SKIN

BRIEF ARTICLE

Dermatologic Presentation of Etanercept-Induced Lupus in Rheumatoid Arthritis

Salma Bennis, BS[1], Emily G. Deehan[1], BS, Joseph Gofman, DO[2,3], Mathew Farbman, DO, FACP[2]

[1] Nova Southeastern University Dr. Kiran C. Patel College of Osteopathic Medicine, Fort Lauderdale, Florida, USA
[2] Department of Internal Medicine, University of Miami at Holy Cross Health, Miami, Florida, USA
[3] Department of Dermatology, St. Barnabas Hospital, Bronx, New York, USA

ABSTRACT

Background Etanercept, a tumor necrosis factor-alpha (TNF-α) inhibitor, is widely used in the management of inflammatory arthropathies. While effective in modulating inflammatory responses, TNF-α inhibitors are associated with rare paradoxical immune-mediated adverse effects, including drug-induced lupus erythematosus (DILE). Although systemic manifestations of DILE in the setting of TNF-α inhibitor use have been well-established in the literature, manifestations of cutaneous etanercept-induced lupus erythematosus (EILE) remain under-reported.

Case We present the case of a 46-year-old male with a past medical history of seropositive rheumatoid arthritis (RA) who reported new onset pruritic, well-demarcated, confluent, erythematous plaques involving the distal left upper and left lower extremity in the course of treatment with etanercept. During the course of treatment, autoantibody testing identified elevated-titers for ANA, dsDNA, Ro/SS-A, and anti-histone antibodies, consistent with a diagnosis of DILE. Discontinuation of etanercept and initiation of alternative therapy led to marked improvement. A subsequent course of prednisone facilitated complete cutaneous recovery at one month following discontinuation. Subsequent labs revealed a decline in anti-histone antibodies, corroborating the diagnosis

Discussion and Conclusions A review of the literature using PubMed and Google Scholar from 1999 to 2025 identified only nine reported cases of cutaneous manifestations associated with EILE. By situating our case of cutaneous EILE within the context of existing literature, we delineate the consistent serologic and systemic findings, underscore the key cutaneous.

INTRODUCTION

Etanercept, a tumor necrosis factor-alpha (TNF-α) inhibitor, is widely used in the management of inflammatory arthropathies, including psoriatic and rheumatoid arthritis (RA). These biologic medications are protein-based therapies which target the inflammatory cascade.[1] Etanercept acts as a soluble p75 TNF receptor, binding TNF-α and TNF-β to block their inflammatory signaling.[1] Prolonged use has been linked to adverse outcomes, including the rare but well-established development of drug-induced lupus erythematosus (DILE), with 2,597 cases reported among etanercept patients to date by the U.S. Food and Drug

Administration.[2] In contrast, cutaneous etanercept-induced lupus erythematosus (EILE) remains under-reported, with only nine cases documented in the literature between 1999 and 2025. Drug-induced cutaneous lupus often resembles the presentation of its idiopathic counterpart with photo distributed, symmetric, nonscarring annular polycyclic or papulosquamous lesions, though typically in a more limited distribution.[3] Notably, cutaneous involvement is reported less frequently in EILE compared with classic DILE.[3] In this report, we present a case of cutaneous EILE, highlight its key features, and compare our findings with current literature to raise awareness of this pathology in patients undergoing rheumatologic care.

CASE REPORT

We present the case of a 46-year-old male treated with etanercept for seropositive RA who developed cutaneous lupus-like symptoms. Five years prior, his RA was poorly controlled on hydroxychloroquine 400 mg daily and low-dose prednisone, prompting the addition of methotrexate 20 mg weekly and folic acid 1 mg daily. This managed his arthralgias for two years, with flares controlled by low-dose prednisone. In February and May 2022, he had persistent arthralgias unresponsive to therapy, prompting initiation of etanercept 50 mg weekly in December 2022, with significant improvement while continuing methotrexate and folic acid.

In September 2024, the patient returned to clinic with complaints of a pruritic, well-demarcated, confluent, erythematous plaques with overlying scale involving the distal left upper (**Figure 1A**) and lower extremity (**Figure 1B**). He denied constitutional symptoms and physical examination was otherwise unremarkable. The cutaneous eruption was first diagnosed as dermatitis, and triamcinolone 0.01% cream was prescribed, relieving the pruritus. The patient was advised to continue etanercept and stop methotrexate and folic acid.

