

Reactivation of Spinal Tuberculosis in a Patient with Rheumatoid Arthritis on Low-dose Methotrexate

Narjust Duma MD*, Jaime Mittal MD, Sobia Nizami

Rutgers-New Jersey Medical School, Newark, NJ, United States

*Corresponding author: narjustperezmd@gmail.com

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Abstract 42 year old Hispanic woman with rheumatoid arthritis who has been taking methotrexate for 24 weeks was admitted for severe, sharp lumbar back pain for 3 weeks. The pain radiated to both legs, worsened with walking or standing and improved at rest. It was accompanied by low grade fevers, anorexia and generalized fatigue. The patient denied cough or shortness of breath. MRI of the spine showed an L4 pathologic deformity with abnormal marrow infiltration and a ring-enhancing lesion within the left psoas muscle suspicious for abscess. CT-guided biopsy of the psoas showed necrotic debris and neutrophilic infiltrates. PPD test was reported negative. Bacterial and fungal cultures were negative after 5 days. She was discharged with an empiric 30-day regimen of intravenous ceftriaxone and oral linezolid due to high suspicion for a bacterial etiology. Twenty-six days later, the patient returned due to worsening of her back pain, she was unable to ambulate, and had a 15 pound interval weight loss. Previous biopsy cultures were positive for acid-fast bacilli and repeat MRI showed pathologic collapse of L4 with a retropulsive fracture, superimposed phlegmons bilaterally, severe spinal stenosis, and compression of the cauda equina. Three sputum specimens for AFB smears were negative. The patient recalled having had a BCG vaccine and a negative PPD in 1995; she denied exposure to TB or international travel for the past 21 years. The patient was placed on a 6 months regimen of isoniazid, rifampin, pyrazinamide, ethambutol, and pyridoxine. Two months after her presentation, she required an L4 corpectomy with a vertebral replacement cage, an L2-L4 laminectomy, and L3-L5 fusion due severe back pain and spine instability.

Keywords: *spinal tuberculosis, methotrexate, rheumatoid arthritis, Pott's disease*

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1. Background

Rheumatoid arthritis (RA) is an inflammatory disease treated with immunomodulatory agents including corticosteroids, methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine. These medications are commonly grouped as disease-modifying anti-rheumatic drugs (DMARDs) [1]. Tumor-necrosis factor (TNF) inhibitors are also used for severe disease not controlled by DMARDs. Methotrexate (MTX) is the most widely used DMARD in rheumatoid arthritis. MTX's adverse effects include myelosuppression, hepatotoxicity, and interstitial lung disease [1]. MTX is generally not associated with opportunistic infections as it does not cause significant immunosuppression. TNF inhibitors, on the other hand, are associated with increased risk of infections including: bacterial, fungal infections, and reactivation of tuberculosis. Several cases of reactivation of tuberculosis have been reported when MTX is used in conjunction with tumor necrosis inhibitors. However, there are only two cases in the English literature reporting activation of tuberculosis in patients treated only with MTX. Here we report the case of a patient with rheumatoid arthritis on

methotrexate therapy, who developed spinal tuberculosis. The role of methotrexate in increasing the risk of active tuberculosis is discussed.

2. Case Presentation

A 42 year-old Hispanic woman with a past medical history of well-controlled rheumatoid arthritis for 5 years, on methotrexate (MTX) monotherapy (15mg/week) for 24 weeks and no history of TNF inhibitors treatment, presented to our emergency department with severe, sharp lumbar back pain for 3 weeks. The patient was seen by her primary care physician one week prior who prescribed oral analgesia and a muscle relaxant (Ibuprofen and cyclobenzaprine) with minimal improvement of symptoms. Her pain progressively worsened and at the time of presentation was rated 10 out of 10, radiated to both lower extremities, worsened with walking and standing and improved with rest. She denied any leg weakness, fecal or urinary incontinence. Her associated symptoms included: low grade fever for 2 weeks, generalized fatigue and decreased appetite with a 5 pound weight loss over the preceding two weeks. She denied any cough or shortness

of breath and the remainder of her review of systems was otherwise unremarkable.

