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Multiple mononeuropathy due to vasculitis associated with anticardiolipin antibodies: a case report

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Abstract

This report illustrates a case of peripheral nerve vasculitis associated with elevated anticardiolipin antibodies. A 49-year-old female with a history of seven spontaneous abortions initially complained of pain and numbness in her right calf that later spread to the left foot and ankle. Over the next few months, she developed a Raynaud phenomenon and livedo reticularis. Clinical examination revealed signs of multiple mononeuropathy. Right sural nerve biopsy performed two months after the beginning of the disease revealed active necrotizing arteritis of the epineural arteries with transmural inflammatory infiltrate and thrombosis. Vasculitis is a rare finding in sural nerve biopsies, usually in patients with systemic vasculits or autoimmune connective tissue diseases. However, vasculitis restricted to the peripheral nerves has also been described. Our patient had no clinical or laboratory features of any autoimmune disorder and also no signs of systemic vasculitis. We discuss the potential role of anticardiolipin antibodies in the pathogenesis of vasculitis.

Key words: *peripheral nerve, antiphospholipid syndrome, anticardiolipin antibodies, vasculitis.*

Introduction

Neurological disorders are among the most prominent clinical manifestations of antiphospholipid syndrome (APS). They are predominantly related to thrombo-occlusive vascular events in the central nervous system, vasculitis playing little or no role [4]. The involvement of the peripheral nervous system in APS is uncommon. Although vasculitis has not been frequently noted in association with APS, some cases have been reported [16]. We report a case of multiple mononeuropathy due to peripheral nerve system vasculitis in association with anticardiolipin antibodies.

Clinical history and examinations

A 49-year-old female, with a history of seven spontaneous abortions, suffered a sudden onset of pain and numbness in her right calf, spreading over her foot up to the knee. A month later, she described similar pain in her left foot and ankle followed by a pruritic rash over her hands and back. She lost 7 kg in two months. Over the next few months, she developed a Raynaud phenomenon and livedo reticularis. There was no previous history of vascular thrombosis or autoimmune systemic disease.

At first examination, her right calf was swollen and cyanotic. Neurological examination revealed impaired

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mobility of the right ankle, the Ahil reflex was non-responsive, and a decrease in touch and pinpick sensation on the same leg was found.

Nerve conduction studies showed signs of moderate axonal injury in both schiatic nerves. MRI of the lumbosacral region was unremarkable. Doppler ultrasonography excluded deep venous thrombosis.

Laboratory tests showed anticardiolipin antibodies of IgG isotype in medium titre at the beginning and in low titre three months later. ANCA, ANA, ENA, anti-DNA, anti-beta2-glycoprotein I were negative, creatinine, urinalysis, platelet count, complement, lupus anticoagulant, cryoglobulins and tumor markers were normal. There were mild lymphopenia and polyclonal hypergammaglobulinemia in the serum; oligoclonal bands were demonstrated in the serum and the cerebrospinal fluid. The cerebrospinal fluid showed normal protein level with three lymphocytes and one monocyte per mm^3.

The patient made a significant recovery when treated with oral corticosteroids (methylprednisolone 48 g daily). At 18 months of follow-up she was doing well, with mild paresis of the right foot. She experienced no thrombotic events, but IgG anticardiolipin antibodies remained present in low titre.

Biopsy findings

Skin biopsy showed moderate perivascular infiltration in the upper dermis, composed mostly of mononuclear cells, but also some granulocytes. Right sural nerve biopsy performed two months after the beginning of the disease revealed active necrotizing arteritis of epineural arteries with transmural inflammatory infiltrate composed mostly of lymphocytes and macrophages, with some plasma cells and polymorphonuclear leukocytes (Fig. 1A) and intimal circular fibrinoid necrosis focally spreading into the media (Fig. 1B). Focal destruction of the internal elastic lamina was present (Fig. 1C). Organized thrombus was observed in some sections. Vasculitis was also present in the endoneurial arterioles and venules. Immunofluorescence studies showed scarce focal granular deposits of IgM, IgA and complement components C3 and C1q in the intima and media of epineural arteries, associated with abundant fibrin deposition. Nerve fascicles showed signs of hypoxic damage with reactive changes: immunohistochemistry showed neural growth factor-receptor expression on all Schwann's cells and a somewhat increased number of endoneurial macrophages; the density of myelinated fibres was diffusely and severely decreased with a few spheroid globules demonstrating an active process (Fig. 1D). There were no regenerating clusters. Electron microscopy revealed a lot of endoneurial tubes stuffed with Schawann cell processes but without axons.

