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Case report

Miliary tuberculosis with cerebral, liver, prostate and retroesophageal involvement

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ABSTRACT

Miliary tuberculosis results from the lymphohematogenous spread of *Mycobacterium tuberculosis* and it is a rare form of this disease. The most affected places are the lymph nodes, pleura, and osteoarticular system, but any organ can be involved. Currently the disease is still endemic in developing countries by its close association with poor living conditions and malnutrition. Other comorbidities, particularly infection by human immunodeficiency virus (HIV), diabetes mellitus, smoking and alcoholism are of great importance in the epidemiology of this disease.

The authors describe the case of an adult man from Guinea-Bissau that has been residing in Portugal for the last few months, admitted with complaints of headache. He was submitted to a computerized tomography (CT) scan of the brain which showed multiple lesions. This led to further study and the diagnosis of a disseminated tuberculosis with cerebral, liver, prostate and retroesophageal involvement. He was started on anti-tuberculosis therapy, achieving good results.

Introduction

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis*, an aerobic bacteria of small dimensions and high infectivity. According to the World Health Organization, in 2013, approximately one third of the global population had latent tuberculosis [1]. The risk of these people progressing to active TB throughout life is 10%, a number that rises in case of HIV infection, malnutrition, diabetes, smoking or alcoholism [2].

In spite of being a curable disease, TB continues to cause high mortality worldwide. According to the Center for Disease Control and Prevention (CDC), in 2014 about 9.6 million people were infected and 1.5 million died of complications of the disease [3].

The most affected organ by this disease is the lung, involved in over 90% of cases. In cases of extrapulmonary disease, the most affected places are the lymph nodes, pleura and osteo-articular and genitourinary systems [4], but any organ can be implicated. Miliary tuberculosis is a rare form of the disease, resulting from the lymphohematogenous spread of mycobacteria, usually comprising extrapulmonary organs [5].

In this report, we present a case of Guinean patient admitted with complaints of headache, confusion and slowness of movement. Further studies concluded the patient suffered from disseminated tuberculosis with cerebral, retroesophageal, liver and prostate involvement.

Clinical case

A 50 years old black male from Guinea-Bissau and living in Portugal for the past seven months presented to the emergency room complaining of persistent frontoparietal headaches for the past week. The headache was non pulsatile, associated with photo and phonophobia, nausea and anorexia, and it disturbed his sleep, leading the patient to wake up several times during the night. The headache didn't worsen with the decubitus position. He denied other symptoms, particularly in terms of the respiratory, gastrointestinal, urinary or cutaneous systems. According to his wife, he had periods of marked disorientation and apathy since 3 years ago, since the time he was diagnosed hypertension (HTA), treated with amlodipine. Other comorbidities included a probable dementia related to multi-infarctions suffered a year earlier, and had no known allergies.

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At examination, the patient presented with apparent slowing of movements, associated with time and space disorientation. He was afebrile, calm, with a blood pressure of 105/78 mmHg, a heart rate of 87 beats per minute and a respiratory rate of 16 cycles per minute. The cardio-pulmonary auscultation, the abdominal inspection and palpation were all normal. He had severe xerodermia, but no other skin lesions. He had no edema and no palpable peripheral lymphadenopathy.

The neurological examination showed the patient was conscious, but uncooperative, without apparent dysarthria, preserved visual fields, isochoric and isoreactive pupils, eye movements with no limitation, without facial palsy or motor lateralization, and without ataxia or neck stiffness.

In the emergency department blood tests showed: leukocytes 5.3×10^9/L (**N**ormal **R**ange: 4–10×10^9/L), platelet count 213×10^9/L (NR 150–400×10^9/L), hemoglobin 14.7G/dL (NR 13–17G/dL), erythrocyte sedimentation rate of 36 mm/1st h (NR: <20 mm/1st h), creatinine 1,28 mg/dl (NR: 0.8–1.3 mg/dL), AST 40 U/L (NR: 5–30U/L), ALT 42 U/L (5–30U/L), gamma glutamyl transferase 346 U/L (NR: 6–50U/L), alkaline phosphatase 249 U/L (50–100U/L), lactate dehydrogenase 261U/L (50–150U/L). An abdominal and renal ultrasound were requested and revealed no hepatic or renal abnormalities. The CT scan of the brain initially performed revealed diffuse brain atrophy, showing multiple small nodular lesions, isodense and a ring enhancement after intravenous injection of iodinated contrast, involving the brain and the cerebellum (Fig. 1). Subsequently, a lumbar puncture was performed, and the cerebrospinal fluid (CSF) showed to be xanthochromic, with an opening pressure of 13cmH_2O. CSF analysis included: glucose 52 mg/dl (NR: >60 mg/dL), protein 43 mg/dl (NR: <42 mg/dL), leukocytes <1/mm^3, erythrocyte 2800/mm^3; India ink test and *Streptococcus pneumoniae* antigen were negative.

