



Case report

Tuberculosis in patient with psoriasis receiving biologic therapy: Case report

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ABSTRACT

Introduction: The introduction of biological therapy has revolutionized the treatment of psoriasis. Due to its immunosuppressive effect, the following side effects might occur: injection-site reactions, exacerbation of autoimmune diseases, increased risk of malignant tumors and infections, including tuberculosis (TB).

Aim: The aim of this report is to present a case of a patient who developed TB during tumornecrosis factor α (TNF- α) inhibitor therapy.

Case study: A 52-year-old man was admitted to the Dermatology Clinic for re-qualification for biological treatment with adalimumab. The patient was treated with cyclosporin A and lefludomide combined with methotrexate with no effect and the adalimumab therapy was initiated with complete remission of psoriatic lesions. The patient was suspended in the drug program because of TB. TNF- α inhibitor therapy was resumed after antimycobacterial treatment, during which lymphadenopathy was observed and serous TB was confirmed. Three months after the treatment, the patient was rehospitalized because of suspicion of TB relapse. It was decided to requalify the patient for biological therapy after completion of antimycobacterial treatment. Due to the high risk of TB recurrence, switch to the interleukin-17 inhibitor was decided.

Results and discussion: The proper qualification and thorough testing before biological treatment ensures patients' safety and satisfactory therapeutic effect. It should be remembered that during longterm therapy with TNF antagonists, both reactivation of latent TB as well as new infection are serious problems. Therefore, regular tests should be performed, especially in countries with high prevalence of this disease.

Conclusions: In patients who develop TB, particularly recurrent, switching to a drug with a different mechanism should be considered.

1. INTRODUCTION

The introduction of biological therapy has revolutionized the treatment of psoriasis. The advantages of biological treatment are: greater effectiveness and a high safety profile compared to drugs used in conventional therapy, fast and longterm remission, and a significant improvement in the quality of life of patients. The first introduced agents for the treatment of severe plaque psoriasis were tumor necrosis factor α (TNF- α) inhibitors (etanercept, infliximab and adalimumab). Due to their immunosuppressive effect, the following side effects might occur: injection-site reactions, exacerbation of autoimmune diseases, gastroenterological disorders, neurological complications, increased risk of malignant tumors and infections, including tuberculosis (TB).¹ The incidence of TB in patients receiving TNF inhibitors (iTNF) is higher than in the general population and depends on the prevalence of TB in the region (in Sweden there was a 4-fold increase in risk, while in Korea 30-fold).² The results of the British Society for Rheumatology Biologics Register analysis show that the TB development rate for adalimumab was the highest among TNF- α inhibitors (144 events / 100000 persons-year), then infliximab (136 events / 100000 persons-year) compared to etanercept (39 events / 100000 persons-year). It was estimated that the median time from the initial dose of the TNF antagonist to the diagnosis of TB was 13.4 months for etanercept, 5.5 months for infliximab and 18.5 months for adalimumab.³ Important risk factors for TB development during treatment are: male gender, age over 60 years, respiratory system disorders, glucocorticosteroid therapy with dose more than 7.5 mg a day and living in regions with high TB prevalence.⁴

Poland is a country with an average TB incidence. In 2019, there were 5321 TB cases, i.e. 13.3 cases / 100000 persons-year – this is more than the European Union average, although a downward incidence trend is observed compared to previous years.⁵ The consequence of exposure to mycobacteria is usually an asymptomatic latent infection and only a small percentage of the infected (around 7%–8% throughout their lives) develop clinically active TB. A significant threat is multi-drug resistant TB, caused by mycobacteria resistant to two main drugs, isoniazid and rifampicin. The prognosis in this case is unfavorable, especially by reinfection. Changes in the number of TB patients may be caused by migration of people from Eastern countries with high prevalence of this disease.⁵

2. AIM

The aim of this report is to present a case of a patient who developed active TB during TNF- α inhibitor therapy.

3. CASE REPORT

Patent, 52-year-old man was admitted to the Dermatology Clinic for requalification for biological treatment with

adalimumab. First psoriatic lesions appeared in 1997 and he was diagnosed with psoriatic arthritis in 2012. In the past, the patient was treated with cyclosporin A and lefludomide in combination with methotrexate with no effect.

In addition, the patient has been obese for over 20 years, and has been suffering from hypertension and type 2 diabetes for 16 years. In December 2008, the patient reached BMI 50.9 (165 kg) and was qualified for bariatric surgery (sleeve gastrectomy). Two months after surgery, hypotensive and hypoglycaemic drugs were discontinued. Six months after surgery, a 60 kg weight reduction (BMI 29.2) was achieved.

