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CASE REPORT

INTRIGUING MANIFESTATION OF MILIARY TUBERCULOSIS - A CASE REPORT.

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Abstract

This report is a case of a 24-year-old immunocompetent lady treated with anti-tuberculous drug for disseminated tuberculosis diagnosed by bone marrow finding. She presented with concurrent intracranial and intramedullary tuberculoma associated with tuberculous spondylodiscitis evidenced by serial magnetic resonance imaging (MRI) screening after a month of anti-tuberculous therapy. These complications are thought to be paradoxical effects of anti-tuberculous therapy. Symptoms resolved with continuation of anti-tuberculous treatment and a course of corticosteroid.

Keywords: *Disseminated tuberculosis, bone marrow, intracranial, intramedullary, anti-tuberculous, paradoxical effect*

Introduction

Tuberculosis (TB) is a centuries old disease; yet it is still a leading cause of illness and death globally, with more cases being reported today than at any previous period of time in history. Extra-pulmonary TB occurs in 10 to 15% of all TB cases[1]. In about 10% of all TB patients, the central nervous system (CNS) is involved[2] and 1 to 3% of skeletal TB frequently affects the spine[1,3] But a combination of intramedullary and intracranial tuberculoma is extremely rare[4,5]. Combination of spondylodiscitis and CNS TB has never been described in previous English literature.

We report a case of a patient who developed concurrent intracranial and intramedullary tuberculoma after a month of anti-TB therapy for disseminated TB. Combination of anti-TB treatment with the addition of steroid helped to improve the symptoms.

Case Report

A 24-year-old lady was admitted for pyrexia of unknown origin. She was treated in another hospital earlier for persistent high grade fever for two weeks associated with constitutional symptoms with non-productive cough. She had no history of night sweat, headache, joint or bone pain, oral ulcer, photosensitivity rashes or alopecia. She had neither a history of traveling nor contact with any tuberculosis patient and denied high risk behavior or history of illicit abuse drugs.

On examination, she was febrile with temperature fluctuating from 37.0^{o}C to 39.5^{o}C. There was neither bony tenderness nor peripheral lymphadenopathy. Splenomegaly was present. Other systems were unremarkable. Laboratory investigation showed low haemoglobin level ranging from 8.6 g/dl to 9.4 g/dl and leucopenia which fell from 4.8x10^{3}/ul to 2.4x103/ul. However, her platelet count remained within normal range. Her erythrocyte sedimentation rate (ESR) was 73mm/1st hr. Liver, renal function tests and electrolytes were normal. Human immunodeficiency virus (HIV), Hepatitis B and C screening, blood film for malaria parasite (BFMP) and screening for connective tissue (Antinuclear antibody (ANA), anti-double stranded DNA and rheumatoid factor) were negative. Screening for tuberculosis (tuberculin skin test and sputum for acid fast bacilli (AFB) was also negative. Septic surveillance was repeatedly negative. Initial chest radiograph was unremarkable and 2D echocardiography revealed no vegetation.

Ultrasound abdomen only showed splenomegaly and computed tomography (CT) of abdomen showed presence of small bowel related mass at the pelvic region. Combinations of broad spectrum antibiotics were given without any improvement and she remained febrile. Based on earlier CT scan report, an exploratory laparotomy was performed but without significant finding. Post-operatively, she required six days intensive care management and had a stormy recovery. Findings of repeat CT abdomen, pelvis and CT thorax were unremarkable.

A month later, in view of the patient's failure to respond to multiple antibiotics, repeated negative septic surveillance, and normal echocardiographic findings, we proceeded with bone marrow aspiration and trephine biopsy. It was done over her right iliac crest. The biopsy showed caseating granulomatous lesion and Ziehl-Neelsen (ZN) staining confirmed presence of acid fast bacilli in the histiocytes (**Fig. 1**). Culture from bone marrow aspiration was negative for M. tuberculosis. Other body fluids including sputum culture for AFB was not done. Treatment with anti-tuberculous drugs (ethambutol, isoniazid, rifampicin, and pyrazinamide) commenced promptly with improvement of her clinical status.

However, she developed progressive lower limbs weakness after a month of anti-TB treatment. She was wheel chair bound. She experienced back pain, worse at night and aggravated by sitting up associated with urinary retention and urge incontinence. Examination revealed tenderness over the area of T10 to L1 vertebral bodies and generalized muscle atrophy and weakness of both lower extremities with muscle power of grade 3 to 4 on the Medical Research Council Scale (MRCS). Her sensation however, was intact. Her higher mental function was still intact. No other remarkable neurological finding was observed.

Repeated chest radiograph showed features consistent with milliary tuberculosis. Magnetic resonance imaging (MRI) of the spines (cervical, lumbosacral, and thoracic) and brain were consistent with intracranial tuberculoma associated with intramedullary tuberculoma and tuberculous spondylodiscitis. (**Fig. 2, 3 and 4**)

She received a course of prednisolone in reducing dose over a period of a month and combination of anti-TB therapy extended for a year for which she was referred to chest physician in a tertiary center. Her symptoms improved gradually with the treatment and she was able to ambulate without residual neurological deficit. She had no symptoms suggestive of reactivation of TB.

