

Tumor Necrosis Factor α Inhibitor–Induced Lupuslike Syndrome in a Patient Prescribed Certolizumab Pegol

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PRACTICE POINTS

- Tumor necrosis factor α (TNF- α) inhibitor–induced lupuslike syndrome (TAILS) is a form of drug-induced lupus specific to patients on anti-TNF- α therapy.
- The underlying mechanism of disease development is unique compared to other types of drug-induced lupus.
- TAILS most commonly is associated with the use of infliximab and etanercept but also has been reported with adalimumab, golimumab, and certolizumab pegol.

To the Editor:

Tumor necrosis factor α (TNF- α) inhibitor–induced lupuslike syndrome (TAILS) is a newly described entity that refers to the onset of subacute cutaneous lupus erythematosus (SCLE) during drug therapy with TNF- α antagonists. The condition is unique because it is thought to occur via a separate pathophysiologic mechanism than all other agents implicated in the development of drug-induced lupus erythematosus (DILE). Infliximab and etanercept are the 2 most common TNF- α antagonists associated with TAILS. Although rare, adalimumab, golimumab, and certolizumab pegol have been reported to induce this state of autoimmunity. We report an uncommon presentation of TAILS in a patient taking certolizumab pegol with a brief discussion of the pathogenesis underlying TAILS.

A 71-year-old woman presented to the dermatology clinic with a rash located on the arms, face, and trunk that she reported as having been present for months. She had a medical history of rheumatoid arthritis and currently was receiving certolizumab pegol injections. Physical examination revealed erythematous patches and plaques with overlying scaling and evidence of atrophic scarring on sun-exposed areas of the body. The lesions predominantly were in a symmetrical distribution across the extensor surfaces of both outer arms as well as the posterior superior thoracic region extending anteriorly along the bilateral supraclavicular area (Figures 1 and 2). A 4-mm punch biopsy was obtained and sent for histologic analysis, along with a sample of the patient's serum for antinuclear antibody (ANA) testing.

Hematoxylin and eosin–stained tissue sections of the right superior thoracic lesions revealed epidermal atrophy, hyperkeratosis, and vacuolar alteration of the basal layer with apoptosis, consistent with a lichenoid tissue reaction. In addition, both superficial and deep perivascular and periadnexal lymphocytic infiltrates were observed as well as increased dermal mucin. Serologic testing was performed with a comprehensive ANA panel of the patient's serum (Table). Of note, there was a speckled ANA pattern (1:1280), with elevated anti–double-stranded DNA (anti-dsDNA) and anti–Sjögren syndrome–related antigen A (anti-SSA) (also called anti-Ro antibodies) levels. The patient's rheumatologist was consulted; certolizumab

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FIGURE 1. Erythematous patches and plaques symmetrically distributed across the extensor surfaces of the arms.

pegol was removed from the current drug regimen and switched to a daily regimen of hydroxychloroquine and prednisone. Seven weeks after discontinuation of certolizumab pegol, the patient was symptom free and without any cutaneous involvement. Based on the histologic analysis, presence of anti-SSA (Ro) autoantibodies, and the resolution of symptoms following withdrawal of anti-TNF- α therapy, a diagnosis of TAILS was made.

Subacute cutaneous lupus erythematosus, the most common subset of DILE, typically presents with annular polycyclic or papulosquamous skin eruptions on the legs; patients often test positive for anti-SSA/Ro and/or anti-Sjögren syndrome–related antigen B (also called anti-La) antibodies. Pharmaceutical agents linked to the development of SCLE are calcium channel blockers, angiotensin-converting enzyme inhibitors, thiazide diuretics, terbinafine, the chemotherapeutic agent gemcitabine, and TNF- α antagonists.^{1,2} Tumor necrosis factor α antagonists are biologic agents that commonly are used in the management of systemic inflammatory diseases such as ulcerative colitis, Crohn disease, seronegative spondyloarthropathies, and rheumatoid arthritis. Among this family of therapeutics includes adalimumab (humanized monoclonal antibody), infliximab (chimeric monoclonal TNF- α antagonist), etanercept (soluble receptor fusion protein), certolizumab pegol (Fab fraction of a human IgG monoclonal antibody), and golimumab (humanized monoclonal antibody).

