

Refractory Sweet's syndrome successfully treated with rituximab

Lucia Seminario-Vidal, MD, PhD, Cesar Guerrero, MD, and Naveed Sami, MD
Birmingham, Alabama

Key words: neutrophilic dermatosis; rituximab; Sweet's syndrome.

INTRODUCTION

Sweet's syndrome (SS) is a neutrophilic dermatosis characterized by an abrupt onset of painful erythematous cutaneous lesions that have a neutrophilic infiltrate typically located in the papillary dermis. Fever and an elevated neutrophil count can accompany the cutaneous manifestations. Systemic corticosteroids are the mainstay of treatment, although steroid-sparing agents are frequently co-administered or substituted. We report a case of a white man in his 60s who had a 5-year history of SS refractory to various conventional treatments. Rituximab, a potent B-cell-depleting anti-CD20 monoclonal antibody, was initiated and resulted in a dramatic improvement.

CASE REPORT

A 60-year-old white man presented to our clinic with a history of abrupt onset of painful plaques with overlying pustules on the knees, upper extremities, and inner thighs (Fig 1). He did not have any associated systemic symptoms. Biopsies found a diffuse neutrophilic infiltrate with cellular debris and edema within the papillary dermis (Fig 2). Results of immunofluorescence studies; other autoimmune diagnostic testing, including autoantibodies to gliadin and transglutaminase; and special stains for microorganisms (fungal, bacterial, acid-fast bacilli) were normal. Although the patient did not have clinical findings consistent with rheumatoid arthritis (RA), laboratory studies found positive serologies for RA, including rheumatoid factor (RF) of 238 U/mL (normal, <20 U/mL) and anticyclic citrullinated peptide antibodies (anti-CCP) of 125 units (normal, <19 units). Age-appropriate malignancy workup and evaluation for other systemic disorders were normal. The clinical and histopathologic findings suggested

Abbreviations used:

IL:	interleukin
PG:	pyoderma gangrenosum
RA:	rheumatoid arthritis
SS:	Sweet's syndrome
TNF:	tumor necrosis factor

the diagnosis of SS. SS was confirmed after the patient was treated with prednisone (1 mg/kg) and dapsone (100 mg/d), and his lesions cleared within a few weeks of therapy.

When prednisone was tapered, he had an exacerbation of his cutaneous SS. Dyspnea also developed, which was initially attributed to the anemia from dapsone. As the dyspnea worsened, he was evaluated by the pulmonology department and was found to have interstitial lung disease. Over the next year, dapsone was discontinued, and the patient did not respond to colchicine (0.12 mg/d) and mycophenolate mofetil (2.5 g/d). Joint pain developed, and RA was diagnosed by his rheumatologist. He subsequently did not respond to hydroxychloroquine (400 mg/d), and developed side effects to both etanercept and adalimumab. Because he was still on prednisone, 20 mg/d, and given his history of RA and interstitial lung disease, he was treated with rituximab (RA protocol, ie, 1000 mg at days 1 and 15).¹ Four months after his initial rituximab treatment, the patient was able to taper his prednisone to 4 mg/d without any relapse of his cutaneous SS along with improvement of his dyspnea. Because of exacerbations of his arthritis, he received 2 additional cycles of rituximab at 6 months and 18 months after the initial dose. His cutaneous and pulmonary symptoms continue to remain under control 22 months after his initial rituximab treatment (Fig 3).

From the Department of Dermatology, University of Alabama at Birmingham.

Funding sources: None.

Conflicts of interest: None declared.

Correspondence to: Naveed Sami, MD, Department of Dermatology, EFH 414, 1530 3rd Ave S, Birmingham, AL 35294. E-mail: nsami@uabmc.edu.

JAAD Case Reports 2015;1:123-5.

2352-5126

© 2015 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<http://dx.doi.org/10.1016/j.jidcr.2015.03.002>



Fig 1. Sweet's syndrome. Scattered erythematous plaques with overlying pustules on the left knee.

