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Anti-Tumor Necrosis Factor-α-Induced Systemic Lupus Erythematosus in Patients with Axial Spondiloarthritis- A Single Center Experience

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ABSTRACT

Lupus induced by a tumor necrosis factor-alpha inhibitor, namely "Anti-TNF-α-Induced Lupus (ATIL)" is commonly seen in patients with Crohn's disease and Rheumatoid Arthritis; however, it is rarely seen in axial spondyloarthropathy (SpA). Here, four cases of ATIL in patients with axial SpA are presented and discussed in the light of literature data.

The files of the patients who used anti-TNF-α drugs regularly for at least one year due to axial SpA were reviewed retrospectively, and four patients with ATIL were analysed.

ATIL developed while the first case was using Adalimumab for 6 years, the second was using Infliximab for 5 years, the third was using Infliximab for 7 years, and the fourth was using Adalimumab for 16 years. In all cases, antinuclear antibodies (ANA) and anti-double stranded DNA (anti-dsDNA) values were positive, while none of the cases had hypocomplementemia. ATIL symptoms were acute mesenteric thrombosis, fever and pleuritis in the first case, arthritis in the small joints of the hand in the second case, deep vein thrombosis, fever, pleuritis and peritoneal fluid accumulation in the third case and malar rash in the fourth one. Anti-TNF-α medication was discontinued in all patients and prednisolone was started. Only in the third case was the switch to another anti-TNF-α agent.

Although anti-TNF-α is an effective and common treatment option in patients with SpA, these patients should be carefully monitored for side effects such as ATIL.

Keywords: Anti-TNF-α induced lupus, Drug-induced lupus erythematosus, Spondyloarthritis, Tumor necrosis factor- α inhibitors

Introduction

Spondyloarthritis (SpAs) comprises a group of inflammatory diseases of the spine and joints, and shows common clinical features such as inflammatory back pain, peripheral arthritis and enthesitis (1). Nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, disease-modifying anti-rheumatic drugs (DMARDs), Tumor necrosis factor-alpha (TNF-α) and Interleukin-17 inhibitors can be used for treatment (2).

Drug-induced lupus erythematosus (DILE) is a clinical entity that is considered to be associated with medication, characterized by development of Systemic Lupus Erythematosus (SLE)-like symptoms such as fever, musculoskeletal involvement and serositis, which resolves within weeks after discontinuation of medication (3,4).

Many drugs, including hydralazine, procaineamide, isoniazid, minocycline and TNF-α inhibitors have been reported to cause DILE (5).

Although there is no defined criterion for DILE, the diagnosis is established by presence of at least one serological SLE marker such as anti-double stranded DNA (anti-dsDNA), antinuclear antibodies (ANA), anti-cardiolipin antibodies (aCL) and at least one non-serologic SLE marker (arthritis, serositis, skin rash, hematologic involvement, thrombosis), no prior history of SLE, and improvement of disease symptoms with discontinuation of the responsible drug (6).

The clinical table that emerges after the use of anti-TNF-α and differs in some aspects from other DILEs is called anti-TNF-α induced lupus (ATIL). The majority of patients with ATIL are patients with

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rheumatoid arthritis (RA) and Crohn's disease (CD) and a few patients with SpA (6-8).

The aim of this study is to determine the frequency of ATIL in our patients receiving anti-TNF-α therapy due to axial SpAs and to reveal the clinical and demographic characteristics and laboratory findings of the patients with this side effect.

Materials and Methods

The patients who were followed up in the Rheumatological Diseases Follow-up Polyclinic and the files of the patients who received anti-TNF-α with the diagnosis of axial SpA were included in our study. Consent was obtained from the Ethics Committee of our hospital before the study and the study was conducted in accordance with the rules of the Declaration of Helsinki.

All files between the dates of 01.01.2015 and 31.12.2022 were scanned and the files of patients aged 18-65 years who had visited at least once in the last year were included in our study. Patients who interrupted their check-up and medication and those with missing data in their files were not included in the study.

