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Original Article

Tuberculosis in patients using biological disease-modifying antirheumatic drugs

Biyolojik hastalık modifiye edici antiromatizmal ilaç kullanan hastalarda tüberküloz

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ABSTRACT

Aim: In rheumatic diseases, the possibility of developing tuberculosis (TB) increases due to both the disease itself and the biological disease-modifying antirheumatic drugs (bDMARDs) used for treatment. In our study, we aimed to investigate the causes and risk factors of TB infection in patients using bDMARDs for rheumatological diseases.
Methods: Demographic, radiological, laboratory data, tuberculin skin test (TST) results, duration of disease, and medications used in TB patients were recorded in 531 patients who were using bDMARD with the diagnosis of rheumatologic disease.
Results: TB developed in 5 (0.9%) of 531 patients. TB was detected in 10% of the anakinra users, 2.4% of the infliximab users, 1.4% of the certolizumab users, 1.2% of the etanercept users, and 0.9% of the adalimumab users. The mean duration of bDMARD use until TB development was 28 months. All the cases were female, and the mean age was 53.8 years.
Conclusion: Our study highlights the importance of routine chest X-ray, cervical-supraclavicular lymphadenopathy (LAP) examination, annual TST follow-up, and symptom questioning in TST-negative or anergic patients using bDMARDs.

Keywords: bDMARD, rheumatologic disease, tuberculin skin test, tuberculosis

ÖZ

Amaç: Romatolojik hastalıklarda hem hastalığın kendisi hem de tedavi için kullanılan biyolojik hastalık modifiye edici antiromatizmal ilaçlar (bDMARD) nedeniyle tüberküloz (TB) gelişme ihtimali artmaktadır. Çalışmamızda romatolojik hastalıkları nedeniyle bDMARD kullanan hastalarda gelişen TB enfeksiyonunun nedenlerini ve risk faktörlerini araştırmayı amaçladık.
Yöntem: Romatolojik hastalık tanısıyla bDMARD kullanan 531 hastadan TB gelişenlerde demografik, radyolojik, laboratuar verileri, tüberkülin cilt testi (TST) sonuçları, hastalık süresi ve kullandığı ilaçları kaydedildi.
Bulgular: 531 hastanın 5'inde (0.9 %) TB gelişti. Anakinra kullananların 10%'unda, infliximab kullananların 2.4%'ünde, sertolizumab kullananların 1.4%'ünde, etanercept kullananların 1.2%'sinde ve adalimumab kullananların 0.9%'unda TB saptandı. TB gelişene kadar geçen ortalama bDMARD kullanım süresi 28 aydı. Olguların tamamı kadın ve ortalama yaş 53.8 idi.
Sonuç: Çalışmamız bDMARD kullanan TST negatif veya anerjik olguların rutin akciğer grafisi, servikal-supraklavikular LAP muayenesi, yıllık TST takibi ve semptom sorgulamasının önemini vurgulamaktadır.

Anahtar kelimeler: bDMARD, tüberküloz, romatolojik hastalık, tüberkülin cilt testi

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INTRODUCTION

The suppression of the immune system with the accompanying autoimmune disease or immunosuppressive treatments (such as glucocorticoids or anti-TNF agents) may reactivate silent infections in the granuloma tissue. While there are many studies (1) showing that the risk of infection has increased since the introduction of biological disease-modifying antirheumatic drugs (bDMARDs) for the treatment of rheumatological diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA), there are also studies reporting that treatment with bDMARDs does not significantly increase the risk of infection (2). It is also known that autoimmune diseases may increase the risk of infection by causing dysfunction in the immune system (3).

Tuberculosis (TB) is one of the diseases that can affect all organs, most commonly the lungs, and cause significant morbidity and mortality worldwide (4). Latent tuberculosis infection is investigated before giving immunosuppressive treatment in rheumatic diseases. The effects of immunosuppressive treatment and autoimmunity can cause false negative tuberculin skin test (TST) results. Therefore, a negative TST result should be considered suspicious, and these patients should be carefully monitored for atypical TB presentation. Anti-TNF therapy should be avoided until active TB is ruled out or treated if detected (5). This issue is very important, especially in Türkiye where the prevalence of latent TB is high. In our study, we aimed to investigate the causes and risk factors of TB infection in patients using bDMARDs for rheumatological diseases.

