Uncommon pathological findings in sural nerve biopsy from a patient with Churg-Strauss related multiple mononeuropathy

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ABSTRACT

We describe a patient with severe multiple mononeuropathy associated with hypereosinophilia, asthma and pulmonary non cavitating micronodules. Sural nerve biopsy revealed marked perineural thickening and microfasciculation with inflammatory infiltrates in the perinerium and in the epinerium. The patient markedly improved with steroid therapy. Our final diagnosis was Churg-Strauss related multiple mononeuropathy. Thus, we report a case of Churg-Strauss related multiple mononeuropathy with uncommon pathological findings on sural nerve and we underline the importance of clinical evaluation for this diagnosis.

Keywords: Nerve biopsy; Multiple mononeuropathy; Churg-Strauss Syndrome; Perineural microfasciculation; Inflammatory infiltrates.

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is essentially a pathological entity characterized by a necrotizing vasculitis with eosinophilic infiltration and extravascular granuloma formation in tissues obtained by biopsy or necropsy[1,2]. Clinically, this disorder is usually referred to as Churg-Strauss syndrome (CSS) a rare and potentially fatal vasculitis characterized by a prodromal phase with allergic rhinitis, chronic sinusitis, bronchial asthma, pulmonary infiltrations and blood and tissue eosinophilia, followed by a vasculitic phase with a generalized multisystemic disease process that often involves peripheral nerves[2].

Herein we describe a patient, affected by a Churg-Strauss related multiple mononeuropathy, in which sural nerve biopsy revealed uncommon pathological findings.

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CASE REPORT

A 64-year-old woman was admitted to our department to investigate a three months history of distal numbness involving hands and feet, associated with lower limbs weakness more pronounced in left leg. Anamnesis revealed only a two years history of asthma, although specific allergic factors were not identified and serum IgE level was within the normal range. Neurological examination revealed a strength weakness in tibialis anterior (TA) and extensor hallucis longus (EHL) graded 2 on the MRC scale in right muscles and 1 in the left ones, paraesthesias and hypoesthesias with stocking-and-glove distribution and the absence of tendon reflexes.

Extensive laboratory studies, including complete blood count, erythrocyte sedimentation rate, concentrations of electrolytes, C-reactive protein, fasting glucose, glycosylated hemoglobin, FT3, FT4, TSH, antithyroid antibodies, serum vitamin B12 and folate, hepatic enzymes, creatinine, urinalysis, immunofixation electrophoresis, serum IgE level, antinuclear antibodies (ANA), anti-extractible nuclear antigens (ENA), anti-DNA antibodies, antineutrophil cytoplasmic antibodies (ANCA), circulating C3 and C4, anti-Hu antibodies, serologic tests for HBV, HCV and HIV and screening for infections, malignancies, malabsorption and systemic autoimmune disorders, revealed only an increase of eosinophils count (1.29 x 10^9/l, normal value: 0.0-0.7) and percentage (23.5%, normal value: 0-5).

Nerve conduction studies were consistent with an axonal multiple mononeuropathy (Table I). Electromyographic examination, performed in TA, EHL, rectus femoris and first digiti interosseous bilaterally, showed in both TA and EHL a neurogenic pattern, more se-

TABLE I. ELECTROPHYSIOLOGICAL EXAMINATION OF THE PATIENT AT THE AGE OF 64

Nerve	Tract	MCV (m/s)	dL (ms)	CMAP (mV)
R Median	E - W	51 (≥45)		8.0 (≥5)
	W - ABP		3.4 (≤4)	8.0 (≥5)
R Ulnar	Ax-Ab. E	60 (≥45)		5.2 (≥5)
	Ab. E-Bel. E	50 (≥45)		5.4 (≥5)
	E - W	62 (≥45)		5.5 (≥5)
	W - ADM		2.9 (≤3)	6.1 (≥5)
R Deep Peronel	PF - FH	47 (≥43)		1.2 (≥3)
	FH -TA		4.3 (≤4)	1.2 (≥3)
L Deep Peronel	PF - FH	38 (≥43)		0.3 (≥3)
	FH -TA		3.3 (≤4)	0.5 (≥3)
R Deep Peronel	A - EDB		4.0 (≤4)	0.3 (≥1)
L Deep Peronel	A - EDB		–	absent
R Tibialis	LM-AH		5.5 (≤5)	1.3 (≥5)
L Tibialis	LM-AH		5.7 (≤5)	0.3 (≥5)

F wave	mL (ms)	
R Median	25.9 (≤30)	
R Ulnar	25.3 (≤31)	

Nerve		SCV (m/s)	SAP (μV)
R Sural	A - SURA	40 (≥40)	0.5 (≥5)
L Sural	A - SURA	44 (≥40)	2.0 (≥5)
R Median	IF - W	35 (≥45)	1.0 (≥5)
	IIIF - W		absent
R Ulnar	VF - W	–	absent
R Radial	IF - W	–	absent