Age, gender, follow-up period due to axial SpA, duration of anti-TNF-α use, types of anti-TNF-α drugs they used, and ANA values before starting anti-TNF-α were recorded from their files. Then, during the follow-up, the side effects thought to be related to the anti-TNF-α and the anti-TNF-α related to this side effect were noted.

The characteristics of patients who developed ATIL were also examined. How long ATIL developed after anti-TNF-α drug use, ATIL symptoms, serology in patients who developed ATIL, symptom resolution times and treatments were examined in detail.

Statistical analysis was performed using the Statistical Package for the Social Sciences version 25.0 for Windows (SPSS, Inc.; Chicago, IL, USA). Descriptive statistics were presented as mean (standard deviation (SD)) or median (minimum-maximum) for continuous variables, and frequencies (%) for nominal and categorical variables.

Results

Of the 77 patients using anti-TNF-α drug due to axial SpA, 29 (37.7%) were female and 48 (62.3%) were male. The mean age was 49.33 (SD 9.65) years. The follow-up period with the diagnosis of Axial SpA was 17 (3.0-46.0) years. The duration of Anti-TNF-α use was 9.0 (1.0-20.0) years. The number of patients using more than one Anti-TNF-α was 32 (41.56%). While ANA level before Anti-TNF-α use was unknown in 68 (88.3%) patients, it was negative in 7 (9.1%) patients and positive in 2 (2.6%) patients. Disease and drug use characteristics of the patients are summarized in Table 1.

Adverse events secondary to anti-TNF-α drug developed in 20 (25.8%) patients and included hypersensitivity reactions, ATIL, skin reactions, infection, non-infectious uveitis, tuberculosis, malignancy, hepatic reaction, and thromboembolic reaction. The drug responsible for the side effects was Infliximab in 10 (13.0%) patients, Adalimumab in 5 (6.5%) patients, Etanercept in 2 (2.6%) patients, Sertolizumab in 2 (2.6%) patients, and Golimumab in 1 (1.3%) patients. Side effects and responsible drug information are summarized in Table 2.

The clinical features of 4 ATIL patients are detailed below and summarized in Table 3.

Case 1: A 49-year-old male patient with a 20-year history of Ankylosing Spondylitis (AS) who had been treated with Adalimumab 40 mg/2 weeks for 6 years, admitted with abdominal pain, fever, leukocytosis, high levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Abdominal computed tomography (CT) investigation showed short-segment partial thrombosis that caused filling defect inside the lumen starting from the proximal region of the superior mesentery artery, and long-segment total occlusion on the distal branches; and high-resolution pulmonary CT showed bilateral pleural effusion. Adalimumab treatment was discontinued, and segmental resection was performed.

Due to the development of thrombotic event, fever and pleuritis, a preliminary diagnosis of ATIL was considered due to Adalimumab treatment. Laboratory investigations demonstrated positive ANA in a weak granular pattern (<1/100 titration), positive anti-dsDNA; normal complement levels; negative anti-histone antibodies (AHAs) and antiphospholipid antibodies. Prednisolone 20 mg/day and anticoagulant treatment were started. Pleural effusion regressed dramatically. Two months later, repeated laboratory investigation demonstrated; negative antibody profile. Prednisolone was shifted to 3x50 mg/g indomethacin after the ESR and CRP values returned to normal in the 7th month. The patient is still under follow-up without inflammatory signs or recurrence of lupus symptoms.

Case 2: A 35-year-old female patient with a 7-year history of axial SpA who had been under treatment with Infliximab 300 mg/6 weeks, for 5 years, presented with peripheral arthritis, including

Table 1: Disease and Drug Use Characteristics of the Patients

	n=77
Age (years) mean (SD)	49.33 (9.65)
Gender n(%)	
Woman	29 (37.7)
Man	48 (62.3)
Follow-up due to Axial SpA (years) median (min-max)	17.0 (3.0-46.0)
Anti-TNF-α usage time (years) median (min-max)	9.0 (1.0-20.0)
Anti-TNF-α drugs used n (%)	
Adalimumab	31 (40.3)
Infliximab	30 (39.0)
Golimumab	28 (36.4)
Etanercept	24 (31.2)
Sertolizumab	5 (6.5)
ANA before anti-TNF-α n (%)	
Unknown	68 (88.3)
Negative	7 (9.1)
Positive	2 (2.6)

left ankle, left 2nd metacarpophalangeal and 3rd proximal interphalangeal joints.