Discussion

Diagnosis of disseminated or milliary TB is often difficult. It may mimic many diseases and in some case series, up to 50% of cases are undiagnosed ante-mortem. It is easily missed and fatal if untreated. Therefore, a high index of clinical suspicion is important. The most common presentations are fever and weight loss. Pulmonary symptoms may be absent and the duration of illness ranges from acute illness to as long as 6 months before the diagnosis is made. As the pathogenesis of the disease is by haematogenous spread, multi-organ involvement may occur. Patients are not always acutely ill. Clinical examination of the chest is usually normal and up to 30% of patients have normal chest radiograph[2].

Since extra pulmonary TB may mimic other diseases, confirmation of diagnosis is usually late. Tuberculin skin test is of limited value: a positive result supports the diagnosis, but a negative result does not exclude TB. Radiographic findings may be suggestive of TB, but they are not mandatory. Microbiological and / or histological findings are required for final diagnosis of TB. Unfortunately, Ziehl-Neelsen (ZN) staining is positive in a minority of extra pulmonary TB cases, and excess time is required before culture results come back. Alsoub et al found that acid-fast bacilli (AFB) were rarely positive in sputum cerebrospinal fluid, bronchial washings and urine but yet the cultures for Mycobacterium tuberculosis were positive in 25% to 55% in these body fluids. Lymph node biopsy yields the highest positivity for AFB as compared to transbronchial, bone marrow and liver in patients without radiographic evidence of milliary pattern[6]. In our case, diagnosis was made by identification of AFB and caseating granulomas seen in bone marrow biopsy. In previous studies the yield of tuberculous granuloma from bone marrow biopsy was highly positive in milliary tuberculosis[7,8]. However, culture for AFB from marrow aspirate has been reported as less sensitive.

The incidence of concurrent CNS TB with skeletal TB is rare in immunocompetent patient but it can be postulated since the spread is via blood. The vertebral column are affected in about 50% of all cases of skeletal TB, especially involving the thoracic and lumbar regions[2, 9]. The different pattern of vertebral TB identified: firstly the spondylodiscitis which characterized by destruction of two or more contiguous vertebrae and opposed end plates disc infection and secondly an atypical form of spondylitis without disc involvement [10]. The common symptoms are pain, limitation of motion and eventually develop spinal deformities in later stages.

Intracranial tuberculoma is commonly found among CNS tuberculoma. The incidence of intramedullary tuberculoma is extremely rare and only few cases were reported in the literatures[4,5, 11,12]. HIV-related multiple CNS tuberculoma has

been well recognized but it is not uncommon among non HIV patients. Bernardino Roca, reviewed 25 cases of intradural extramedullary tuberculoma and found 25% of them were HIV-infected patients. This finding showed that disseminated TB occurs regardless of the HIV status.

Radiological evaluation has gained importance in diagnosis of extra pulmonary TB. Conventional radiograph is important in the initial imaging study, however generally the finding occurs late. The sensitivity and specificity of the plain spine radiographs are very low[1,13]. Conventional CT scan has played a minor role for the diagnosis of early spondylitis and disc infection. MRI is superior to both plain radiograph and CT scan in detection of early spondylitis and disc infections[13]. The intracranial tuberculoma MRI image of this patient is typical of central liquid caseating type. This is characterized by centrally hypo-intense on T1W1 and hyper-intense on T2-weighted images with peripheral hypo-intense ring which represent the capsule of tuberculoma. Images after contrast administration show ring enhancement. This finding is consistent with what has been described in previous literatures[1,7,11,13]. With the emergence of newer and sophisticated imaging techniques, there will be more reporting of cases, previously thought to be rare. It has been observed and documented frequently in several literatures that intracranial tuberculoma appears or paradoxically increase in size while patients are being treated with anti-TB therapy. These lesions are usually discovered accidentally when follow up imaging is performed routinely or when new neurological signs develop during the course of anti-TB therapy probably related to an immune response to antigen released as bacilli are destroyed by chemotherapy[2,12,14,15,16,17]. However, such paradoxical effect on neurological system may also be due to haematogenous dissemination even before the commencement of anti-TB medication. Unfortunately, MRI or CT scan of the brain and spinal cord was not performed prior to anti-TB treatment and while she was being investigated for fever of unknown origin.

Development of intracranial tuberculoma during anti-TB therapy does not represent treatment failure and continuation of anti-TB drugs, with or without the addition of steroids will usually resolve the lesion[2,12,14,15,18]. Steroids may be used to reduce the oedema and subsequent mass effect associated with tuberculoma. In this case prednisolone was given at a dose of 1.5mg/kg/day and gradually tapered down over a period of a month and continuation of anti-TB therapy for a period of 12 months.

Various manifestations of disseminated TB, previously was considered rare, has now become more common as the whole spectrum of these disorders being reported worldwide. Early recognition of tubercle bacilli or caseating granulomatous lesion in the bone marrow is essential for prompt treatment. Delay or dismissal of the diagnosis may end up with catastrophe as illustrated in the early part of this patient's management. Hence, the morbidity and mortality can be prevented by early intervention.

