

SHORT COMMUNICATION

Cryoglobulinaemia (IgG- κ -type and IgM- γ -type) with Occluding Leukocytoclastic Vasculitis in a Patient with Vitiligo and Demyelinating PolyneuropathyMasako Sato¹, Naoki Oiso^{1*}, Toshihiko Shiga², Ryoko Morita¹, Masatomo Kimura³, Masanori Funauchi², Itaru Matsumura² and Akira Kawada¹Departments of ¹Dermatology, ²Hematology and Rheumatology and ³Pathology, Kindai University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan. *E-mail: naoiso@med.kindai.ac.jp

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Cryoglobulinaemia is defined as the presence of circulating immunoglobulins that precipitate with cold temperature (1, 2). Type-1 cryoglobulinaemia is induced by monoclonal immunoglobulin, whereas type-2 is induced by polyclonal IgG and monoclonal IgM and type-3 by polyclonal IgG and polyclonal IgM. Type-1 cryoglobulinaemia has no rheumatoid factor (RF) activity and usually occurs in patients with lymphoproliferative disorders. It is often associated with vascular occlusion and rarely presents as leukocytoclastic (neutrophilic small-vessel) vasculitis (3–5). Type-2 and type-3 mixed cryoglobulinaemias have RF activity and generally occur in patients with chronic infections, mostly hepatitis C virus (HCV) infection, connective tissue diseases and lymphoproliferative disorders. They are usually related to leukocytoclastic vasculitis.

We report here a case of type-1 cryoglobulinaemia with leukocytoclastic vasculitis and vascular occlusion in a patient with vitiligo and chronic inflammatory demyelinating polyneuropathy (CIDP). This is the first known reported case of cryoglobulinaemia with vitiligo.

CASE REPORT

A 47-year-old Japanese man with non-segmental vitiligo was referred to us in August 2013 with painful eruptions on the bilateral lower legs and dorsal hands, which he had noticed 4 days previously. He was not taking any medicines at the first examination. He had experienced vitiligo and CIDP simultaneously 8 years previously. The diagnosis of CIDP had been made by neurologists, based on clinical features, electromyography and magnetic resonance imaging. Intravenous and, subsequently, oral corticosteroids for CIDP had been administered and then tapered for 2 years. No recurrence of CIDP occurred after termination of corticosteroids. Physical examination revealed: (i) purpura on the bilateral lower legs, and dorsal feet and hands

(Fig. 1a–c); (ii) ecchymosis with peripheral purpura on the right lower leg (Fig. 1d); and (iii) complete depigmented macules on the lip, neck, right leg, feet, toes and fingers (Fig. 1a–c).

Laboratory examinations revealed blood erythrocyte sedimentation rate 30 mm/h (normal, 0–10 mm) and C-reactive protein 2.208 mg/dl (normal <0.3 mg/dl), leukocytes $5,200/\mu\text{l}$ (normal 3,900–9,300/ μl), erythrocytes $3.65 \times 10^6/\mu\text{l}$ (normal $4.43\text{--}5.73 \times 10^6/\mu\text{l}$), haemoglobin 12.7 g/dl (normal 13.9–17.0 g/dl), platelets $12.3 \times 10^4/\mu\text{l}$ (normal $16.7\text{--}36.2 \times 10^4/\mu\text{l}$), lactic dehydrogenase 255 IU/l (normal 100–225 IU/l), C3 63 mg/dl (normal 82–145 mg/dl), C4 8 mg/dl (normal 12–33 mg/dl), CH50 <7 U/ml (normal 24.2–52.8 U/ml), immunoglobulin G (IgG) 1,060 mg/dl (normal 870–1,700 mg/dl), IgA 112 mg/dl (normal 110–410 mg/dl), IgM 428 mg/dl (normal 33–190 mg/dl), IgG4 25.5 mg/dl (normal 4.8–105 mg/dl), cryoglobulin positive (normal, negative), cryofibrinogen undetectable (normal, negative), RF <7 IU/ml (normal 0–15 IU/ml), RF-IgG 0.5 INDEX (normal <2.0 INDEX), proteinase-3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) <1.0 U/ml (normal <3.5 U/ml), myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) <1.0 U/ml (normal <3.5 U/ml), anti-streptolysin O antibody (ASO) 98 IU/ml (normal <239 IU/ml) and anti-streptokinase antibody (ASK) 640 times (normal <2,560 times). Anti-nuclear, anti-RNP, anti-double strand DNA, anti-Sm, anti-SS-A/Ro, anti-SS-B/La, anti-SCL-70, anti-cardiolipin, anti-centromere, anti-cyclic citrullinated peptide and anti-glomerular basement membrane autoantibodies were not detected. Infection with HCV, hepatitis type B virus, human immunodeficiency virus, human T-cell lymphotropic/leukaemia virus, syphilis and tuberculosis were not detected. Immunoelectrophoresis did not identify monoclonal protein (M-protein). Immunofixation electrophoresis (IFE) detected IgG- κ -type and IgM- γ -type M-proteins.

