Type II cryoglobulinaemic vasculitis with primary Sjögren's syndrome successfully treated with belimumab and hydroxychloroquine

Sir,

Cryoglobulinaemic vasculitis is a small-to-medium vessel vasculitis caused by cryoglobulin-containing immune complexes. Sjögren's syndrome (SS) is associated with type II cryoglobulinaemic vasculitis. Chevalier *et al*. previously reported three patients with refractory cryoglobulinaemic vasculitis with primary SS (pSS) treated with anti-CD20 therapy and belimumab (1). Additionally, De Vita *et al*. reported a patient with severe SS-related parotid low-grade B-cell mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) and cryoglobulinaemic vasculitis treated with belimumab followed by rituximab, who had been in remission for three and a half years (2). Herein, we report a patient with type II cryoglobulinaemic vasculitis with pSS, successfully treated with belimumab and hydroxychloroquine.

A 27-year-old woman presented with poly-arthralgia, dry eye, dry mouth, and purpura on both the extensor surfaces of the lower legs. Laboratory findings included: 1.67 mg/dL C-reactive protein level, 0.57 mg/dL creatine level, 2,432 mg/dL immunoglobulin G level, cryoglobulin positivity, 93.4 U/mL rheumatoid factor level, and hypocomplementaemia (C3 38.0 mg/dL, C4 6.1 mg/dL), while the patient was negative for anti-Ro/SS-A, anti-La/SS-B, and anti-hepatitis C virus antibodies. Urinalysis with urinary sediment examination revealed proteinuria, haematuria, red blood cell casts, white blood cell casts and granular casts. Renal biopsy revealed membranoproliferative glomerulonephritis and computed tomography revealed bilateral bronchiectasis. The patient fulfilled the classification criteria for pSS according to the 2016 American College of Rheumatology/European League Against Rheumatism (3) as follows: salivary gland biopsy (focus score 1), Schirmer's test <5 mm/min, and an unstimulated whole saliva flow rate <0.1mL/min. After diagnosis with type II cryoglobulinaemic vasculitis with pSS, the patient was treated with rituximab monotherapy at a dose of 375 mg/m^2/week for 4 consecutive weeks as induction therapy. After induction therapy, proteinuria, poly-arthralgia, and purpura improved; however, hematuria, red blood cell casts, and dysmorphic casts persisted. Maintenance therapy with rituximab at a dose of 375 mg/m^2 every 6 months was continued. However, she also suffered frequent episodes of *Pseudomonas aeruginosa* pneumonia due to bronchiectasis, possibly due to pSS; thus, rituximab maintenance therapy was discontinued. Subsequently, she developed purpura and polyarthralgia, and her haematuria and dysmorphic casts again worsened. Hence, remission reinduction therapy with rituximab (375 mg/m^2/week) was readministered for 4 consecutive weeks. Six months after the subsequent maintenance therapy with rituximab, the patient experienced anaphylactic shock due to the infusion reaction of rituximab and *P. aeruginosa* pneumonia. Twelve months after the second induction therapy, subcutaneous belimumab (200 mg/week) and hydroxychloroquine (200 mg) were initiated as alternative maintenance therapies. Surprisingly, fatigue, purpura (Fig. 1A), poly-arthralgia, proteinuria, haematuria, and dysmorphic casts (Fig. 1B) abated after the combination therapy, and the patient has not experienced a relapse of cryoglobulinaemic vasculitis or bacterial pneumonia for >6 months. Moreover, chest computed tomography revealed improved ground-glass opacity and consoli-

