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Acute Encephalomyelitis due to Treatment for Tuberculous Meningitis

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Abstract

Tuberculous meningitis develops when granulomas formed by bacillus release their content in the subarachoid space, triggering an inflammatory activity. After beginning treatment with anti-tuberculosis drugs, some patients may have a paradoxical reaction which has different clinical manifestations. Here we present a case of a severe acute encephalomyelitis. A 38-years-old female presented with refractory headache. CSF analysis of admission showed 235 cel/mm^3 (85% lymphocytes) and glucose 5 mg/dl. Two days after beginning anti-tuberculosis treatment, she developed mental confusion, bradypsychism, paraparesis and bilateral Babinsk sing. Electroencephalogram showed a slow base rhythm and MRI demonstrate a pattern suggestive of myelitis. Endotracheal intubation was necessary due to decreased level of consciousness secondary to hydrocephalus. Despite external ventricular shunt and clinical measures, intracranial pressure remained high. After two weeks of treatment, patient died. The paradoxical reaction is not so rare and should not be confused with failure of anti-tuberculosis treatment.

Keywords: Tuberculosis; Tuberculosis meningitis; Encephalomyelitis acute; Paradoxal Reaction; Case report.

Introduction

World Health Organization (WHO) estimated that in 2016 there were 6.3 million new cases of active Tuberculosis (TB) in the world and, in immunocompetent adults, the *Mycobacterium tuberculosis* is the second most common cause of death due to infectious disease (in HIV patients, it is the first) [1].

TB can affect any organ, including the nervous system. The most common form of neurologic involvement is tuberculous meningitis, followed by granuloma (tuberculous) in the central nervous system and spinalcord [2]. When the diagnosis is made early, before irreversible neurological deficits have been established, the clinical response to anti-tuberculosis therapy in all forms of nervous system tuberculosis is excellent [3].

It´s important to recognize the paradoxical reaction that can arise after the beginning of treatment, since it can be assigned to diagnostic error and/or therapeutic failure.

Here we present a case of a severe acute encephalomyelitis after beginning treatment for tuberculous meningitis.

Case report

A 38-years-old female, physical education teacher, no known comorbidities, began fever, headache, which worsened in the supine position, and episodes of disorientation and mental confusion, with spontaneous reversal after a few minutes. She went to medical appointments more than once and always re-

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ceived the same diagnosis: Migraine. The symptoms persisted for six days after the beginning of treatment with analgesics and so she was hospitalized for investigation.

On admission, she had normal neurological examination and cranial Computerized Tomography (CT), but in the CSF analysis a pattern of lymphocytic pleocytosis (235 cels/mm^3, 85% lymphocytes), high levels of protein (98 mg/dl) and low glucose level (5 mg/dl) were observed.

It was started empiricaly ampicillin and acyclovir for treatment of meningitis caused by *L. monocytogenes* and herpes, respectively. After seven days, the results of the CSF revealed a positive PCR for *M. tuberculosis* and ampicillin and acyclovir were suspended. It was also started treatment with anti-tuberculosis drugs (rifampicin, isoniazid, pyrazinamide and ethambutol), maintained dexamethasone, which was in use since admission for headache control. HIV serology was non-reactive.

After two days of the onset of the anti-tuberculosis treatment, the patient complained of low back pain, paresthesias, reduced muscle strength in the lower limbs and urinary retention. In addition, a family member witnessed a short episode of loss of awareness, after which the patient became bradypsychic. She was then transferred to intensive care unit for closer neurological monitoring.

On the next day, it was evidenced paraparesis with sensory level in the T2 and bilateral Babinski sign. The magnetic resonance imaging (MRI) of the thoracic spine was performed (Figure 1).

Anti-tuberculosis treatment was maintained and after a week the patient presented with sudden decrease in level of consciousness, was submitted to endotracheal intubation and referred for emergency CT that showed important supratentorial hydrocephalus.

Emergency external ventricular shunt was performed. Despite the procedure and the clinical strategies adopted to normalize intracranial pressure, its levels remained varying between 30-36 mmHg. The transcranial Doppler showed hemodynamic signs of vasospasm and she developed bilateral late ischemia of the basal ganglia.

Fifteen days after beginning of anti-tuberculosis treatment, the patient died.

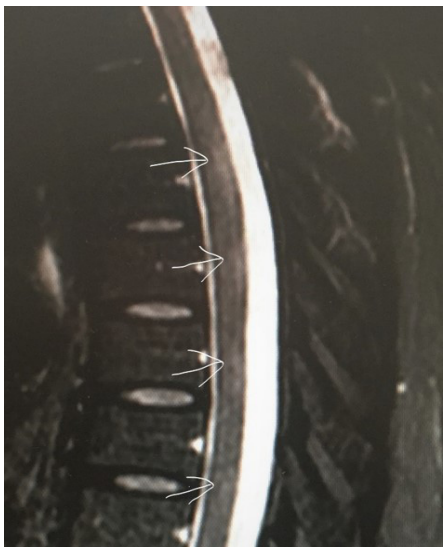

Figure 1: MRI T2 hypersignal areas suggestive of myelitis.

