Clinical features of tumor necrosis factor-alpha-inhibitor induced chilblain lupus: A case series

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INTRODUCTION

Lupus erythematosus is an autoimmune disorder with variable presentations and extent of involvement, including systemic lupus erythematosus (SLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE). SLE is a multisystem disorder, with malar erythema and photosensitivity as common findings. Chilblain lupus is a rare variant of CCLE, manifesting clinically as erythematous, dusky papules on acral sites, which can be pruritic or painful. Chilblain lupus is associated with SLE in up to 20% of cases, particularly if discoid lupus plaques are present.1

Drug-induced lupus erythematosus (DILE) may present as classic drug-induced SLE, drug-induced SCLE, and rarely as drug-induced CCLE (eg, chilblain lupus). A distinct form of tumor necrosis factor (TNF)-alpha-inhibitor induced lupus has emerged.2 Chilblain lupus is an uncommon presentation of anti-TNF-alpha-induced lupus (ATIL), with 8 published cases to date.3 We present 3 cases of ATIL with chilblain lupus to add to the literature. These patients presented at least 1 year prior to the pernio-like eruption related to COVID-19.

CASE SERIES

Case 1

A 36-year-old woman with HLA-B27 spondyloarthropathy on etanercept for 10 weeks presented with 2 weeks of painful and pruritic lesions involving the fingers and oral mucosa. The patient had pleuritic chest pain, Raynaud disease, and cytopenia. There were 2-3-mm light pink papules on multiple fingers, aphthous ulcers of the hard palate, and crusting of the nares (Fig 1). Antinuclear antibody (ANA) testing was previously negative; however, the patient seroconverted to 1:160. The anti-histone antibody level was 0.9 (reference value < 1.0). The following tests were normal: anti-double-stranded-DNA (anti-ds-DNA), complements C3 and C4, anti-Jo, Scl-70, anti-ribonucleoprotein, anti-Smith, anti-Ro and anti-La antibodies, and urinalysis.

Punch biopsy showed a superficial and deep, perivascular and periadnexal lymphocytic infiltrate, which focally obscured the dermal-epidermal junction (Fig 2).

The patient was diagnosed with chilblain lupus induced by etanercept, which was stopped. Prednisone provided >80% symptom resolution. As it was tapered, the patient developed nasal and
oral aphthous ulcers. Hydroxychloroquine 400 mg daily and potent topical steroids controlled the cutaneous symptoms, but the patient continues to have ANA positivity, aphthosis, and joint pain.

**Case 2**

A 59-year-old woman with anticyclic citrullinated peptide-positive rheumatoid arthritis on adalimumab for over 15 years presented with a 3-week history of painful, erythematosus-to-violaceous papules and plaques on the bilateral fingertips unrelated to cold exposure. Most were on the volar and lateral edges, with some along the dorsal proximal nailfold (Fig 1). The patient’s cuticles were ragged. She denied fevers, chills, joint pain, oral ulcers, or urinary symptoms but did report tongue swelling. She was positive for ANA (1:640) and atypical anti-neutrophil cytoplasmic antibodies.

Punch biopsy revealed a superficial and deep perivascular and periadnexal lymphocytic infiltrate, and Alcian-blue stain showed mucin in the interstitial dermis (Fig 3). The superficial dermis exhibited subtle stromal alteration with no substantial papillary dermal edema.

The patient was diagnosed with chilblain lupus induced by adalimumab, which was continued because it controlled her arthritis. Cutaneous symptoms resolved with potent topical steroids andhydroxychloroquine 400 mg daily.

**Case 3**

A 33-year-old female with Behçet disease on infliximab for 7.5 years, colchicine, and methotrexate presented with a 6-month history of recurrent tender erythematos papules on the dorsal and
palmar bilateral fingers and elbows; some were ulcerated.

