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CASE BASED REVIEW

Diverse patterns of anti-TNF-α-induced lupus: case series and review of the literature

Ora Shovman[1,2] · **Shalev Tamar**[3] · **Howard Amital**[1,2,4] · **Abdulla Watad**[1,2,4] · **Yehuda Shoenfeld**[1,4,5]

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Abstract The induction of autoantibodies is common following therapy with anti-TNF-α agents. However, anti-TNF-α-induced lupus (ATIL) is rare. We assessed the clinical characteristics of three patients with inflammatory bowel disease (IBD) who were treated with infliximab and developed distinct subsets of ATIL. Also, we searched for similar cases in the published literature. We describe three patients with ATIL. The first patient had a classical drug-induced lupus (DIL) presented by thrombocytopenia that resolved after infliximab discontinuation. The second case experienced symmetric polyarthritis of 14 joints in rheumatoid arthritis (RA)-like distribution accompanied by lymphopenia. The third one had a severe serositis including ascites and pleural and pericardial effusions along with pancytopenia. In this patient, ATIL coexisted with anti-TNF-α-induced hepatitis. The second and third patients met the American College of Rheumatology classification criteria for SLE. Nevertheless, all three cases exhibited ANA and anti-dsDNA positivity, and only the second patient had anticardiolipin (aCL IgG) and anti-histone antibodies. The coexistence of both lupus-like syndrome and hepatitis following anti-TNF-α therapy in the same patient is very rare, and to the best of our knowledge, only four such case reports are mentioned in literature. Patients with mild ATIL may tolerate another anti-TNF-α agent without recurrence of the disease. Rheumatologists should be aware of the distinct clinical presentations of ATIL and its coexistence with other rare anti-TNF-alpha complications such as hepatitis.

Keywords Anti-TNF-induced lupus (ATIL) · Autoantibodies · Hepatitis · Lupus · TNF-α blockers

Introduction

Anti-TNF-α therapies are widely used in a variety of inflammatory diseases including rheumatoid arthritis (RA), psoriatic arthritis (PA), ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), and inflammatory bowel disease (IBD). This group of drugs includes infliximab, etanercept, adalimumab, and more recently, certolizumab pegol and golimumab. The serious adverse effects of these agents are immunogenicity along with infections and reactivation of tuberculosis.

Anti-TNF-α agents are known to induce autoimmunity in the form of antinuclear antibodies and/or anti-dsDNA antibodies [1–4]. It has been shown that these drugs may induce new onset ANA positivity in previously ANA-negative patients or increase ANA titers in previously positive ANA patients [3]. For instance, a high prevalence of ANA and anti-dsDNA antibodies was found in 53 and 35% of patients with Crohn's disease (CD) respectively, following treatment with infliximab [5].

Despite the high prevalence of autoantibodies production, anti-TNF-α-induced lupus (ATIL) is rare. Hence, post marketing studies have shown that the estimated incidence of

Ora Shovman and Shalev Tamar contributed equally to this work.

✉ Yehuda Shoenfeld
shoenfel@post.tau.ac.il

[1] Zabludowicz Center for Autoimmune Diseases, Chaim Sheba Medical Center, 52621 Tel-Hashomer, Israel

[2] Department of Medicine 'B', Sheba Medical Center, Tel-Hashomer, Israel

[3] Department of Gastroenterology, The E. Wolfson Medical Center, Holon, Israel

[4] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[5] Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel

ATIL was 0.19–0.22% for infliximab, 0.18% for etanercept, and 0.10% for adalimumab [1, 6]. Furthermore, golimumab and certolizumab were also reported to induce ATIL in a manner similar to that of other anti-TNF-α agents [7, 8]. According to the latest update of the Spanish Study Group of Biological Agents in Autoimmune Diseases (BIOGEAS), only 140 cases with lupus-like syndrome have been reported following treatment of millions of patients with biologic drugs including TNF-α blockers [9]. Likewise, cases of ATIL in IBD patients treated either with infliximab [10, 11] or adalimumab [12, 13] have been rarely reported.

However, the true incidence of ATIL is yet unknown due to the paucity of data and the lack of unique definition for this relatively new clinical entity [14].

In this report, we present three females with inflammatory bowel disease (IBD) who were treated with infliximab and developed distinct clinical subsets of lupus. The first patient had a classical drug-induced lupus (DIL). The second and third patients met the American College of Rheumatology (ACR) classification criteria for a full-blown SLE. Additionally, in the third patient, ATIL coexisted with anti-TNF-α-induced hepatitis.