Complete blood count, ESR, CRP, complete urinalysis, and biochemical parameters were normal. ANA was positive in the homogenous pattern (1/100-1/320 titration); anti-dsDNA was positive and AHAs were negative, complement levels were normal. The patient was potentially considered to have ATIL due to the presence of arthritis in the small joints of the hand and positive antibody results. Infliximab was shifted to prednisolone 15 mg/day. Seventeen months after drug discontinuation, anti-dsDNA and ANA became negative. The steroid dose was reduced and stopped approximately 18 months after the diagnosis of ATIL. The patient is under follow-up in remission under NSAID.

Case 3: A 47-year-old female patient with a 17-year history of AS, was hospitalized with the complaints of fever, morning stiffness lasting almost all day, severe neck and low back pain also pain in the right thigh and hip.

She was treated with infliximab 5mg/kg/6 weeks and indomethacin for 7 years. Her right thigh diameter was 3 cm higher than her left thigh. There were rales in the right middle-lower section of the lungs. Laboratory investigation demonstrated: elaveted ESR and CRP, leukocytosis, positive ANA in homogenous and granular pattern (>1/3200), positive anti-dsDNA and negative AHAs and aCL, normal lupus anticoagulant and complement levels. Methicillin-resistant staphylococcus aureus growth was observed in blood culture. A chest X-ray showed an infiltrative appearance in the right middle-lower section. Venous doppler ultrasonography (USG) of the right lower extremity revelaed hypoechogenic thrombus patches in the femoral vein. Abdominal CT revealed splenomegaly and free fluid in the Douglas space. Thoracic CT showed infectious bronchiolitis and bilateral pleural effusion. Deep vein thrombosis, fever, pleuritis and peritoneal fluid accumulation, positive ANA and anti-dsDNA values, occurring during the use of Infliximab, resulted in diagnosis of ATIL. Infliximab treatment was discontinued, anticoagulant and 30 mg/day prednisolone was started. Antibioterapy was added for treatment of lung infection. Since disease activity increased and at 6 months of drug discontinuation, antibody profile illustrated negative results, Adalimumab 40 mg/2 weeks treatment was started. ATIL due to adalimumab did not develop, but the patient died about a year later due to septicemia.

Case 4: A 48-year-old female patient presented with complaints of inflammatory low back pain 8 years ago. There was no significant finding other than psoriathic skin lesions in her systemic examination. Skin biopsy performed in dermatology was reported as "psoriasis vulgaris". The patient, who was ANA and HLA B-27 negative, showed bone marrow edema in the left sacroiliac joint in the sacroiliac MRI and was followed up with the diagnosis of Psoriatic Artritis. Methotrexate 15 mg/week was started but was stopped due to nausea and intolerance. Due to the increase in psoriatic skin lesions, leflunamide 20 mg/day was started.

Table 2: Side Effects Properties

	n=20
Side effect due to anti-TNF-α n (%)	
Hipersensitivity reaction	5 (25)
ATIL	4 (20)
Skin reactions	3 (15)
Infection	2 (10)
Non-infectious uveitis	2 (10)
Tuberculosis	1 (5)
Malignancy	1 (5)
Hepatic reaction	1 (5)
Tromboembolic reaction	1 (5)
Anti-TNF-α responsible for the side effect n (%)	
Infliximab	10 (50)
Adalimumab	5 (25)
Etanercept	2 (10)
Sertolizumab	2 (10)
Golimumab	1 (5)

The patient received psoralen plus ultraviolet light (PUVA) treatment for skin lesions, but when there was no improvement, adalimumab 40 mg / 2 weeks was added to her treatment. 16 months ago. She was in our follow-up with low disease activity. When she came to the last control, she had a malar rash on her face. ANA and anti-dsDNA were positive. AHAs negative, complement levels were normal. Skin biopsy result as "Histomorphological findings include aspects consistent with SLE." Considering ATIL, adalimumab was discontinued in the patient and prednisolon 20 mg/day was added to leflunamid. The patient is still under our follow-up.

