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Severe cryoglobulinemia with cerebral infarction successfully treated with steroid and rituximab: A case report

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Abstract

We report the case of severe cryoglobulinemia with cerebral infarction and ischemic cardiac disease successfully treated with steroid and rituximab.

KEYWORDS

cryoglobulinemia, cryoglobulinemic vasculitis, purpura, refractory skin ulcers, rituximab

1 | INTRODUCTION

Cryoglobulinemia causes systemic small vasculitis and presents various symptoms. Limited data are available regarding the treatment of severe cryoglobulinemic vasculitis. We present that severe cryoglobulinemia with cerebral infarction and ischemic cardiac disease is successfully treated with steroid and rituximab.

Cryoglobulin is a serum immunoglobulin (Ig) that precipitates in the cold and redissolves when heated to 37°C. Cryoglobulinemia is an immune complex-type small vasculitis caused by deposits of cryoglobulins in endothelial cells, which usually presents with various symptoms, such as purpura, peripheral neuropathy, arthritis, renal disorder, skin ulcer, and necrosis.[1]

Cryoglobulinemia is classified into three according to the type of Ig composing the cryoglobulin. Type I consists of monoclonal Ig only, type II polyclonal IgG and monoclonal IgM, and type III polyclonal IgG and polyclonal IgM. Types II and III are called mixed types. Most of the mixed cryoglobulinemia types are caused by hepatitis C virus (HCV) infection.[1] Essential cryoglobulinemia is relatively rare, accounting for 2.5%-11% of all cryoglobulinemia,[2] and is based on the continuous activation of B lymphocytes.[3]

Neurologic manifestations of cryoglobulinemia include peripheral neuropathy, mostly sensorimotor mononeuritis multiplex. The attack on the central nervous system (CNS) is rare. Ramos et al[4] reported that 3 of 209 consecutive patients with cryoglobulinemic vasculitis (CryoVas) involved the CNS. The most commonly involved domains were those of attention. Distinguishing these symptoms from the most common atherosclerotic manifestations is often difficult.

The treatment of noninfectious CryoVas is based on a combination of steroids and immunosuppressants or plasmapheresis. More recently, the effectiveness of rituximab, an anti-CD20 monoclonal antibody targeting B cells, has emerged.[3,5] Limited data on the treatment of severe nonviral cryoglobulinemia are available. We report a case of severe cryoglobulinemia with cerebral infarction and ischemic cardiac disease successfully treated with steroid and rituximab.

2 | CASE REPORT

A 73-year-old female complained of purpura and pain in the lower legs. This purpura has been observed since about 20XX. Five years later, she noticed a right cervical lymphadenopathy. A biopsy revealed diffuse large B-cell lymphoma (DLBCL); thus, she underwent six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), achieving complete remission. Two years after the end of treatment, a delay on the recovery of her lower limb bruise was noted, and she was admitted to our dermatology department. Upon admission, she had purpura, skin ulcer, and edema on both her lower legs (Figure 1A). A history of hypertension, osteoporosis, and cholecystectomy was recorded.

Her blood count and biochemical examinations were almost normal. The C-reactive protein level increased to 1.99 mg/dL, and IgM and soluble interleukin-2 receptor (sIL-2R) levels were 534 mg/dL and 1310 U/mL, respectively. The renal function is normal. Complements were low, C3 67.1 mg/dL, C4 <5.0 mg/dL, and CH50 7.2 U/mL, with a positive cryoglobulin qualitative.

The biopsy of her skin ulcer showed an infiltration of inflammatory cells in the small blood vessels of the superficial dermis, which was showing an image of leukocytoclastic vasculitis. Fluorescent antibody staining revealed a strong C3 deposition on the vascular wall of the superficial dermis (Figure 1B,C).