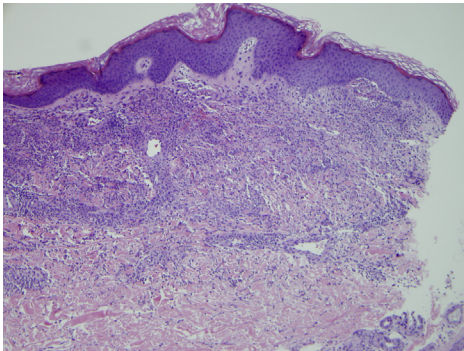


Fig 2. Spongiosis and a diffuse neutrophilic infiltrate with cellular debris and edema within the dermis. (Hematoxylin-eosin stain; original magnification, $\times 40$.)

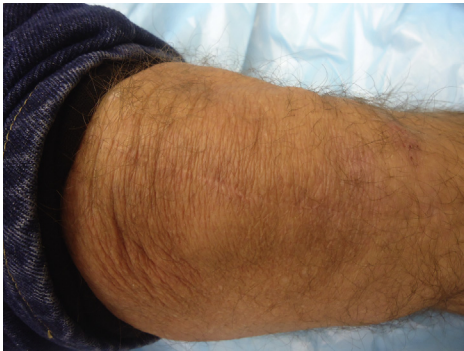


Fig 3. Left knee 22 months after initial rituximab dose.

DISCUSSION

SS, or acute febrile neutrophilic dermatosis, is a cutaneous disorder initially described in 1964 by Dr Robert Sweet.² The diagnosis of SS is established by the presence of 2 major and 2 minor criteria.³ Major criteria include (1) abrupt onset of painful erythematous plaques or nodules, occasionally with vesicles, pustules, or bullae and (2) a neutrophilic infiltrate in the dermis without leukocytoclastic vasculitis. Minor criteria include (1) preceding nonspecific respiratory or gastrointestinal tract infection or vaccination or

association with inflammatory disease, hemoproliferative disorder, solid malignant tumor, or pregnancy; (2) constitutional symptoms and fever; (3) leukocytosis; and (4) excellent response to treatment with systemic corticosteroids.³

Several therapies have been described for the management of SS. In addition to high-dose systemic corticosteroids (1 mg/kg/d), colchicine and potassium iodide are first-line treatment options.⁴ Second-line therapies include nonsteroidal anti-inflammatory drugs (eg, indomethacin, naproxen, sulindac), dapsone, clofazimine, cyclosporine, and thalidomide. There are reports of efficacy with methotrexate, danazol, interferon- α , intravenous immunoglobulins, and etetrinate.⁴ Lastly, biologics, including anakinra and anti-tumor necrosis factor (TNF)- α agents, are therapeutic alternatives.^{4,5} Infliximab, adalimumab, and etanercept are used mainly in patients with an associated inflammatory disease, such as inflammatory bowel disorder or RA.⁴ However, TNF- α inhibitors have also been implicated in drug-induced SS,⁶ and their use remains controversial.

This case shows that rituximab could be a treatment option for recalcitrant SS. Rituximab is a chimeric monoclonal antibody against CD20 that causes B-cell depletion. Although it was originally developed for the treatment of B-cell malignancies,^{7,8} it is also US Food and Drug Administration approved for the treatment of RA.⁹ The first case report of successful therapy of RA with rituximab was in a patient with B-cell lymphoma and erosive arthritis who became free of musculoskeletal symptoms and joint inflammation.¹⁰ Subsequent randomized, controlled studies showed response rates in RA between 50% and 85%.^{1,11} It has been proposed that rituximab improves RA by reducing the production of T-cell-modulating cytokines, interfering with the presentation and processing of autoantigens, and decreasing the activation of autoreactive T cells.⁹ In our patient, treatment with rituximab resulted in the simultaneous improvement of RA and SS, suggesting an association of these entities. However, it is unclear why he continues to have periodic relapses of his arthritis but no exacerbations of his cutaneous SS.