Biopsy showed a superficial-to-mid-dermal peri-vascular and periadnexal lymphocytic infiltrate, with focal interface changes and few necrotic keratinocytes (Fig 3). Periodic acid-Schiff with diastase stain revealed a focally thickened basement membrane. Alcian-blue stain did not show definite increased mucin.

The ANA titer was 1:640. Anti-Smith and anti-Ro antibody testing was negative.

Infliximab was continued to control Behçet disease. The cutaneous symptoms improved with hydroxychloroquine 400 mg daily and potent topical steroids.

**DISCUSSION**

Chilblain lupus may be exacerbated by cold exposure and can ulcerate. Patients often have underlying Raynaud disease. Chilblains (syn. pernio) unrelated to autoimmune disease cannot definitively be differentiated from chilblain lupus based on histopathologic criteria alone. Both can have superficial and deep lymphocytic inflammation and interface dermatitis. However, substantial interface dermatitis may be seen in chilblain lupus. Whether the presence of interface dermatitis is a clue of chilblain lupus as opposed to ATIL remains unclear. This question may be answered as additional cases of ATIL are reported.

Persistent lesions in the absence of cold exposure may suggest chilblain lupus. When considering a diagnosis of chilblain lupus, providers should obtain a review of systems and consider laboratory evaluation of autoimmune connective tissue disease. Family history is important to exclude autosomal dominant mutations in 3 prime repair exonuclease 1, which present in childhood and may be associated with SLE. The main differential diagnosis considered for our patients was idiopathic chilblains unrelated to medications, as this can be seen with autoimmune disease.

DILE is a lupus-like syndrome occurring 1 month to 10 years after initial medication exposure. No clear-cut DILE diagnostic criteria exist. The condition can be caused by more than 100 medications. DILE mirrors its idiopathic counterparts, consisting of SLE, SCLE, and CCLE. Drug-induced SCLE is the most common. The key features of each type of DILE are summarized below.

Drug-induced SLE affects men and women equally. Although cutaneous symptoms are rare, the most common ones are photosensitivity and purpura. Serologically, ANA and anti-histone antibodies are detected in >99% and in up to 95%, respectively. Unlike idiopathic SLE, renal and neurologic manifestations are rare.2

Drug-induced SCLE affects women more than men in a 3:1 ratio. Cutaneous symptoms are seen in nearly all patients and are similar to idiopathic SCLE. Antibody positivity includes ANA (>80%), anti-Ro (>80%), and anti-La (>45%).2

ATIL affects women more than men in a 5:1 ratio. Cutaneous symptoms are seen in about two-thirds of patients, with photosensitivity being most common. Antibody positivity includes ANA (>99%) and anti-double-stranded-DNA antibody (70%-90%).2

The diagnosis of ATIL is often based on symptoms consistent with lupus erythematosus with no prior history of idiopathic lupus erythematosus, a temporal relationship with TNF-α inhibitor use (a mean of 40 weeks after initiation), and subsequent resolution after discontinuing medication. Most ATIL cases are
associated with the use of etanercept, infliximab, or adalimumab. This may be due to how long the medications have been available; etanercept and infliximab were both approved for use in the United States in 1998, while adalimumab was not approved until 2002. No cases of drug-induced lupus caused by biologic agents other than TNF-α inhibitors have been reported thus far. Systemic symptoms are similar to classic non-TNF-α DILE, although cutaneous involvement is more common in ATIL. SCLE and CCLE are more common with etanercept, while serositis and ANA positivity are more common with infliximab. Usually, the medication is stopped, and clinical and serological markers often resolve with time. However, TNF-α inhibitors can be continued if the symptoms are tolerated. Systemic treatment with steroids or immunosuppressants may be required. Our patients were treated with potent topical steroids. In case 1, the symptoms were severe enough to stop the TNF-α inhibitor, and the patient was treated with systemic steroids and hydroxychloroquine. In our other 2 cases, the underlying inflammatory conditions were well controlled. TNF-α inhibition was continued and hydroxychloroquine added.