On physical examination, the patient was in acute distress due to back pain. She was appropriately alert and oriented; her body temperature was 100.8F, heart rate was 115 beats per minute and respiratory rate was 18 breaths per minute. Her examination was notable for mild conjunctival pallor, dry mucous membranes, and severe pain with palpation of the para-spinal muscles of the thoracic and lumbar spine. Muscle strength in the upper and lower extremities was preserved, and peripheral reflexes were within normal limits. Her respiratory and cardiovascular examinations were normal. Her complete blood count was significant for anemia (hemoglobin: 10.2 g/dL), normal mean corpuscular volume (88.7 fL), mild leukopenia (WBC of 3.6×10^3 ; neutrophils: 52%, lymphocytes: 29%, monocytes: 15% and eosinophils 2%) and platelets of 169,000. Her chemistry was notable for C-reactive protein of 16.6. Other laboratory tests were within normal limits, including chest x-rays (Figure A). Initial magnetic resonance imaging (MRI) of the lumbar spine revealed extensive fragmentation and lytic destruction of the L4 vertebral body compatible with a moderate pathologic compression deformity, possible osteomyelitis (Figure B), and a left psoas muscle abscess. CT-guided biopsy of the psoas showed necrotic debris and neutrophilic infiltrates. A tuberculin skin test (PPD) was placed and reported negative. Bacterial and fungal cultures from the psoas abscess were negative. The patient was discharged with an empiric 30-day regimen of intravenous ceftriaxone and oral linezolid due to a high suspicion for abacterial etiology.



Figure A. Chest X-ray shows normal lung volumes, without infiltrates, pleural effusions or pneumothorax.

Twenty-six days later, the patient returned with worsening back pain, and a 15 pound interval weight loss. Previous biopsy cultures returned positive for acid-fast bacilli. Repeat MRI showed pathologic collapse of L4 with a retropulsive fracture, superimposed phlegmons bilaterally, severe spinal stenosis, and compression of the cauda equina, as well as L3-L4 foraminal stenosis (Figure C-D). Three sputum specimens for AFB smears were negative. The patient recalled having a BCG vaccine and a negative PPD in 1995; she denied exposure to TB or international travel for the past 21 years. During further questioning the patient reported steroids therapy for her rheumatoid arthritis 3 years prior for total of 2 months but

denied any recent steroid use. The patient was placed on a 6 months regimen of isoniazid, rifampin, pyrazinamide, ethambutol, and pyridoxine. After 1 week on this regimen the fevers improved but she continued to have severe back pain for which she was not able to ambulate. She was evaluated by neurosurgery and underwent an L4 corpectomy with an intervertebral replacement cage, a posterior L2-L4 laminectomy, and posterior segmental instrumented fusion from L3-L5, two months after starting the anti-tuberculosis regimen (Figure E). On 6 month follow up the patient's back pain was better controlled but she continues to have reduced range of motion in the lumbar spine and requires walker for ambulation. The final diagnosis is spinal tuberculosis (Pott's disease) secondary to low dose methotrexate.



Figure B. Lumbar spine MRI, displays extensive fragmentation and lytic destruction of the L4 vertebral body



Figure C. Spine MRI 26 days after initial presentation reveals pathologic collapse of L4 with a retropulsive fracture, superimposed phlegmons bilaterally, severe spinal stenosis, and compression of the cauda equina, as well as L3-L4 foraminal stenosis



Figure D. Spine MRI 26 days after initial presentation reveals pathologic collapse of L4 with a retropulsive fracture, superimposed phlegmons bilaterally, severe spinal stenosis, and compression of the cauda equina, as well as L3-L4 foraminal stenosis.

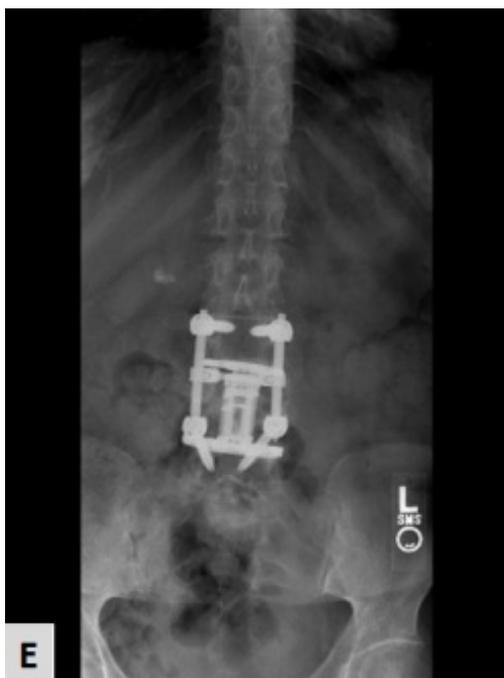


Figure E. Lumbar spine x-rays shows post-surgical changes including: intervertebral replacement cage, and a posterior segmental instrumented fusion from L3-L5.

