Central nervous system tuberculosis following delayed and initially missed lung miliary tuberculosis: a case report

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SUMMARY

Central nervous system (CNS) tuberculosis includes three clinical entities: tuberculous meningitis, intracranial tuberculoma, and spinal tuberculous arachnoiditis. All three categories are encountered frequently in regions of the world where the incidence of TB is high. Meningeal tuberculosis is a medical emergency: it is the most severe, lethal and disabling form of tuberculosis. Early diagnosis and treatment can be lifesaving. Even, in developed countries the diagnosis of tuberculous meningitis is difficult, frequently delayed or missed, and is often not microbiologically confirmed. Here I report a case of miliary tuberculosis, in a patient with diabetes mellitus and chronic kidney disease, but without HIV infection. Although the patient had regular contact with healthcare staff (hemodialysis), miliary tuberculosis diagnosis was considerably delayed. This patient, subsequently evolved into tuberculous meningitis. In spite of quadruple anti-tuberculosis treatment, corticosteroids, and general supportive care, this case resulted in death.

Keywords: tuberculosis, central nervous system tuberculosis, miliary tuberculosis, diagnosis, delayed diagnosis.

■ INTRODUCTION

Tuberculosis (TB) is a global public health problem [1, 2]. According to the World Health Organization, Peru is a country of high endemicity and belongs to the top 30 high burden countries for resistant TB. About 20% of all TB cases are extrapulmonary [1]. Central Nervous System (CNS) tuberculosis (TB) accounts for 1% of all TB cases and 5% of extrapulmonary TB cases. In resource limited countries, though is highly endemic, TB diagnosis remains very difficult. So, a high index of suspicious is required [2-5]. Here, I present a case of miliary TB that subsequently evolved into CNS tuberculosis (tuberculous meningitis and intracranial tuberculomas).

■ CASE PRESENTATION

A 63-year-old woman was admitted to Emergency Department on February 09th 2018 with a 3-week history of headache, drowsiness, hypoactivity, anorexia, and asthenia. She had previous history of diabetes mellitus (DM), hypertension (HTN), and Chronic Renal Disease (CRD) on regular hemodialysis (HD). *Physical examination*: blood pressure 160/90 mmHg, respiratory rate 20 bpm, heart rate 84 bpm, T 37.8 °C, Sat. O_2 95% (FiO_2 0.21). Body weight 50 kg, height 1.65 m, BMI 18.3 kg/m²; respiratory, cardiovascular, and gastrointestinal system were unremarkable. Neurologic examination showed stupor (Glasgow Coma Scale 13), unre-

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Figure 1 - CXR (February 9th, 2018) showing enlarged heart shadow and miliary pattern of pulmonary opacities suggestive of interstitial lung disease, including fibrosis.

sponsive to calling, no focal deficit, isochoric pupils with normal reaction to light, no meningeal signs, the Babinski's sign was positive bilaterally. Basic analysis, Chest X-ray (CXR) (Figure 1), and non-contrast head computed tomography (CT)

were performed (Figure 2 and Figure 3). *Evolution*: on February 10th, 2018, the patient remained with stupor and low-grade fever. Based on head CT a provisional diagnosis of neurocysticercosis was entertained, and Western Blot serology and contrast-enhanced brain magnetic resonance imaging (MRI) were ordered. On February 15th 2018, the patient became comatose. She was intubated and connected to mechanical ventilation (MV). On February 18th 2018, a diagnosis of miliary TB was made based upon an "unexpected finding" of a CXR taken three months before (Figure 4). There was no evidence in the patient's medical record of the reason why this CXR was taken. But is probable that it was indicated by nephrologist for checking proper position of central venous catheter for hemodialysis after it was inserted, because this is a routine practice.