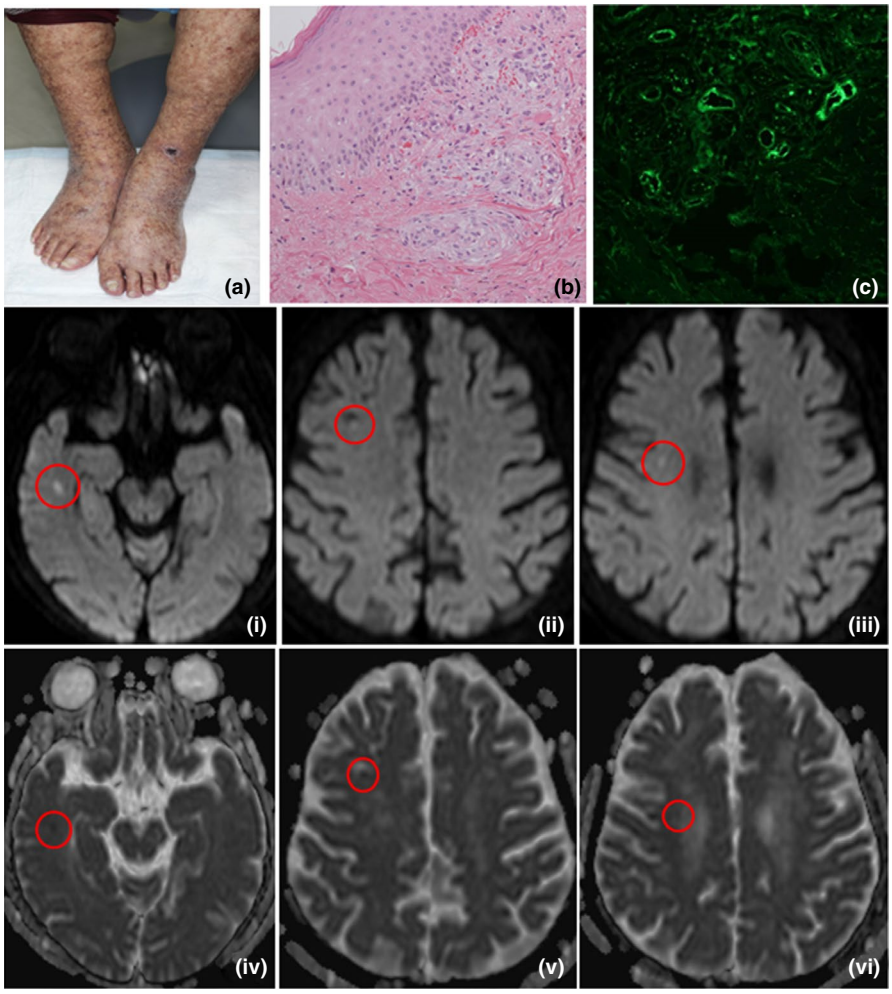

FIGURE 1 A, Skin purpura and ulcer. B, Skin biopsy of the left leg ulcer (H.E). Leukocytoclastic vasculitis in dermal microvessels. Inflammatory cell infiltrate, red blood cell extravasation, and fibrinoid degeneration were found. C, Skin biopsy of the left leg ulcer (fluorescent antibody staining). Deposition of C3 complement in dermal vessels. (i)-(vi): High signal intensity is seen on diffusion-weighted image (i)-(iii), and low signal intensity is seen on apparent diffusion coefficient map (iv)-(vi). Multiple microcerebral infarctions in the right temporal and right frontal lobes

Monoclonal IgM-κ increased, and polyclonal IgG and IgA mixed cryoglobulin were observed in immunoelectrophoresis; therefore, she was diagnosed with type II cryoglobulinemia.

She was treated with 15 mg/day prednisolone (PSL). Her clinical course was good, but on the 29th hospital day, her speech became slurred, and head magnetic resonance imaging revealed acute cerebral infarctions in the right temporal and right frontal lobes (Figures 1i-vi and 2). To suppress the vasculitis, we doubled PSL from 15 to 30 mg/day and added rituximab. And then, she experienced chest pain attacks on the 58th and 71st hospital days. Troponin T was slightly elevated at 0.033 ng/mL during the first attack, and the second ST-segment decreased at V5 and V6. Coronary angiography and an acetylcholine tolerance test were performed, but no significant stenosis and coronary spasm were noted. Also, neuralgia of the lower extremities, which was thought to be caused by vasculitis, was observed on the 78th hospital day. We continued PSL and rituximab, adjusting the dose of the PSL. On the 82nd hospital day, the cryoglobulin semiquantitative value was low at 1%, so rituximab was terminated after four cycles. The IgM level was reduced from 534 to 182 mg/dL, and the sIL-2R level decreased from 1310 to 214 U/mL Her skin ulcer became smaller than in the beginning, and the pain was resolved. Therefore, PSL and rituximab controlled the vasculitis. After that, we gradually reduced PSL to 6 mg/day. Two years after, her skin ulcers were almost epithelialized, with no vasculitis relapse.

