# Two Cases of Tuberculosis Complicating Treatment With Tumor Necrosis Factor-α Inhibitors

## Tümör Nekrozis Faktör-α İnhibitörleri İle Tedavi Komplikasyonu Olan İki Tüberküloz Olgusu

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**ABSTRACT**

TNF-α blocking agents have been increasingly used in the treatment of systemic inflammatory diseases. The main adverse effect of these drugs is susceptibility to infections, mainly reactivation of latent tuberculous infection (LTBI). In this paper we described two cases of TNF-α inhibitor-associated TB. Because LTBI and BCG vaccination are widespread in the Turkish population, a stringent pre-treatment screening protocol for LTBI should be used. In such patients, TB frequently presents as an extrapulmonary or disseminated and life-threatening disease. Physicians should be aware of the risk of the reactivation of TB, despite isoniazid chemoprophylaxis, with unusual clinical manifestations and a paradoxical response.

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**Key words:** Tuberculosis, anti TNF-α agents, latent infection

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**ÖZET**

TNF-α bloke edici ajanlar sistemik inflamatuvar hastalıkların tedavisinde artan bir şekilde kullanılmaktadır. Bu ilaçların temel yan etkisi başta latent tüberküloz (LTBİ) olmak üzere infeksiyonlara duyarlılıktır. Bu makalede TNF-α inhibitörleri ile ilişkili iki olguyu tanımladık. Türk halkında LTBİ ve BCG aşılaması yaygın olması nedeniyle tedavi öncesi dikkatli bir LTBİ tarama protokolü kullanılmalıdır. Bu hastalarda tüberküloz sıklıkla ekstrapulmoner veya yaygın ve hayatı tehtid eden bir hastalık olarak ortaya çıkar. Klinisyenler izoniazid ile koruyucu tedaviye karşın LTBI reaktivasyonu riski, hastalığın sık izlenmeyen klinik formları ve paradoksal yanıt açısından uyanık olmalıdır.

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**Anahtar sözcükler:** Tüberküloz, anti TNF-α ajanlar, latent infeksiyon

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### INTRODUCTION

Anti TNF-α agents have been used in an increasing number of autoimmune diseases in recent years [1]. TNF-α is a cytokine produced mainly by macrophages, which plays a major role in the immune response to infections via recruitment of inflammatory cells to the site of infection and in the formation and maintenance of granulomas [2]. Since the introduction of these drugs into clinical practice, a wide range of infections have been reported in many countries [3-5]. Reactivation of LTBI has been recognized to be the most serious side-effect [5,6].

TNF-α inhibitors have also been used in an increasing number of autoimmune diseases in our country in recent years.

In this paper we described two cases of TNF-α inhibitors-associated TB.

### CASE 1

A 29-yr-old male using infliximab for Chron's disease for 3 months was admitted to hospital with a 2-week history of fever up to 38.6 °C, chills, night sweats and cough. Prior to the initiation of infliximab, he had had a normal chest radiography and physical examination, but the tuberculin skin test (TST) had not been performed. He had no other comorbid disease or exposure to TB. Infliximab was stopped. Physical examination was normal except for the high temperature. A laboratory work-up revealed anemia (Hb: 9.9 g/dl, haematocrit:28%), high erythrocyte sedimention rate (ESR) of 120 mm/h, and high C-reactive protein (CRP:154 mg/L) with no other abnormal findings. A chest radiograph showed bilateral hilar enlargement especially on the right hilus, reticulonodular shadows associated with the hilus in the right paracardiac region (Figure 1). Computed tomography (CT) scan of the chest revealed bilateral diffuse micronodular shadows, enlargement lymphadenopaty in the right paratracheal and subcarinal regions (Figure 2).

The diagnosis of TB was established with positive acid-fast bacillus (AFB) stain on gastric lavage and

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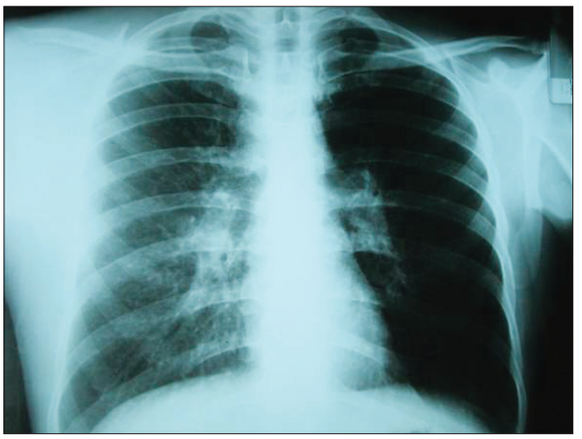

**Figure 1.** A chest radiograph showed bilateral hilar enlargement and reticulonodular shadows associated with hilus in the right paracardiac region

Mycobacterium tuberculosis was identified in BACTEC culture. It was sensitive to all primary antiTB drugs. In addition, the patient had a positive AFB stain in his urine specimen and he had cervical caseating granulomatous lymphadenopathy. Abdominopelvic USG showed grade 1 splenomegaly and multiple granulomatous nodular lesions in the spleen. We described this situation as disseminated TB. AntiTB treatment (isoniazid, rifampin, pyrazinamide, ethambutol) was given for 9 months, with complete resolution.