MATERIAL AND METHODS

The bDMARDs used by the patients included in our study were: etanercept, adalimumab, infliximab, golimumab, abatacept, rituximab, tocilizumab, certolizumab, secukinumab, and anakinra. Patients using targeted synthetic DMARDs (tofacitinib, baricitinib) were also included in the study. Demographic, radiological, laboratory data, TST test results, duration of disease, and medications used in patients who developed TB among 531 patients reciveing bDMARD treatment with the diagnosis of rheumatological disease in the Rheumatology outpatient clinic between February 2019 and December 2022 were recorded. Approval was obtained from the ethics committee of our institution for our study (no: 2023/28, date: 21.02.2023).

RESULTS

The drug distribution of 531 patients using bDMARD with the diagnosis of rheumatologic disease was as follows; abatacept: 11, adalimumab: 113, baricitinib: 27, etanercept: 85, golimumab: 93, infliximab: 41, rituximab: 39, secukinumab: 66, certolizumab: 73, tofacitinib: 57, tocilizumab: 33, and anakinra: 10 people. Some patients had a history of more than one bDMARD use. The general characteristics of the patients are shown in Table 1.

TB developed in 5 patients (0.9%). TB was detected in 1 (10%) of the anakinra users, 1 (2.4%) of infliximab users, 1 (1.4%) of the certolizumab users, 1 (1.2%) of the etanercept users, and 1 (0.9%) of the adalimumab users. The mean duration of bDMARD use until TB development was 28 months. All the cases were female, and the mean age was 53.8 years. Since the Bacillus Calmette-Guérin (BCG) vaccine was routinely

Table 1. General characteristics of patients using biologic agent therapy.

Age	51 (19-86)
Gender (F/M)	300 /231
Disease duration (years)	8 (1-44)
Diagnosis	**n (%)**
Rheumatoid arthritis	215 (40.5%)
Ankylosing spondylitis	213 (40.1%)
Psoriatic arthritis	33 (6.2%)
Vasculitis	24 (4.5%)
Overlap syndrome	23 (4.3%)
Sjogren's syndrome	6 (0.9%)
Undifferentiated spondyloarthritis	3 (0.6%)
Systemic sclerosis	1 (0.2%)
Other	14 (2.6%)

Table 2. Demographic, laboratory, radiological, and clinical findings of patients diagnosed with tuberculosis.

	Case 1	Case 2	Case 3	Case 4	Case 5
Gender	Female	Female	Female	Female	Female
Age (year)	67	64	69	33	36
Rheumatological disease	RA	RA	Psoriatic Arthritis	Still's Disease	Behcet's Disease
Rheumatological disease duration	6 years	5 years	3 years	1 year	15 years
History of TB	no	no	no	no	no
TB theme	No	no	no	no	no
TST (mm)	2	anergic	anergic	15	2
Chest X-ray before bDMARD	Normal	Normal	Normal	Hilar fullness	Normal
BCG scar	yes	yes	yes	yes	yes
INH prophylaxis	no	no	no	unknown	no
bDMARD	Etanercept	Infliximab	Certolizumab	Anakinra	Adalimumab
bDMARD duration used until TB develops	5 years	4 years	2 months	6 months	2 years
Immunosuppressive drug	sulfasalazine, leflunomide, prednisolone	methotrexate, prednisolone, leflunomide	methotrexate, prednisolone, leflunomide	methylprednisolone	Azathioprine, Cyclosporine, prednisolone
Previous bDMARD use	no	Tofacitinib	no	no	Infliximab
Symptom	cough	no	dyspnea, fatigue	dyspnea	cough, sputum
Radiology in the diagnosis of TB	cavity	cavitary nodule, infiltration	infiltration	normal	Hilar LAP
Diagnostic method	Microbiology (Sputum culture)	Microbiology (Sputum culture)	Microbiology (Gastric lavage)	Pathology (Lymph node biopsy)	Pathology (Lymph node biopsy)
ARB	negative	negative	negative	unknown	unstudied
Mycobacteria culture	reproduction (+)	reproduction (+)	reproduction (+)	unknown	unstudied
Mortality	no	no	yes (1st month)	no	no
Comorbidity	DM, HT, asthma, OSAS	goiter	HT, dementia	HT, CRF	Bipolar