The mechanism of ATIL might differ from that of classic DILE. One hypothesis is that TNF-α inhibitors interfere with cell apoptosis, leading to decreased clearance of nuclear debris and development of autoantibodies. Another explanation is that TNF-α inhibitors block TH1 cytokine production, causing increased levels of TH2 cytokines and autoantibodies. A third mechanism suggests that TNF-α inhibitors block cytotoxic T cells, reducing their ability to clear autoantibodies produced by B cells. Finally, as bacterial infections are increased with TNF-α inhibitors, this may lead to polyclonal B cell activation and autoantibody formation.

CONCLUSION

DILE is a clinical spectrum of systemic and cutaneous findings. ATIL is a distinct form of DILE, which presents on average 40 weeks after initiation of TNF-α inhibitor therapy. There are similar systemic findings in DILE and ATIL, although cutaneous findings are more common in ATIL. ATIL is most frequently caused by etanercept and infliximab, followed by adalimumab.

ANA and anti-dsDNA antibody positivity is common. We present 3 cases of chilblain lupus as a manifestation of ATIL, which were treated with potent topical steroids and hydroxychloroquine. Two patients continued treatment with TNF-α inhibitors, while one stopped treatment given the severity of symptoms. Dermatologists should have a high index of suspicion for this condition.

Conflicts of interest

None declared.

REFERENCES

1. Hedrich CM, Fiebig B, Hauck FH, et al. Chilblain lupus erythematosus—a review of literature. Clin Rheumatol. 2008; 27(8):949-954.
2. Dalle Vedove C, Simon JC, Girolomoni G. Drug-induced lupus erythematosus with emphasis on skin manifestations and the role of anti-TNFα agents. J Dtsch Dermatol Ges. 2012;10(12): 889-897.
3. Sifuentes Giraldo WA, Ahijón Lana M, García Villanueva MJ, González García C, Vázquez Diaz M. Chilblain lupus induced by TNF-α antagonists: a case report and literature review. Clin Rheumatol. 2012;31(3):563-568.
4. Boada A, Bielsa I, Fernández-Figuera MT, Ferrándiz C. Perniosis: clinical and histopathological analysis. Am J Dermatopathol. 2010;32(1):19-23.
5. Cribier B, Djendji N, Peltre B, Grosshans E. A histologic and immunohistochemical study of chilblains. J Am Acad Dermatol. 2001;45(6):924-929.
6. Zimmerman N, Wolf C, Schwenke R, et al. Assessment of clinical response to Janus kinase inhibition in patients with familial chilblain lupus and TREX1 mutation. JAMA Dermatol. 2019;155(3):342-346.
7. Rubin RL. Drug-induced lupus. Expert Opin Drug Saf. 2015;14(3):361-378.
8. Almoallim H, Al-Ghamdi Y, Almarghabi H, Alyasi O. Anti-tumor necrosis factor-α induced systemic lupus erythematosus. Open Rheumatol J. 2012;6:315-319.
9. Chadwick L, Zhao S, Mysler E, Moots RJ. Review of biosimilar trials and data on etanercept in rheumatoid arthritis. Curr Rheumatol Rep. 2018;20(12):84.
10. Melsheimer R, Geldhof A, Apaolaza I, Schaible T. Remicade (infliximab): 20 years of contributions to science and medicine. Biologics. 2019;13:139-178.
11. Frenzel A, Schirmann T, Hust M. Phage display-derived human antibodies in clinical development and therapy. mAbs. 2016;8(7):1177-1194.
12. Ramos-Casals M, Brito-Zerón P, Muñoz S, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. Med (Baltimore). 2007;86(4):242-251.
13. Quaresma MV, Bernardes Filho F, Oliveira FB, Rockstaller MP, Dias MF, Azulay DR. Anti-TNF-α and hydralazine drug-induced lupus. An Bras Dermatol. 2015;90(3 Suppl 1):125-129.