3 | DISCUSSION

This case provided two important clinical suggestions. First, essential cryoglobulinemia can occur in DLBCL patients who have achieved complete remission. In general, cryoglobulinemia is secondarily caused by some underlying disease.[1] We suspected this case to be associated with DLBCL recurrence at first because the sIL-2R level was high upon admission. However, no lymphadenopathy was observed, and positron emission tomography/computed tomography and bone marrow examination results did not suggest DLBCL relapse. Furthermore, the purpura has been recognized before the diagnosis of DLBCL. Hepatitis B virus and HCV were also negative. Although antinuclear antibodies and anti-ds-DNA antibodies were positive, the diagnostic criteria, such as systemic lupus erythematosus and Sjogren's syndrome, were not met. Based on the above, our diagnosis was essential cryoglobulinemia.

Second, steroid and rituximab successfully treats severe cryoglobulinemia. This case unusually presented with the CNS attack and chest pain. Coronary angiography was normal; however, we considered her cryoglobulinemia to be the cause of microangiopathy, and the fine branch of the coronary artery was narrowed or occluded. Her vasculitis was resistant to steroid monotherapy, so we used steroid and rituximab as a second-line therapy. Terrier et al[5] compared steroid monotherapy, steroid plus alkylating agent combination therapy, and steroid plus rituximab combination therapy in 242 cases of nonviral mixed CryoVas (of which 117 were essential). The steroid plus rituximab combination group had the highest remission rate with no increase in mortality. Also in our case, steroid and rituximab combination therapy was effective.

In conclusion, we should note that CryoVas can present as cerebral infarction and ischemic cardiac disease. Severe cryoglobulinemia requires treatment with steroid and rituximab.

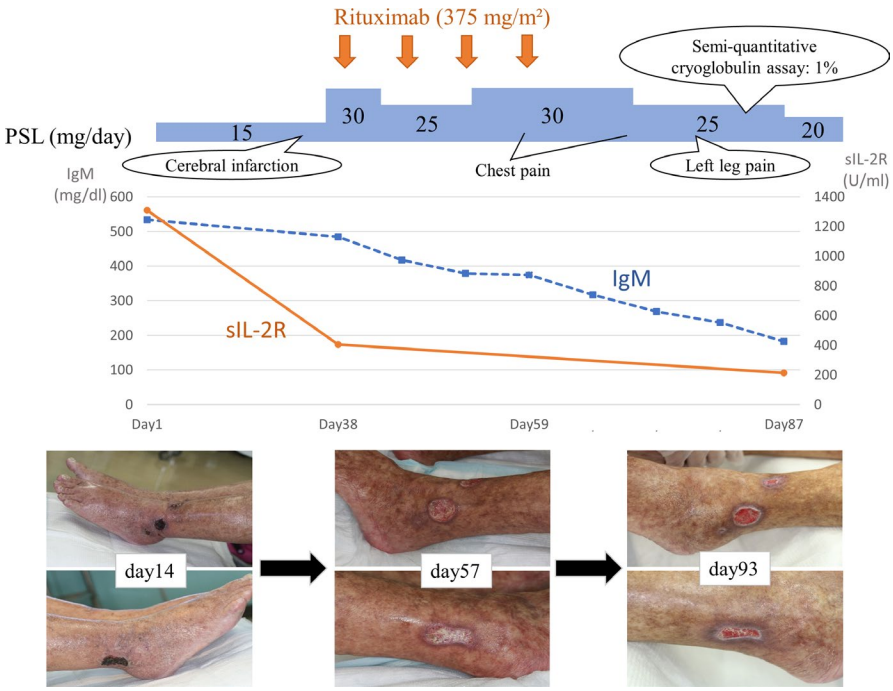

FIGURE 2 Clinical course

Further reports should be accumulated to establish the standard treatment for nonviral cryoglobulinemia, especially for those with cerebral infarction and ischemic cardiac disease.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

NY: conceived presented idea and wrote the manuscript with support from coauthors. TY: made substantial contributions to conception of idea and drafting of manuscript. HN: participated in drafting the article and revising it for important intellectual content. DH: encouraged primary author to investigate skin ulcer. YT and YI: encouraged primary author to investigate cardiovascular diseases. MH: made substantial contributions to supervise the Clinical Case Reports Page 6 of 10 findings of this work. All authors provided critical feedback and contributed to the final manuscript.

ETHICAL APPROVAL

The use of materials and clinical information was approved by the Ethics Committee of Osaka City University and was in accordance with the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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