In April 2025, the patient returned with a persistent but stable rash, prompting hematologic evaluation. Results were notable for elevated dsDNA antibodies (19.0 IU/mL), elevated Ro/SS-A antibodies (149 U/mL), +ANA with homogenous pattern at titer > 1:1280, and elevated histone IgG

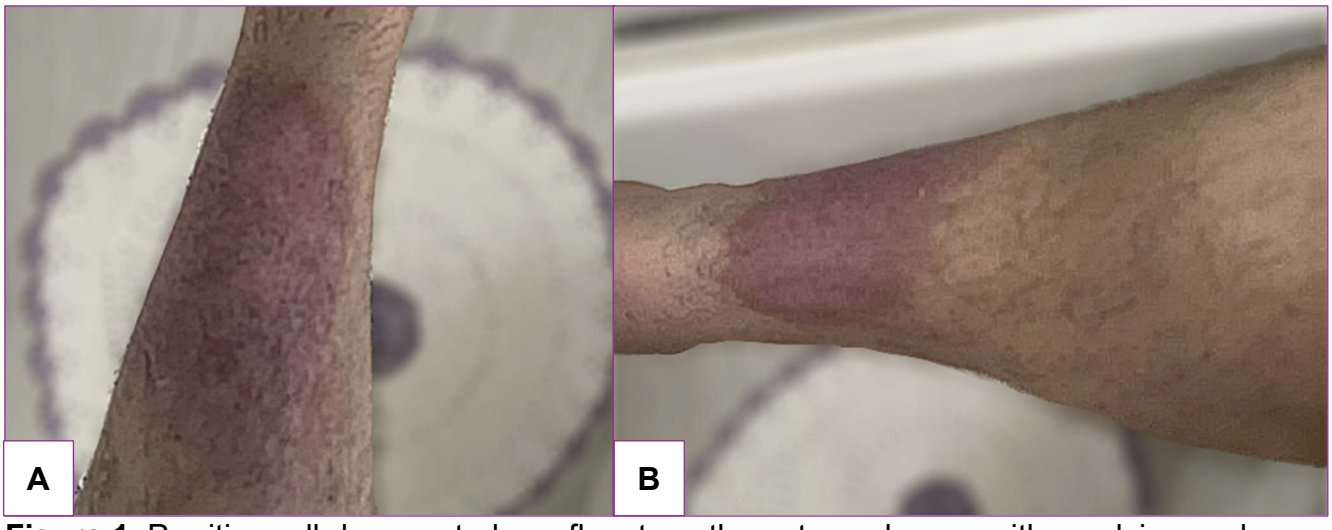

Figure 1. Pruritic, well-demarcated, confluent, erythematous plaques with overlying scale involving the **(A)** distal left upper extremity and **(B)** distal left lower extremity.

antibodies > 9.9 U. ESR (29 mm/hr) and CRP (10 mg/L) were elevated. EILE was suspected, leading to discontinuation of etanercept and initiation of once weekly 125 mg subcutaneous abatacept injections in July 2025.

At follow-up in August 2025, the patient reported tolerance of abatacept, with significant improvement in arthralgia and initial improvement in the rash. A notable decline in anti-histone IgG antibodies, from > 9.9 U (above the assay's upper limit) to 9.4 U, finalized the diagnosis of DILE. Serologies remained positive (dsDNA, Ro-SS-A, histone IgG, ANA >1:1280), with elevated CRP, ESR, and C3 consumption, suggesting an evolving lupus-like overlap syndrome. One week later, the rash nearly resolved, and arthritis symptoms subsided. The patient continued weekly abatacept, used triamcinolone ointment as needed, and started a short course of prednisone 5 mg.

DISCUSSION

A review of the literature using PubMed and Google Scholar from 1999 to 2025 identified only nine reported cases of cutaneous manifestations associated with EILE. While the association between etanercept and DILE is well-established, reports focusing specifically on cutaneous manifestations remain limited, as summarized in **Table 1**.

Table 1. Cutaneous Presentations of Etanercept-Associated Lupus: Reported Cases 1999-2025

Citation	Patient Demo-graphics	Time to Onset of DILE	Autoanti-body Testing	Cutaneous Involvement	Systemic Involvement	Treatment Attempted	Outcome Following Attempted Treatment
Santos et al. 2021	39 y.o. F with seropositive RA	2 months	+ANA +anti-dsDNA +anti-Ro/SSA low C3	pruritic photo-distributed erythematous rash in her forearms, back and chest	leukopenia, renal insufficiency	D/C etanercept, add hydroxychloroquine 200 mg 2x/day, add prednisolone 10 mg/day tapered over 6 weeks	leukopenia, renal insufficiency and skin lesions improved ANA, anti-dsDNA and complement consumption normalized
De Bandt et al. 2003	38 y.o. F with seropositive RA	3.5 months	+ANA +anti-dsDNA +anticardiolipin low C4	scattered discrete round to oval, well demarcated, scaling and erythematous	diffuse muscle pain and fatigue	D/C etanercept, add topical steroid	1 month: skin lesions cleared, active polyarthritis returned, ANA remained positive and anti-DNA

