (HIV) infected patients is threatening to compromise tuberculosis control worldwide.

Here we report a rare case of disseminated tuberculosis, presenting with a wide spectrum of extra pulmonary involvement including prostate and leptomeningeal, and evolving to a fatal outcome due to lack of response to all tuberculostatic drugs used.

This paper highlights the clinical complexity of this disease, and the diagnostic and therapeutic challenges that one faces when treating patients with tuberculosis.

Keywords: Disseminated tuberculosis; Prostatic involvement; Leptomeningeal involvement; HIV

Introduction

Tuberculosis (TB) continues to be a leading cause of morbidity and mortality in the world. In 2009 there were an estimated 9.4 million new cases of tuberculosis globally, equivalent to 137 cases per 100 000 habitants [1]. The majority of these cases occurred in Asia (55%) and Africa (30%), with a smaller percentage occurring in the European region (4%). In Portugal, 2686 new cases of tuberculosis were diagnosed in 2008, corresponding to 25.3 cases per 100,000 habitants, an inferior number to the global incidence and, in particular, to the European mean incidence [2].

In 1958, Sir John Crofton read to a plenary session during the Annual Meeting of the British Medical Association: "The development of drug resistance may be a tragedy not only for the patient himself but for others. For he can infect other people with his drug-resistant organisms. In such patients the disease would not be sensitive to the drug in question. A recent survey by the Medical Research Council in various clinics all over the country has shown that no less than 5% of newly diagnosed patients were infected with organisms resistant to at least one of the three main drugs. If physicians come to apply thoroughly the present knowledge about preventing drug resistance, this percentage should steadily diminish" [3].

Despite this warning, the "percentage" didn't diminish, and fifty years later the existence of Multi-Drug Resistant TB (MDR-TB), caused by strains of *Mycobacterium tuberculosis* that are resistant to both isoniazid and rifampicin with or without resistant to other drugs, is a worldwide problem that threatens to destabilize tuberculosis control [4].

Of the total number of incident TB cases globally, 3.6% are estimated to have MDR-TB strains [5]. In 2008, there were an estimated 440,000 MDR-TB cases worldwide, with 58 countries reporting at least one case of Extensively Drug-Resistant TB (XDR-TB) by July 2010 [1]. Recent investigations on six different continents showed that 10% of MDR-TB cases became XDR-TB strains [6], and there are even reports of a more dangerous form of disease named Totally Drug-Resistant strain (TDR) or super-XDR-TB isolates and defined as MDR strains resistant to all second-line drug classes that were tested (i.e., aminoglycosides, cyclic polypeptides, fluoroquinolones, thioamides, serine analogues, and salicylic acid derivatives) [7]. In Portugal this has also become a very important healthcare issue - 34% of the MDR-TB cases diagnosed in Portugal during 2008 had criteria of XDR-TB [2].

The clinical presentation of TB varies dramatically, is very unspecific and can mimic several other disorders, reason why it has earned the nickname of "the great pretender". It can present either in an indolent or fulminant manner, with overwhelming systemic symptoms or with scant complaints and can affect one or several organ systems. Disseminated TB was defined as having two or more non-contiguous sites resulting from lymphohematogenous dissemination of *Mycobacterium tuberculosis* [8]. The advent of Human Immunodeficiency Virus (HIV) infection led to an increase in the number of cases of disseminated TB because HIV renders the host immune system impoverished, resulting in an incompetence to contain the infection and allowing therefore dissemination throughout the organism. It can result from two distinct pathogenic sequences, occurring either as an early consequence of initial infection and bacillemia or as a result of endogenous reactivation and blood stream invasion [9]. Nevertheless, disseminated TB is still uncommon.

Here we present a rare clinical case of disseminated TB with central nervous system, spleen, kidney and prostatic involvement that we believe can be representative of the challenges in diagnosing and treating TB in our days.

Case Report

A 37-year-old melanodermic male patient, born in Guine-Bissau but resident in Lisbon for the past 16 years, married, with four children, was admitted to the infectious diseases department of Hospital de Santa Maria in Lisbon with fever, asthenia and weight loss of 15%. He

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was diagnosed with HIV infection 7-months before, in the context of his spouse's diagnosis during pregnancy surveillance. Antiretroviral therapy was started with Tenofir DF/ Emtricitabina + Nevirapina (TDF/FTC + NVP). The genotypic testing of the infecting strain did not show any resistance mutations.