Because, no cause of coma could be determined at this point, negative serology for cysticercosis, and an established diagnosis of miliary TB, a diagnosis of CNS tuberculosis was entertained and spinal tap was performed. Based on clinical grounds and preliminary cerebrospinal fluid (CSF) laboratory results, anti-TB therapy was initiated. CSF adenosine deaminase (ADA) result was obtained 2 days after spinal tap. During the following days,
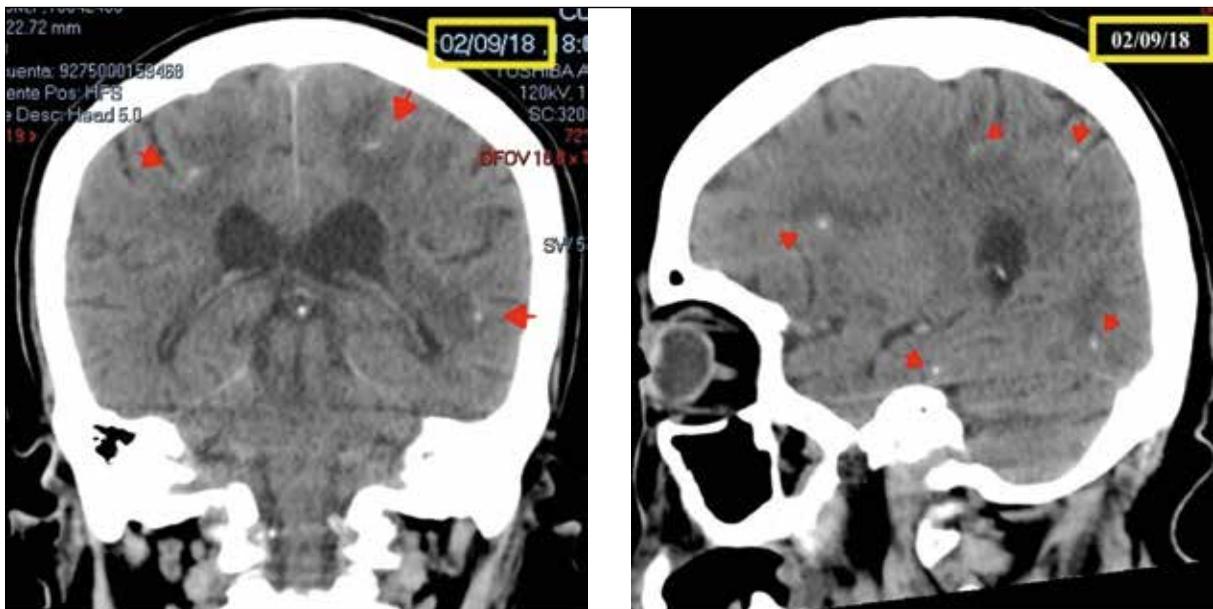
Figure 2 and Figure 3 - Non-contrast head CT (February 09th, 2018), coronal (left) and sagittal (right) views showing multiples hyperdense lesions (calcifications) compatible with tuberculomas and prominent perilesional edema.

Figure 4 - Chest X-Ray (November 23th, 2017) showing a typical miliary pattern of pulmonary opacities and cardiomegaly.

this patient continued with MV and general supportive care, including broad spectrum antibiotics and vasopressors. She died 20 days after initiation of anti-TB treatment.

Lab Tests: remarkable basic hematology and biochemistry were hypoproteinemia (6.1 g/dL), hypoalbuminemia (2.79 g/dL), moderate anemia (9 g/dL), and severe lymphopenia (252 lymphocytes/µL or 4% out of 6 300 white blood cells). Serologies for cysticercosis (Western Blot), human immunodeficiency virus (HIV), hepatitis B and C, and VDRL were also negative. CSF: turbid, 310 leucocytes/uL, polymorphonuclear 85%; Gram smear, china ink smear, Ziehl-Neelsen (ZN) smear were negative; glucose 18 mg/dL, proteins 272.3 mg/dL, ADA 38.2 U/L. Non-contrast head CT: Normal. ZN smear and culture for *M. tuberculosis* in urine (two samples), gastric aspirate (two samples), bronchial secretion (two samples), feces (one sample), all were negative. *Cultures for common pathogens:* bronchial secretion, urine, and CSF were also negative. Electrocardiogram was compatible with left ventricular (LV) hypertrophy; echocardiography showed LV hypertrophy, LV ejection fraction (by modified Simpson's rule) of 52%, grade II diastolic dysfunction, no valvular abnormalities, no pericardial effusion, and borderline pulmonary artery pressure. Polymerase chain reaction (PCR) was not available in our institution at the time of the case presentation; and

because of the denial of patient's family autopsy was not performed.