Tumor necrosis factor α inhibitor–induced lupuslike syndrome most commonly occurs in women in the fifth decade of life, and it is seen more often in those using infliximab or etanercept.³ Although reports do exist, TAILS rarely complicates treatment with adalimumab, golimumab, or certolizumab.^{4,5} Due to the lack of reports, there are no diagnostic criteria nor an acceptable theory regarding the pathogenesis. In one study in France, the estimated incidence was thought to be 0.19% for infliximab and 0.18% for etanercept.⁶ Tumor necrosis



FIGURE 2. A and B, Clavicular region with erythematous papules and plaques at the base of the neck (left and right, respectively).

factor α inhibitor–induced lupuslike syndrome is unique in that it is thought to occur by a different mechanism than that of other known offending agents in the development of DILE. Molecular mimicry, direct cytotoxicity, altered T-cell gene expression, and disruption of central immune tolerance have all been hypothesized to cause drug-induced systemic lupus erythematosus, SCLE, and chronic cutaneous lupus erythematosus. Tumor necrosis factor α inhibitors, are postulated to cause the induction of SCLE via an independent route separate from not only other drugs that cause SCLE but also all forms of DILE as a whole, making it a distinctive player within the realm of agents known to cause a lupuslike syndrome. The following hypotheses may explain this occurrence:

1. *Increased humoral autoimmunity:* Under normal circumstances, TNF- α activation leads to upregulation in the production of cytotoxic CD8⁺ T lymphocytes. The upregulation of CD8⁺ T lymphocytes concurrently leads to a simultaneous suppression of B lymphocytes. Inhibiting the effects of TNF- α on the other hand promotes cytotoxic T-lymphocyte suppression, leading to an increased synthesis of B cells and subsequently a state of increased humoral autoimmunity.⁷

Patient's Laboratory Values With Complete Antinuclear Antibody Panel

Serologic test	Patient's serum values (reference range)
ESR	68 mm/h (0–30 mm/h)
C-reactive protein	0.84 mg/dL (0.02–0.50 mg/dL)
Vitamin B ₁₂	562 pg/mL (211–911 pg/mL)
Rheumatoid factor	<15 IU/mL (0–29 IU/mL)
Anti-CCP IgG/IgA	<0.5 U/mL (0.0–4.9 U/mL)
ANA (homogenous)	1:80 (<1:80)
ANA (speckled)	1:1280 (<1:80)
Anti-dsDNA	17 IU/mL (0–9 IU/mL)
Anti-RNP	0.4 AI (0.0–0.9 AI)
Anti-Smith	<0.2 AI (0.0–0.9 AI)
Anti-SCL-70	<0.2 AI (0.0–0.9 AI)
Anti-SSA (anti-Ro)	>8.0 AI (0.0–0.9 AI)
Anti-SSB (anti-La)	<0.2 AI (0.0–0.9 AI)
Anti-Jo-1	<0.2 AI (0.0–0.9 AI)
Anticentromere-B	<0.2 AI (0.0–0.9 AI)
Antichromatin IgG	<0.2 AI (0.0–0.9 AI)
QuantiFERON-TB Gold assay	Negative
HCV antibody	Nonreactive
HBV core antibody	Negative
HBV surface antigen	Nonreactive

Abbreviations: ANA, antinuclear antibody; CCP, cyclic citrullinated peptide; dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; HBV, hepatitis B virus; HCV, hepatitis C virus; RNP, ribonucleoprotein; SCL-70, scleroderma 70 kD protein; SSA, Sjögren syndrome-related antigen A; SSB, Sjögren syndrome-related antigen B.

