Case Report

Pleural Tuberculosis following Infliximab Therapy for Ankylosing Spondylitis

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Abstract

We present a case of pleural tuberculosis (TB) in a patient on infliximab for ankylosing spondylitis. A 36-year-old male presented to our hospital with low back ache of inflammatory type along with multiple symmetric inflammatory type of joint pain. Further clinical examination, laboratory and radiological investigations were suggestive of ankylosing spondylitis. He was initially treated with nonsteroidal anti-inflammatory drugs but citing poor response it was decided to initiate biologic therapy using infliximab (antitumor necrosis factor-alpha). Mantoux test and chest radiograph were done before the therapy to rule out TB. Following three doses of infliximab, patient came with complaints of fever and cough for 1 week. On investigation, it was found to be a case of pulmonary TB. This shows the importance of close monitoring of patient for TB among patients on infliximab even though the screening test has come out to be negative.

Keywords: Ankylosing spondylitis, antitumor necrosis factor-alpha, infliximab, tuberculosis

Introduction

Ankylosing spondylitis is a spondyloarthropathy seen commonly among males.[1] Tumor necrosis factor-alpha (TNF-α) inhibitor is the drug of choice. Opportunistic infections following therapy are well known.[2] Reactivation of latent tuberculosis (TB) is a serious hindrance to continuation of therapy. We present here a case of pleural TB in a patient on infliximab for ankylosing spondylitis.

Case Report

A 36-year-old male presented to our hospital in 2006 with low back ache inflammatory type with symmetric joint pains involving large joints such as shoulder joints, hip joints, knee joints, and small joints such as metacarpophalangeal joints, elbow joints, and metatarsophalangeal joints. There was associated early morning stiffness for over an hour. On examination, synovitis was present in peripheral joints with restriction of movement in all joints. Modified Schober's test was positive, and the chest expansion (<3 cm) was restricted.

On evaluation, he had anemia and elevated erythrocyte sedimentation rate (ESR) (46 mm/h) and C-reactive protein (CRP) (18 mg/L). Liver function tests and renal function tests were normal. Imaging revealed kyphoscoliosis of thoracic spine, syndesmophytes at multiple levels giving the appearance of bamboo spine [Figure 1]. Diffuse ossification of interspinous and paraspinal ligaments with fusion of thoracic and lower cervical vertebra was present. Human leukocyte antigen-B27 (HLA-B27) was positive.

In view of HLA-B27, more than 2 SpA features and typical radiological features, ankylosing spondylitis was considered. He was started on nonsteroidal anti-inflammatory drugs (NSAIDs) and dose escalated for symptomatic relief. In view of persisting symptoms and elevated ESR and CRP in spite of optimal NSAIDs, option of biologics was given. He was initially not willing but later accepted for therapy. Before biologic therapy, TB workup was done. Mantoux test was negative, and chest radiography was normal. Patient was administered infliximab by intravenous infusion. Subsequent

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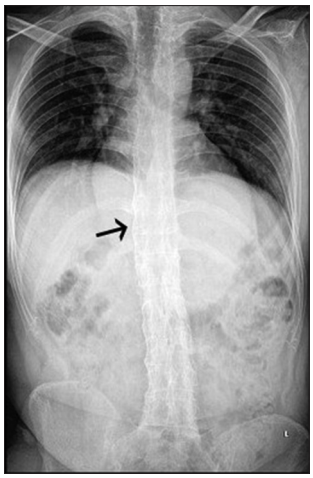

Figure 1: Radiograph showing bamboo spine

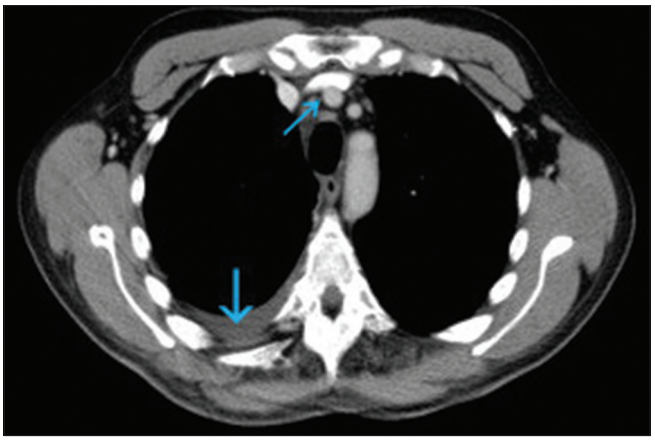

Figure 2: Computed tomography chest showing right-sided pleural effusion and enlarged mediastinal lymph nodes

doses were planned at 2 and 6 weeks and then every 8 weeks. There was an improvement in symptoms.