Final diagnosis: tuberculosis miliary and CNS tuberculosis (tuberculous meningitis and intracranial tuberculomas).

Standard quadruple anti-TB therapy included isoniazid 5 mg/kg, rifampicin 15 mg/kg, ethambutol 20 mg/kg, pyrazinamide 25 mg/kg adjustment for CRD in HD. Dexamethasone 0.4 mg/kg/d was administered concomitantly. CSF culture in solid media yielded *Mycobacterium tuberculosis* (MTB) susceptible to all first line anti-TB drugs, which was obtained 6 weeks after death.

■ DISCUSSION

Tuberculosis remains one of the leading causes of adult deaths from infectious diseases worldwide. During last years, a constant proportional increase of extrapulmonary disease has been reported [1, 2]. This case emphasizes the importance of clinicians' awareness on life-threatening forms of extrapulmonary TB, especially CNS disease, because it is hard to diagnose without having it constantly in mind. Delayed diagnosis and treatment is associated with a poor prognosis such as in the presented case [2-5].

CNS tuberculosis (TB) includes three clinical categories: tuberculous meningitis (TBM), intracranial tuberculoma, and spinal tuberculous arachnoiditis. All three categories are encountered frequently in endemic regions such as Peru [6]. During the bacillaemia that follows primary infection or late reactivation tuberculosis (TB), scattered tuberculous foci (tubercles) are established in the brain, meninges, or adjacent bone. The chance occurrence of a subependymal tubercle, with progression and rupture into the subarachnoid space, is the critical event in the development of tuberculous meningitis. The widespread and dense distribution of infectious foci seen in association with progressive miliary tuberculosis greatly increases the chance that juxta-ependymal tubercles will be established. Consequently, meningitis develops most commonly as a complication of progressive primary infection in infants and young children and from chronic reactivation bacillaemia in older adults with immune deficiency caused by aging, alcoholism, malnutrition, malignancy, HIV infection, etc. [2-4]. The case presented here, had sever-

al risk factors (DM, CRD on HD, elderly), but no HIV infection.

TBM evolves into three phases:

1) *prodromal phase*, presents insidiously (2-3 weeks) with malaise, asthenia, headache, fever, and personality changes;
2) *meningitic phase* follows with meningismus, protracted headache, vomiting, lethargy, confusion, and cranial nerve and long-tract signs;
3) *paralytic phase* supervenes with stupor, coma, seizures, and hemiparesis.

Several TBM severity scales have been developed. One of the most useful and extensively used is the Modified Medical Research Council Scale (mMRC). This system classifies:

1) *Grade I:* GCS 15, no focal neurologic deficit;
2) *Grade II:* GCS 11-14, or 15 with focal neurologic deficit;
3) *Grade III:* GCS ≤10 [2-4].

MTB is the most severe, lethal, and disabling form of TB. Mortality ranges from 20 to 50% but can be 100% in patients with resistant TB and HIV coinfection. Clinical outcomes depend mainly on stage when treatment is initiated. Therefore, early TBM diagnosis has critical importance [2]. Death rate or severe neurologic disability in stage mMRC I, II, y III is 15%, 30% and 50%, respectively for non-HIV-infected patients [3]. Our patient presented on paralytic phase and began treatment in mMRC stage III. This explains, at least in part, its adverse outcome. Other prognostic factors are age, and duration of disease. Mortality is higher in patients less than 5 years (20%) and more than 50 years (60%), and in those with symptoms lasting more than 2 months (80%) [2, 4]. It is evidence based that BCG vaccination at birth protects newborns and infants from the most serious manifestation of disseminated TB [2].