Discussion

Vasculitis is a rare finding in sural nerve biopsies [6]. The disease typically affects the 50- to 400-µm vessels of the vasa nervorum, leading to randomly distributed ischemia along the course of the nerve [9]. The clinical presentation in most patients is multiple mononeuropathy or sensorimotor polyneuropathy [6,8,12,13,17].

The major causes of vasculitic neuropathy are systemic vasculitides such as polyarteritis nodosa (PAN), PAN associated with hepatitis B and C, Wegener's granulomatosis, Churg-Strauss syndrome or autoimmune connective tissue diseases (systemic lupus erythematosus (SLE), Sjögren syndrome, rheumatoid arthritis) [9]. However, Kissel et al [13] and Harati and Niakan [10] demonstrated that typical autoimmune systemic diseases are not the most common cause of vasculitic neuropathy, since most patients in their studies had no underlying disease. In some cases, vasculitis may be restricted to the peripheral nerves. Some authors believe that localized vasculitis of the muscle and nerve is a distinct clinicopathological entity [6,8,17]. A variant of non-systemic vasculitic neuropathy with the vasculitis confined to the small vessels in both the peripheral nerve and the skin has also been described [20]. Others suggest that, rather than being an organ specific vasculitis, it is a mild form of systemic vasculitis, in which the nerves are most affected because their long course makes them especially vulnerable to small areas of ischemia [18]. Puechal and Said [18] reported that 34% of patients with isolated peripheral vasculitic neuropathy at initial presentation developed involvement of other organ systems during follow-up.

Our patient had no previous history of a systemic illness and no clinical or laboratory features of any autoimmune disorder known to be associated with vasculitic neuropathy. She also had no signs of systemic vasculitis. It is therefore possible that she suffered from non-systemic vasculitic neuropathy. However, a history of 7 spontaneous abortions, anticardiolipin antibodies once in the medim and several times in low titre and livedo reticularis made the diagnosis of primary APS highly possible.