Discussion

Anti-TNF-α treatments are a group of drugs that are being used effectively in the treatment of SpA. This group of drugs has side effects such as injection or infusion site reactions, hepatotoxicity, opportunistic infections, congestive heart failure, and malignancies such as lymphoma, as well as some paradoxical side effects such as ATIL, vasculitis, psoriasis, demyelinating diseases, sarcoidosis, uveitis, optic neuritis, autoimmune hepatitis, and interstitial lung disease (9). Various side effects occurred in 20 (25.97%) of 77 patients examined in this study who received anti-TNF-α therapy for Axial SpA.

While the exact mechanism is not clear yet, several hypotheses have been suggested about ATIL. The first is the "cytokine shift" which indicates suppression of the Th1 cells by such drugs and thus occurrence of an excessive Th2 response. The second hypothesis is the predisposition of the patients, who use these drugs, to bacterial infection, and associated auto-antibody formation (7). Another hypothesis is based on the effect via CD44 molecule and its expression is enhanced by TNF-α. Anti-TNF-α drugs lead to reduction both in the expression of the CD44 molecule and in the clearance of apoptotic cells, thereby releasing nucleosomal auto-antibodies and forming anti-dsDNA (10). Slow acetylator status, HLA-DR2, HLA-DR3, HLA-DR4 and complement factor C4 null allele are risk factors for DILE, too (11).

Most of the patients with ATIL are observed to have rheumatoid arthritis (RA) and Crohn's disease (6,7). In a series of 92 patients with lupus-like symptoms induced by anti-TNF-α drugs, only four patients had axial SpA while the majority had RA (12). The low incidence in SpA is attributed to the absence of circulating autoantibodies in these patients (11). While it is reported to be rarer, all four of our patients had axial SpA.

In the series of 92 patients who developed ATIL, which we mentioned earlier, Infliximab was responsible for 44% of the patients, Etanercept for 40% and Adalimumab for 16% (11). In another study, the incidence of ATIL was reported to be 0.10% for Adalimumab, 0.18% for Etanercept, and 0.19-0.22% for Infliximab (13). In one study, it was stated that the clinical features of ATIL appeared after an average of 19 months of anti-TNF-α therapy, but the primary diagnosis of these patients was Chron (14).

Table 3: Clinical Characteristics of Patients with Anti-TNF-α-Induced Lupus

	Case-1	Case-2	Case-3	Case-4
Age	49	35	47	48
Sex	Male	Female	Female	Female
Disease	Axial SpA	Axial SpA	Axial SpA	Axial SpA
Duration of anti-TNF-α treatment before ATIL	6 years	7 years	17 years	16 months
The drug responsible for ATIL	Adalimumab	Infliximab	Infliximab	Adalimumab
ANA before anti-TNF- α	Unknown	Unknown	Negative	Negative
ATIL symptoms	Acute mesenteric thrombosis, fever, pleuritis	Arthritis in the small joints of the hand	Deep vein thrombosis, fever, pleuritis, peritoneal fluid accumulation	Malar rash
ANA	Positive in a weak granular pattern (<1/100 titration)	Positive in the homogenous pattern (1/100-1/320 titration)	Positive in homogenous and granular pattern (>1/3200)	Positive in the homogenous pattern (1/320-1/3200 titration)
Anti-dsDNA	Positive	Positive	Positive	Positive
AHAs	Negative	Negative	Negative	Negative
Complement	Normal	Normal	Normal	Normal
Anti-TNF-α withdrawal	Yes	Yes	Yes	Yes
Treatment	Prednisolon 20 mg/day	Prednisolon 15 mg/day	Prednisolon 30 mg/day	Prednisolon 20 mg/day
Resolution of ATIL symptoms	7 months	16 months	6 months	Following up
Alternative with anti-TNF-α blockers	No	No	Adalimumab 40 mg/2 weeks, no ATIL symptoms, but died due to septicemia	No

The first case we presented was using Adalimumab for 6 years, the second case was using Infliximab for 5 years, the third one was using Infliximab for 7 years, and the fourth was using Adalimumab for 16 months. None were using Etanercept. These periods are observed to be quite long compared to the overall average times. Although this suggests that ATIL may occur later in axial SpA, larger case series examining only patients with SpA are needed.

