Microscopic Polyangiitis Associated with Antiphospholipid Antibodies and Immune Complex Mediated Cutaneous Vasculitis

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Microscopic polyangiitis (MPA) is a systemic antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis that affects small-sized blood vessels, almost invariably affects the lungs and kidneys, and is often associated with cutaneous involvement. Antiphospholipid (aPL) antibodies, including anti-phosphatidylserine-prothrombin complex (anti-PS/PT) antibodies, are thought to activate endothelial cells, thus creating a hypercoagulable state that leads to thrombosis. Lupus anticoagulant (LAC) activity detected by a phospholipid-dependent coagulation assay is heterogeneous with respect to the specificities and functional capacities of the antibodies. Some studies have suggested that anti-PS/PT antibodies are associated with symptoms of LAC activity (1, 2). In previous studies, we speculated that anti-PS/PT antibodies might be implicated in disease detection for cutaneous vasculitis (3, 4). We further suggested that anti-PS/PT antibodies are closely related to the pathogenic factors that trigger the development of cutaneous vasculitis. We report here an unusual case of a patient with MPA with aPL antibodies who developed cutaneous vasculitis.

CASE REPORT

A 72-year-old man was admitted to our hospital with a 4-month history of skin lesions with myalgias, arthralgias, swelling on his extremities, and gait disturbance. He complained of bilateral numbness in his upper and lower extremities, general fatigue, a mid-grade fever, and a headache. He had been diagnosed with idiopathic hypertrophic pachymeningitis that had persisted for 7 years. He had begun to experience cutaneous manifestations, arthralgias, myalgias and numbness on his extremities. His symptoms were being managed with intermittent administration of low-dose steroids. Although steroid-responsive, these clinical manifestations had frequently recurred with corticosteroid taper. Examination revealed livedo racemosa (irregular broken circles), erythematous macules, purpuric lesions, and nodules scattered over his extremities. The cutaneous ulcerations had necrotic bases surrounded by rubor on his lower extremities (Fig. 1). Microscopic examination of the lower extremity eruption on his left leg revealed fibrinoid degeneration, nuclear dust, neutrophilic infiltration and erythrocyte extravasation (which is characteristic of necrotizing vasculitis) in the upper and mid-dermis. We also found thrombi and capillary dilatation at the same levels of the dermis (Fig. 2A). Direct immunofluorescence (DIF) analysis showed prominent deposits of IgM and complement 3 (C3) in the cutaneous capillary walls (Fig. 2B).

The laboratory findings were as follows: complete blood cell analysis showed a white blood cell count of 9100/μl (normal 4000–9000/μl), a red blood cell count of 3.3×10^6/μl ($4.5–5.6 \times 10^6$/μl) and a platelet count of 305×10^3/μl ($180–370 \times 10^3$/μl).

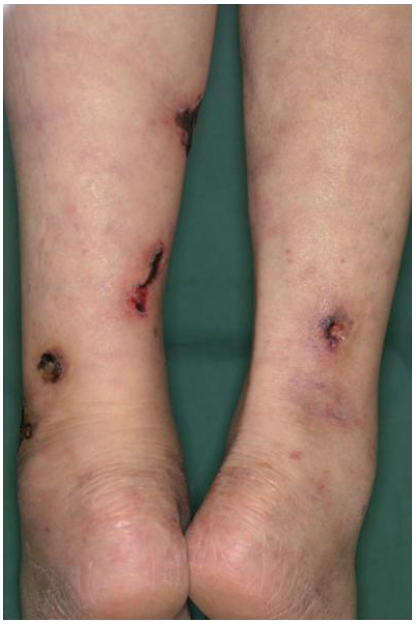

Fig. 1. Erythematous macules, livedo racemosa, purpuric lesions and ulcerations on the lower legs.

Non-specific indicators of inflammation were elevated C-reactive protein (6.34 mg/dl; < 0.3 mg/dl). Urinalysis results were normal except for erythrocyturia. An enzyme-linked immunosorbent assay (ELISA) revealed an antimyeloperoxidase (MPO)-ANCA of 31.9 EU and was negative for antiproteinase-3 (PR3)-ANCA. Plasma samples for LAC were collected and immediately centrifuged at 1500 g for 30 min at 4ºC. After filtration, aliquots of platelet-free plasma were stored at –70ºC until used for the LAC clotting tests. According to guidelines recommended by the Subcommittee on Lupus Anticoagulant/Phospholipid Dependent antibodies, LAC was screened by measuring diluted Russell's viper venom time and kaolin clotting time, and was confirmed by mixing studies and demonstration of phospholipid dependence (3–5). The patient was positive for LAC. Anti-PS/PT antibodies were measured with a specific ELISA (Medical & Biological Laboratories, Nagoya, Japan) according to the manufacturer's protocol. The patient was positive for serum IgM anti-PS/PT antibodies (15 U/ml; < 10 U/ml). Cryoglobulinaemia, anticardiolipin antibodies, antinuclear antibodies, hepatitis C virus antibodies and hepatitis B virus surface antigen were normal or negative. An electromyogram revealed abnormal findings, indicating loss of both motor and sensory functions in peripheral nerves of the upper and lower extremities. Mononeuritis multiplex was diagnosed based on his clinical and electromyogram findings. A chest radiograph and computed tomography showed bilateral consolidations with dilated bronchi in the lingual segment, middle lobe and basal segments of both lungs. These findings were consistent with pulmonary fibrosis. Brain magnetic resonance imaging

