

Anti-TNF- α drug-induced lupus: A Case Report

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Abstract

Background: It is expected that incidence of anti-TNF α induced lupus (ATIL) will probably increase with more widespread use of anti-tumor necrosis factor- α (anti-TNF α) agents.

Case Report: We report a rare presentation of ATIL with hepatitis for a woman who has Crohn's disease and was treated with infliximab for 9 months. She had clinical and biochemical improvement after discontinuation of infliximab and starting steroid therapy.

Conclusion: Treatment with Infliximab may cause a lupus-like syndrome, which can be reversed upon its discontinuation.

Key words: Drug-induced lupus erythematosus, anti-TNF α , hepatitis, infliximab.

Introduction

Drug-induced lupus erythematosus (DILE) is a syndrome with symptoms, signs and laboratory findings similar to idiopathic systemic lupus erythematosus (SLE). Sulfadiazine was the first medication reported to cause drug-induced lupus (1). Since then, more than 80 drugs have been implicated in the onset of DILE (2).

In 1998, the introduction of tumor necrosis factor- α blocking therapies (anti-TNF α) marked the beginning of a new era in the treatment of chronic inflammatory human diseases, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) and Crohn's disease (CD) (3). The relationship between anti-TNF α agents and DILE was confirmed by the disappearance of symptoms after withdrawal of the implicated drugs. Treatment with infliximab and etanercept has been commonly associated with drug-induced lupus erythematosus, but it is rarely related to adalimumab (4,5) as infliximab and etanercept have been widely used for relatively longer periods (6).

According to post-marketing studies, anti-TNF α induced lupus (ATIL) has an estimated prevalence of 0.19–0.22% for infliximab, 0.18% for etanercept, and 0.10% for adalimumab. Nevertheless, in randomized controlled trials, the prevalence is higher, reaching 0.78% (7).

We report a Saudi female patient, who developed drug-induced lupus erythematosus after being treated with infliximab for management of refractory Crohn's disease.

Case Report

In September 2019, a 35-year-old woman presented to the outpatient clinic in McMaster University Hospital, with malaise, body aches and polyarthralgia affecting the ankles, knees, the shoulder, elbows, and wrists.

She was diagnosed with Crohn's disease in 2004, based on consistent symptoms and colonoscopy with biopsies. Colonoscopy showed ulceration in terminal ileum with highly suggestive histology focal crypt irregularity, focal inflammatory infiltration and pyloric metaplasia. She had no past medical history apart from Crohn's disease. She reported a family history of colon cancer in her father at the age of 50 years.

Her prior medications included multiple courses of prednisone (40 mg/day) and azathioprine (150 mg/day). In May 2012, she developed a perianal abscess that was treated with antibiotics with complete response. However, in May 2018, she had recurrent perianal symptoms with perianal fistula drainage that did not respond to antibiotics. She was initiated on infliximab at standard induction and maintenance dose (5 mg/kg every 8 weeks) concurrent with ongoing azathioprine. Unfortunately, she did not respond after her induction doses with infliximab. Therapeutic drug level monitoring was sent at week 6 and was 16 AU/ml. The patient was referred to a colorectal surgeon for further management and consideration of Seton insertion.

On regular blood work conducted to monitor her while on azathioprine, serum ALT was raised to 63 U/L (normal <30 U/L). Therefore, azathioprine was withheld and her serum ALT was normalized.

In May 2019, a follow-up drug trough level of infliximab was 1.6 µg/mL. Subsequently, her infliximab dose was increased to 7 mg/kg every 6 weeks. In September 2019, she developed body aches, joint pains involving most of the small joints of her hands, wrists and large joints of lower limbs including knees and ankles.

