CENTRAL DIABETES INSIPIDUS INDUCED BY TUBERCULOSIS IN A RHEUMATOID ARTHRITIS PATIENT

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Abstract

Tuberculosis, a polymorphic disease, is a diagnostic challenge, particularly when arises concomitantly to an autoimmune disease such as rheumatoid arthritis (RA). Herein, the authors describe a 33-year-old woman with nodular RA who was being treated with methotrexate, sulfasalazine and corticosteroids and presented with subcutaneous nodules simultaneously with aseptic meningitis. *Mycobacterium tuberculosis* was identified in cultures from a biopsy of an axillary nodule. The patient also developed polyuria and polydipsia with normal glycemia; antidiuretic hormone (ADH) treatment before and after a 3% saline infusion test was performed and diabetes insipidus was diagnosed. An encephalic MRI showed sellar and suprasellar masses, suggesting central diabetes insipidus (CDI). The patient received standard tuberculosis (TB) treatment for 6 months and also DDAVP (desmopressin acetate) during this period. Control of CDI was observed. A pre-surgical magnetic resonance imaging (MRI) showed no pituitary mass. It is known that intrasellar tuberculoma occurs in only 1% of TB patients. TB should be considered in the differential diagnosis of CDI, especially in immunosupressed patients and in countries where this infection is a serious public health problem.

Keywords: Diabetes Insipidus; Rheumatoid Arthritis; Tuberculosis; Tuberculoma; Nodulosis.

Introduction

Tuberculosis (TB) is a granulomatous disease caused by *Mycobacterium tuberculosis* bacilli that mainly affects the lungs. Before the era of HIV, the risk of contracting this infection in most developing countries had been declining by 1-5% per year. Since the mid-1980s, however, with the explosion of HIV, the incidence of TB has increased considerably. Even in industrialized countries, significant TB incidences are observed due to increased immigration from developing countries, the interaction between tuberculosis and HIV infection and the decline in the health care infrastructure related to tuberculosis control programs[1].

The most common form of infection is by inhalation of bacilli, which are then engulfed by alveolar macrophages. These bacilli continue replicating and are disseminated throughout the body inside infected macrophages. Once a cell-mediated immune response develops, the infection is brought under control, and granulomas develop in a process mediated by cytokines, primarily tumor necrosis factor (TNF). In approximately 90% of affected individuals, the infection remains latent, with the bacilli inside the granulomas. In some patients (particularly those who are immunocompromised), the infection progresses to tuberculosis disease[2]. Due to its polymorphic presentation, tuberculosis is always a difficult diagnosis, a statement that is supported by epidemiological data.

Aside from concern about co-infection of tuberculosis and HIV, another serious issue is the development of active tuberculosis disease in patients receiving anti-TNF therapy, which is primarily used to treat rheumatoid arthritis[3]. TNF is the crucial cytokine in responding to a variety of infectious agents, particularly intracellular pathogens such as *Mycobacterium tuberculosis*. TNF is essential in the formation and maintenance of the granulomas that physically contain the infection[2]. Moreover, TNF directly activates macrophages, which are responsible for phagocytosis and pathogen death[4]. As with HIV-positive individuals, TB frequently occurs in anti-TNF-treated patients in an atypical fashion, with extra-pulmonary manifestations or dissemi-

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nated disease, resulting in a serious diagnostic challenge[5].

We describe the occurrence of a pituitary tuberculoma that manifested as central diabetes insipidus (CDI) in a patient with RA and nodulosis. In this case, the main goal was to differentiate the rheumatoid nodule in the CNS from other mass lesions, primarily tumors or infections.

Case Report

A 33-year-old woman was admitted to investigate an asymptomatic pulmonary nodule. She had suffered from Rheumatoid Arthritis (RA) for 10 years (ACR criteria). The disease was controlled with methotrexate (MTX) (17.5 mg weekly), sulfasalazine (SSA) (1 g daily), deflazacort (15 mg daily) and nonsteroidal anti-inflammatory drugs. The histopathology of the nodule, obtained by open lung biopsy, was compatible with a rheumatoid nodule. At that time, chloroquine (250 mg daily) was introduced, the SSA dose was increased to 2 g daily and MTX was maintained at a lower dose (10 mg weekly).

After remaining asymptomatic for the next seven months, the patient developed subcutaneous nodules in the left axilla, supraclavicular area, right arm, forearms and legs. Some of the nodules in the arms and legs became painfully ulcerated, and their biopsy result was suggestive of rheumatoid nodules with negative cultures. The axillary nodule evolved into an abscess, which was submitted to surgical intervention, after which the material was sent for culture (fungus and mycobacterium included). Antibiotic therapy led to complete resolution of the abscess.

