Subacute cutaneous lupus erythematosus and systemic lupus erythematosus associated with abatacept

Meera Tarazi, BA,[a,b,c] Kumpol Aiempanakit, MD,[b,d] and Victoria P. Werth, MD[a,b]
Philadelphia, Pennsylvania, and Songkhla, Thailand

Key words: abatacept; drug-induced lupus erythematosus; subacute cutaneous lupus erythematosus; systemic lupus erythematosus.

INTRODUCTION

Subacute cutaneous lupus erythematosus (SCLE) is a subtype of cutaneous lupus erythematosus (CLE) with distinct clinical and immunologic features. It can be associated with Sjogren syndrome and rheumatoid arthritis (RA) as well as several classes of medications. Here we present a patient with new-onset SCLE and systemic lupus erythematosus (SLE) after treatment with abatacept. There is one other case of SCLE and one of SLE associated with abatacept described in the literature.[1,2]

Abbreviations used:

ANA:	antinuclear antibodies
CLE:	cutaneous lupus erythematosus
CTLA-4:	cytotoxic T-lymphocyte—associated antigen-4
HCQ:	hydroxychloroquine
RA:	rheumatoid arthritis
SCLE:	subacute cutaneous lupus erythematosus
SLE:	systemic lupus erythematosus

CASE REPORT

This case is of a 66-year-old woman who was referred by her rheumatologist to the autoimmune dermatology clinic at the University of Pennsylvania with a widespread rash suspicious for SCLE. This pruritic eruption began in April (3 months before presentation) on her face and spread to her upper chest and the extensor surfaces of both arms. She also reported hair loss and fatigue. The patient had a longstanding history of RA, which had been previously well controlled on hydroxychloroquine (HCQ). She recently experienced worsening swelling and pain in her hands, for which she had begun treatment with abatacept 4 months before the onset of her rash. She denied starting any other new medications around that period. A skin biopsy performed a month after her rash developed found interface dermatitis. The patient had SCLE diagnosed at that time, possibly caused by abatacept, and the drug was discontinued. She received her last dose of abatacept 2 months after the onset of her rash and 1 month before presenting to our clinic. At the time of diagnosis, her rheumatologist prescribed 20 mg of oral prednisone, which was increased to 40 mg/d 1 week before being seen at our office and quinacrine, 100 mg/d, and kept her on 200 mg/d of HCQ. Her rash did not improve after 6 weeks on this regimen, and she was referred to our clinic.

The patient had a history of primary biliary cirrhosis (PBC). Her medications included bupropion, ursodiol, denosumab, and HCQ, none of which was newly initiated. On physical examination, the patient had generalized, erythematous, annular plaques and patches with scale that were present in

From the Corporal Michael J. Crescenz VAMC[a]; Department of Dermatology, University of Pennsylvania, Perelman School of Medicine[b]; Sidney Kimmel Medical College, Thomas Jefferson University[c]; and Division of Dermatology, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hatyai.[d]

Ms Tarazi and Dr Aiempanakit contributed equally to this article.

Funding sources: This work was supported by the United States Department of Veterans Affairs (Veterans Health Administration, Office of Research and Development and Biomedical Laboratory Research and Development)..

Conflicts of interest: None disclosed.

Correspondence to: Victoria P. Werth, MD, Department of Dermatology, University of Pennsylvania, Perelman Center for Advanced Medicine, Suite 1-330A, 3400 Civic Center Boulevard, Philadelphia, PA 19104. E-mail: werth@pennmedicine.upenn.edu.

JAAD Case Reports 2018;4:698-700.
2352-5126

https://doi.org/10.1016/j.jdcr.2018.03.008

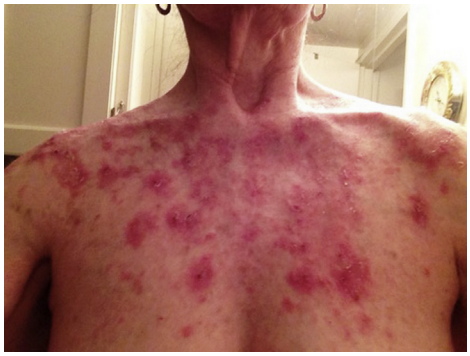

Fig 1. Clinical features of SCLE show erythematous, annular, and scaly plaques on chest.