Discussion

Some of the predisposing factors for the development of Tuberculous Meningitis (TM), include poverty, malnutrition, alcoholism, use of illicit substances, immunosuppressive treatment and infection by the human immunodeficiency virus. *M. tuberculosis* transmission is carried out through the air, and in the lungs, the bacillus multiplies in the alveolar macrophages [4].

Within 2 to 4 weeks, through the bloodstream, the bacillus spread to extrapulmonary sites, such as the central nervous system, and produce small granulomas in the meninges and adjacent brain parenchyma, known as *Rich focus*. It usually remain inactive for years on the subpial surface or subependymal brain. The TM develops when one of these granulomas releases its contents into the subarachnoid space, triggering inflammatory activity. The high levels of tumor necrosis factor and interferon gamma in the CSF are related with disease severity [4].

The exact incidence and prevalence of TM is unknown, but it is estimated to be responsible for approximately 5% of all TB cases in immunocompetent individuals [5]. Its clinical spectrum is wide and this tends to make early diagnosis difficult. Just as it happened to our patient, it includes fever for about 7 days, malaise, headache and some episodes of mental confusion. In adults, meningeal signs are less frequent. Cranial nerves paralysis, particularly VI nerve (25% of the cases) and other neurologic signs, like radiculomyelitis, are present in advanced stages of the disease [3].

The Tuberculous Radiculomyelitis (TBRM) usually manifests insidiously with paraparesis progressing over one to two months, unlike what happened to our patient. Symptoms include radicular pain, paresthesias, sphincter dysfunction, weakness of the lower limbs and response in extension to the plantar skin reflex. Dastur and Wadia [6] described four mechanisms that lead to the spinal involvement: 1) edema of the border zone regions of the spinal cord, probably secondary to venous stasis due to the pressure associated with meningitis; 2) Ischemic myelomalacea resulting from vasculitis or post-thrombotic occlusion of the meningeal vessels; 3) Spinal cord ischemia due to vascular occlusion; 4) Formation of intramedullary tuberculomas with pericentral necrosis.

CSF analysis is essential for the diagnosis of TM. Typical changes consist of lymphocytic pleocytosis (100-500 cells/mm^3), high levels of protein (100-500 mg/dl) and low glucose level (<45 mg/dl). However, the “gold standard” for diagnosis is the recognition of the bacillus in the CSF [7]. Althoughour patient´s CSF showed all these biochemical characteristics, it was not started immediate empirical treatment for TM because there were no systemics clinical features suggesting tuberculosis and the PCR for *M. tuberculosis* was not available.

The first-line drugs for treating TM include rifampicin, isoniazid, pyrazinamide and ethambutol [8]. The use of corticosteroids reduces the process of arachnoiditis and modulates production of cytokines and chemokines, decreasing the mortality rate and severe neurological deficits among survivors [9].

After beginning of treatment with anti-tuberculosis drugs, some patients can develop a Paradoxical Reaction (PR) which is characterized by worsening of pre-existing tuberculous lesions or the appearance of new lesions. Possible explanations for this PR are the recovery of the patient's late hypersensitivity response and increased response to mycobacterial antigens released with treatment [10].

There are a variety of clinical and radiological manifestations of PR, mainly known from reports and/or small case series. In general, according to Garcia-Moncoet al. [11], these manifestations are interpreted as a clinical deterioration that appears a few weeks after the beginning of treatment. Expansion of brain tuberculomas or emerging of new tuberculomas, hydrocephalus and spinal arachnoiditis are common manifestations [10], as it happened in the patient of this report.

The time to start PR involving the central nervous system seems to be longer when compared to other sites. This can be explained by the lower penetration of anti-tuberculosis drugs on the blood-brain barrier of non-inflamed meninges [12]. Our patient, however, had clinical and radiological signs of encephalomyelitis due to PR, less than five days after the beginning of treatment.

Usually, the PR does not affect the clinical outcome of TM, but it was not what happened to our patient. She evolved to death 15 days after the beginning of the anti-tuberculosis treatment, despite the use of high-dose corticosteroids, considered the most suitable approach for the treatment of PR [10].

Conclusion

PR is not such a rare phenomenon. The present report demonstrates that this reaction requires significant attention from the attending physician, given its variety of clinical presentations and uncertain time for the onset of symptoms in the central nervous system, thus avoiding the precipitated diagnosis of failure of anti-tuberculosis treatment.

Authors' contributions: All authors have read, revised, and approved the manuscript.

Compliance with ethical standards

Conflict of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Consent for publication: We took a written informed consent from the patient's guardian to publish his case.

Ethical Approval: Approval from an institutional board review is not required for a case report.

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