Considered the possibility of an infectious etiology, the patient was transferred to the Infectious Diseases ward for further studies. These included: negative HIV and syphilis screening tests, immunity (IgG presence and absence of IgM) for toxoplasmosis, cytomegalovirus, Borrelia and hepatitis A virus; natural immunity to hepatitis B virus; absence of antibody for hepatitis C virus, amebiasis, hydatidosis or cysticercosis. The lymphocyte populations were normal, with lymphocyte T-CD4+ of 600 cells/mm^3 (NR: >700cells/mm^3) and a CD4/CD8 ratio of 2.48. Interferon gamma test (QuantiFERON TB Gold®) was strongly positive.

By the 7th day at the ward, a brain magnetic resonance was performed and it confirmed the presence of multiple nodular intra-axial lesions with intense enhancement, predominantly homogeneous, but in form of "ring" in the larger ones, and surrounding edema relatively large for their small dimensions, although with no significant mass effect. Given the characteristics of the lesions, the differential diagnosis of secondary brain (metastatic) lesions, or an infectious etiology with hematogenous spread, including tuberculosis, were considered. The lumbar puncture was repeated, with a normal cytochemical examination, as it was the adenosine deaminase (ADA). At that time, CSF was also collected for cultures and polymerase chain reaction in real time (PCR-rt) screening for mycobacteria.

By the 11th day in the ward, the liver enzymes remained elevated (AST 51U/L, ALT 54 U/L, GGT 375 U/L, alkaline phosphatase 328 U/L) and a liver biopsy was performed. Histological result of the sample revealed necrotizing granulomatous inflammation, setting the diagnostis of tuberculosis as the main one. Given these results, antituberculosis drugs (ethambutol, rifampicin, isoniazid and pyrazinamide) were initiated.

At that time, a bronchoscopy with bronchoalveolar lavage was performed, as well as CT scans of the thorax, abdomen and pelvis. These last exams revealed a mass in the posterior mediastinum with 2.6×2.3 cm in contact with the esophagus, multiple adenopathies above and below the diaphragm, micronodules in the lung, and an increased heterogeneous prostate. After these findings, a gastrointestinal ecoendoscopy and a prostate ultrasound were performed. The first test confirmed the presence of a retroesophageal mass and it was sent to histology and microbiological study. The direct examination (with Ziehl-Nielsen staining) was strongly positive (>10bacilis/field). On the other hand, transrectal prostatic ultrasonography showed a gland of increased dimensions (54cc) with symmetrical and regular borders, and several well-defined hypoechoic nodular formations (Fig. 2), some with internal calcifications. Given the clinical information, and after discussion with the Urology department, a tuberculous etiology was actually considered as the most likely.

Among the ongoing tests performed since the beginning of hospitalization, we highlight the negative results of mycobacterial research (cultures and PCR-rt) in CSF, blood, urine or bronchoalveolar liquid.