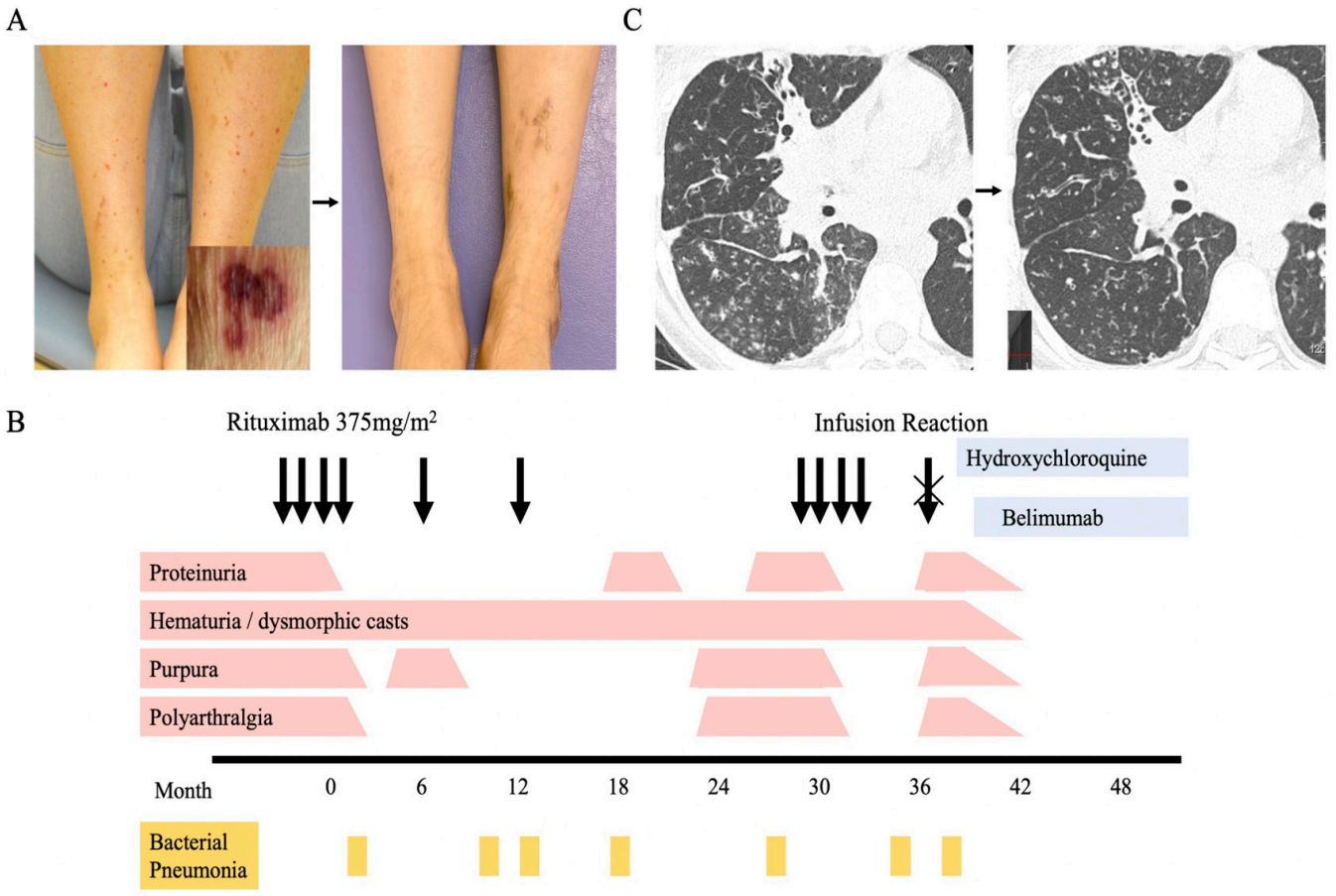

Fig. 1. (**A**) Purpura on the lower legs before and 5 months after the hydroxychloroquine and belimumab administration. (**B**) The clinical course of the present patient. (**C**) Chest CT before and 5 months after the hydroxychloroquine and belimumab administration showing improvement of ground-grass opacity, granular shadow, and consolidation in both lungs.

dation (Fig. 1C).

This is the first reported case of refractory type II cryoglobulinaemic vasculitis associated with pSS successfully controlled with belimumab and hydroxychloroquine, even after discontinuation of rituximab. Serum B-lymphocyte stimulator (BLys) levels are elevated in patients with mixed-cryoglobulinaemic syndrome (4). Therefore, belimumab has been indicated as a potential therapy for cryoglobulinaemic vasculitis (5). Combination therapy with rituximab and belimumab has also been suggested as a potential therapy for SS (6, 7), as rituximab accelerates BLyS upregulation. In patients with systemic lupus erythematosus, belimumab and hydroxychloroquine are recommended therapies for cutaneous manifestations (8). Additionally, hydroxychloroquine is sometimes used for the treatment of arthritis in hepatitis C-associated mixed cryoglobulinaemic vasculitis (9). This patient experienced a relapse of cryoglobulinemic vasculitis approximately ten months after the second induction therapy with rituximab and successfully achieved remission with belimumab and hydroxychloroquine. This case also implies that this treatment is recommended for patients susceptible to infection or allergic to rituximab.

Acknowledgement

We would like to thank Editage (www.editage.com) for English language editing.

S. Izuka, *MD*
H. Yamashita, *MD, PhD*
Y. Takahashi, *MD, PhD*
H. Kaneko, *MD, PhD*

Division of Rheumatic Diseases, National Center for Global Health and Medicine, Shinjuku, Tokyo, Japan.

Please address correspondence to:
Shinji Izuka,
Division of Rheumatic Diseases,
National Center for Global Health and Medicine,
1-21-1 Toyama, Shinjuku,
Tokyo 162-8655 Japan.
E-mail: cmt3cts@gmail.com

Competing interests: none declared.

References

1. CHEVALIER K, BELKHIR R, SEROR R, MARIETTE X, NOCTURNE G: Efficacity of a sequential treatment by anti-CD 20 monoclonal antibody and belimumab in type II cryoglobulinaemia associated with primary Sjögren syndrome refractory to rituximab alone. *Ann Rheum Dis* 2020; 79: 1257-9.
2. DE VITA S, QUARTUCCIO L, SALVIN S *et al.*: Sequential therapy with belimumab followed by rituximab in Sjögren's syndrome associated with B-cell lymphoproliferation and overexpression of BAFF: evidence for long-term efficacy. *Clin Exp Rheumatol* 2014; 32: 490-4.
3. SHIBOSKI CH, SHIBOSKI SC, SEROR R *et al.*: International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis* 2017; 76: 9-16.
4. FABRIS M, QUARTUCCIO L, SACCO S *et al.*: B-Lymphocyte stimulator (BLyS) up-regulation in mixed cryoglobulinaemia syndrome and hepatitis-C virus infection. *Rheumatology* (Oxford) 2007; 46: 37-43.
5. OSTOJIC P, JEREMIC IR: Managing refractory cryoglobulinemic vasculitis: challenges and solutions. *J Inflamm Res* 2017; 10: 49-54.
6. FOX RI, FOX CM, GOTTENBERG JE, DÖRNER T: Treatment of Sjögren's syndrome: current therapy and future directions. *Rheumatology* (Oxford) 2019; kez142.
7. REED JH, VERSTAPPEN GM, RISCHMUELLER M, BRYANT VL: When B cells break bad: development of pathogenic B cells in Sjögren's syndrome. *Clin Exp Rheumatol* 2020; 38 (Suppl. 126): S271-82.
8. FANOURIAKIS A, KOSTOPOULOU M, ALUNNO A *et al.*: 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019; 78: 736-45.
9. FERRI C, SEBASTIANI M, ANTONELLI A, COLACI M, MANFREDI A, GIUGGIOLI D: Current treatment of hepatitis C-associated rheumatic diseases. *Arthritis Res Ther* 2012; 14: 215.