Concomitantly, the patient presented with headache, vomiting and photophobia. Examination of the cerebrospinal fluid revealed lymphocytic meningitis (550 cells, 69% lymphocytes, 19% monocytes, protein 72 mg/dL, glucose 46 mg/dL). Thoracic radiographs were unremarkable, tuberculin and anti-HIV tests were negative, but *Mycobacterium tuberculosis* was identified in the material from the axillary abscess. Next, the patient developed polyuria and polydipsia with normal glycemia; a saline 3% infusion test and antidiuretic hormone (ADH) treatment before and after infusion were performed, and diagnosis of diabetes insipidus was presupposed. Encephalic magnetic resonance imaging (MRI) showed sellar and suprasellar masses (Figs. 1 and 2), strengthening the diagnosis of central diabetes insipidus (CDI). Surgery was scheduled and the patient was placed under careful medical supervision while receiving standard TB treatment (Rifampin, Isoniazid and Pyrazinamide) for 6 months and DDAVP (desmopressin acetate) during diabetes insipidus symptoms. Regression of the subcutaneous lesions and control of CDI were observed. A pre-surgical MRI showed no pituitary mass (Figs. 1 and 2). At the time of the last visit, the patient's RA activity was controlled with SSA and chloroquine diphosphate. No new nodules or CDI manifestations were reported.

Discussion

More than 34 cases of intrasellar tuberculoma have been documented in the literature, most of them in India. It is an unusual condition, reported in autopsy series, rarely with clinical manifestations[6].

TB central nervous system (CNS) involvement, more commonly manifested as meningitis, results from a distant focus of *Mycobacterium tuberculo-*

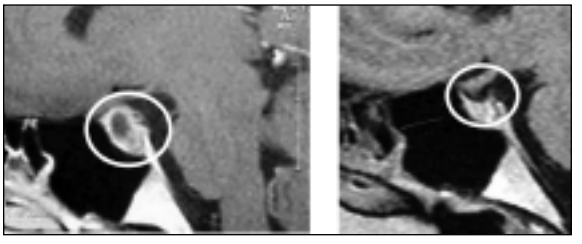

Figure 1. Mass lesion with cystic aspect in sellar and suprasellar regions before and after treatment. Magnetic resonance imaging (MRI) on T1 sequence, sagittal incidence.

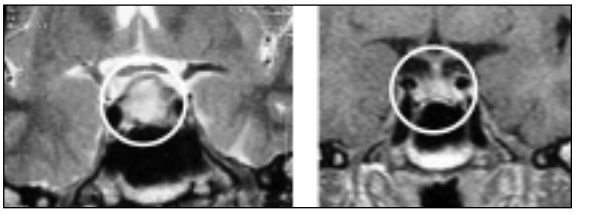

Figure 2. Mass lesion with cystic aspect in sellar and suprasellar regions before and after treatment. Gadolinium-enhanced Magnetic resonance imaging (MRI), coronal incidence.

sis, secondary to hematogenous spreading. In developing countries such as Brazil, CNS is affected in about 20% of the cases of extra-pulmonary infection. Even in these endemic areas, intracranial tuberculoma is uncommon (1% of TB patients) and is frequently associated with miliary tuberculosis. It is usually located in the cerebral cortex and cerebellum but has also been reported in the thalamus, cavernous sinus, cerebellopontine angle and very rarely in the pituitary[6].

This is the first case of pituitary tuberculoma in an immunosuppressed patient with RA. The majority of cases described in the literature were observed in healthy individuals with no evidence of immunosuppression[6].

Similar to the symptoms of our patient, headache and visual symptoms were the most frequent initial complaints[6]. Hypopituitarism was observed in about 60% of the cases. Other cases presented with hypogonadism, hyperprolactinemia or no endocrine manifestations. CID has already been reported as occurring subsequent to successfully treated tuberculosis meningitis[7] but not as a consequence of pituitary compression by tuberculoma.

This patient had ganglionary and cutaneous TB, in addition to a cerebrospinal fluid examination compatible with lymphocytic meningitis. Clinical or laboratory evidence of concomitant meningitis in patients with CNS tuberculoma is extremely variable and is observed in 10% to 50% of patient[8,9]. The recommended treatment for tuberculoma is an anti-tuberculosis traditional therapeutic scheme (Isoniazid, Rifampicin and Pyrazinamide), adding ethambutol or other drugs only in the presence of previous treatment for TB or antibiotic-resistant *Mycobacterium*[10]. During follow-up, cases demonstrated a reduction in size or disappearance of the lesion or, in cases of mass persistence, surgical excision.

