CASE REPORT

Peroneal nerve involvement as initial manifestation of primary systemic vasculitis

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SUMMARY

We report a case of two patients with foot drop due to peroneal nerve infarct as early sign of two different forms of primary systemic vasculitides: a predominantly small-vessel p-antineutrophil cytoplasmic antibody-positive vasculitis (microscopic polyangiitis) and a predominantly medium-vessel vasculitis (polyarteritis nodosa).

BACKGROUND

Systemic vasculitis is a disease that should be treated vigorously because of its tumultuous evolution. Clinical features of systemic vasculitides are determined by location and size of the affected vessels, severity of the inflammatory process and comorbid conditions.¹

The diagnostic process is sometimes challenging because of the presentation with aspecific signs (fever, loss of weight, sweating) that are later followed by progressive multiple organ involvement (kidney, lung, gut and peripheral nerves).

Overall, in about 25% of patients with systemic vasculitis,^{2–4} the vasa nervorum infarcts due to occlusion of small epineurial arteries lead to acute or subacute axonal painful and multifocal neuropathy, which is an important alert for neurologists.⁵

However, the rate of neuropathic complications varies among the different types of systemic vasculitis, because at baseline it occurs in about 10% of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis,⁶ whereas this percentage is higher in advanced cases, that is, 45% in microscopic polyangiitis, in a recent series,^{7 8} and 60–70% in polyarteritis nodosa (PAN).⁹

CASE PRESENTATION

Case 1

A 52-year-old man, who had been on a holiday in North Africa 2 months before, started to suffer from high fever unresponsive to antibiotics. He lost 5 kg in 6 weeks and was referred to the infectious diseases department. Few days after hospitalisation, he experienced tingling in the four extremities and became unable to walk because of a bilateral foot drop. The neurological examination documented mild weakness in the upper limbs (Medical Research Council (MRC) scale 4/5 in proximal muscles and 3/5 in distal muscles) and severe weakness in the lower limbs, with asymmetric and distal-dominant distribution (MRC 3/5 leg flexors, 2/5 right tibialis anterior and right extensor digitorum brevis), absence of deep tendon reflexes in the

lower limbs, stocking-gloves hypoesthesia and reduced distal vibratory sense. During the next few weeks, the patient developed severe peripheral oedema due to acute kidney failure.

Case 2

A 46-year-old man was hospitalised in the urology department because of an acute orchialgia with the clinical suspect for infectious orchitis. The epididymus was removed (figure 1), but no pyogenous or mycotic infection was detected, although he had constant fever and leukocytosis. The patient started to suffer from numbness and tingling in the lower limbs, and after 2 weeks, suddenly a right foot drop (preceded by acute pain in the leg) appeared; therefore, the patient was transferred to the neurology department. Ankle reflexes were absent in the lower limbs and the patient reported distal stocking hypoesthesia. The distal strength worsened in few days, preventing the patient to bilaterally move his feet (MRC 0/5 in foot dorsiflexion). Few days later, the pain involved the abdomen and an emergency surgical operation was required because of peritonitis.

INVESTIGATIONS

On admission, patient 1 had C reactive protein (CRP) 15 mg/dL, leukocytosis (white cell count (WCC) 13 000 /μL; eosinophils 500 /μL), rheumatoid factor 103 mg/dL, normal complement dosage (C3, C4), perinuclear antibodies directed against cytoplasmic protein antigens in neutrophils and

Figure 1 Testis tissue from patient 2. On the right, vasculitic infiltrates (→) with fibrinoid necrosis (*) can be appreciated. The wall of small-sized and medium-sized arteries showing necrotising and hyaline degeneration and the inner elastic lamina is destroyed, leading to complete vessel occlusion. On the left, a peripheral nerve is surrounded by inflammatory cells (○) (H&E, ×200).

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Figure 2 Chest X-ray of patient 1 on admission. Diffuse bilateral small-vessel infiltrates can be appreciated.

monocytes¹⁰ (p-ANCA) 423, HCV-abs positivity, proteinuria (>1.5 g/die) and small size pulmonary infiltrates (figure 2). Cerebrospinal fluid protein levels and cell counts were normal. Patient 2 had erythrocyte sedimentation rates 95 mm/h, CRP 20 mg/dL, leucocytosis (WCC 10 000), increased β 2-microglobulin

and monoclonal gammopathy (detected at serum protein electrophoresis), but serum immunofixation and Bence-Jones protein were negative. Serological screening for HIV, HCV and HBV was negative. The electromyography (EMG) recordings in both cases showed a severe axonal multineuropathy with patchy distribution (figure 3). Motor and sensory peripheral nerves of the upper and lower limbs were asymmetrically involved (eg, ulnar nerve on one side and tibial or peroneal nerve on the other side). Compound muscle action potentials (CMAPs) were deeply reduced, whereas the conduction velocities and distal latencies were preserved. This pattern was consistent with multiplex axonal degeneration of nerve fibres caused by ischaemia. For patient 1, a kidney biopsy (figure 4) and a right sural nerve biopsy (figure 5) were performed and led us to diagnose definite microscopic polyangiitis (MPA) according to the Peripheral Nerve Society criteria for systemic vasculitic neuropathy.¹¹ For patient 2, the histological analysis of tissues removed after surgical operations (testis and bowel) was diagnostic of PAN.