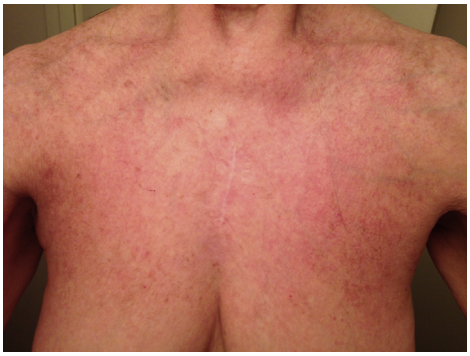

Fig 2. Clinical improvement of chest 3 months after discontinuation of abatacept and treatment with antimalarials and systemic steroids.

photodistributed areas, including the face, chest, and arms (Fig 1). Notable laboratory results included a complete blood count showing a hemoglobin level of 10.3 g/dL, hematocrit value of 32.7%, and white blood cell count of 2.4×10^3 cells/mm^3. Serology values checked 4 months before initiation of abatacept showed positive antinuclear antibodies (ANA) with a titer of 1:640 and positive anti-Smith, anti-RNP, anti-dsDNA, and antihistone antibodies. Anti-Ro/SS-A and anti- La/SS-B antibodies were not present.

At presentation to our clinic, her HCQ dose was increased from 200 mg/d to 400 mg/d, and she remained on 40 mg of oral prednisone and 100 mg/d of quinacrine. Her rash began to improve 1 month later and 3 months after discontinuation of abatacept (Fig 2). Quinacrine was successfully discontinued upon improvement of her rash, and she completed her prednisone taper 1 month later.

DISCUSSION

Drug-induced SCLE is seen in approximately 20% of patients with CLE.[3] The duration between drug exposure and onset of skin lesions ranges from 3 days to 10 years, and the resolution time after withdrawal of medication ranges between 1 week and 1 year.[3,4] In the last 10 years, there have been more reports of proton pump inhibitors inducing SCLE, as well as biological agents, especially tumor necrosis factor-α inhibitors.[3]

Abatacept is a recombinant fusion protein of cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) and human immunoglobulin, selectively inhibiting T-cell activation and proliferation, and also reducing serum immunoglobulin levels.[5] There has been 1 other report of SCLE and 1 of SLE with membranous nephropathy associated with abatacept (Table I).[1,2] Interestingly, the reported patient with SLE associated with abatacept also had PBC.[2] Although it is well established that autoimmune diseases often coexist in individuals and families, there is no reported association between PBC and SLE or PBC and CLE.[6]

The mechanism by which abatacept may induce SLE/SCLE remains unclear. In fact, initial hypotheses proposed that this drug could potentially treat lupus by suppressing T-cell activation and its downstream effects. Subsequent studies looking at the efficacy of abatacept in the treatment of lupus nephritis showed no difference in treatment response between the treatment and control groups.[7] Although the mechanism by which abatacept may induce SCLE and SLE is unknown, previous studies found that 4.8% of patients on abatacept had antibodies to the drug while on treatment, and 5.5% of patients had antibodies to the abatacept molecule after treatment was discontinued.[5] Moreover, 50% of patients who had antibodies to the CTLA-4 portion of the molecule showed neutralizing effects. CTLA-4 is an antigen expressed on T-regulatory cells, which act by interfering with the costimulatory signal between antigen-presenting cells and CD4 T cells and suppressing T-cell activation and its downstream effects. Interestingly, studies found that patients with lupus have dysregulation of their T-regulatory cells.[8] One proposed mechanism could be that our patient formed antibodies to the CTLA-4 portion of the abatacept molecule, which consequently also interfered with the CTLA-4 antigen on her T-regulatory cells, inducing SCLE and a SLE-like syndrome. This hypothesis is further supported by the fact that ipilimumab, a monoclonal antibody that targets CTLA-4, is reported to induce autoimmune disorders, including lupus nephritis and dermatomyositis.[9,10]