RA: rheumatoid arthritis, TB: tuberculosis, INH: isoniazid, BCG: bacillus Calmette-Guérin, TST: tuberculin skin test, bDMARD: Biological Disease-Modifying Antirheumatic Drug, ARB: acid-resistant bacteria, DM: diabetes mellitus, HT: hypertension, OSAS: obstructive sleep apnea syndrome, CRF: chronic renal failure, LAP: lymphadenopathy.

administered during childhood in Türkiye, all the cases had at least one BCG scar. The clinical findings of each case are shown in Table 2 and presented in detail below.

Case 1, GK

A 67-year-old female patient, who has been followed up with the diagnosis of RA for 6 years, had diabetes mellitus (DM), hypertension (HT), asthma, and severe obstructive apnea syndrome diagnoses. TST of the patient who used prednisolone, leflunomide, and sulfasalazine before using etanercept was evaluated as 2 mm. Isoniazid (INH) prophylaxis was not given to the patient who had a normal chest X-ray and had no TB contact. Since the control TST was anergic 3 years later, it was evaluated as anergic again when the booster reaction test was performed. On a thorax CT taken upon detection of nodules on a chest X-ray during routine control, a 22x23 mm nodule was observed in the middle lobe of the right lung (Figure 1a). The nodule was measured as SUV max 2.0 in PET-CT, and when wedge resection was performed, the pathology was reported as necrotizing granuloma, anthracosis, and rheumatoid nodule. Prednisolone, leflunomide, and etanercept treatment were continued. When the patient was admitted with cough complaints in the 5th year of anti-TNF treatment, centrally located cavitary lesions in the right lung were observed on a thorax CT (Figure 1b), and sputum was negative for acid-resistant bacteria (ARB), but M. tuberculosis reproduction was detected in mycobacterial culture. Anti-tuberculosis (HRZE: isoniazid, rifampicin, pyrazinamide, ethambutol) treatment was started by continuing with

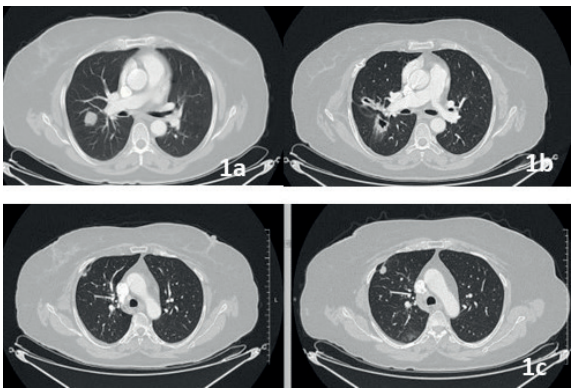

Figure 1. a: 22x23 mm nodule in the middle lobe of the right lung on the thorax CT, b: Cavity lesions on the thorax CT, c: Progression of the peripheral nodule in the right upper lobe on the thorax CT.

prednisolone, one of the rheumatic drugs. A transthoracic tru-cut biopsy was performed 1 year after the end of the treatment due to the detection of the progression of the peripheral nodule in the right upper lobe on a thorax CT during the follow-up (Figure 1c). A transthoracic fine needle biopsy was performed but was not diagnostic; therefore, wedge resection was performed, and the pathology result was reported as granuloma with caseification necrosis. However, rituximab and steroid treatment were continued, considering that the patient had no clinical complaints, CRP and sedimentation were normal, and sputum ARB was negative, considering that it might be secondary to tuberculosis infection of the granuloma tissue.