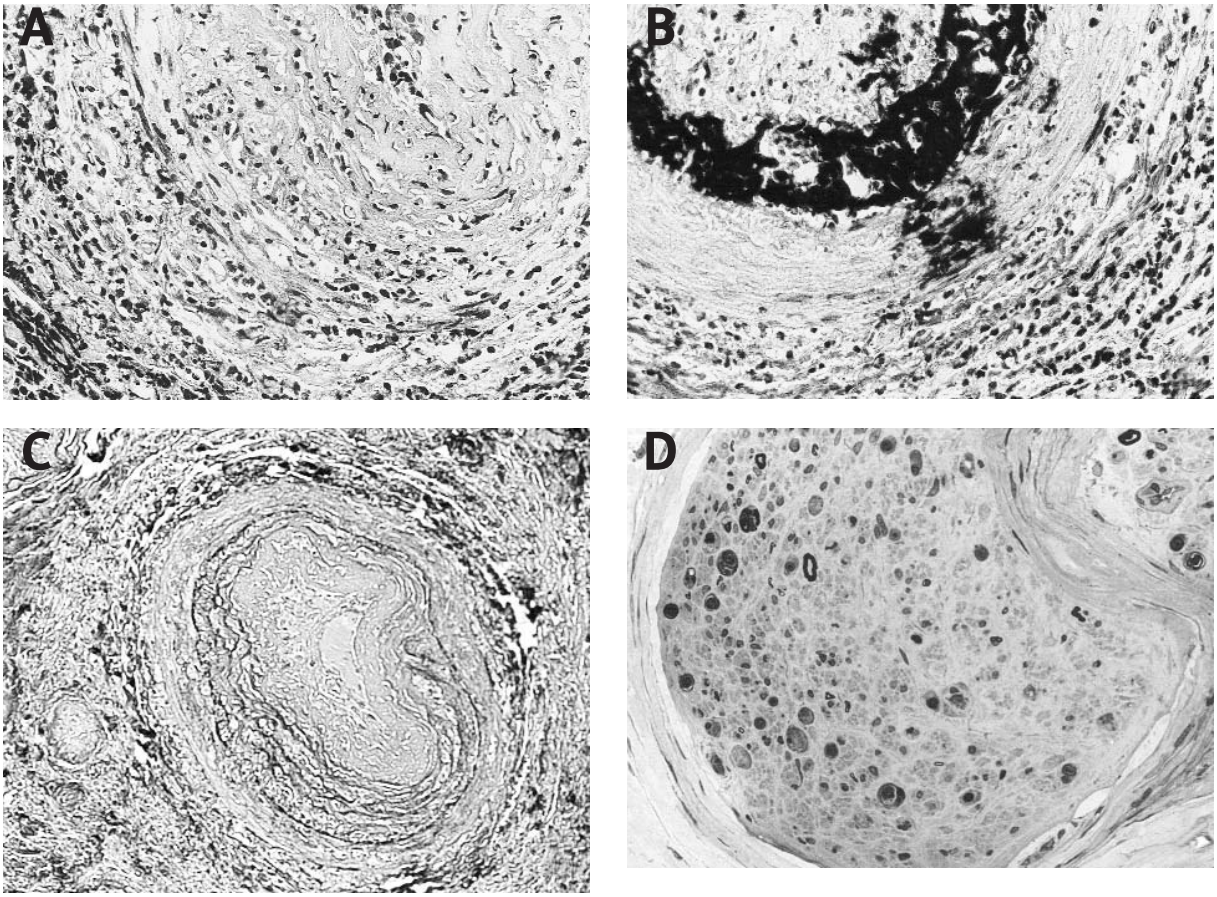

Fig. 1. Vasculitis of the epineurial artery **(A, B, C)** with subsequent pathology in the sural nerve **(D)**. **(A)** Transmural inflammatory infiltration of the arterial wall, HE, original magnification x 400. **(B)** Intimal fibrinoid necrosis focally spreading into the media, Pycro-Mallory, original magnification x 400. **(C)** Eccentrically replicated and focally destroyed internal elastic lamina, van Gieson-Weigert, original magnification x 200. **(D)** Severe reduction of myelinated fibres in the sural nerve fascicle, semi-thin section, original magnification x 400

Vasculopathy associated with APS is thought to be thrombotic in origin. Typical features of vasculitis with histological finding of transmural lymphocytic infiltrate responsive to corticosteroids have been reported in only a few patients with APS, usually in association with an underlying disease such as SLE [19]. It has therefore been suggested that APS can not be the cause of vasculitis [15]. On the other hand, peripheral neuropathy, as an uncommon manifestation of pediatric SLE, has already been associated with the presence of anticardiolipin antibodies [11]. Vasculitis in patients with SLE, with multiple mononeuropathy as the most common manifestation of visceral involvement with vasculitis, has also been associated with clinical manifestations of APS including livedo reticularis [7]. Alarcon-Segovia et al [2] reported that SLE patients with definite APS have an increased risk of cutaneous vasculitis, peripheral neuropathy and leukopenia.

We speculate that the peripheral nerve vasculitis in our patient is associated with anticardiolipin antibodies, especially since the highest titres were observed at the time when the neurological manifestations were the most prominent. During the follow-up, she did not fulfil the criteria for any systemic autoimmune disease or systemic vasculitis, although some mild systemic symptoms and findings were observed that could be explained by APS. The patient reported weight loss, showed mild leukopenia, and also developed a skin rash, possibly due to the vasculitis. During the two years of follow-up, she also developed a mild Raynaud's phenomenon and livedo reticularis, which is frequently associated with APS.

It may also be argued that our patient had a primary vasculitis with a secondary elevation of antiphospholipid antibodies (aPL). Cuchacovich and Espinoza [5] suggested that the high prevalence of aPL in the sera of patients with giant cell arteritis may be due to an existing endothelial injury, resulting in the exposure of membrane phospholipids leading to stimulation of aPL and the subsequent development of vascular thrombosis. They have also detected aPL in patients with Wegener's granulomatosis and polyarteritis nodosa, but without a clear association with thrombotic events. However, the history of seven spontaneous abortions, livedo reticularis and the fact that aPL were still detectable 18 months after the vasculitic event, increase the possibility of primary APS in our patient.

Cuchacovich and Espinoza [5] suggested that the determination of aPL is not indicated in the diagnostic work-up of vasculitis, because they do not have a pathogenic role or influence the clinical manifestations. On the other hand, Castellino et al [3] believe that anticardiolipin antibodies should be assessed in ANCA-associated vasculitis because they may contribute to life-threatening events superimposed on vascular damage. Norden et al [16] also stressed that vasculitis, whether coincidental with or causally related to APS, often has a stormy course and is important to recognize, because it may require a different treatment strategy.

Many authors agree that patients with isolated peripheral nervous system vasculitis have a more benign course than patients with generalized vasculitis with systemic involvement [6,8]. The surprisingly high rate of long-term recovery in patients with isolated peripheral nerve vasculitis in which the peripheral nerves have been severely damaged, has already been reported [6]. On the other hand, several cases of severe and relapsing localized vasculitic neuropathies have been reported [1] and, in a recent study, the relapse rate in 48 patients was 46% [4]. The same study showed that corticosteroid/cytotoxic therapy is more effective in inducing remission and improving the disability than corticosteroid monotherapy.

This case illustrates how the peripheral nerve system can be affected in a patient with signs of APS. Although vasculopathy associated with APS is thought to be thrombotic in origin, a full spectrum of vascular changes associated with anticardiolipin antibodies remains to be determined.

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