**Abstract**

Tumor necrosis factor (TNF) alpha inhibitors play an important role in the treatment of immune mediated diseases including rheumatoid arthritis, the seronegative spondyloarthopathies, psoriasis, and inflammatory bowel disease. These agents have significant potential for adverse effects that lead to reactivation and dissemination of latent tuberculosis infection. We present a patient with miliary tuberculosis occurring during treatment with certolizumab for ankylosing spondylitis under INH prophylaxis.

A 57 old female patient presented with dry cough, fever, loss of appetite, and chest pain present for three weeks. Chest x-ray showed diffuse miliary nodules and right pleural effusion. Computed tomography revealed diffuse miliary nodules, infiltration in the right lower lobe, and right pleural effusion. Pleural effusion was exudative in character and had a 74% lymphocyte ratio with a high level (114 U/L) of adenosine deaminase. Sputum smear was positive for acid-fast bacilli and mycobactrium tubeculosis grew in culture. The diagnosis was miliary tuberculosis associated with certolizumab treatment. Four weeks after with antituberculous drug treatment the symptoms completely resolved while the radiologic lesions diminished significantly.

TNF alpha inhibitors are potent anti-inflammatory agents. Alpha inhibition may result in severe complications and adverse effects. Clinicians should bear in mind that severe immunosuppression leading to mycobacterial infection may occur even if the patient is under prophylactic treatment for tuberculosis and current screening methods for latent tuberculosis may be inadequate to identify the latent infection.

**Keywords:** Certolizumab; Miliary tuberculosis; TNF-alfa antagonists; Tuberculosis

**Introduction**

TNF-alpha inhibitors serve as important treatment options for a variety of immune mediated diseases with a major impact on the treatment of disabling inflammatory disorders. These agents submit a targeted strategy that contrasts with the nonspecific traditional immunosuppressive agents. However, significant complications and severe adverse effects may occur during treatment with these targeted TNF-alpha inhibitor drugs. One of the important side effect of TNF-alpha blockers is increased risk for reactivation of latent tuberculosis and dissemination of tuberculosis infection [1-4].

Screening and identification of tuberculosis infection may be challenging and troublesome in patients treated with the TNF-alpha antagonists. Although screening for latent tuberculosis is routinely performed before treatment with these agents, de novo tuberculosis infection may come out even under prophylactic treatment.

We present a patient under isoniazid prophylaxis in whom certolizumab treatment led to dissemination of latent tuberculosis infection resulting in miliary tuberculosis. This case report illustrates the clinical hazards and complications [1,4,5] associated with tuberculosis that emerged during anti-TNF-alpha treatment. Current surveying tools for latent tuberculosis [6-9] may be inconclusive and thereby significant consequences of pulmonary tuberculosis like miliary dissemination cannot be prevented by using the prevailing laboratory techniques in some cases. Patients may develop de novo miliary disease even if they had received prophylaxis against latent infection. Routine screening for latent tuberculosis is not reliable to preclude the serious complications of latent tuberculosis.

**Case Report**

A 57 year old Caucasian female was admitted for dry cough, fever, loss of appetite and chest pain for three weeks. She had a history of tonsillectomy, ankylozing spondylitis, uveitis, pelvis fracture and tibia fracture. Her father died of colonic carcinoma. Her mother had hypertension and previous pulmonary tuberculosis. The patient was under treatment with certolizumab, methotrexate, and prednisolone for ankylosing spondylitis and uveitis. Daily 300 mg isoniazid was also given simultaneously.

Her family history is positive for diabetes, hypertension, and tuberculosis. She had no specific previous drug history. She is a non-smoker. Her current medications include isoniazid, prednisolone, methotrexate, and certolizumab.

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353 U/L, and albumine 3.56 g/dl. Pleural fluid had 1540 cells/mm³ with a 74% lymphocyte ratio. Pleural fluid ADA was 114 U/L (normal 0-40 U/L). The pleural fluid was exudative compatible with tuberculosis. Computed tomography of the thorax revealed diffuse miliary nodules, infiltration in the right anterior segment of the lower lobe, and right pleural effusion (Figures 2–4). Sputum stains was positive for acid-fast bacilli. Mycobacterium tuberculosis was isolated from the sputum culture. The final diagnosis was miliary tuberculosis associated with certolizumab occurring on the third month of treatment. The patient was commenced on pyrazinamide, isoniazid, rifampicine, and ethambutol treatment for tuberculosis while certolizumab treatment was stopped.

**Discussion**

TNF-alpha-antagonists are remarkably effective agents in the treatment of various immune mediated diseases like rheumatoid arthritis, inflammatory bowel disease, and psoriasis [10-13]. TNF-alpha constitutes an important role of defence against tuberculosis and mechanisms of anti-TNF-α agents lead to tuberculosis by impairing tuberculosis immune response [14,15]. This case report illustrates the various clinical pitfalls and complications that can be encountered during anti-TNF-α treatment.

The patient had a negative tuberculine test and a normal chest x-ray before certolizumab treatment. She was commenced on prophylactic isoniazid treatment because the patient had an
exposure to active tuberculosis. Miliary tuberculosis with pleural effusion and right lower lobe infiltration occurred on the third month of treatment. The patient had an appropriate screening for tuberculosis including medical history, tuberculosis test, and chest x-ray before anti-TNF-α treatment was started. The sensitivity of the tuberculine test may have been restricted or diminished by the previous immunosuppressive treatment in our patient. The normal chest x-ray before treatment had also a low diagnostic yield for revealing sequelae of past or current infection. Following treatment the right lower anterior segment infiltration was only identified at the computed tomography coronal image and was not detected in chest x-ray.

Our case shows the inadequacy of current screening tools for tuberculosis before commencing anti-TNF-α agents. Second, a serious complication like miliary tuberculosis developed in this patient while the patient was under prophylactic isoniazid regimen. And as far as we know, this is the first case of miliary tuberculosis occurring in association with certolizumab treatment.

The role of TNF-α associated with the immune defence mechanisms against tuberculosis are not clear. The pathologic contrivance produced by the anti-TNF-α agents is not explicit either. Thereby, the current screening tools including patient history, tuberculosis test, and chest x-ray for latent tuberculosis are apparently incompetent and unreliable for identifying the patients at risk who are prone to develop tuberculosis or its complications associated with TNF-alpha antagonists.

Conflict of Interest

None.

Acknowledgment

None.

References