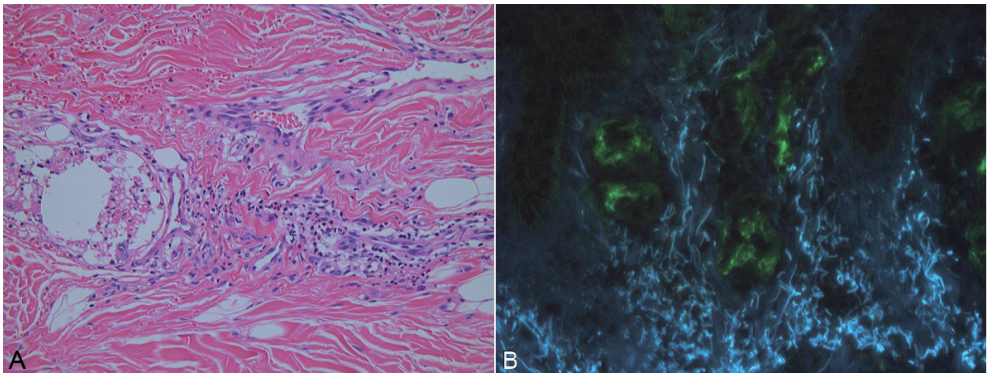

Fig. 2. (A) Microscopic examination of a skin biopsy specimen from the patient's left leg revealed necrotizing vasculitis with moderate neutrophilic infiltrations and thrombi in the upper to middle dermis (haematoxylin-eosin stain; original magnification ×200). (B) Direct immunofluorescence revealing perivascular deposits of C3 within the affected vasculitis (original magnification ×200).

showed diffuse thickening and enhancement of the dura mater, which led to a diagnosis of hypertrophic pachymeningitis. The patient was diagnosed with MPA according to the Chapel Hill Consensus Conference definition (6) and Japanese criteria (7), and was classified as a case with a slowly progressive clinical course. The patient was started on oral prednisone (30 mg/day) and intravenous lipoprostaglandin E1 (Lipo-PGE1). Within one month of initiation of the combination therapy, there was improvement in his clinical manifestations, including the cutaneous eruptions. After discharge from the hospital, the patient was commenced on an adjunct therapy of oral administration of warfarin as an alternative to intravenous Lipo-PGE1 on an out-patient basis. Following the start of warfarin treatment, there was a remarkable decrease in cutaneous eruptions accompanied by a reduction in joint pain and swelling.

DISCUSSION

The presence of MPO-ANCA and the absence of immunoglobulin and complement localized on the vessel walls reportedly distinguish MPA from immune complex mediated small vessel vasculitis (6). The presence of aPL antibodies is not a feature usually seen in association with MPA. Rees et al. (8) reported a 17% point prevalence of aPL antibodies in patients with primary systemic vasculitis. On the other hand, we previously suggested that small vessel vasculitis, especially immune complex mediated cutaneous vasculitis, could be dependently associated with the presence of aPL antibodies (3, 4). While the full clinical spectrum of MPA is still being defined, these additional features in our patient suggest an association between microvascular occlusions and vasculitis in the presence of aPL antibodies and ANCA. Some recent studies have suggested that tissue injury in antiphospholipid syndrome related to aPL antibodies may be caused by a complement-mediated inflammatory process, rather than by thrombosis alone (9). Complement activation may participate in coagulation processes and contribute to tissue damage in patients with aPL syndrome (10). This complement activation might be due, in part, to immunoglobulin aggregates, which would probably be locally produced. We believe that aPL antibodies are involved in the activation of endothelial cells, thus creating a hypercoagulable state that can lead to complement activation and vasculitis in the dermis.

Hypertrophic pachymeningitis (HPM) is an uncommon disorder that causes a localized or diffuse thickening of the dura mater and has been associated with MPA (11, 12). Our patient showed HPM as an initial manifestation of MPA. The patient first visited our dermatological department for his cutaneous manifestations approximately 7 years after the appearance of his initial manifestations. MPA generally has a rapid to intermediate progressive clinical course. However, a slowly progressive clinical course, also known as the smouldering type of MPA, is currently believed to account for approximately 30% of MPA cases (13). The slowly progressive type is generally manifested by gradual increases in serum MPO-ANCA levels as previously described (13, 14). In a previous study, we found that moderate and superficial dermal necrotizing vasculitis corresponds to MPA cases with a slowly progressive clinical course (14). Livedo racemosa is characterized by a striking violaceous net-like pattern on the skin similar to livedo reticularis, but differs according to its shape (irregular or broken). We reported previously that IgM anti-PS/PT antibodies and cutaneous vasculitis might be implicated in disease susceptibility for livedo racemosa (15).

This case demonstrates that MPA can be treated effectively using Lipo-PGE_1 and warfarin with moderate doses of oral corticosteroid. PGE_1 is a prostanoid that has numerous biological actions, such as the inhibition of receptor-mediated stimulation of platelet aggregation, vasodilation, and the suppression of antibody formation (16). Disease progression was halted in this patient by sustained warfarin therapy during the resolution of his skin manifestations. Warfarin is the best available and most effective treatment for recurrent thrombosis in aPL syndrome. These features favour a thrombo-occlusive vasculopathy caused by aPL antibodies rather than a vasculitis *per se*. Our case shows that the two entities can co-exist and explains, at least in part, the pathogenesis of microvascular occlusion.

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