Conflict of interest: None

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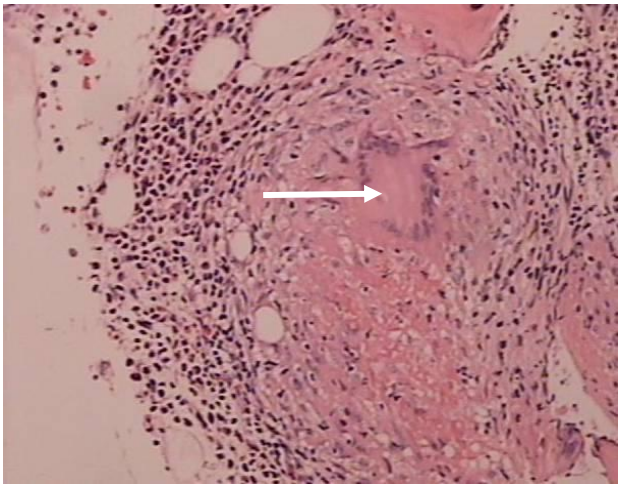

Figure 1: Trephine biopsy of bone marrow: Aggregates of epitheliod histiocytes with central necrosis suggestive of Langhan's giant cells (*arrow*) within islands of hypercellular haematopoeitic cells.

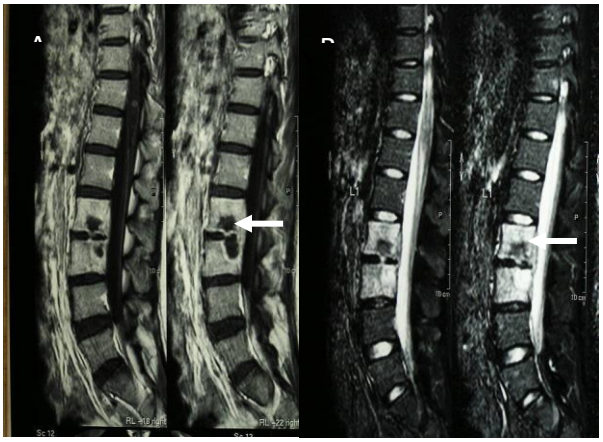

Figure 2: MR Imaging of lumbar spine**.** Post-contrast, sagittal view, T1W1 (Panel B) shows rim enhancement within vertebral body of L3. The lesion appears hyperintense in T2W1 image. Arrow indicates subligamentous or epidural phlegma situated posterior to the vertebral body of L2 and L3 that enhanced in post-contrast film.

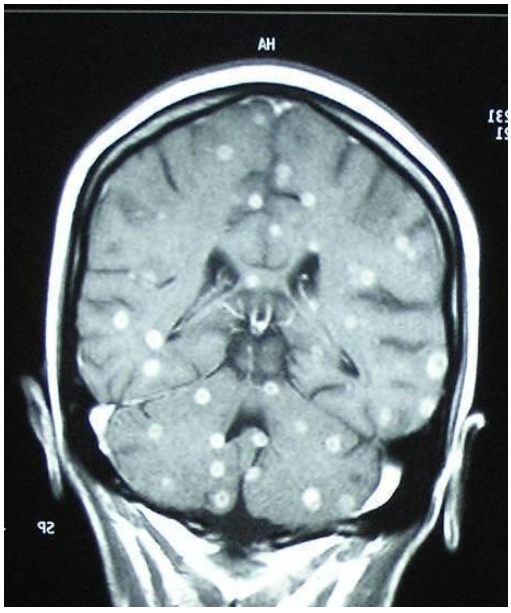

Figure 3: MR imaging of the brain, T1W1, post contrast (coronal view) shows multiple small ring enhancing lesions involving the cerebrum, brain stem, pons and cerebellum.

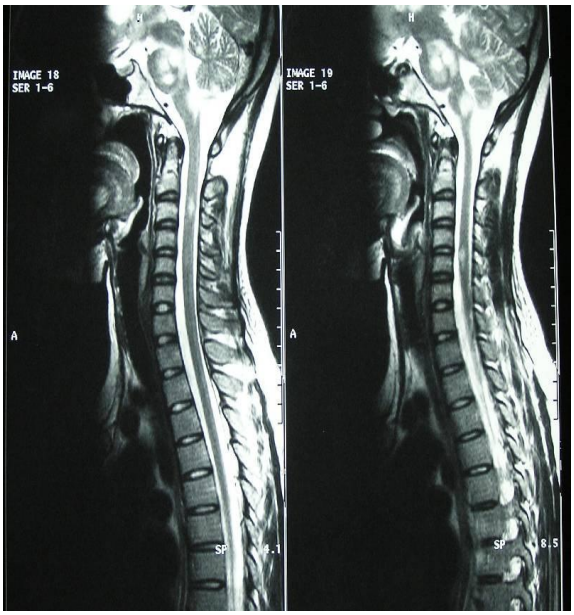

Figure 4: MRI of the cervical and thoracic spine, T1W1 sagittal view show lesion in the spinal cord that enhanced post-contrast noted at C2 and C4/C5 levels.

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