Case 2, SE

A 64-year-old female patient had been followed up with the diagnosis of RA for 5 years and had goiter as an additional disease. INH prophylaxis was not used because the patient who used tofacitinib for 4 years was found to have anergic TST two times. Prednisolone 10 mg and leflunomide were also continued. It was learned that the patient had previously used methotrexate and discontinued the drug. Since the patient's arthritis was not under control, infliximab and methotrexate treatments were started. The patient, whose TST was performed twice before, was anergic, and had a normal chest X-ray, and had no TB contact. After 7 months, during the routine control, an increase in density in the bilateral middle-upper zone (Figure 2a) was observed in the chest X-ray, a nodule in the right upper lobe, and a cavitary nodule in the left upper lobe, and consolidation (Figure 2b) was observed in the thorax CT. Sputum was ARB negative and M. tuberculosis reproduction was detected in mycobacteria culture. The patient was given anti-tuberculosis (HRZE) treatment. Sulfasalazine and prednisolone treatments were also continued. After the completion of TB treatment, nodules developed in the lung, rituximab treatment was started, and the nodular lesions regressed completely (Figure 2c).

Case 3, HB

A 69-year-old female patient had been followed up with the diagnosis of psoriatic arthritis for 3 years and also had HT and dementia. The patient was treated with prednisolone and methotrexate, and leflunomide was started 6 months ago. As the patient did not tolerate leflunomide treatment, she was switched to certolizumab treatment. It was observed that the patient, who was anergic to the TST before, was again anergic when the TST was repeated with the booster reaction. INH prophylaxis was not given to the patient who had no pathology in the chest X-ray and had no TB contact. Since the patient who did not follow the treatment regularly complained

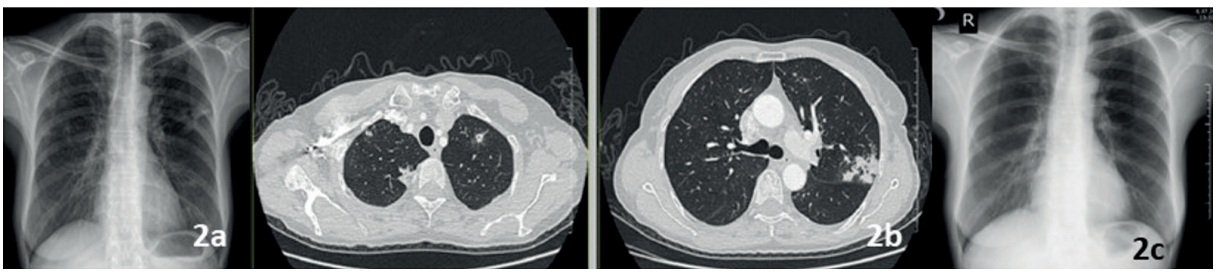

Figure 2. a: Density increase in bilateral mid-upper zone on chest X-ray, b: Nodule in the right upper lobe, cavitary nodule in the left upper lobe, and consolidation in thorax CT, c: Nodules are observed to regress in chest X-ray control.