The cornerstone in TBM diagnosis is CFS analysis. Protein concentration is elevated; glucose concentration is low (CSF/serum plasma glucose ratio <0.5 in 90% of cases); cell count ranges from 0 to 1 500 cells/mm^3; pleocytosis lymphomononuclear (LMN) is typical, but polymorphonuclear (PMN) predominance may occur in up to 25-34% of TBM patients, especially at the beginning of the disease, as occurred in our case [2-6]. This CSF pattern, usually changes rapidly to LMN response in subsequent CSF examinations. After initiation of anti-TB therapy, CSF changes rapidly to a PMN response in approximately 30% of TBM, which is

associated with transient clinical deterioration. This phenomenon is known as "paradoxical reaction", and according to some experts, is pathognomonic of TBM [2, 4, 7, 8].

It is required at least 10^4 microorganisms so that ZN smear becomes positive. This fact explains why microscopy sensitivity is poor in paucibacillary forms of TB, such as TBM [5]. In order to increase sensitivity, it is necessary to examine a large volume of CSF in repeated lumbar punctures. CSF analysis showed acid fast bacilli in 10-37% of an initial exam; but, increases up to 87% when large volume (~10 mL) of four lumbar taps are examined [4]. Another way, is to obtain a large volume of CSF and centrifuge it at 3 000g, which can improve sensitivity to more than 80%. This technique can also increase culture yield for *M. tuberculosis* [2-5]. Nonetheless, these methods are not practical for use in resource-limited settings, because ideally, they should be performed in biosecurity tertiary-level facilities [5, 9]. Cultures are more sensible and specific than ZNS, but they take at least 10 days on liquid media and up to 8-12 weeks on solid media [2-5]. Both, ZN smear and culture can be positive even after treatment has begun [2].

The sensitivity of PCR for TB is low in the CSF: only 60-90% [2-5]. The adenosine deaminase (ADA) test is useful to support a TBM diagnosis and to start treatment, but its diagnostic yield depends on the cut-off value used. Using a cut-off value ≥10 U/L, is 92.5% and specificity 97% [2, 3, 5, 10].

In about 75% of TBM cases, there are extra-meningeal TB concomitantly; miliary lung TB is the most common finding, as presented in our Case [2, 4, 11, 12]. In fact, miliary TB could be an indicator for TBM in countries with high prevalence of TB [13]. So, as meningitis reactivation may be presented in miliary TB, TBM should be kept in mind in differential diagnosis of miliary TB.

In order to improve diagnostic accuracy of TBM, several clinical prediction rules have been described. One of the main pitfalls of Twaites' scoring system is that it has been developed and validated manly in populations with low prevalence of HIV infection [3-5, 14-16]. In Latin America and Peru, validation studies have shown inconsistent results. So, in general, this tool has a limited utility for diagnosis of TBM and differential diagnosis with other etiologies of meningitis [17-21].

In a similar way to TBM, for patients with lung miliary TB, predictors of adverse outcomes have been described [22-24]. According to Kim et al., a high nutritional risk score (NRS ≥3) is an independent predictor of acute respiratory failure and mortality. NRS was defined by the total number of the following risk factors (one point assigned for each factor present): 1) BMI <18.5 kg/m^2, 2) serum albumin <3.0 mg/dL, 3) serum cholesterol <90 mg/dL, 4) total lymphocyte count <7×105 cells/L [24]. Our patient has at least three of these adverse risk factors.

TBM is a medical emergency, therapy should be initiated immediately in every patient with meningeal syndrome and a typical CSF pattern, especially if there is evidence (past or current) of TB in another organ; or if there is no convincing alternative diagnosis [2-6, 11, 12]. In our case, anti-TB treatment was initiated based on clinical suspicion without waiting for confirmation for TBM nor even CFS ADA result. Finally, this case exemplifies the difficulty in diagnosing TB. In spite of having regular health care contact (hemodialysis), TB diagnosis was delayed three months.

Conflict of interest
None to declare

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