3. Discussion

The incidence of tuberculosis in RA patients is considered the same as in the general population, unless they receive anti-TNF therapy [2], or prolonged glucocorticoid exposure [3,4] Carmona et al. [5] reported in Spain a 4-fold increase in the risk of TB infection in patients with RA, but this figure did not take into account the proportion of RA patients on biologic agents. The American College of Rheumatology currently

recommends screening for TB in RA patients before starting anti-TNF therapy, but not before starting DMARDS such as methotrexate [6]. The National Psoriasis Foundation however, recommends screening for latent TB infection before initiating treatment with TNF-alpha inhibitors, T-cell blockers, cyclosporine, and methotrexate [7].

Methotrexate is used in the treatment of several inflammatory disorders, including RA, psoriasis, and eczema [8]. It is a folic acid antagonist that arrests cell proliferation and suppresses B cell and macrophage function, inhibits IL-1, and TNF production [9]. Weekly low doses of MTX have become the therapy of choice for patients with RA. Myelosuppression is a well-known adverse effect; although this is not linked to an increased risk of infections. There are several reasons for the wide acceptance of MTX, including good disease control and low toxicity [10]. However, despite its wide use, previous studies have shown disparities in the patterns of prescriptions. Some patients are started on high doses instead of a progressive tapering process, we found this in our patient who was started on 15mg weekly instead of a lower dose and we hypothesize that this may have contributed to the reactivation of the tuberculosis [11,12,13].

To date, only 2 cases of active tuberculosis [4,14] and one case of *Mycobacterium intracellulare* [15] have been reported in RA patients in connection with methotrexate monotherapy. One of these cases was described by Binyamin and Cooper [4] who reported a patient with history of spinal tuberculosis at the age of 7 and developed a relapse at age of 57 after MTX monotherapy. In our case, the patient had no prior history or recent exposure to tuberculosis. Furthermore, our case shows an extensive vertebral damage secondary to the TB infection; this extent of disease is rarely seen in developed countries where health departments have strict policies and direct observation therapy is widely available.

In our patient, the tuberculin skin test was negative when the patient first presented with back pain, which lowered the suspicion of spinal tuberculosis, until the cultures from the bone biopsy proved otherwise. A similar observation was reported by Binyamin et al. [4]. The American College of Rheumatology recommends using either a two-step skin test or the immunoglobulin release assay (IGRA) for screening [6]. However, IGRAs are reported to be more sensitive compared to TB skin testing in patients with immune-mediated inflammatory diseases like RA, and the sensitivity of the skin test is further reduced in patients on steroid therapy [16,17]. Isoniazid treatment is indicated for RA patients found to have latent TB, and may be safe and well tolerated alongside methotrexate, as reported by Mor et al. [10]. Latent TB should be treated before patients are started on TNF inhibitors.

Reactivation of latent TB in patients with systemic illness is frequently extra-pulmonary or disseminated [16]. As in our case, these patients usually do not have pulmonary findings which could represent a real challenge for an early diagnosis. Particularly in skeletal TB since there is no evidence of active chest disease in more than 90% of the cases. Tung et al. [18] studied over 700 cases of spinal TB with only 2.7% of patients having any pulmonary findings at the time of diagnosis. As 20% of

tuberculosis cases reactivate at an extrapulmonary site, clinicians must maintain high clinical suspicion for tuberculosis even in the absence of respiratory or any constitutional symptoms.

In summary, we report an unusual case of spinal tuberculosis secondary to low dose methotrexate, in a patient with RA, with no pulmonary findings and a negative tuberculin skin test. According to our findings patients should be tested for latent tuberculosis, not only when starting TNF-inhibitors therapy but also when starting any immunosuppressant agent like MTX.

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