The optimal therapy for drug-induced SCLE is discontinuation of the culprit medication. Topical corticosteroids and topical calcineurin inhibitors can also be used in combination with systemic treatment, such as oral glucocorticoids or HCQ, as seen in our patient.[4]

Table I. Summary of reports resulting in abatacept-associated lupus erythematosus

Study	Year	Age/sex	Duration of treatment before reaction	Reaction	Histopathology	Relevant medical history	Treatment
Alrifai[1]	2015	80 M	2 doses	SCLE	Skin biopsy for DIF: granular deposition of IgG at DEJ with dusting pattern of the lower epidermis	RA (RF^+, high titer ANA)	Discontinue abatacept, topical hydrocortisone
Asami et al[2]	2016	59 F	7 mo	SLE (nephrotic syndrome, AIHA, lymphopenia, low complement, ANA 1:1280, positive anti-dsDNA)	Renal biopsy: membranous nephropathy Renal biopsy for DIF: positive for IgM and IgA	RA (RF^+), Sjogren syndrome, PBC	Discontinue abatacept, methylprednisolone with oral prednisolone

AIHA, Autoimmune hemolytic anemia; *DEJ*, dermal-epidermal junction; *DIF*, direct immunofluorescence; *HCQ*, hydroxychloroquine; *PBC*, primary biliary cirrhosis; *RF*, rheumatoid factor; *SCLE*, subacute cutaneous lupus erythematosus; *SLE*, systemic lupus erythematosus.

CONCLUSION

To our knowledge, this is the second reported case of SCLE associated with use of abatacept and the second case of drug-induced SLE, meeting the following criteria: positive ANA, anti-dsDNA, photosensitivity, and leukopenia. Skin lesions developed on this patient 4 months after starting treatment with abatacept and improved within 3 months of discontinuation under a regimen of antimalarials and systemic steroids. Given the 3 presented cases of abatacept-associated lupus, physicians should consider a potential association with triggering lupus when seen in patients taking abatacept.

REFERENCES

1. Alrifai A. Cutaneous lupus erythematosus induced by rheumatoid arthritis medication (Abatacept) [abstract]. *J Hosp Med*. 2015;10(suppl 2).
2. Asami Y, Ishiguro H, Ueda A, Nakajima H. First report of membranous nephropathy and systemic lupus erythematosus associated with abatacept in rheumatoid arthritis. *Clin Exp Rheumatol*. 2016;34:1122.
3. Laurinaviciene R, Sandholdt LH, Bygum A. Drug-induced cutaneous lupus erythematosus: 88 new cases. *Eur J Dermatol*. 2017;27:28-33.
4. Lowe GC, Henderson CL, Grau RH, et al. A systematic review of drug-induced subacute cutaneous lupus erythematosus. *Br J Dermatol*. 2011;164:465-472.
5. Blair HA, Deeks ED. Abatacept: a review in rheumatoid arthritis. *Drugs*. 2017;77:1221-1233.
6. Watt FE, James OF, Jones DE. Patterns of autoimmunity in primary biliary cirrhosis patients and their families: a population-based cohort study. *QJM*. 2004;97:397-406.
7. Furie R, Nicholls K, Cheng TT, et al. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. *Arthritis Rheumatol*. 2014;66:379-389.
8. Ohl K, Tenbrock K. Regulatory T cells in systemic lupus erythematosus. *Eur J Immunol*. 2015;45:344-355.
9. Fadel F, El Karoui K, Knebelmann B. Anti-CTLA4 antibody-induced lupus nephritis. *N Engl J Med*. 2009;361:211-212.
10. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. *PLoS One*. 2016;7:e0160221.