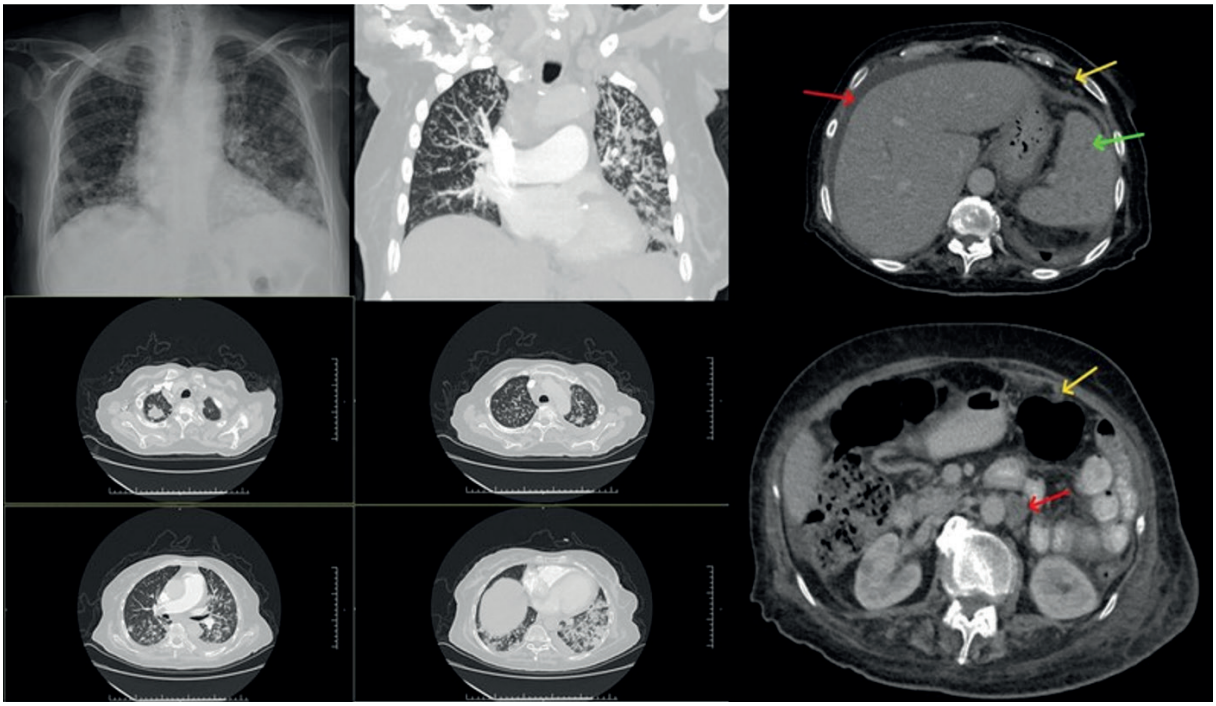

Figure 3. Diffuse nodular and infiltrative lesions on the thorax CT, paraaortic LAP, ascites, pulmonary embolism, and multiple lesions in the spleen.

of weakness and dyspnea, newly developed widespread nodular and infiltrative lesions, paraaortic lymphadenopathy (LAP), ascites, pulmonary embolism, and multiple lesions in the spleen were observed in the thorax CT taken (Figure 3). ARB was negative in the gastric lavage taken from the patient, who did not produce sputum. When the biopsy was taken from the supraclavicular lymph node, granuloma structure, including caseification necrosis, was observed in the pathology. Anti-tuberculosis (HRZE) treatment was started due to the reproduction of M. tuberculosis in the mycobacteria culture. The patient with involvement in the peritoneum, spleen, lung, and lymph nodes was evaluated as having multisystemic TB. The patient, who was intubated in the intensive care unit due to the development of respiratory failure during his follow-up, died.

Case 4, MO

A 33-year-old female patient was being followed up with the diagnosis of adult-onset Still's disease, and her comorbidities were HT and end-stage chronic renal failure (CRF). She had used glucocorticoids and anakinra for a year. Two years ago, endobronchial ultrasound (EBUS) was performed with the preliminary diagnosis of intermittent fever, some calcified lymphadenomegaly on a thorax CT, and a right hilar mass. The patient, who developed a complication of hemopneumothorax during the procedure and had an arrest, responded to cardiopulmonary resuscitation. TST was performed on the patient in an external center whose lymph node biopsy result was reported as benign: TST was recorded as 15 mm, but INH usage information could not be obtained. Latent TB screening is also not recommended for anakinra use by the local health committee of our country. Right supraclavicular lymphadenomegaly was detected in thorax CT, which was requested due to right supraclavicular fullness during routine control in the 1st year of

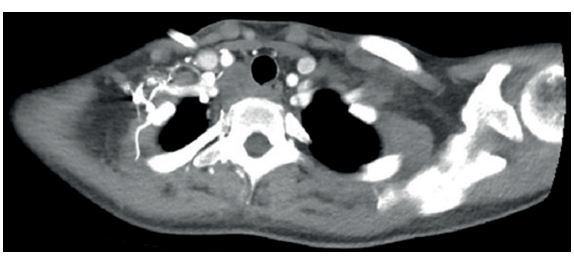

Figure 4. Right supraclavicular lymphadenomegaly on the thorax CT.

anakinra treatment (Figure 4). A fine-needle aspiration biopsy performed on the lymph node was reported as a granulomatous infection with caseification. The patient was started on anti-tuberculosis treatment, and anti-rheumatic drugs were discontinued. During this period, no major problems were encountered, except for mild adult Still's disease attacks.