Serologic workup revealed elevated titers of antinuclear antibodies (ANA): 1/640 (negative <1/160) and anti-double stranded (ds) DNA: 69 IU/mL (normal <7 IU/mL). Her other serological workup was negative including anti-ENA, anti-Ro, La, Sm, RNP, Scl-70, Jo1, and anti-histone. She also had elevated transaminitis with serum alanine aminotransferase (ALT) 450 U/L, aspartate aminotransferase (AST) 411 U/L, alkaline phosphatase (ALP) 106 U/L, total bilirubin 6 mg/dL, with negative serology for viral hepatitis (Anti-HAV, HBsAg, Anti-HCV).

Infliximab was discontinued and she was started on oral steroid therapy. She responded well and liver enzymes improved afterward. Our followed plan was to watch and see, monitor her liver enzymes and other relevant parameters.

Discussion

Our case presented with Crohn's disease in 2004, and was treated with azathioprine. However, in 2018, she had a recurrent perianal fistula which did not respond to treatment. Therefore, she was initiated on infliximab, after which she developed DILE.

Infliximab is a chimeric monoclonal antibody which targets TNF-α. It is efficacious in treatment of patients with Crohn's disease (8). It has been noted that treatment with infliximab is known to produce an increase of autoantibodies, but not clinical disease (10). However, the serologic workup of our patient showed elevated titers of antinuclear antibodies, associated with symptoms suggestive of SLE, i.e., body and joint pains.

In cases of CD, anti-TNFα agents have been implicated (1). In the first years after the introduction of anti-TNFα, most cases of ATIL were reported in infliximab-treated patients with RA (9-10), PsA or CD (9-11). RA and CD are the two most commonly autoimmune diseases associated with this syndrome, with a 2:1 risk for women compared with men for DILE-like syndrome (12).

Several pathogenic hypotheses have been suggested for ATIL development. Some authors suggest that it results from decreased CD44 expression, which interferes with apoptosis, affects the clearance of apoptotic neutrophils and nuclear debris by phagocytes and promotes autoantibody production against other nuclear antigens and DNA (13-18). Another hypothesis states that immunosuppression by anti-TNF increases infection rates, and in turn activates polyclonal B-lymphocytes and drives autoantibody production. A third hypothesis implies 'cytokine shift' by which anti-TNF alpha suppresses T-helper 1 immune responses and favors T-helper 2 cytokine production, IL-10, and INF-alpha, and promotes humoral autoimmunity (19-23).

Recently, it has been reported that the rate of clearance of dead cells, increased number of plasmacytoid dendritic cells, along with decreased levels of TNFα may influence who will develop autoimmunity and eventually SLE, after treatment with anti-TNFα (24).

ATIL manifestations include malaise, fever, weight loss, polyarthrititis, serositis with pleurisy and pericarditis, myositis, hematological (anemia, leukopenia), renal and neurological disorders (10). Cutaneous manifestations like skin rashes are more common in ATIL compared to DILE, whereas myalgias are more common in DILE compared to ATIL (10). The incidence of fever is similar in both diseases. ATIL can occur within months or even years after exposure. Usually full remission of symptoms follows the discontinuation of the inciting drug within weeks (1).

Some authors have suggested there should be a temporal relationship between symptoms and therapy, and at least four American Congress of Rheumatology criteria met for diagnosis of SLE (25). However, most cases do not meet

the full criteria for this diagnosis. The clinical presentations of ATIL associated with adalimumab, etanercept, and infliximab are all similar (7,9, 26).

Case series from the USA reported significant differences between classical DILE and ATIL, with regard to autoantibody profiles (10). Classical DILE was strongly associated with ANA (>99%) and anti-histone antibodies (>95%), while anti-dsDNA antibodies were essentially absent (<1%) (7). In contrast, of the 33 ATIL cases only 57% were anti-histone positive, while 90% were anti-dsDNA positive. Positive ENAs and hypocomplementemia were also more common in ATIL compared with classical DIL in the US study (10).