3-months prior to the admission into our hospital, the patient travelled to Guine-Bissau, where he stayed for 2 months. Since the beginning of his visit he refers diarrhoea without blood or mucus, daily vespertine non-quantified fever, headache, myalgias, anorexia and weight loss.

Upon presentation, the patient was conscious, coherent and co-operative, undernourished and febrile. There were no lymphadenopathies detected. The lungs were clear, cardiac auscultation showed tachycardia. Abdominal examination didn't reveal any palpable masses or any other alterations.

Laboratory examination revealed an increase in inflammatory parameters with a C-reactive protein of 15.2 mg/dl and VS of 120 mm, with no other analytic alterations. The serologies were negative for acute infection for Hepatitis B, Hepatitis C, CMV, toxoplasmosis, and cryptococcal antigen, *Legionella*, VDRL and Widal. The pulmonary x-ray didn't show any alterations suggestive of active disease.

He was admitted for further investigation of this clinical presentation of fever of unknown origin, weight loss and intense asthenia.

The body CT scan performed at admission showed multiple pre-tracheal calcified lymph nodes, probably of residual nature, and multiple cystic pulmonary images suggestive of previous *Pneumocystis* infection, with no other pulmonary alterations. A discrete hepatomegaly was evident, with a hypodense lesion of 8 mm, and also a heterogeneous splenomegaly was noted with multiple nodular hypodense lesions measuring between 3 and 15 mm (Figure 1A). Heterogeneity of the inferior pole of the right kidney was evident, with aspects suggesting the presence of a renal abscess (Figure 1B). The prostate was also heterogeneous with evidence of several hypodense areas, suggestive of a prostatic abscess with multiple loci (Figure 1C). Intraabdominally, several adenopathies were noted, the biggest with 2.5 cm of diameter.

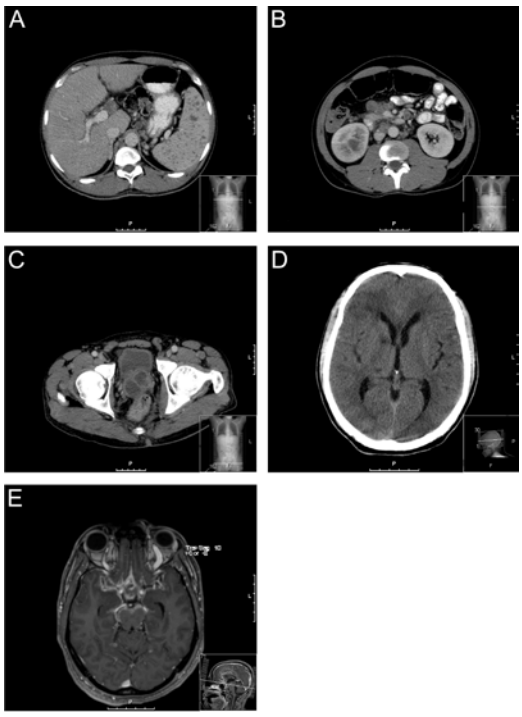

Figure 1:
A. Body CT scan showing multiple nodular hypodense lesions scattered in the spleen
B. Renal abcess of the right kidney
C. Imagiologic evidence of a complex prostatic abscess, with multiple loci
D. Cranioencephalic CT showing several cerebral parenchymal hypodensities
E. Cranioencephalic MRI demonstrating leptomeningeal involvement

Next, an echo-guided splenic biopsy was performed, but the anatomopathologic exam was inconclusive and the microbiology analysis was negative. He was also submitted to a bronchofibroscopy with BAL, but the bacteriology and mycologic exams were also negative. Similarly, the bone marrow biopsy and myelogram performed didn't show any evidence of infection.

During his permanence in our department, clinical deterioration occurred with installation of neurologic alterations suggestive of meningoencephalitis. A lumbar puncture was performed, with removal of liquor under tension, Pandy+++, glycorrhachia of 32 mg/dL (glycemia of 99 mg/dL), proteinorrhachia of 212 mg/dL and lymphocyte-predominant pleocytosis of 82 cells/μL.