Case 5, GU

A 36-year-old female patient, who has been followed up with the diagnosis of Behcet's disease for 15 years, had no comorbidities other than bipolar personality disorder. The patient was followed up with azathioprine and cyclosporine, and because of the development of macular edema and ischemic optic neuropathy in the right eye, a pulse steroid was administered. However, due to the inability to control her complaints, she was started on infliximab treatment. The TST before the treatment was 2 mm, and the chest X-ray was normal. Due to the development of toxic hepatitis 15 days after the treatment, adalimumab treatment was started. A max diameter of 14 mm mediastinal LAP was detected in the thorax CT taken after the right hilar fullness was observed in the chest X-ray in the routine control 1 year later (Figure 5a). PET-CT was requested, but the patient did not come to the control visits. In PET-CT taken 1 year later, lymphanetopaties in the anterior mediastinum, prevascular area, and subcarinal area (SUV max 11.2) and supraclavicular 2.5 cm LAP (SUV max 19.2) were observed (Figure 5b). The patient, who had cough and sputum complaints for 1 month, underwent a biopsy of the supraclavicular lymph node. As a result, granuloma with caseification formed by epithelioid histiocytes and Langerhans-type giant multinuclear cells was detected. Renal dose anti-TB treatment was started. The patient, who completed the anti-TB treatment, is being followed up in our rheumatology clinic.

DISCUSSION

In patients with rheumatic disease using anti-TNF therapy, the average TB incidence is 9.62 cases per 1000 patients in all countries (6). Similar to this result, in our study, the overall TB incidence was 0.9%. TB development was observed with anakinra (10%), infliximab (2.4%), certolizumab (1.4%), etanercept (1.2%), and adalimumab (0.9%) of bDMARDs. The patient using infliximab had used tofacitinib, and the patient using adalimumab had previously used infliximab. Bongartz et al.[7] analyzed randomized controlled trials of infliximab and adalimumab and reported a significant increase in the risk of infection. On the contrary, meta-analyses evaluating patients treated with adalimumab, etanercept, infliximab, rituximab, abatacept, and anakinra concluded that the risk of severe infection did not increase (8-10). In the study by Alaşan et al.[11] conducted in Türkiye, it was reported that TB developed in 2 cases (1.8%) due to the use of etanercept and infliximab among 110 patients who were under anti-TNF therapy. Since mycobacterial infections have been reported very rarely in patients receiving rituximab, there is no recommendation to screen for latent TB before using rituximab

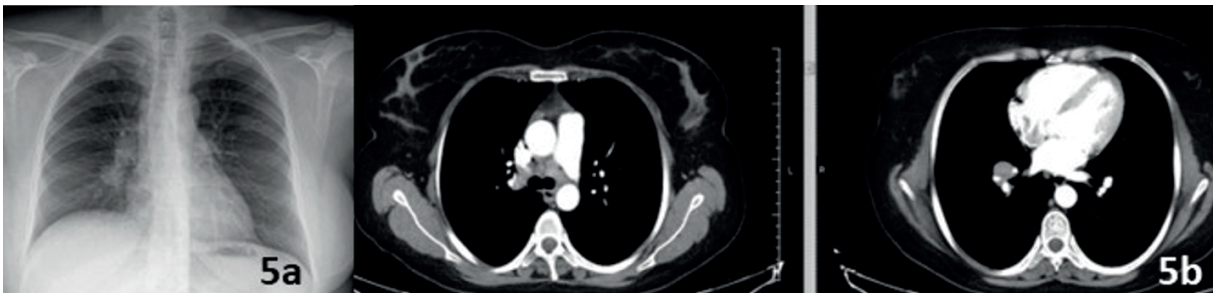

Figure 5. a: Newly formed right hilar fullness on chest X-ray, b: In the PET-CT, In the anterior mediastinum, prevascular area, subcarinal, and supraclavicular LAP is observed.

treatment (12). In our country, screening for latent TB is not recommended before the use of Anakinra. In our study, it was observed that TB developed in one patient after the use of anakinra. This case was investigated in a different institution for the investigation of the etiology of the LAP, but TB could not be completely excluded.