**CASE 2**

This case was a 30 yr-old woman who developed TB following etanercept treatment for rheumatoid arthritis despite isoniazid prophylaxis for LTBI. Prior to the initiation of etanercept, she had had no symptom or findings associated with TB. She had no TB exposure history, but she had lived in an orphanage for 18 years. Diagnosis of active TB was excluded with negative AFB stains and BACTEC cultures on sputum for three examinations and normal chest X-ray. As her TST was 16 mm, isoniazid was given at a dose of 300 mg/day and after 1 month of isoniazid treatment etanercept was initiated. On the fourth month of etanercept therapy, her chest radiograpy releaved a homogenous density in the right middle-lower zone laterally and elevation of the right diaphragm (Figure 3). CT scan of the chest revealed nodular consolidation in the right middle zone laterally (Figure 4).

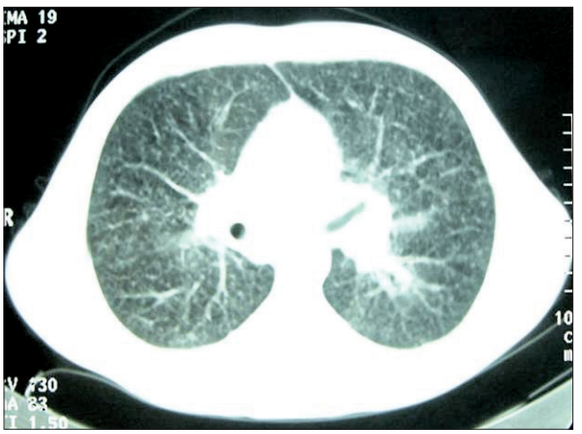


**Figure 2.** Computed tomography scan of the chest revealed bilaterally diffuse micronodular shadows, enlargement LAP in the right paratracheal and subcarinal regions

Etanercept and isoniazid were discontinued and advanced investigations were begun. She had systemic symptoms such as weakness, lack of appetite and sweating but no pulmonary symptoms. Her physical examination was normal. A laboratory work-up revealed anemia (Haematocrit: 33.8%), high ESR (18 mm/h), CRP (11.6 mg/L) and no other abnormal findings.

Three sputum specimens did not stain for AFB. BACTEC culture of sputum specimens were negative. She did not respond to oral antibiotherapy for 14 days and transthoracic needle aspiration was made under thorax CT and the aspiration specimen was negative for fungal, bacterial and mycobacterial investigation. Lung biopsy was obtained by videothorascopy and histopathological examination revealed caseating granulomas. AFB stain and culture were negative, but PCR was positive for M.Tb on lung tissue. Anti TB therapy was initiated (isoniazid, rifampin, ethambutol and pyrazinamide) with progressive clinical improvment. The patient was readmitted to hospital with recurrence of high fever, cough and malasia after 6 weeks. Thorax CT scan revealed progression of the previous infiltrate, multiple new nodular infiltrates and bilateral axillary lymphadenopathy. Smears and cultures of three sputum samples were negative for AFB. We described this situation as a paradoxical response to treatment, and prednisone (1 mg/kg q.d.) was added to her anti TB regimen for 4 weeks. Anti TB treatment was given for 6 months with excellent clinical improvement, but incomplete radiological resolution of TB was seen.

**DISCUSSION**

TNF-α inhibitors have been proven highly effective against a number of autoimmune diseases, but a major concern surrounding the use of TNF-α inhibitors is their potential to increase the risk of opportunistic infections, especially tuberculosis [7]. Screening for LTBI is advised in all patients before the use of TNF-α inhibitors [8].

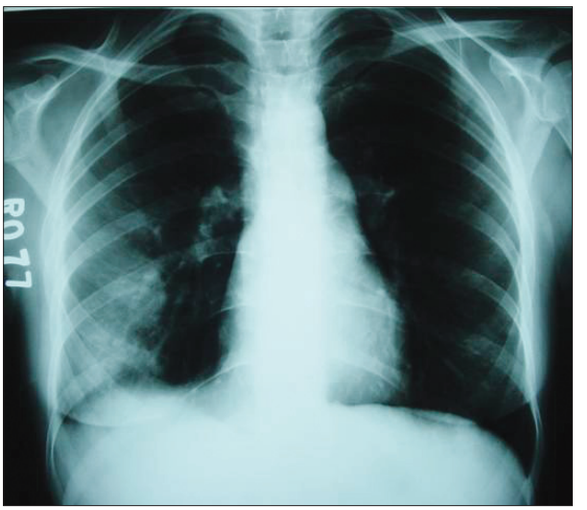

**Figure 3.** Chest radiograpy releaved a homogen density in the right middle-lower zone laterally and elevation of the right diaphragm

In the first case, LTBI had not been investigated in detail before using anti TNF-α agents. It should be considered a remarkable feature.

