Refractory rheumatoid vasculitis complicated by cytomegalovirus reactivation as a manifestation of immune reconstitution inflammatory syndrome

Michie Katsuta, MD, PhD,[a] Tetsuo Shiohara, MD, PhD,[b] and Akihiko Asahina, MD, PhD[a]
Tokyo, Japan

Key words: cutaneous ulcers; cytomegalovirus reactivation; immune reconstitution inflammatory syndrome; rheumatoid arthritis; rheumatoid vasculitis.

INTRODUCTION

Rheumatoid vasculitis (RV) is among most serious cutaneous complications of long-standing rheumatoid arthritis (RA). Many sporadic case reports document localized infections caused by opportunistic microorganisms in patients with RV on immunosuppressive therapy. The prevailing dogma shaped by clinical observations depicts impairment of immune responses as the inducers of such opportunistic infections. Recent studies, however, have revised this dogma and suggested that opportunistic infections may paradoxically occur upon a rapid restoration of immune responses.[1-3] The rapid restoration by abrupt reduction or withdrawal of immunosuppressive agents would have the potential to promote excessive inflammatory conditions, termed *immune reconstitution inflammatory syndrome* (IRIS).[4]

We present a case of 59-year-old woman who underwent immunosuppressive treatment for RA. After reduction of immunosuppressive agents, her multiple cutaneous and mucosal ulcers rapidly worsened, consistent with the detection of cytomegalovirus (CMV) antigenemia and immunohistochemical identification of CMV antigens in the lesions.

Abbreviations used:

CMV:	cytomegalovirus
IRIS:	immune reconstitution inflammatory syndrome
RA:	rheumatoid arthritis
RV:	Rheumatoid vasculitis
VGCV:	valganciclovir

CASE REPORT

In October 2017, a 59-year-old woman with known history of RA presented to our department with painful erythematous nodules in her face and leg, which developed in the last month. RA was diagnosed and treated 15 years ago. Her medications included prednisone, 3 mg/d, and methotrexate, 8 mg/wk. Skin examination found well-defined erythematous nodules localized to her left cheek and left thigh. The erythematous nodules rapidly became ulcerated. The ulcers evolved through coalescence of multiple discrete small ulcers and extended to the lower legs and buttock. Her RA was in a remission state. C-reactive protein was slightly elevated at 0.69 mg/dL. Rheumatoid factor was elevated at 333 IU/mL. The rest of the workup was negative, including antinuclear antibodies and hepatic panel. Histopathologic findings were consistent with necrotizing vasculitis in small and medium-sized vessels. The arterial walls showed fibrinoid necrosis with infiltration of lymphocytes, histiocytes, and neutrophils. RV was the diagnosis, and prednisone and methotrexate were increased to 20 mg/d and 10 mg/wk, respectively. These doses were maintained for 7 weeks. Although joint swelling and

From the Department of Dermatology, The Jikei University School of Medicine[a] and the Department of Dermatology, Kyorin University School of Medicine.[b]
Funding sources: None.
Conflicts of interest: None disclosed.
Correspondence to: Michie Katsuta, MD, PhD, Department of Dermatology, The Jikei University School of Medicine, 3-25-8 Nishishimbashi, Minato-ku, Tokyo, 105-8461, Japan. E-mail: mkatta1219@gmail.com.

JAAD Case Reports 2020;6:652-5.
2352-5126

https://doi.org/10.1016/j.jdcr.2020.05.003

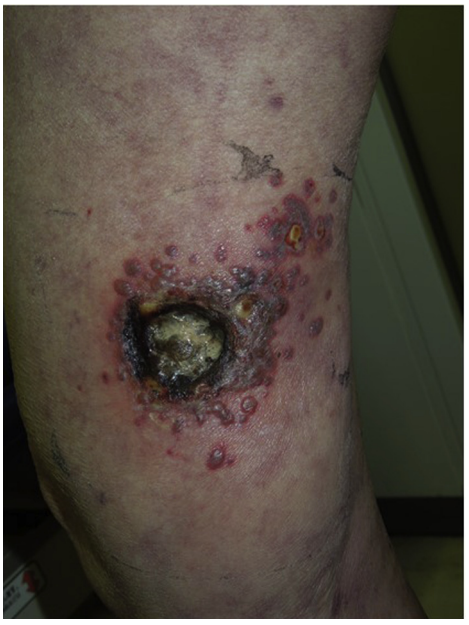

Fig 1. Upon a tapering of her prednisone, the patient's thigh ulcer diameter increased with peripheral numerous hemorrhagic bullae.