In 2015 the patient was diagnosed with cystic retinitis and uveitis of the right eye. The adalimumab therapy was initiated (June 2015 – March 2016) with complete remission of psoriatic lesions. In the 12th week of treatment there was a complete remission of inflammation in the area of right macula.

Due to recurrence of psoriatic lesions and changes in the right eye the patient was requalified for biological treatment in January 2017. Because of the positive IGRA test the patient received chemoprophylaxis – rifampicin a month before the therapy. The treatment was resumed, initially according to the drug program with a dose of 40 mg twice a month, then the dose was increased to 40 mg once a week due to the lack of the reduction in psoriasis area and severity index (PASI) and inflammatory changes in the eye. At 16th week of treatment, the patient developed atrial fibrillation and transient ischaemic attack (TIA) with aphasia and hemiparesis – thrombophilia (MTHFR mutation) was diagnosed during further diagnostics, adalimumab therapy was continued.

In October 2017, the patient was suspended in the drug program due to persistent fevers up to 38°C, malaise and excessive sweating. The performed tests revealed Quantiferon-TB⁺, high-resolution computed tomography of the chest and pleural fluid examination confirmed pleural TB. Anti-mycobacterial treatment (rifampicin, pyrazinamide, ethambutol) was initiated and ended in April 2018. In May 2018 adalimumab treatment was resumed, during which enlargement of the right supraclavicular lymph nodes was observed. Histopathological examination of the node from September 2018 confirmed serous TB and the genetic examination revealed the presence of genetic material *Mycobacterium tuberculosis* complex. The patient received again anti-TB treatment, completed in December 2018.

In June 2019, the patient was rehospitalized because of suspicion of TB relapse. The patient was disqualified from ethambutol treatment after ophthalmologic consultation due to necrotizing scleritis and was treated with rifampicin only until October 2019.

Physical examination at the admission to the Clinic revealed well-demarcated, inflammatory plaques with scales on the trunk, upper and lower limbs (Figures 1 and 2), as well as disseminated erythematous scaling lesions on the head (PASI 26, BSA 37%, DLQI 25). There was a palpable lymph node and a purple scar after biopsy in the right su-



Figure 1. Severe inflammatory plaques on the trunk.



Figure 2. Plaques with scales on the lower limbs.



Figure 3. Purple scar after lymph node biopsy.

praclavicular fossa (Figure 3). The right eye was slightly red. The patient reported joints pain and deterioration of vision of the right eye. Qualification tests were performed, the only abnormalities were slightly elevated inflammation makers (CRP 16.54 mg/L, OB 14 mm). Chest X-ray showed no deviation from the norm, in abdominal ultrasound renal cortical cysts up to 28 mm were found. The X-ray of the hands showed distortion of the tuberosity of the distal IV phalanx and the fingertip of the right hand; the pelvic X-ray revealed sclerotization of the acetabular roof and sacroiliac joint surfaces. Rheumatological consultation described limitation of right shoulder joint mobility, positive Patrick's test on both sides, with no joint edema. Ophthalmological examination found scleral fistula, iris adhesions, subcapsular cataract and cystoid macular edema of the right eye and cataract surgery was recommended. During hospitalization, topical treatment was applied with a slight improvement of skin lesions.

Due to the high risk of TB recurrence, switch to the interleukin-17 inhibitor was decided. The therapeutic effect after the first administration of secukinumab was satisfactory. On the first monitoring visit significant reduction of scaling and inflammation of psoriatic plaques was observed: PASI 11.6, BSA 26%, DLQI 10 (Figure 4) and laboratory tests showed no abnormalities. The treatment is very well tolerated, the patient reports no side effects and is regularly monitored by pulmonologist and ophthalmologist.