DIFFERENTIAL DIAGNOSIS

In both cases, high fever was the first symptom and was initially related to an infectious cause, unresponsive to antibiotics. For patient 1, a tropical infection was suspected. For patient 2, instead, lymphoma was initially compatible with laboratory examinations, but this diagnosis was excluded after positron emission tomography-total body and osteomedullary biopsy.

Figure 3 Neurophysiological recordings from patient 1 in the acute phase. (A) The left peroneal nerve study showing undetectable compound muscle action potentials (CMAPs) at ankle and popliteal fossa recording from extensor digitorum brevis (EBD) muscle and still evocable, but very low amplitude CMAPs recording from tibialis anterior (TA) muscle. (B) The right ulnar nerve study, recording from abductor digiti minimi (ADM) muscle, showing very low amplitude CMAPs at distal and proximal stimulation sites. The severe decrease in amplitude is not coupled with a reduction of conduction velocity. Fibrillation potentials were recorded with concentric EMG needle in peroneal innervated muscles (EBD and TA) and in ulnar innervated muscles (ADM, first dorsal interosseous or FDI), suggesting prominent denervation due to a severe and acute axonal multiplex mononeuropathy. Sensory nerve action potentials of the left median, the right and left sural, and the right ulnar nerve had very low amplitude as well (not represented).

Figure 4 Kidney biopsy from patient 1. Typical features of microscopic polyangiitis are shown in (A): destruction of the internal elastic lamina of an artery and fibrocellular crescent in a glomerulus (+). In the Masson's trichrome staining (B) fibrinoid necrosis of a glomerulus is shown at higher magnification ((A) H&E, $\times 200$; (B) Masson's trichrome staining, $\times 400$).

Vasculitis could mimic many diseases because of the multi-organ involvement, but in our cases the clinical sign that essentially led to diagnosis was peripheral neuropathy.

The involvement of peroneal nerve occurs more frequently than others,⁴ followed by sural and tibial nerve. The pain localised in the area of affected nerve is also typical, as experienced by our patients.

TREATMENT

As soon as the diagnosis was confirmed by histological analysis, in both cases, high-dose intravenous steroids (methylprednisolone 1 g for 10 days) were started and followed by intravenously pulsed cyclophosphamide (6 cycles at the standard dose of 500 mg/m²). According to the Chaper Hill criteria,¹ both patients received intravenous high-dose steroids and a prolonged immunosuppression of oral steroids combined with immunosuppressive agents (azathioprine and then mycophenolate mofetil in patient 1, cyclophosphamide in patient 2). Both patients started intense physiotherapy before being discharged.

OUTCOME AND FOLLOW-UP

Although the hospitalisation of patient 2 was complicated by a bowel perforation that required intensive care unit monitoring, both patients had an overall good long-term prognosis as described in the literature,¹² with a partial neurological improvement. They started to walk unassisted after few months and are still performing physiotherapy, but remained slightly disabled; the effect of axonal damage is still detectable with EMG recordings after more than 2 years. Both patients receive periodically clinical and neurophysiological follow-up,

with constant control of p-ANCA antibodies and kidney function for patient 1.

DISCUSSION

Certain nerves have a propensity for vasculitic involvement, probably due to their poor collateral vessel supply. The most frequently affected individual nerve is the common peroneal nerve.¹³ In MPA, the ischaemic zone that directly damages nerve fibres is present in the proximal-middle portion of peripheral nerve trunks.¹⁴

In a large cohort of patients with ANCA, called EUVAS trial, no correlation could be found between peripheral neuropathy at diagnosis and the occurrence of life-threatening organ involvement (chest, renal, cardiovascular and abdominal).⁶ During the first 5 years after diagnosis of granulomatosis with polyangiitis

Learning points

- ▶ Peripheral nerve involvement with an axonal patchy pattern (mononeuritis multiplex) should raise a suspicion of a vasculitis, a life-threatening disorder that needs urgent treatment.
- ▶ Histological confirmation is strongly recommended because escalating immunosuppressive treatments are needed and prolonged for a long time.
- ▶ Peroneal nerve involvement is a classical feature of small-vessel and medium-vessel vasculitis as microscopic polyangiitis and polyarteritis nodosa.

Figure 5 Sural nerve biopsy of patient 1. (A) Peripheral nerve biopsy showing vasculitic infiltrates that consist predominantly of T lymphocytes stained by anti-CD3 antibodies ((A) H&E, $\times 200$; (B) and (C) CD3 staining, $\times 400$ and $\times 600$, respectively).

and MPA, 15% of patients developed chronic peripheral neuropathy lasting over 3 months.⁶

Although nerve involvement is not life-threatening, it can impair the quality of life of patients because of weakness or pain in the extremities.¹⁵

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