The recent increase in morbidity and mortality from tuberculosis is mainly related to HIV infection, but is also related to age-related immunosuppression or immunosuppressive drugs used for autoimmune diseases[3], as was the case of our patient. This RA patient did not receive anti-TNF therapy, but she could be considered immunosuppressed due to methotrexate and corticosteroid treatment, as well as to RA itself. Anergy or decreased delayed--type hypersensitive responses to recall antigens, including tuberculin, has been observed in RA patients and could explain the negative PPD test even in the presence of active TB[11,12].

In this case, one important differential diagnosis was the CNS rheumatoid nodule, especially under MTX therapy, which accelerates nodulosis formation. Nodules in RA occur in 50-60% of patients and are commonly localized in the subcutaneous tissue, but have also been described in the heart, lungs, gastrointestinal tract and CNS[13].

Jackson et al[14], in their review of 14 cases of CNS rheumatoid nodules, reported that RA was long-standing and erosive. Subcutaneous nodules were also observed concomitantly in most reported cases. CNS nodulosis was largely asymptomatic unless there was concomitant vasculitis or meningitis. In this series, meningeal involvement was more common than parenchymal disease, which was observed in only 1 patient with nodules in the left cerebral hemisphere.

In another review of inflammatory CNS involvement in RA[15], less than half of the patients had active articular RA when CNS nodulosis was diagnosed. The majority of cases had debilitating cutaneous disease with important subcutaneous nodulosis, leg ulcers and gangrene, although the frequency of other RA extraarticular features was not reported. Our patient did not have aggressive RA and had been in remission when the neurological problem developed.

This case highlighted the importance of tuberculoma in the differential diagnosis of an intracranial mass lesion. It also should be considered an alert for considering a TB diagnosis in the most varied clinical settings, particularly in immunosuppressed patients, and especially at the present time with the widespread use of anti-TNF drugs.

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References

1. Porter JDH, McAdam KPWJ. The re-emergence of tuberculosis. Rev. Public Health 1994; 15: 303-323.
2. Gardam MA et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis 2003; 3: 148–155.
3. Winthrop KL. Risk and prevention of tuberculosis and other serious opportunistic infections associated

with the inhibition of tumor necrosis factor. Nat Clin Pract Rheumatol 2006; 2: 602-610.
4. Bekker LG et al. TNF-a controls intracellular mycobacterial growth by both inducible nitric oxide synthase-dependent and inducible nitric oxide synthase-independent pathways. J Immunol 2001; 166: 6728–6734.
5. Keane J et al. Tuberculosis associated with infliximab, a tumor necrosis factor-a neutralizing agent. N Engl J Med 2001; 345: 1098–1104.
6. Sharma MC, Arora R, Mahapatra AK, Sarat-Chandra P, Gaikwad SB, Sarkar C. Intrasellar tuberculoma – an enigmatic pituitary infection: a series of 18 cases. Clin Neurol Neurosurg 2000; 102:72-77.
7. Hay DR. Diabetes insipidus after tuberculous meningitis. Br Med J 1960; 1: 707.
8. Giese A, Kucinsli T, Hagel C, Lohmann F. Intracranial tuberculomas mimicking a malignant disease in an immunocompetant patient. Acta Neurochir 2003; 145: 513-519.
9. Wasay M, Moolani MK, Zaheer J, Kheleani BA, Smego RA, Sarwari RA. Prognostic indicators in patients with intracranial tuberculoma: a review of 102 cases. J Pak Med Assoc 2004; 54: 83-87.
10. Bayindir C, Mete O, Bilgic B. Retrospective study of 23 pathologically proven cases of central nervous system tuberculomas. Clin Neurol Neurosurg 2006; 108: 353-357.
11. Emery P, Panayi G, Symmons D, Brown G. Mechanisms of depressed delayed-type hypersensitivity in rheumatoid arthritis: the role of protein energy malnutrition. Ann Rheum Dis 1984;4:430-434.
12. Pope RM, Kniker WT, Talal N, Dauphinee M. Delayed type hypersensitivity in patients with rheumatoid arthritis. J Rheumatol 1993;20:17-20.
13. Karam NE, Roger L, Hankins LL, Reveille JD. Rheumatoid nodulosis of the meninges. J Rheumatol 1994; 21: 1960-1963.
14. Jackson CG, Chess RL, Ward JR. A case of rheumatoid nodule formation within the central nervous system and review of the literature. J Rheumatol 1984; 11:237-240.
15. Bathon JM, Moreland LW, DiBartolomeo AG. Inflammatory central nervous system involvement in Rheumatoid Arthritis. Semin Arthritis Rheum 1989; 18: 258-266.

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