4. DISCUSSION

TNF- α is a cytokine that plays a key role in maintaining the inflammatory response against infections and takes part in the formation of TB granuloma.⁶ *Mycobacterium tuberculosis* reaches the alveoli and is absorbed by alveolar macrophages with TNF- α release, which stimulates the excretion of other proinflammatory cytokines and chemokines to mobilize and activate CD4⁺, CD8⁺ and γ/δ lymphocytes. IFN- γ is released by these activated cells, which accelerates antigen presentation and induces the processes of intracellular mycobacterial killing and macrophage apoptosis. TNF- α blockade causes a disruption of the natural response to mycobacterial infection, the granuloma cannot be formed nor maintained, which leads to dissemination of the disease.^{7,8} Therefore, more than 50% of TB cases during TNF- α antagonist treatment develop as extrapulmonary, and 25% as disseminated as a consequence of impaired tuberculous formation. Atypical forms of the disease might cause a delay in the correct diagnosis.^{9,10} In addition, it was also found that infliximab and adalimumab suppress IFN- γ production, significantly inhibiting T cell activation and reducing CD4⁺ by up to 70% for infliximab and 50% for adalimumab. Such effect was not described for etanercept.^{7,11}

Due to the increased risk of TB during anti-TNF therapy, it is required to take measures to reduce this risk. Before the therapy it is crucial to: exclude active TB, perform a test for TB infection and start treatment of latent infection, if indicated. In addition, it is recommended to have a history of TB and exposure to infection factors, a physical examination, chest X-ray and a test based on INF level measurement in blood serum (e.g. Quantiferon TB-Gold) – IGRA.¹² A positive test result should not be the conclusive to confirm *M. tuberculosis* infection, it is required to perform culture for acid-resistant mycobacteria. A negative one does not exclude the possibility of infection or active TB. False negative results may occur due to the stage of infection (sample collected before the immune response) and the coexistence of diseases that affect the immune system.

There are case reports of active TB development during adalimumab therapy, despite negative screening for active and latent TB before the treatment.⁹ In our case report, before the second cycle of adalimumab the patient received rifampicin one month before the therapy due to the positive IGRA test, although the chest X-ray showed no deviation from the norm. Before the first cycle the above tests were negative.

The latest metaanalysis on the reactivation of latent TB infection in biologically treated psoriasis patients included 51 studies in which 78 patients with active TB were evaluated. The majority of patients (73%) with active TB were male, the average age was 48 ± 13 years, and 85% were Europeans or Asians. Interestingly, pretreatment screening for latent TB was negative in up to 63% of patients. The disease occurred in 33% of patients in the first 3 months of therapy and in 51% in the first 6 months. Most patients (72%) had extrapulmonary TB and 49% had disseminated disease. The mortality rate was estimated as 7%.¹³



Figure 4. First monitoring visit: significant reduction of scaling and inflammation of psoriatic plaques.

According to Polish guidelines, patients with latent TB infection should receive chemoprophylaxis, which includes:

- (1) isoniazid at a dose of 5 mg/kg once a day, not more than 300 mg, administered for 9 months (therapy of choice);
- (2) isoniazid in a dose as above and rifampicin at a dose of 10 mg a day, not more than 600 mg, administered for a total of 3 months;
- (3) rifampicin in a dose as above administered for 4 months, in case of intolerance to isoniazid;
- (4) one month before TNF antagonist treatment, provided that there are no prophylactic treatment interruptions.¹⁴

In addition, chemoprophylaxis should be administered regardless of the outcome of the IGRA or tuberculin skin test in patients who: (1) recently had contact with TB patients, (2) immigrants from countries with a high prevalence of TB, (3) had TB in the past and have not been treated or insufficiently treated, (4) have tuberculous lesions in radiological examination of the lungs (fibrous changes, calcification in the lungs and lymph nodes, pleural thickening) and have not been treated for this.^{14–16} Treatment of latent TB infection reduces the risk of reactivation of TB associated with anti-TNF- α inhibitors, but no chemoprophylaxis is completely protective¹⁷.

The diagnosis of TB during anti-TNF treatment is an indication for discontinuation of the therapy. TNF antagonist agent can be administered at the earliest one month after properly conducted antimycobacterial therapy if drug resistance has not been proved.¹⁵ However, it is worth paying attention to literature reports on that IL-17 inhibitors do not increase the risk of TB – in a group of over 5000 patients treated with secukinumab where there were no new cases

after one year of therapy.¹⁸ No cases of TB reactivation were reported within 2.5 years of ixekizumab therapy.¹⁹ Therefore, in patients with previous TB infection, the treatment of psoriasis or psoriatic arthritis should be continued with IL-17 antagonists.

5. CONCLUSIONS

The proper qualification and thorough testing before biological treatment ensures patients' safety and satisfactory therapeutic effect. It should be remembered that during longterm therapy with TNF antagonists, both reactivation of latent TB as well as new infection are serious problems. Therefore, regular tests should be performed, especially in countries with high prevalence of this disease.

In patients who develop TB, particularly recurrent, switching to a drug with a different mechanism should be considered.

Conflict of interest

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