Currently, there are no diagnostic criteria for ATIL. However, physicians should look for the presence of one or more of the following: (i) temporal relationship between anti-TNF α and symptoms, (ii) at least one serological finding, such as ANA or anti-dsDNA compatible with American College of Rheumatology (ACR) and (iii) one non-serological finding, including arthritis, serositis, hematological disorders, malar rash compatible with ACR. In clinical practice, these findings can be considered for early diagnosis (19).

Our patient met these criteria including arthritis with high ANA, anti-dsDNA. Moreover, she had elevated transaminitis with high serum ALT. We believe that transaminitis is a part of ATIL. However, Shovman et al. (25) noted that ATIL-associated transaminitis is a rare presentation. Only one other case report of ATIL has been reported which was associated with serositis and hepatitis.

After discontinuation of Infliximab, our patient's condition improved. Ramos-Casals et al. (7) stated that discontinuation of the offending drug is usually the first action to be taken for management of DILE. In nearly all cases, this leads to resolution of symptoms. This is usually accompanied by a decrease in the levels of autoantibodies. Some cases may require further management for improving their symptoms, which includes corticosteroids, and immunosuppressive agents, like azathioprine, cyclophosphamide, methotrexate or mycophenolate.

There is limited evidence, in terms of whether patients diagnosed with ATIL can receive an alternative anti-TNF α . One study reported four out of five patients who tolerated alternative agents after discontinuation of infliximab (27).

Conclusion

Patients with Crohn's disease may develop DILE after being treated with infliximab. However, this developed condition can be reversed upon discontinuation of this agent.

References

- 1- Vasoo S. Drug-induced lupus: an update. *Lupus* 2006; 15(11): 757-61.
- 2- Vedove CD, Simon JC, Girolomoni G. Drug-induced lupus erythematosus with emphasis on skin manifestations and the role of anti-TNF α agents. *J Dtsch Dermatol Ges.* 2012; 10(12): 889–897.
- 3- Desai SB, Furst DE. Problems encountered during anti-tumour necrosis factor therapy. *Best Pract Res Clin Rheumatol* 2006;20:757–90.
- 4- Haraoui B, Keystone E. Musculoskeletal manifestations and autoimmune diseases related to new biologic agents. *Curr Opin Rheumatol* 2006; 18(1): 96-100.
- 5- van Rijthoven AW, Bijlsma JW, Canninga-van Dijk M, Derksen RH, van Roon JA. Onset of systemic lupus erythematosus after conversion of infliximab to adalimumab treatment in rheumatoid arthritis with a pre-existing anti-dsDNA antibody level. *Rheumatology* 2006; 45(10): 1317-9.
- 6- Arnaud L, Mertz P, Gavand PE, Martin T, Chasset F, Tebacher-Alt M, Lambert A, Muller C, Sibilia J, Lebrun-Vignes B, Salem JE. Drug-induced systemic lupus: revisiting the ever-changing spectrum of the disease using the WHO pharmacovigilance database. *Ann. Rheum. Dis.* 2019;78(4):504-508.
- 7- Ramos-Casals M, Roberto-Perez-Alvarez C, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by biological agents: a double-edged sword? *Autoimmun Rev* 2010; 9:188–193.
- 8- Klapman JB, Ene-Stroscu D, Becker MA, Hanauer SB. A lupus-like syndrome associated with infliximab therapy. *Inflamm Bowel Dis* 2003;9:176–8.
- 9- Favalli EG, Sinigaglia L, Varenna M, Arnoldi C. Drug-induced lupus following treatment with infliximab in rheumatoid arthritis. *Lupus* 2002;11:753–5.
- 10- Costa MF, Said NR, Zimmermann B. Drug-induced lupus due to anti-tumor necrosis factor alpha agents. *Semin Arthritis Rheum* 2008;37:381–7.
- 11- Sarzi-Puttini P, Ardizzone S, Manzionna G et al. Infliximab-induced lupus in Crohn's disease: a case report. *Dig Liver Dis* 2003;35:814–17.
- 12- Moulis G, Sommet A, Lapeyre-Mestre M, Montastruc JL. Is the risk of tumour necrosis factor inhibitor-induced lupus or lupus-like syndrome the same with monoclonal antibodies and soluble receptor? A case/non-case study in a nationwide pharmacovigilance database. *Rheumatology (Oxford)*. 2014, Vol. 10, 53: 1864-1871.
- 13- Kang M-J, Lee Y-H, Lee J. Etanercept-induced systemic lupus erythematosus in a patient with rheumatoid arthritis. *J Korean Med Sci.* 2006;21(5):946–949.
- 14- Cairns AP, Duncan MK, Hinder AE, et al. New onset systemic lupus erythematosus in a patient receiving etanercept for rheumatoid arthritis. *Ann Rheum Dis.* 2002;61(11):1031–1032.
- 15- Hart SP, Dougherty GJ, Haslett C, et al. CD44 regulates phagocytosis of apoptotic neutrophil granulocytes, but not apoptotic lymphocytes, by human macrophages. *J Immunol.* 1997;159(2):919–925.