Among the immunosuppressive agents, glucocorticoids increase the risk of infection the most (13). Delayed addition of bDMARDs to treatment leads to longer duration and higher dose use of glucocorticoids, and secondary to this, an increase in severe infection rates may occur (2,3). In this paper, 4 of our 5 cases had glucocorticoid use. Pulse steroid was used in one of these cases. Anakinra and TNF inhibitors are associated with an increased risk of infection compared to conventional DMARDs, especially in the early stages of treatment. The most common sites of infection are the respiratory tract, skin, soft tissue, and urinary tract. The risk of TB has been reported to be higher with TNF inhibitors (especially infliximab) than with traditional DMARDs (14).

Since the effects of immunosuppressive therapy and autoimmunity may cause false negative TST results, a negative TST result should be considered suspicious, and these patients should be followed for an atypical TB presentation closely (15). Since isoniazid is a hepatotoxic drug, a preventive treatment can be avoided in countries with low TB prevalence. However, in countries with a high prevalence of latent TB, such as our country, if we do not treat latent TB, disseminated disease may develop that may be resistant to treatment due to TNF blockers (5). TST was anergic or negative, except for case number 4. No positivity was achieved with the booster reaction either. Interferon-gamma release assay (IGRA) tests were not performed in any of the patients. All of our cases had BCG vaccination scars, and there was no previous TB history or TB contact. However, case number 4 had hilar LAP; therefore, EBUS was performed and no TB was detected. Although respiratory symptoms suggest the diagnosis of TB presence in most of our cases, we also had a case that was detected only by chest X-ray in the routine control. This result draws attention to the importance of routine check-ups every six months and good questioning of pulmonary symptoms.

TB tends to be extrapulmonary and systemic in immunosuppressive patients. However, there is also data showing that the pulmonary form is dominant (6). The disease progressed with pulmonary involvement in 2 of our 5 cases, lymph nodes in two, and multisystemic involvement in one patient. It is recommended to carefully evaluate especially newly formed nodules, cavitation, and hilar enlargement in the chest X-rays of patients who are using bDMARDs and to palpate accessible lymph nodes, especially cervical-supraclavicular LAP, keeping in mind extrapulmonary TB. As in our case with multisystemic TB, other organ involvements should be evaluated with a prediagnosis of TB. The sensitivity of ARB microscopy is low (50-60%), and it decreases distinctly in patients who are co-infected with human immunodeficiency virus (HIV), in children, and in patients with non-pulmonary TB (16). The method accepted as the gold standard in the diagnosis of TB is mycobacterial culture, which requires an incubation period of 6-8 weeks. In 3 of our cases, growth was detected in mycobacterial cultures despite ARB negativity. Therefore, although ARB negativity is detected in patients using bDMARD therapy, the result of the mycobacterial culture should be expected in cases of suspected TB.

It is known that additional diseases such as chronic obstructive pulmonary disease, chronic kidney diseases, and DM increase the risk of infection in patients with rheumatic diseases (3). In our study, there were comorbidities such as DM, asthma, and CRF. In general, it is known that patients with psoriatic arthritis, ankylosing spondylitis, and primary Sjögren's syndrome are relatively younger, have fewer comorbidities, and are generally treated with fewer immunosuppressive treatments than RA patients (17). For these reasons, TB development

can be expected to be less common in this group of patients. However, data show that there is no difference in the incidence of TB between different rheumatic diseases in which patients receive anti-TNF agents (6). Two of our cases also had RA. The mean duration of rheumatologic disease was 6 years. The duration of bDMARD use until the development of TB is 28 months, and it has been reported in the literature that TB develops in the first 20th month in most cases (6).

Our limitations include the lack of information about the comorbidities and other immunosuppressive treatments of patients using bDMARDs and the unequal distribution of patients using bDMARDs. However, our study on cases highlights what should be considered regarding TB development in bDMARD use.