tenderness were reduced, her RV gradually worsened; however, immunohistochemical studies did not show CMV antigen reactivity in the ulcers. Because *Mycobacterium avium* complex was detected by polymerase chain reaction of the saliva, the prednisone dose was reduced to 17.5 mg/d while maintaining methotrexate dose. Two days after the reduction of prednisone, a marked flare of cutaneous lesions was detected immediately. The ulcer extended to the periphery and deeper skin and was covered with yellow-green necrotic crusts and surrounded by numerous hemorrhagic bullae (Fig 1). Importantly, this exacerbation was not associated with an increase in inflammatory parameters. Blood testing at this point found positive CMV antigenemia (C7-HRP). A skin biopsy found typical "owl's eye" nuclear inclusions in the endothelium, and immunohistochemical staining confirmed them to be CMV-related inclusion bodies (Figs 2 and 3). After we started oral valganciclovir (VGCV), 15 mg/kg/d, while maintaining prednisone doses, there was a significant improvement of her ulcers on her face and thigh. Methotrexate, 10 mg/wk, was then decreased to 8 mg/wk, and prednisone was tapered down to 12.5 mg/d. Despite prednisone tapering over 2 weeks, her ulcers continued to improve. Anti-CMV treatment was stopped after 5 weeks, when CMV DNA polymerase chain reaction results became negative. Five days after withdrawal of VGCV, her oral ulcer relapsed. The onset of oral ulcers was coincident with tapering of her prednisone and

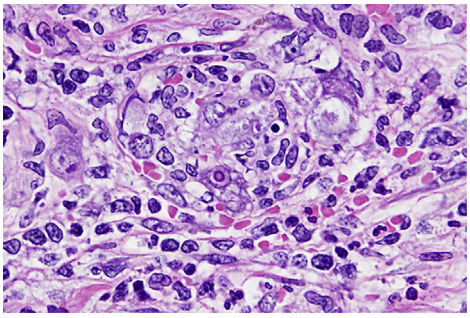

Fig 2. The endothelium shows the characteristic viral cytopathic changes with intranuclear inclusions surrounded by a clear halo (owl's eye appearance).

methotrexate doses to 10 mg/d and 6 mg/wk, respectively. Multiple ulcers in her oral mucosa were covered with a layer of yellowish slough (Fig 4). Resurgence of joint swelling and tenderness during a prednisone and methotrexate taper was associated with the onset of oral ulcers, coincident with positivity of CMV antigenemia. Patient management included the resumption of anti-CMV therapy, and the dose of methotrexate was increased to 8 mg/wk, with a marked response to treatment. Over the next 2 months, her cutaneous lesions gradually resolved, and her prednisone dose was slowly tapered to 5 mg/d, and VGCV treatment was discontinued.

DISCUSSION

Therapy-refractory RV and CMV vasculitis share many clinical symptoms, both leading to severe ulcers, making it difficult to distinguish them clinically.[5-7] Our patient showed exacerbation of RV immediately after reduction of immunosuppressive agents rather than during immunosuppressive therapy. Thus, the paradoxical induction of vasculitis by immunosuppressive therapy was indicative of IRIS. Our patient experienced 2 episodes of CMV reactivation, occurring after reduction of immunosuppressive agents but not their commencement. Because CMV reactivation is facilitated by rapid recovery of immune responses, reduction of immunosuppressive therapy given for RV must be considered causative. Our findings that continued treatment with VGCV was needed to prevent CMV reactivation while maintaining immunosuppressive doses suggested that RV lesions refractory to conventional therapies can be resolved completely only when sufficient doses of immunosuppressive agents are combined with anti-CMV agents but not without the latter. Thus, the principal of management for IRIS is achieving a fine balance between host immune responses and infectious agents. Our patient is

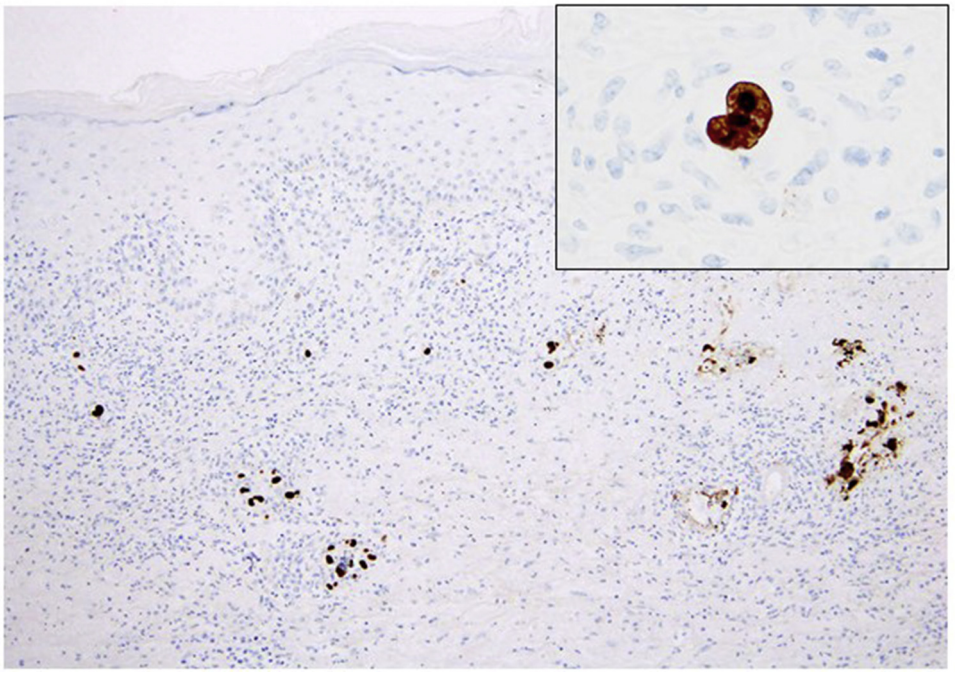

Fig 3. Positive CMV immunohistochemical stain of the infected cells. **Inset**, Higher magnification of positive CMV immunohistochemical stain.