Our aim is to draw attention to the variety of the clinical symptoms in ATIL, because it may occasionally be a severe disease and cause diagnostic and therapeutic difficulties.

Patient description

Case 1

A 14-year-old female patient, bearer of ulcerative colitis (UC) for 2 years, presented with persistent thrombocytopenia of 72,000/mm^3, ANA of 1:320 (homogeneous nuclear pattern), and positive anti-dsDNA antibodies after 7-month therapy with infliximab.

The ANA status before infliximab treatment is unknown. The diagnosis of DIL was based on hematologic manifestations and the presence of autoantibodies. Following the discontinuation of infliximab, her thrombocytopenia resolved and she was successfully treated with adalimumab. After 2 years, the patient remained asymptomatic with no recurrence of lupus symptoms. ANA results are still positive and anti-dsDNA antibodies are undetectable.

Case 2

A 64-year-old female with CD accompanied with asymmetric oligoarthritis was treated with infliximab and parenteral methotrexate at a dosage of 15 mg per week for 11 months and was asymptomatic. The patient had no history suggestive of idiopathic SLE, and no presence of autoantibodies was reported before the initiation of the drug. Eleven months later, she developed symmetric polyarthritis of 14 joints in RA-like distribution involving the elbows, knees, MTP joints, and the PIP and MCP joints of hands. Her abnormal laboratory findings included a normochromic normocytic anemia (Hb 10.4 g/dl), lymphopenia (800/mm^3), ESR of 52 mm/h, and CRP of 15.3 mg/dl (normal range, 0–5 mg/dl). Urinalysis test and liver and kidney functions were all normal. Immunological evaluation is summarized as follows: positive serology fore ANA (1:640, homogeneous nuclear pattern), anti-histone, anti-dsDNA, and anticardiolipin antibodies (aCL IgG, confirmed by a second assay 3 months later). Serum complement levels were within normal limits. Therefore, she satisfied the ACR criteria for the classification of SLE (polyarthritis, lymphopenia, anemia, and the existence of described above autoantibodies). Treatment with infliximab was discontinued. She was treated with prednisone at a dosage of 20 mg per day, and the dosage of parental methotrexate was increased to 25 mg per week for 7 months until her polyarthritis completely resolved. Prednisone dosage was slowly tapered with a complete withdrawal after 6 months. Due to exacerbation of CD, methotrexate was stopped and azathioprine at a dosage of 150 mg per day was initiated. The patient returned for follow-up after an interval of 1 year. She did not have any symptoms of CD or SLE and her colonoscopy was normal. ANA and anti-histone antibodies remained positive.

Case 3

A 67-year-old female suffering from ulcerative colitis developed polyserositis including right side pleural effusion, pericardial effusion, and ascites detected by abdominal and chest CT and echocardiography 3 months after the initiation of infliximab. ANA was negative and liver functions were within normal limits before the treatment with the drug was started. Prior to infliximab, she was unsuccessfully treated with corticosteroids, mesalazine, and mercaptopurine. Her abnormal laboratory analysis included new onset leucopenia (WBC 3000/mm^3), neutropenia (1200/mm^3), and normochromic normocytic anemia (Hb 10.4 g/dl). Liver function tests showed a marked elevation in liver enzymes as follows: SGPT 566 u/l, SGOT 650 u/l, and GGT-800 u/l. The bilirubin, prothrombin time, and INR were all within normal ranges. Urinalysis test, kidney functions, immunoglobulins levels, serum compliment levels, and tumor markers were within normal limits. Screening for viral hepatitis (A, B, C, and E) was negative. Anti-liver-kidney microsomal, anti-mitochondrial, smooth-muscle antibodies, ANCA, and anti-soluble liver antigen antibodies were all negative. ANA (1/320, pattern unknown) and anti-dsDNA were detected. Alpha-1 antitrypsin, iron saturation, ferritin, and ceruloplasmin were within normal limits. Liver ultrasound was normal. The patient met the ACR criteria for the classification of SLE (serositis, hematological manifestations, and positive autoantibodies). Liver biopsy

was not performed owing to the rapid spontaneous improvement of liver function after infliximab cessation, even before the initiation of steroid therapy. The diagnosis of coexistence of ATIL and anti-TNF-α-induced hepatitis was determined. Under prednisone at a dosage 15 mg per day and diuretics, the pericardial effusion, pleural effusion, and ascites regressed dramatically. Liver functions normalized completely, and the leucopenia and neutropenia resolved during the following 2 months. Rectal corticosteroids and methotrexate 15 mg/week orally were started with good clinical response. The clinical characteristics of all three patients with ATIL are summarized in Table 1.