Although the pathogenesis of SS is poorly understood, studies have found increased levels of pro-inflammatory cytokines and chemokines, such as interleukin (IL)-1, IL-8, IL-6, and IL-17; chemokine (C-X-C motif) ligand (CXCL)-1, CXCL-2, CXCL-3, and CXCL-16; TNF- α ; and metalloproteinases.¹²⁻¹⁴ Many of these mediators can be released from B cells¹⁵ and may contribute to disease progression by recruitment and activation of neutrophils; therefore, rituximab could exert a positive effect by inhibiting the B cells involved in the release of these mediators.

Rituximab has been used in the treatment of rheumatoid arthritis along with many dermatologic disorders including autoimmune blistering diseases, cutaneous B-cell lymphoma, dermatomyositis, and graft-versus-host disease.⁹ Until now, one other case report has discussed the use of rituximab in neutrophilic dermatoses. Donmez et al¹⁶ reported on a patient with pyoderma gangrenosum (PG) associated with granulomatous polyangiitis successfully treated with a combination of rituximab and infliximab. The authors suggested that treatment of the underlying disorder resulted in resolution of PG; however, it is also possible that rituximab exerts a direct action on PG by a mechanism that remains to be elucidated.

Based on our observations, we propose consideration of rituximab as an alternative therapy in cases of SS and other neutrophilic dermatoses unresponsive to conventional therapies.

REFERENCES

1. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med*. 2004;350:2572-2581.
2. Sweet RD. An acute febrile neutrophilic dermatosis. *Br J Dermatol*. 1964;76:349-356.
3. Fett DL, Gibson LE, Su WP. Sweet's syndrome: signs and symptoms and associated disorders. *Mayo Clin Proc*. 1995;70:234-240.
4. Schadt CR, Callen JP. Management of neutrophilic dermatoses. *Dermatol Ther*. 2012;25:158-172.
5. Kluger N, Gil-Bistes D, Guillot B, et al. Efficacy of anti-interleukin-1 receptor antagonist anakinra (Kineret®) in a case of refractory Sweet's syndrome. *Dermatology*. 2011;222(2):123-127.
6. Keidel S, McColl A, Edmonds S. Sweet's syndrome after adalimumab therapy for refractory relapsing polychondritis. *BMJ Case Rep*. 2011;21:2011.
7. Maloney DG, Grillo-Lopez AJ, Bodkin DJ, et al. IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. *J Clin Oncol*. 1997;15:3266-3274.
8. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol*. 1998;16:2825-2833.
9. Bhandari PR, Pai VV. Novel applications of Rituximab in dermatological disorders. *Indian Dermatol Online J*. 2014;5(3):250-259.
10. Protheroe A, Edwards JC, Simmons A, et al. Remission of inflammatory arthropathy in association with anti-CD20 therapy for non-Hodgkin's lymphoma. *Rheumatology (Oxford)*. 1999;38:1150-1152.
11. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum*. 2006;54:2793-2806.
12. Reuss-Borst MA, Pawelec G, Saal JG, et al. Sweet's syndrome associated with myelodysplasia: possible role of cytokines in the pathogenesis of the disease. *Br J Haematol*. 1993;84:356-358.
13. Fielding CA, McLoughlin RM, McLeod L, et al. IL-6 regulates neutrophil trafficking during acute inflammation via STAT3. *J Immunol*. 2008;181(3):2189-2195.
14. Marzano AV, Fanoni D, Antiga E, et al. Expression of cytokines, chemokines and other effector molecules in two prototypic autoinflammatory skin diseases, pyoderma gangrenosum and sweet's syndrome. *Clin Exp Immunol*. 2014;178:48-56.
15. Chan VS, Tsang HH, Tam RC, et al. B-cell-targeted therapies in systemic lupus erythematosus. *Cell Mol Immunol*. 2013;10(2):133-134.
16. Donmez S, Pamuk ON, Gedik M, et al. A case of granulomatosis with polyangiitis and pyoderma gangrenosum successfully treated with infliximab and rituximab. *Int J Rheum Dis*. 2014;17(4):471-475.