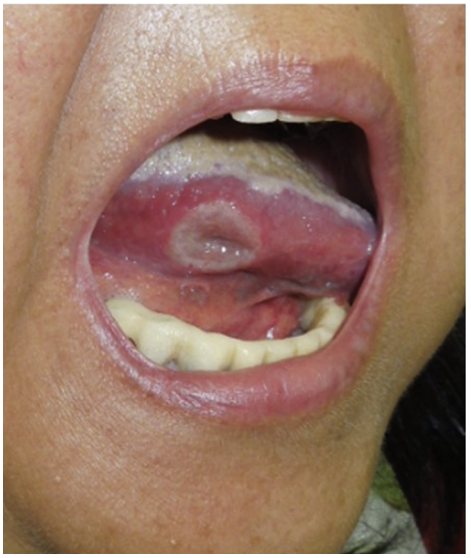

Fig 4. The patient's oral ulcer coincident with a tapering of her prednisone and valganciclovir. After 3 months, when her prednisone was slowly reduced, her oral ulcers gradually resolved.

unique in that in the 2 episodes of CMV reactivation, CMV ulcers on the thigh and oral mucosa developed immediately after a reduction of prednisone or methotrexate and discontinuation of anti-CMV agents, respectively, and that initiation of anti-CMV therapy subsequently led to complete resolution of CMV vasculitis. These findings suggest that CMV reactivation would have occurred as a manifestation of IRIS (CMV-IRIS) in at least the 2 episodes. CMV reactivation was confirmed immediately after the detection of infection in this case. Previous studies suggested that CMV-IRIS develops 3 to 4 days after tapering corticosteroids in severe drug eruptions and bullous pemphigoid.[4,8,9]

When patients have an apparent flare that cannot be explained by an increase in inflammatory parameters and RA symptoms, CMV-IRIS should be suspected, and a more thorough clinical evaluation of CMV reactivation should be done immediately. To identify CMV reactivation, repetitive diagnostic measures with taking of tissue samples and CMV-specific immunohistochemical staining of the tissue samples are necessary.

CMV reactivation should be regarded as potentially etiologic in patients with RV lesions refractory to conventional therapy. RV lesions complicated by CMV reactivation often mimic severe therapy-refractory RV, posing a diagnostic challenge to clinicians.

REFERENCES

1. Hakki M, Riddell SR, Storek J, et al. Immune reconstitution to cytomegalovirus after allogeneic hematopoietic stem cell transplantation: impact of host factors, drug therapy, and subclinical reactivation. *Blood*. 2003;102:3060-3067.
2. Sun HY, Singh N. Opportunistic infection-associated immune reconstitution syndrome in transplant recipients. *Clin Infect Dis*. 2011;53:168-176.

3. Ravimohan S, Tamuhla N, Steenhoff AP, et al. Immunological profiling of tuberculosis-associated immune reconstitution inflammatory syndrome and non-immune reconstitution inflammatory syndrome death in HIV-infected adults with pulmonary tuberculosis starting antiretroviral therapy: a prospective observational cohort study. *Lancet Infect Dis*. 2015;15:429-438.
4. Shiohara T, Kurata M, Mizukawa Y, Kano Y. Recognition of immune reconstitution syndrome necessary for better management of patients with severe drug eruptions and those under immunosuppressive therapy. *Allergol Int*. 2010;59:333-343.
5. Takizawa Y, Inokuma S, Tanaka Y, et al. Clinical characteristics of cytomegalovirus infection in rheumatic diseases: multicentre survey in a large patient population. *Rheumatology (Oxford)*. 2008;47:1373-1378.
6. Lambert EM, Strasswimmer J, Lazova R, Antaya RJ. Cytomegalovirus ulcer. Successful treatment with valganciclovir. *Arch Dermatol*. 2004;140:1199-1201.
7. Grushchak S, Hutchens KA, Joy C, Peterson A, Speiser J, Mudaliar K. Cutaneous cytomegalovirus infection in an immunocompetent patient: innocent bystander or culprit? *Am J Dermatopathol*. 2018;40:295-298.
8. Narita YM, Horie C, Hirahara K, Kano Y, Shiohara T, Mizukawa Y. Bullous pemphigoid complicated by cytomegalovirus disease as a manifestation of immune reconstitution inflammatory syndrome: retrospective analyses of our institutional cases and literature review. *Int J Dermatol*. 2018;57:202-208.
9. Mizukawa Y, Hirahara K, Kano Y, Shiohara T. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms severity score: a useful tool for assessing disease severity and predicting fatal cytomegalovirus disease. *J Am Acad Dermatol*. 2019;80:670-678.e2.