				lesions, on face and scalp			decreased (ELISA, 68 UI/ml) 8 months: biological abnormalities returned to normal value
	50 y.o. Female with active seronegative RA and family history of RA	4 months	+ANA	diffuse erythematous and purpuric skin eruption with fine scaling well demarcated red plaques on the face, with erosions and crusts involving the ear and the dorsa of fingers and the hands	lymphopenia, thrombocytopenia, elevated erythrocyte sedimentation rate, abnormal liver function test (aspartate aminotransferase: 3.5 times normal value and alanine amino-transferase: 2.5 times normal value)	D/C etanercept	5 months: skin manifestations and biological abnormalities (lymphopenia, thrombopenia and liver enzymes) resolved
Swale et al. 2003	58 y.o F with seropositive RA	12 months	+ANA +anti-dsDNA +anti-Ro/SSA low C4	DLE Scaly erythematous eruption over forearms, forehead, and right ear Eczematous eruption in photosensitive distribution over face, forearms,	none reported	D/C etanercept	4 weeks: very rapid improvement of all cutaneous abnormalities

				upper anterior chest and lower legs			
Shakoor et al. 2002	47 y.o. F with seropositive RA	3 months	+ANA +anti-dsDNA	rash on face, arms, and thighs skin biopsy confirmed discoid lupus	none reported	D/C etanercept	6 weeks: rash resolved
	39 y.o. F with RA	6 weeks	+anti-histone	diffuse facial erythema	hypertension (150/100 mm Hg), peripheral oedema, symmetric polyarthralgia of the hands and wrists	D/C etanercept	2 weeks: all symptoms resolved
	50 y.o. F with polyarthritis and symmetric synovitis of hands and wrist	5 months	+ANA +anti-dsDNA +anti-histone +anti-ribonucleoprotein +anti-smith low C3	malar rash, diffuse skin erythema developed	pleuritic chest pain	D/C etanercept	2 weeks: all symptoms resolved
Bleumink et al. 2001	54 y.o F with	4 months	+ANA +anti-dsDNA	Annular polycyclic erythemato-squamous lesions on back and front of trunk, some lesions on upper arms and legs, periungual telangiectasias of fingers	none reported	add moderate potency topical corticosteroids, no discontinuation of etanercept	6 months: rash resolved

Brion et al. 1999	78 y.o F with erosive RA	4.5 weeks	no positivities	diffuse erythematous, papular lesions skin biopsy confirmed discoid lupus	none reported	D/C etanercept, add corticosteroid	2 weeks: rash resolved
Our Case	46 y.o. M with seropositive RA	21 months	+ANA +anti-dsDNA +anti-histone +anti-Ro/SS-A	pruritic, well-demarcated, confluent, erythematous plaques with overlying scale involving the distal left upper extremity and left lower extremity	none reported	D/C etanercept, start abatacept, add prednisone	2 weeks: Initial improvement in rash Improved but still positive auto-antibody levels Increased levels of inflammatory markers Resolved leukopenia 4 weeks: Nearly complete resolution of all cutaneous manifestations

Santos et al. reports the only other case of EILE in the past two decades, detailing an RA patient with cutaneous eruptions and lupus-like serologies two months after initiating etanercept.[4] The remaining literature on cutaneous EILE dates from 1999 to 2003. Brion et al. reported a case of discoid lupus erythematosus (DLE) following etanercept initiation, and was notably seronegative.[5] Swale et al. described a patient with seropositive RA who developed worsening DLE after initiating etanercept, with similar serologic findings later reported in a case of subacute cutaneous lupus erythematosus by Bleumink et al.[6,7] De Bandt et al. reported two cases of EILE, both characterized by seropositivity and varying degrees of systemic and cutaneous involvement.[8] Shakoor et al. reported three seropositive cases of EILE with cutaneous manifestations, two of which were anti-histone antibody positive, the only such reports found in our review.[9]

Across reported EILE cases, ANA and anti-dsDNA positivity were the most consistent findings, while no clear pattern emerged for other autoantibodies (**Figure 2**). Notably, anti-histone antibodies, a well-established marker of DILE, have been shown to possess less sensitivity in the case of EILE.[10] On average, symptoms appeared 4 months after starting etanercept and resolved within 8 weeks of discontinuation. The most commonly reported adjunctive therapies

prescribed alongside drug withdrawal were topical and oral corticosteroids.