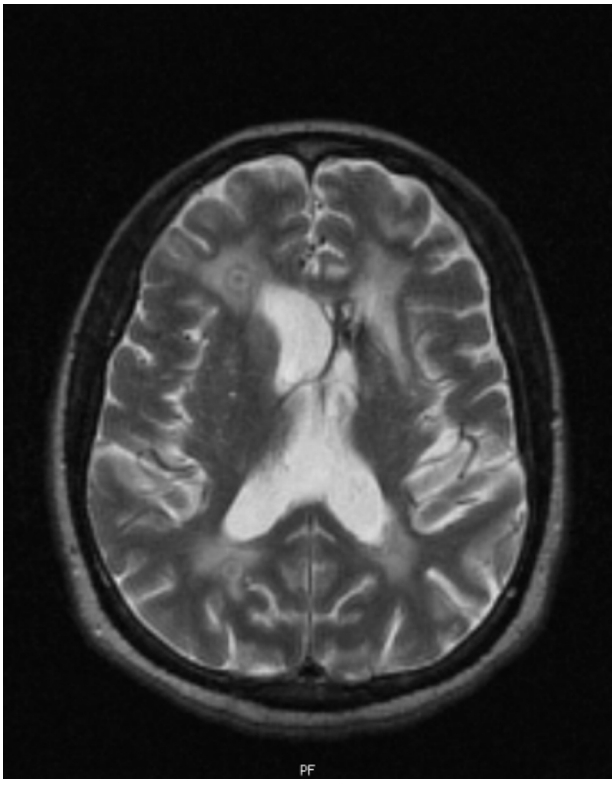

Fig. 1. CT scan of the brain showing two lesions with a ring shaped enhancement.

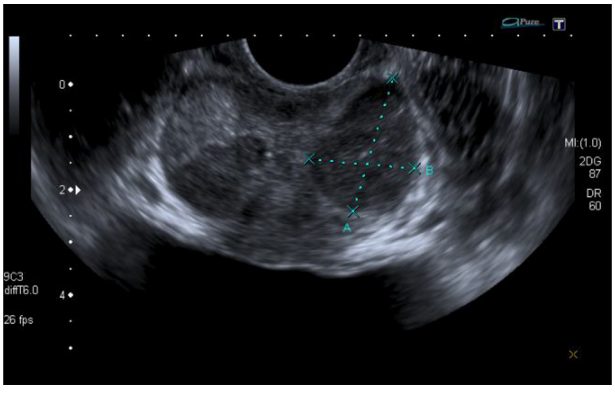

Fig. 2. Ultrasound showing an enlarged prostate with nodular lesions.

During his stay on the ward, the patient had a slight improvement in his cognitive functions, being able to communicate easier. Another CT scan of the brain was performed after one month of antituberculosis drugs, and it showed a change in the enhancement pattern, now more diffuse, an aspect that, combined with the absence of worsenning, favored the hypothesis of tuberculosis in opposition of neoplastic etiology.

The patient was discharged from the hospital at that time, clinically and hemodynamically stable. He remains in follow-up by the Infectious Diseases team as an outpatient, and shows improvement of his overall status, specially his cognitive functions.

Discussion

Tuberculosis remains a disease associated with poor living conditions, facilitated by the high population density of some areas. Although many advances in medicine have been made, this disease remains a major cause of morbidity and mortality worldwide and is still endemic in many parts of the world.

Mycobacterium tuberculosis bacillus generally enters the human body through inhalation, leading to the formation of a pulmonary focus which is either combated and/or contained by cellular immunity. If infection occurs at this time, it is called primary infection. Late reactivation is called secondary tuberculosis. In both forms, hematogenous spread can occur, which is facilitated by the presence of several risk factors: alcoholism, heart failure, poorly controlled diabetes, chronic lung disease or a state of immunosuppression by HIV infection, prolonged use of corticosteroids, malnutrition, neoplasms or genetic defects of the cellular immunity [6].

Disseminated tuberculosis is characterized by concurrent engagement of two or more non-adjacent organs [7]. It is a rare presentation, particularly in immunocompetent patients. The clinical presentation is variable, with symptoms depending on the involved organs. Usually of indolent course, at an early stage it can be asymptomatic and, even at more advanced stages, the constitutional symptoms are nonspecific and clinical suspicion is the main point for an assertive diagnosis. The most common symptoms are malaise, fever, chills and weight loss.

Most patients with genitourinary involvement complain with dysuria, changes in urinary flow, urinary urgency or pollakiuria [8], The presented patient had no complaints regarding this system, and the prostatic involvement was only an imaging finding.

The incidence of tuberculosis in the country of origin of the presented patient in this case is very high (369 per 100,000 persons), compared to that of Portugal (25 per 100,000) [9]. Combining the findings in patient history, laboratory and imaging data, as well as cytology, polymerase chain-reaction and tuberculin skin test/TB blood tests such as QuantiFERON-TB Gold, they all led to the correct diagnosis and allowed to establish the focalizations of the disease.

Conclusion

The uniqueness of this case lies in its presentation, which can be considered atypical because the symptoms and signs were only neurological. Only the subsequent study allowed the diagnosis of miliary tuberculosis with focalizations in uncommon locations. It also aims to reinforce the idea that tuberculosis is a current disease that should be taken into account in the case of migrants from countries with high rates of incidence and prevalence, even in the absence of immunosuppression.

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