On the basis of clinical, physical, laboratory and imagiologic findings, a diagnosis of disseminated TB was made, and tuberculostatic drugs were initiated with the HRZE regimen. No isolation of mycobaterias was made in the CRL, however the PCR in the liquor was positive. He also started systemic corticotherapy, but the behavioural alterations persisted with no changes in the neurologic status, being then administered intrathecal corticotherapy (10 mg/weekly). The cranioencephalic CT showed cerebral parenchymatous hypodensities probably of infectious nature, with incipient hydrocephalus (Figure 1D). He was also submitted to a cranioencephalic MRI that demonstrated leptomeningeal involvement with predominant expression in the pentagonal cistern, with signs of reactive meningitis (Figure 1E). These alterations were compatible with leptomeningeal involvement by TB.

A prostatic biopsy was performed, being positive for mycobacteria by direct examination and by PCR. However, culture was negative. IGRA was also performed, and it was positive.

In spite of the anti-tuberculostatic therapy, the patient continued to present clinical deterioration with neurological alterations, and second line antibacilars were associated, namely levofloxacin, amycacin and cycloserin.

No improvement was seen, and clinical deterioration continued with progressive neurological degradation, resulting in a fatal outcome after 10-months of therapy.

Discussion

TB is a broad spectrum disease that may involve pulmonary and several extra pulmonary locations. A high index of suspicion is necessary in making the diagnosis of disseminated TB. Since the clinical manifestations of TB can be so diverse, it is crucial that all patients that present with a clinical story and physical exam suggestive of TB be considered as TB and prompt treatment is initiated.

Fever, anorexia, night sweats and weight loss are present at diagnosis in a great percentage of patients. Various hematologic and serum abnormalities like thrombocytopenia, anemia, monocytosis,

eosinophilia, leukocytosis, leukopenia, hyponatremia, and alkaline phosphatase elevation, have been implicated. Physical examination is also crucial in making the diagnosis: hepatomegaly, lymph nodes enlargement and subcutaneous nodules can direct to TB diagnosis.

Our patient presented with fever, asthenia, anorexia and weight loss of 15%, which raised the hypothesis of TB infection.

TB can involve any organ system in the body. Genitourinary TB is the second most common extra pulmonary form of TB, and it may involve the kidneys, ureter, bladder and genital organs. Up to 20% of the patients with pulmonary TB have genitourinary lesions, particularly in the kidneys. It usually results from haematogenous dissemination from an active site of infection, although the most frequent cause of genital organs infection is urologic spread from renal foci [8]. Prostatic TB also occurs by haematogenic spread, but involvement is rare [10]. Concomitant renal involvement is present in 85% of patients. Persistent sterile pyuria and hematuria are the most classical findings to be seen in urogenital TB, but severe cases of prostatic involvement may present as abscesses, as in our patient. Splenic TB, also present in this patient, is likewise an unusual manifestation and usually occurs in patients with concurrent HIV infection [11].

We present this case for its rare disseminated involvement of CNS, prostate, kidney and spleen, and for its indolent but fatal course. Although we had imagiologic and clinical evidence of disseminated TB, and several specimens were collected and sent for acid fast bacilli staining, mycobacterial culture and histopathological examination, TB definitive diagnosis was only possible after acid fast resistant bacilli was shown in direct examination of the prostatic drainage material. Unfortunately, mycobacterial culture was negative not allowing the determination of pharmacologic sensibility of this strain. However, the clinical evolution of this patient, with no evidence of response to TB treatment and progression of disease after alteration of the regimen to one adequate to MDR-TB, associated with the high prevalence of XDR-TB in our country [2], raises the hypothesis of infection by a XDR-TB or even a TDR-TB *M. Tuberculosis* strain.

Although incredible advances have been made in the last decades in our radiologic diagnostic capacity, in the *M. tuberculosis* detection techniques, and in the treatment of this disease, TB continues to be a fatal disease. As Keshavjee and Farmer [12] stated "Facing this epidemic will require engaging new players in the fight against tuberculosis; it will require courageous steps and a globalized approach, drawing on new public and private partnerships. We may not have much time before this epidemic overtakes our capacity to stop tuberculosis".

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