Common findings also vary depending on the Anti-TNF-α drug causing ATIL. For example, cutaneous findings are most common in etanercept-induced ATIL, while serositis is more common in patients receiving infliximab treatment (15). Our third case was also using infliximab and developed serositis, which was consistent with the literature.

Reviewing the DILE laboratory values, positive ANA is reported at a rate of 95% and AHAs are observed at a rate of 90% (16). ATIL is different from the classical DILE in terms of certain features. Skin findings, positive anti-dsDNA, and hypocomplementemia are more common and major organ involvement is rarer in ATIL than DILE due to other drugs. AHAs are described in classic DILE more often than in ATIL (>95% versus 57%, respectively) (17).In all four cases we presented, anti-

dsDNA values were positive, similar to those reported previously, and differently, none of them had hypocomplementemia. Although skin findings were more common in ATIL, malar rash was present only in our fourth case.

Two types of ATIL were described based on the severity of the clinical symptoms: the first is the mild form that doesn't require treatment discontinuation, involves arthralgia, myalgia and can be treated with NSAIDs or analgesics while the second is the severe form that cannot be managed with NSAIDs alone, corticosteroids and other immunosuppressant agents such as methotrexate, or cyclophosphamide should be recommended for patients with polyserositis, leukopenia, thrombocytopenia, thrombotic event, hypocomplementemia, unknown-cause fever, and neuropsychiatric lupus (18). In a previously mentioned study, it was stated that lupus-like symptoms disappeared after discontinuation of the drug in most of the cases, 40% of the patients received additional corticosteroids, and 12% needed additional immunosuppressive therapy (13). In our case series, all patients except the second patient had severe ATIL, but we discontinued anti-TNF-α treatment and started immunosuppressive therapy in four patients appropriate to their clinical condition.

It was reported that ANA and anti-dsDNA values turn to normal within a mean of 1 month to 2 years following diagnosis of DILE and drug discontinuation (18). In our cases, ANA and anti-dsDNA values returned to negative values 7 months after the diagnosis in our first patient, 17 months in our second patient, and 6 months in the third. Our fourth case is still in the follow-up phase.

After resolution of all clinical symptoms or resolution of lupus serology, one of the most important questions in ATIL therapy is whether it would be safe to switch to an alternative anti-TNF-α in these patients. There are no high-quality studies, but there are several case series published on this subject (18-20). In a series of 20 patients, fourteen were switched to an alternative anti-TNF-α agent, and only one of these patients ATIL has developed again (21). It was stated that Infliximab and Adalimumab were the responsible drugs in all of these 20 patients. In an article examining 14 cases that developed ATIL, an alternative Anti-TNF-α agent was used in 5 cases and no new adverse effects were observed in 4 cases, whereas ATIL recurrence was reported in one patient (19). In this study, the time to start another anti-TNF-α agent ranged from 2 months to 38 months. According to clinical and laboratory results, we only had to switch to another anti-TNF-α in the third patient and ATIL recurrence was not seen; however, this case died of another cause such as septicemia.

Our study examines in depth four patients with axial SpA, where ATIL is rarely seen, so we think that it will make an important contribution to this field. On the other hand, being retrospective is one of the limitations of our study, and prospective studies with larger patient populations are needed, in which the long-term results of switching to other anti-TNF-α agents are also examined.

In conclusion, while anti-TNF-α is an effective and common treatment option in SpA patients, one should keep in mind that these patients may develop ATIL; and in case of small joint involvement in SpA patients without peripheral joint involvement or in the presence of lupus findings, such as malar rash, thrombotic events or serositis patients should be carefully monitored.

Conflicts of interest: The authors declare no conflict of interest.

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