Discussion

More than 50 systemic and organ-specific autoimmune complications have been reported in patients with autoimmune conditions treated by biologic therapies [3].

Anti-TNF-α-induced lupus (ATIL) is rare but it may sometimes present with serious complications. The clinical presentation of lupus secondary to TNF-α blockers may vary, and specific diagnostic criteria have not been recognized yet.

In most reported cases, the diagnosis of ATIL was based on the criteria for classical DIL and incorporated the presence of one or more symptoms compatible with SLE, ongoing exposure to a drug known to cause DIL, no prior history of SLE, and resolution of symptoms after treatment with this drug was discontinued [15]. However, some patients treated with TNF-α blockers have developed a lupus-like syndrome similar to an idiopathic SLE that resolved after the treatment with corticosteroids and immunosuppressive drugs)1–3, 15). Thus, it was established that ATIL represents a distinct clinical entity, and later studies have defined ATIL by using the ACR classification criteria for SLE [16]. Nevertheless, this strict set of criteria led to the exclusion of ATIL in some patients receiving anti-TNF-α therapy. Therefore, for an early diagnosis, an additional set of criteria has been proposed: at least one serologic ACR criteria of SLE such as ANA or anti-dsDNA antibodies; at least one non-serologic ACR criteria, such as arthritis, serositis, hematologic disorder, or malar rash; a temporal relationship between symptoms and the initiation of anti-TNF-α therapy [1]. As of today, there is no unifying definition and different studies use different sets of criteria.

In our case series, all patients were female, had IBD, and were treated with infliximab.

Table 1 Clinical characteristics of patients with anti-TNF-α-induced lupus (ATIL)

Age (years), race	14, Caucasian	64, Caucasian	67, Caucasian
Sex	Female	Female	Female
Disease	UC	CD, oligoarthritis (resolved with initiation of IFX)	UC
Duration of IFX treatment before ATIL	7 months	11 months	3 months
Concomitant drugs	No	SC MTX 15 mg/week	No
ANA before INX	Unknown	Negative	Negative
ATIL symptoms	Thrombocytopenia of 72,000 platelets/mm^3)	Polyarthritis, lymphopenia, anemia	Pleural effusion, pericardial effusion, and ascites leucopenia (3000/mm^3), neutropenia (1200 /mm^3), anemia (Hb 10.4 mg/dl)
ATIL serology	ANA 1:320 (homogeneous pattern), anti-dsDNA	ANA 1:640 (homogeneous pattern), anti-dsDNA, anti-histone antibodies, anticardiolipin, antibodies (aCL IgG)	ANA 1:320 anti-dsDNA
Hepatitis	–	–	SGOT 650, SGPT 566, GGT-800 u/l alkaline phosphatase, bilirubin, and albumin—normal
IFX withdrawal	Yes	Yes	Yes
Treatment	No	Prednisone 20 mg/day and SC MTX 25 mg/week	Prednisone 15 mg/day
Resolution of ATIL symptoms	3 months	7 months	2 months
Resolution of hepatitis	–	–	Improvement after IFX withdrawal. Complete resolution after 2 months
Alternative with anti-TNF-α blockers	Adalimumab (2 year follow-up), no ATIL symptoms	No	No

CD Crohn's disease, *UC* ulcerative colitis, *IFX* infliximab

Disease onset ranged from 3 months to 1 year after the first drug exposure. All the patients had different hematologic involvement. The first patient had thrombocytopenia that resolved after infliximab discontinuation and therefore met the diagnostic criteria for DIL. The second patient experienced IBD arthropathy, presented as asymmetric oligoarthritis that has previously disappeared while receiving infliximab and reappeared in a distinct distribution in addition to the lymphopenia and anemia. The third patient had severe serositis including ascites and pleural and pericardial effusions along with pancytopenia. All of them exhibited ANA and anti-dsDNA positivity, and only the second patient had anticardiolipin (aCL IgG) and anti-histone antibodies. The second and third patients met ACR classification criteria for SLE.

The clinical features of ATIL in our IBD patients are similar to features reported in CD patients who developed infliximab-induced ATIL, including musculoskeletal manifestations and hematological features [10, 17–19].