- 16- Eriksson C, Engstrand S, Sundqvist KG, et al. Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. *Ann Rheum Dis.* 2005;64(3):403–407.
- 17- Bickerstaff MC, Botto M, Hutchinson WL, et al. Serum amyloid P component controls chromatin degradation and prevents antinuclear autoimmunity. *Nat Med.* 1999; 5(6):694–697.
- 18- Lorenz HM, Herrmann M, Winkler T, et al. Role of apoptosis in autoimmunity. *Apoptosis.* 2000;5(5):443–449.
- 19- Williams EL, Gadola S, Edwards CJ. Anti-TNF-induced lupus. *Rheumatology (Oxford).* 2009;48(7):716–720.
- 20- Gonnet-Gracia C, Barnetche T, Richez C, et al. Anti-nuclear antibodies, anti-DNA and C4 complement evolution in rheumatoid arthritis and ankylosing spondylitis treated with TNF-alpha blockers. *Clin Exp Rheumatol.* 2008;26(3):401–407.
- 21- Singh VK, Mehrotra S, Agarwal SS. The paradigm of Th1 and Th2 cytokines: its relevance to autoimmunity and allergy. *Immunol Res.* 1999;20(2):147–161.
- 22- Romagnani S. Th1/Th2 cells. *Inflamm Bowel Dis.* 1999;5(4):285–294.
- 23- Maczynska I, Millo B, Ratajczak-Stefanska V, et al. Proinflammatory cytokine (IL-1beta, IL-6, IL-12, IL-18 and TNFalpha) levels in sera of patients with subacute cutaneous lupus erythematosus (SCLE). *Immunol Lett.* 2006;102(1):79–82.
- 24- Xu Y, Zhuang H, Han S, Liu C, Wang H, Mathews CE, Massini J, Yang L, Reeves WH. Mechanisms of Tumor Necrosis Factor α Antagonist-Induced Lupus in a Murine Model. *Arthritis Rheumatol.* 2015, Vol. 1, 67: 225-37.
- 25- Shovman O, Tamar S, Amital H, Watad A, Shoenfeld Y. Diverse patterns of anti-TNF- α -induced lupus: case series and review of the literature. *Clinical Rheumatology*, 2018; 37(2): 563-568.
- 26- De Bant M, Sibilia J, Le Loet X, et al. Systemic Lupus Erythematosus Induced by Anti-Tumour Necrosis Factor Alpha Therapy: A French National Survey. *Arthritis Res Ther* 2005;7(3):R545-51.
- 27- Wetter DA, Davis MDP. Lupus-like syndrome attributable to antitumor necrosis factor alpha therapy in 14 patients during an 8-year period at Mayo Clinic. *Mayo Clinic Proc.* 2009 Nov;84(11):979–984.