The mechanism of EILE remains unclear, but one theory suggests TNF-α inhibitors impair apoptosis, reducing clearance of nuclear debris and autoreactive cells, leading to autoantibody formation in genetically susceptible individuals.[11] This may be due to TNF-α inhibitors downregulating leukocyte CD44, which mediates phagocytic clearance of apoptotic neutrophils.[12]

Due to symptom overlap with RA, DILE is often overlooked in etanercept-treated patients presenting only with cutaneous symptoms. In our case, this was not suspected until seven months after rash onset, underscoring the need for timely recognition and greater awareness of EILE, as well as further research into its mechanisms.

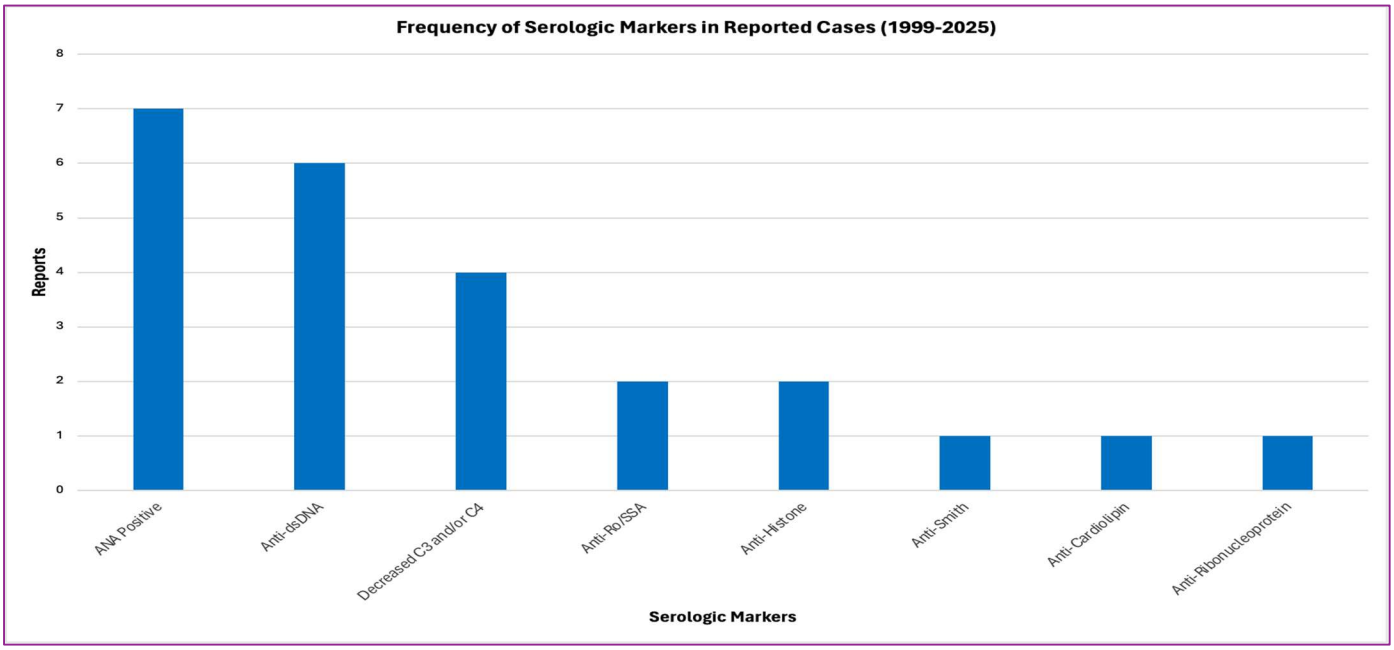

Figure 2. Frequency of Serologic Markers in Reported Cases (1999–2025)

CONCLUSION

Our case highlights the rare instance of cutaneous EILE in a patient who began therapy for RA. This patient case emphasizes the need for heightened suspicion among dermatologists when evaluating persistent, refractory, or atypical rashes in patients receiving TNF-inhibitors including etanercept. Early recognition can facilitate immediate discontinuation of the offending biologic, prevent lupus progression, and inform physicians on effective therapeutic options while remaining vigilant about the original autoimmune presentation, which in our case was RA. A multidisciplinary effort between dermatology and rheumatology is the optimal way to provide tailored care to a patient experiencing cutaneous EILE.

Conflict of Interest Disclosures: None
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Corresponding Author:
Hannah R. Riva, MD
512-897-4095
Email: Hriva0915@gmail.com

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