Likewise, the clinical presentations of ATIL in our patients resemble those described in patients with rheumatic diseases from two large studies: a French nationwide survey and a British study based on the BSR Biologics Register (BSRBR). Notably, these studies depicted additional manifestations of ATIL such as fever, systemic features, rash, and oral ulcers that were not observed in our patients [1, 11]. Furthermore, cerebral and renal involvement has been also found in some ATIL patients. For example, neurological and renal involvement was seen in 3 and 7% of ATIL patients, respectively, in a large study conducted in Spain [3]. Moreover, a higher incidence of renal involvement (9%) was reported in a study conducted in the USA [2]. In addition, various unusual ATIL presentations such as pneumonitis, valvulitis, deep vein thrombosis, neuritis, or inflammatory myositis have been observed in isolated case reports and studies [2, 20].

Hepatotoxicity is a well-known side effect of TNF-α blockers. Asymptomatic mild to moderate elevations of liver enzymes have been often observed while severe hepatitis is very rarely reported [21]. Recently, TNF-α blockers have been considered as a potential cause for drug-induced autoimmune hepatitis (AIH) [22–26] or autoimmune-like drug-induced liver injury (DILI) [27]. Although most of the AIH reports are associated with infliximab, AIH has been also reported in patients treated with adalimumab and etanercept [25, 27]. Immune-mediated DILI is characterized by clinical, biochemical, and histological signs similar to AIH. Unlike AIH, DILI may be successfully treated by steroids with sustained remission following steroids withdrawal, and no treatment with immunosuppressive therapy is required. The differential diagnosis between AIH and immune-mediated DILI is important because they require different treatment and have a distinct disease progression and prognosis.

The occurrence of both lupus-like syndrome and hepatitis following anti-TNF-α therapy in the same patient is very rare. To the best of our knowledge, only four such case reports following treatment with infliximab were mentioned in literature [28–31]. These reports describe three patients with psoriasis [28–30] and one patient with ulcerative colitis [31]. The common feature of ATIL in all these patients was musculoskeletal manifestations. In contrast, our third patient presented with severe polyserositis and pancytopenia. All four patients in these case reports presented elevation of transaminases and emergence of autoantibodies (ANA) and have been diagnosed with a concomitant AIH. In three patients, the diagnosis of AIH was proven by liver biopsy that showed chronic lymphoplasmacytic infiltrate and interface hepatitis [28, 29, 31]. In three reports, ATIL and AIH developed simultaneously as in our third patient, and in the fourth report, hepatitis occurred first and the lupus-like syndrome appeared more than 1 year afterwards. Withdrawal of infliximab and initiation of steroids in standard dose for AIH was followed by normalization of liver function within several months in all the patients.

After negative screening for viral hepatitis, the differential diagnosis of hepatitis in our third patient included autoimmune-like DILI, AIH, or direct liver toxicity. Although liver biopsy was not performed, spontaneous improvement of the liver function after infliximab cessation with subsequent complete normalization following treatment with low dosage prednisone decreases the probability of autoimmune liver disease. As mentioned above, the hepatitis may be explained by direct drug liver toxicity [32, 33], but this condition is not normally associated with positive autoantibodies.

The treatment of ATIL as well as in severe hepatotoxicity (transaminases levels five times greater than upper limit of normal) entails withdrawal of the offending drug. ATIL symptoms usually resolve during 3 to 6 months. In some patients, corticosteroids and immunosuppressive agents might be required to achieve full resolution of ATIL [3]. Patients with DILI and drug-induced AIH following anti-TNF-α usage generally have a good response to a short-term immunosuppressive therapy without relapse. There is partial evidence concerning the safety of switching to another anti-TNF-α agent in patients with ATIL and autoimmune liver disease. Patients with mild ATIL may tolerate another anti-TNF-α agent without recurrence of lupus [34–37]. In cases of infliximab-induced AIH, switching to adalimumab or etanercept without relapse has been reported to be successful [38–40].

In conclusion, rheumatologists should be aware of the distinct clinical subsets of ATIL that may present as classical DIL or lupus-like syndrome similar to idiopathic SLE. Based on our experience and review of the literature, patients with mild ATIL may tolerate another anti-TNF-α agent without recurrence of the disease. Further investigation should be conducted regarding the safety of alternative anti-TNF-α agents in

patients that developed ATIL similar to idiopathic SLE especially if it coexisted with other anti-TNF-α complications such as hepatitis.

Compliance with ethical standards

Disclosures None.

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