Following three doses of infliximab and 10 months after initiation of therapy, patient came with complaints of fever and cough for 1 week. On examination, breath sounds were reduced over the right side, and there was dullness on percussion. Chest radiograph showed features suggestive of pleural effusion [Figure 2]. Diagnostic thoracocentesis showed lymphocytic (total leukocyte count - 4800 cells/cumm, lymphocytes - 90%) exudative type of effusion with high adenosine deaminase (ADA) (114 IU/L). According to light's criteria (effusion protein - 6 g/dL, serum protein - 3.37 g/dL, effusion lactate dehydrogenase (LDH) - 575 U/L, and serum LDH - 325 U/L), it is an exudative type of pleural effusion. Pleural fluid showed elevated ADA levels (114 IU/L) indicating tuberculous pleural effusion. Anti-TB therapy was started.

Discussion

Ankylosing spondylitis is a chronic, systemic, inflammatory disease that affects primarily the sacroiliac joints and spine. It is a spondyloarthropathy with a prevalence of 0.1%–0.4% globally.[1] Data from India are sparse. Its more commonly seen among males under 30 years of age. Diagnosis is made after thorough clinical examination and radiography.

Management is by the use of NSAIDs. If they are refractory to the above treatment, then biologic therapy is initiated. Infliximab is one such biologic which acts by inhibiting a pro-inflammatory cytokine TNF-α and reducing inflammation.

Target-related adverse effects with TNF inhibitors are infections, opportunistic infections, malignancies, demyelinating conditions, hematologic abnormalities, congestive heart failure, autoantibodies (antinuclear antibody and anti-double-stranded DNA), hepatotoxicity, dermatologic reactions, and lupus-like syndromes, whereas the agent-related adverse effects are administration reactions and immunogenicity.[2]

TNF-α is a cytokine that plays an important role in the mediation of inflammation and immune regulation. They are required for inflammatory response against intracellular organisms. In experimental models, fungal and bacterial infections were noted following TNF blockade. *Pneumocystis carinii*[3] and *Histoplasma capsulatum*[4] are some of the fungal pathogens, whereas the bacterial agents are *Listeria monocytogene*,[5] *Mycobacterium tuberculosis,*[6] and *Mycobacterium avium*.[7] Upper and lower respiratory tract infections are the most commonly seen ones.[8,9] There was also an increased risk of serious infections compared with controls (3.6% vs. 1.7%). The risk of serious infections was greater with higher doses of TNF inhibitor.[9]

Confounding factors include comorbidities and concomitant medications. Registries of rheumatoid arthritis patients have shown that the relative risk for infection (3.3–4.1) as well as serious infection (2.7–2.8) was significantly higher among patients receiving TNF inhibitors.[8] To conclude, severity of disease, use of other medications such as corticosteroids, and the presence of comorbidities also contribute to infections in addition to TNF inhibitors alone.

Opportunistic infections following TNF inhibitor therapy include disseminated *M. tuberculosis*. In a study of seventy cases of TB following infliximab therapy, thirty were pulmonary TB and of forty were extrapulmonary disease, only two were cases of pleural TB. Around a quarter of the cases were disseminated disease.[10] The majority of cases of TB were observed within a median period of 12 weeks after initiation of therapy and is likely due to reactivation of latent TB. Incidence of TB following infliximab therapy has been found to be 0.09%.[11,12] A study by Grover *et al*. in India has shown a high incidence of TB (21%) following biologic therapy. It was also seen that among those who received low doses of infliximab (3 mg/kg body weight) did not develop TB.[13] Another study by Malaviya *et al*. has found a lower incidence (9.4%) of TB among those on TNF inhibitors.[14]

This emphasizes the importance of screening for TB. According to a Spanish registry, the rate of development of active TB among rheumatoid arthritis patients on anti-TNF therapy has dropped by 83% with the help of screening.[15] Screening may be done with Mantoux test and chest radiograph.

Suppressing the action of TNF-α can help in relieving the symptoms of ankylosing spondylitis by reducing the inflammatory process, but at the same time, it weakens immune response to microbes such as tubercle bacilli. This could have been the reason for patients developing TB following infliximab therapy.

Hence, meticulous screening and close monitoring of patients on infliximab for any symptoms and signs of TB are important as there is a risk even though the screening tests have come out be negative. This may help in early diagnosis and treatment.

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Conflicts of interest

There are no conflicts of interest.

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