CONCLUSION

TB development was observed with bDMARDs infliximab, certolizumab, etanercept, anakinra, and adalimumab. Since the duration of bDMARD use until the development of TB is 28 months, routine chest X-rays, cervical-supraclavicular LAP examinations, annual TST follow-up, and symptom examinations should not be avoided, especially in TST-negative or anergic cases.

Ethics Committee Approval: The study protocol was approved by the Bolu Abant İzzet Baysal University Clinical Research Ethics Committee Ethics Committee (21.02.2023 / 2023/28).

Conflict of Interest: The authors have declared that they have no conflict of interest.

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REFERENCES

1. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011; 2011(2): CD008794. https://doi.org/10.1002/14651858
2. Cipriani P, Berardicurti O, Masedu F, et al. Biologic therapies and infections in the daily practice of three Italian rheumatologic units: a prospective, observational study. Clin Rheumatol. 2017; 36(2): 251-60. https://doi.org/10.1007/s10067-016-3444-1
3. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology (Oxford). 2013; 52(1): 53-61. https://doi.org/10.1093/rheumatology/kes305
4. Gulhan PY, Elverisli MF, Ercelik M, Aytekin F, Balbay O, Arbak P. Relationship between Diagnosis Period and Internal and External Air Quality in Patients with Tuberculosis. Eurasian J Med. 2020; 52(1): 77-80. https://doi.org/10.5152/eurasianjmed.2020.19226
5. Taylor JC, Orkin R, Lanham J. Tuberculosis following therapy with infliximab may be refractory to antibiotic therapy. Rheumatology (Oxford). 2003; 42(7): 901-2. https://doi.org/10.1093/rheumatology/keg158
6. Sartori NS, de Andrade NPB, da Silva Chakr RM. Incidence of tuberculosis in patients receiving anti-TNF therapy for rheumatic diseases: a systematic review. Clin Rheumatol. 2020; 39(5): 1439-47. https://doi.org/10.1007/s10067-019-04866-x
7. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006; 295(19): 2275-85. https://doi.org/10.1001/jama.295.19.2275.
8. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis. 2009; 68(7): 1136-45. https://doi.org/10.1136/ard.2008.091025
9. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis. 2009; 68(1): 25-32. https://doi.org/10.1136/ard.2007.083188
10. Thompson AE, Rieder SW, Pope JE. Tumor necrosis factor therapy and the risk of serious infection and malignancy in patients with early rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis Rheum. 2011; 63(6): 1479-85. https://doi.org/10.1002/art.30310
11. Alaşan F, Güleç Balbay E, Cangür Ş, Balbay Ö, Yılmaz Aydın L, Annakkaya AN. Should isoniazid prophylaxis be prescribed to the patients under tumor necrosis factor-alpha antagonists independent of tuberculin skin test? Aging Male. 2020; 23(5): 1109-14. https://doi.org/10.1080/13685538.2019.1678582

12. Winthrop KL, Yamashita S, Beekmann SE, Polgreen PM; Infectious Diseases Society of America Emerging Infections Network. Mycobacterial and other serious infections in patients receiving anti-tumor necrosis factor and other newly approved biologic therapies: case finding through the Emerging Infections Network. Clin Infect Dis. 2008; 46(11): 1738-40. https://doi.org/10.1086/587989
13. Dixon WG, Abrahamowicz M, Beauchamp ME, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. Ann Rheum Dis. 2012; 71(7): 1128-33. https://doi.org/10.1136/annrheumdis-2011-200702
14. Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. Semin Arthritis Rheum. 2010; 39(5): 327-46. https://doi.org/10.1016/j.semarthrit.2008.10.002
15. Mohan AK, Coté TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis. 2004; 39(3): 295-9. https://doi.org/10.1086/421494
16. Perkins MD, Cunningham J. Facing the crisis: improving the diagnosis of tuberculosis in the HIV era. J Infect Dis. 2007; 196(Suppl 1): S15-27. https://doi.org/10.1086/518656
17. Cantini F, Niccoli L, Goletti D. Adalimumab, etanercept, infliximab, and the risk of tuberculosis: data from clinical trials, national registries, and postmarketing surveillance. J Rheumatol Suppl. 2014; 91: 47-55. https://doi.org/10.3899/jrheum.140102