In the specimen from the purpuric lesion, fibrinoid degeneration (swelling of the endothelial cells and deposits of fibrin), perivascular infiltration of neutrophils and mononuclear cells, fragments of neutrophil nuclei, extravasation of red blood cells and intravascular eosinophilic crystal deposits were detected in the dermis (Figs. 2a, b, arrow). In the specimen from the lesion of ecchymosis, swelling of the endothelial cells, perivascular infiltration of neutrophils, mononuclear cells and faint eosinophils, excess extravasation of

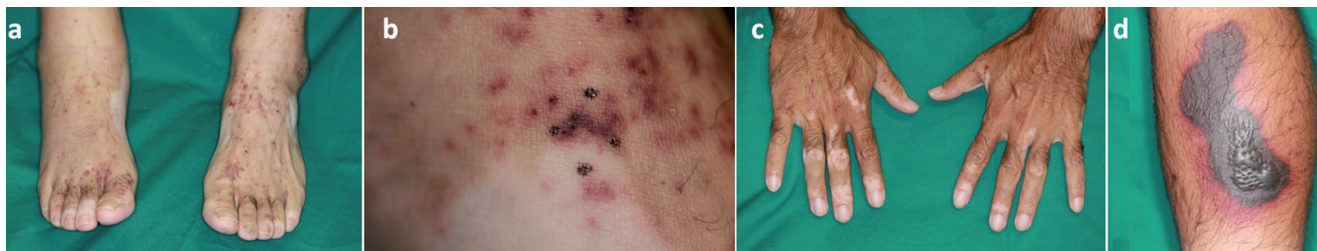


Fig. 1. (a–c) Painful purpura and asymptomatic complete depigmented macules on the dorsal feet and hands. (d) Ecchymosis with peripheral purpura on the right lower leg.

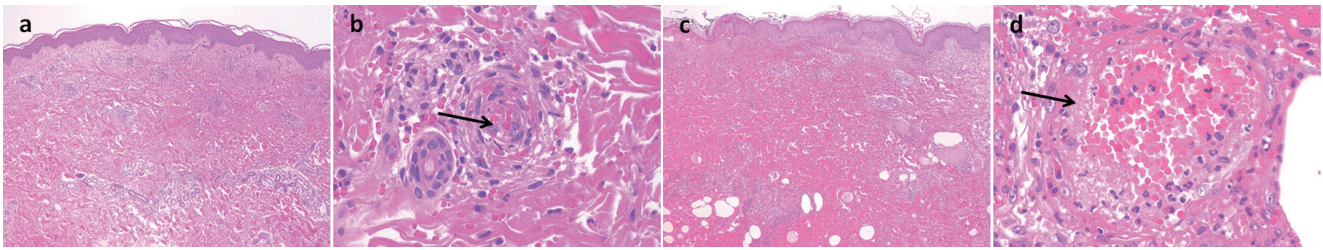


Fig. 2. (a, b) Histopathological examination of the purpuric lesion revealed fibrinoid degeneration, perivascular infiltration of neutrophils and mononuclear cells, nuclear dusts, extravasation of red blood cells and intravascular eosinophilic crystal deposits (arrow) were detected in the dermis (haematoxylin and eosin staining; a: $\times 40$, b: $\times 400$). (c, d) Histopathological examination of the lesion of ecchymosis showed swelling of the endothelial cells, perivascular infiltration of neutrophils, mononuclear cells and faint eosinophils, excess extravasation of red blood cells and intravascular eosinophilic crystal deposits (arrow) in the dermis and the subcutis (haematoxylin and eosin staining; c: $\times 40$, d: $\times 400$).

red blood cells and intravascular eosinophilic crystal deposits were seen in the dermis and the subcutis (Fig. 2c, d, arrow).

A bone marrow aspiration detected no abnormal cells with bone marrow hypoplasia in myeloid cells, erythroblastic cells and megakaryocytes. Computed tomography showed no malignant neoplasms from the brain to the pelvis.

Treatment with oral prednisolone, 40 mg/day, was effective and tapered. Recurrence of purpura and subsequent ulcer occurred with oral prednisolone, 10 mg/day. The eruptions were controlled with oral prednisolone, 12 mg/day.

DISCUSSION

The presence of monoclonal IgG- κ -type and IgM- γ -type cryoglobulins with no RF activity suggested a diagnosis of type-1 cryoglobulinaemia. A positive monoclonal protein can be detected in patients with a normal immunoelectrophoresis pattern with no obvious M spike (6). Concurrent presence of 2 types of monoclonal IgG- κ -type and IgM- γ -type cryoglobulins is extremely rare. It is not known why 2 types of monoclonal cryoglobulins developed concomitantly. We could not detect any lymphoproliferative disorders, chronic infections or malignant tumours.

This case was characterized by the concurrent occurrence of leukocytoclastic vasculitis-associated purpura and vascular occlusion-related ecchymosis due to intravascular crystal deposits derived from the precipitation of cryoglobulin. Our case supports Gammon's suggestion that intravascular crystal deposits are an early clue to the diagnosis of type 1 cryoglobulinaemic vasculitis (4) and showed that deposits can concomitantly cause leukocytoclastic vasculitis and vascular occlusion. Direct immunofluorescence would reveal whether the deposits in leukocytoclastic vasculitis and vascular occlusion are composed of monoclonal IgG- κ -type cryoglobulin, monoclonal IgM- γ -type cryoglobulin or both.

This is the first known reported case of cryoglobulinaemia with vitiligo. It is not currently known whether type-1 cryoglobulinaemia and vitiligo are accidentally concurrent or pathologically associated. Type-2 and -3 mixed cryoglobulinaemias may occur in patients with autoimmune disorders. Vitiligo is epidemiologically and genetically shown to be associated with autoimmune diseases, including systemic lupus erythematosus and

autoimmune thyroiditis (7, 8). In this case, CIDP would be a preceding symptom of type-1 cryoglobulinaemia, because it is highly associated with dysglobulinaemia including cryoglobulinaemia (9). Two reported cases of vitiligo with melanoma and CIDP indicate linked anti-tumour- and auto-immunoreactivity to shared surface antigens in melanocytes, melanoma cells and Schwann cells (10). We speculate that the occurrence of vitiligo, CIDP and type-1 cryoglobulinaemia are associated sequential phenomena. Further accumulation of case series is needed to determine these issues.

The authors declare no conflicts of interest.

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