Guidelines on LTBI screening strategies which are used may differ between geographical regions because they will take into account the local tuberculosis rate, the conditions of tuberculosis care delivery and other factors, such as BCG usage and drug sensitivities [8,9]. In Turkey, LTBI screening strategies also described the reduced occurrence of anti TNF-α agents associated with TB in 2005. In general, it encompasses a careful history (looking for exposure to TB), with conventional radiographs of the chest and TST [10].

The presence of LTBI is considered likely if the TST is positive and the chest X-ray is normal. LTBI should be treated with prophylaxis if possible, and a good option is 9 months of isoniazid. However, we know it is not the optimum strategy for the detection and treatment of LTBI. In our opinion, a more stringent pre-treatment screening protocol, especially for LTBI, should be used by clinicians. Using the TST has some shortcomings (negative results in systemically ill or immunosuppressed patients, dificulty of interpretation, positive results due to BCG). The inadequacies of the TST have been the impetus behind the development of newer T-cell stimulation tests for LTBI, such as QuantiFERON and ELISpot test [9,11-13].

In the second patient, isoniazid chemoprophylaxis could not prevent reactivation of LTBI. There are a number of case reports (11 patients) describing the association of TNF-α inhibitors and TB patients who are on anti TB chemoprophylaxis [14]. Complete prevention is not possible with INH [15], so patients receiving INH and anti TNF-α agent should be closely followed from the aspect of efficiency of chemoprophylaxis and early diagnosis of TB. The efficiency of prophylactic INH therapy is 25-92%, depending on the underlying disease, compliance and type of study [16]. Recently, attention has been drawn to poor completion rates for LTBI in the general population (about 30%) [17]. In some cases, directly observed treatment of LTBI may be required, or two anti TB drugs (e.g. rifampicin and INH) may decrease the change in reactivation [18].

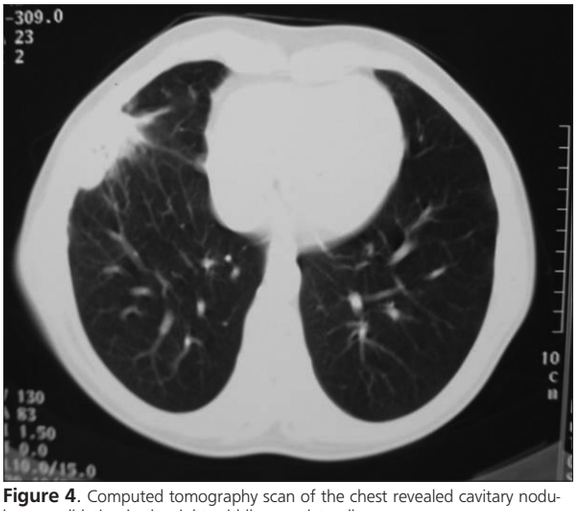


**Figure 4**. Computed tomography scan of the chest revealed cavitary nodular consolidation in the right middle zone laterally.gm

The second important point for the first case: TB in such patients frequently presents as an extrapulmonary or disseminated and life-threatening disease. Clinical presentation of TB in the setting of TNF-α inhibitor treatment is usually atypical with more than 50% of patients presenting with extrapulmonary disease. Approximately 25% have disseminated disease, and the reminder have isolated pulmonary disease [5,19]. Therefore, clinicians should be vigilant for TB in the patient groups who develop fever and weight lose, since TB frequently presents as an atypical and life-threatening disease.

In the second patient, we report a case of etanercept-associated TB with worsening of clinical and radiological condition during effective antiTB therapy. No other causes have been found for explaining the deterioration. We believe that the relapse in this patient may represent a similar immune reconstitution after recovery from iatrogenic immunusupression. Paradoxical reaction that can occur under appropriate antiTB treatment after stopping TNF-α inhibitors which raises the question of an immune restoration phenomenon [20] and has been described in up to 55% of these patients [21]. It has even been reported as 67% by Vidal et al. [22]. Physicians should be aware of the increased risk of paradoxical response in this population and should consider use of corticosteroid when it is suspected. No changes in or discontinuation of anti TB treatment are necessary when it occurs. Early diagnosis and treatment of this complication with systemic steroid may result in a favorable outcome [21,22].

In conclusion, TNF-α inhibitors are effective agents for many debilitating diseases when other treatments are inadequate. However, due to the high rate of (20-30%) LTBI, a stringent pre-treatment screening protocol for LTBI should be used by clinicians in the Turkish population. In addition, physicians should also be aware of the risk of reactivation of TB despite isoniazid prophylaxis, with unusual clinical manifestations of the disease and a paradoxical response.

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