2. *Infection*: The immunosuppressive effects of TNF- α inhibitors are well known, and the propensity to develop microbial infections, such as tuberculosis, is markedly increased on the use of these agents. Infections brought on by TNF- α inhibitor usage are hypothesized to induce a widespread activation of polyclonal B lymphocytes, eventually leading to the formation of antibodies against these polyclonal B lymphocytes and subsequently SCLÉ.⁸

3. *Helper T cell (TH2) response*: The inhibition of T_H1 CD4⁺ lymphocytes by TNF- α inversely leads to an increased production of T_H2 CD4⁺ lymphocytes. This increase in the levels of circulating T_H2 CD4⁺ lymphocytes brought on by the action of anti-TNF- α agents is thought to promote the development of SCLÉ.^{9,10}

4. *Apoptosis theory*: Molecules of TNF- α inhibitors are capable of binding to TNF- α receptors on the cell surface. In doing so, cellular apoptosis is triggered, resulting in the release of nucleosomal autoantigens from the apoptotic cells. In susceptible individuals, autoantibodies then begin to form against the nucleosomal autoantigens, leading to an autoimmune reaction that is characterized by SCLÉ.^{11,12}

Major histone compatibility (MHC) antigen testing performed by Sontheimer et al¹² established the presence of the HLA class I, HLA-B8, and/or HLA-DR3 haplotypes in patients with SCLÉ.^{13,14} Furthermore, there is a well-known association between the antinuclear profile of known SCLÉ patients and the presence of anti-SSA (Ro) antibodies.¹³ Therefore, we propose that in susceptible individuals, such as those with the HLA class I, HLA-B8, or HLA-DR3 haplotypes, the initiation of a TNF- α inhibitor causes cellular apoptosis with the subsequent release of nucleosomal and cytoplasmic components (namely that of the Ro autoantigens), inducing a state of autoimmunity. An ensuing immunogenic response is then initiated in predisposed individuals for which anti-SSA (Ro) autoantibodies are produced against these previously mentioned autoantigens.

Drug-induced SCLÉ is most common in females (71%), with a median age of 58 years. The most common site of cutaneous manifestations is the legs.¹⁵ Although our patient was in the eighth decade of life with predominant cutaneous involvement of the upper extremity, the erythematous plaques with a symmetric, annular, polycyclic appearance in photosensitive regions raised a heightened suspicion for lupus erythematosus. Histology classically involves an interface dermatitis with vacuolar or hydropic change and lymphocytic infiltrates,¹⁶ consistent with the analysis of tissue sections from our patient. Moreover, the speckled ANA profile with positive anti-dsDNA and anti-SSA (Ro) antibodies in the absence of a negative rheumatoid factor and anticyclic citrullinated peptide antibodies strongly favored the diagnosis of SCLÉ over alternative diagnoses.²

The supraclavicular rash in our patient raises clinical suspicion for the shawl sign of dermatomyositis, which also is associated with musculoskeletal pain and photosensitivity. In addition, skin biopsy revealed vacuolar alteration of the basement membrane zone and dermal mucin in both lupus erythematosus and dermatomyositis; therefore, skin biopsy is of little use in distinguishing the 2 conditions, and antibody testing must be performed. Although anti-SSA (Ro) antibodies commonly are associated with SCLÉ, there are reports involving positivity for the extractable

nuclear antigen in cases of dermatomyositis.¹⁷ Based on our patient's current drug regimen, including that of a known offending agent for SCLE, a presumptive diagnosis of TAILS was made. Following withdrawal of certolizumab pegol injections and subsequent resolution of the skin lesions, our patient was given a definitive diagnosis of TAILS based on clinical and pathological assessments.

The clinical diagnosis of TAILS should be made according to the triad of at least 1 serologic and 1 nonserologic American College of Rheumatology criteria, such as anti-SSA (Ro) antibodies and a photosensitive rash, respectively, as well as a relationship between the onset of symptoms and TNF- α inhibitor therapy.¹⁸ Both the definitive diagnosis and the treatment of TAILS can be made via withdrawal of the TNF- α inhibitor, which was true in our case whereby chronologically the onset of use with a TNF- α inhibitor was associated with disease onset. Furthermore, withdrawal led to complete improvement of all signs and symptoms, collectively supporting a diagnosis of TAILS. Notably, switching to a different TNF- α inhibitor has been shown to be safe and effective.¹⁹

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