Legend: **NE**, not examined; **MCV**, motor conduction velocity; **dL**, distal latency; **CMAP**, compound muscle action potential; **mL**, mean latency; **SCV**, sensory conduction velocity; **SAP**, sensory action potential; **R**, right; **L**, left; **Ax**, axilla; **E**, elbow; **W**, wrist; **Ab. E- Bel. E**, above elbow-below elbow; **ABP**, abductor brevis pollicis; **ADM**, abductor digiti minimi; **PF**, popliteal fossa; **FH**, fibula head; **A**, ankle; **TA**, tibialis anterior; **EDB**, extensor digitorum brevis; **LM**, lateral malleolus; **AH**, abductor hallucis; **IF**, first finger; **IIIF**, third finger; **VF**, fifth finger. Normal values are given in brackets.

vere in left side: denervation (fibrillation potentials and positive sharp waves) and high amplitude rapidly firing motor unit potentials.

Cranial and spinal gadolinium-enhanced MRI were unremarkable. Total body contrast-enhanced CT scan detected multiple noncavitating micronodules (<10 mm in diameter) in both lungs.

Considering clinical, neurophysiological and radiological data a diagnosis of a Churg-Strauss related multiple mononeuropathy was made.

After obtaining the patient's informed consent, left sural nerve biopsy was performed to confirm the diagnosis. HE staining documented in two fascicles a marked perineural thickening (Figures 1 and 2), conversely the remaining fascicules were not altered and showed a normal fiber density (Figure 3). Inflammatory infiltrates were noted in the epineurium (Figure 3) and in the perineurium of one fascicule (Figure 2). No alterations of epineural vessel were documented. Semithin sections stained with Toluidine blue revealed a slight loss of myelinated fibers only in the two fascicules with perineural thickening and showed in these fascicules a marked perineural microfasciculation (Figure 4).

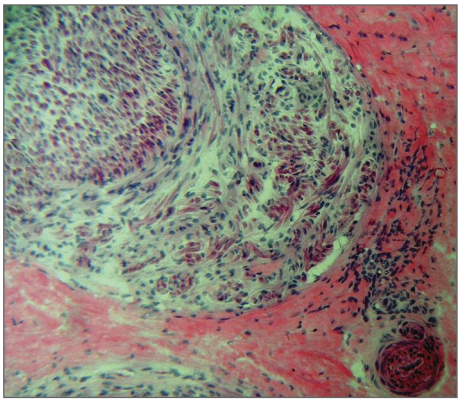

FIGURE 1. Sural nerve biopsy. HE staining. Perineural thickening is noted in this fascicle with presence of an epineural inflammatory infiltrate.

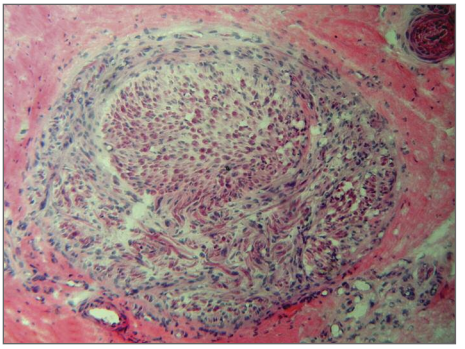

FIGURE 2. Sural nerve biopsy. HE staining. Perineural thickening is noted in this fascicule with presence of scattered perineural inflammatory cells

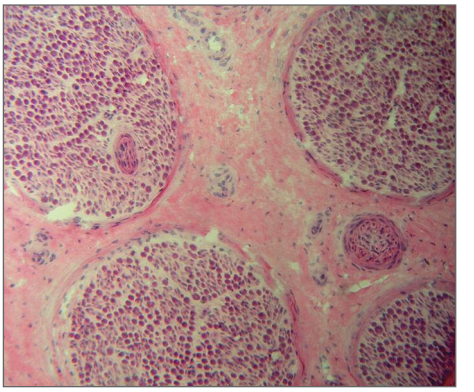

FIGURE 3. Sural nerve biopsy. HE staining. Normal fascicules with normal fibre density and normal epineural vessels are evident

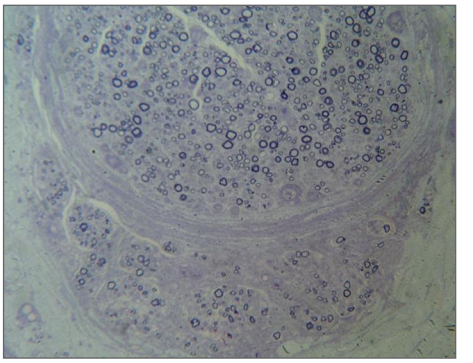

FIGURE 4. Sural nerve biopsy. Semithin section stained with Toluidine blue. Perineural thickening corresponds to an abundant perineural microfasciculation

The patient was discharged with oral steroids therapy (Prednisone 50 mg daily). After six months follow-up evaluation showed the resolution of sensory symptoms and a marked improvement of weakness with a strength graded 3 in left TA and EHL and 4 in right ones. Steroid therapy was gradually tapered down to suspension in one year. After eighteen months, follow-up evaluation showed a complete resolution of strength impairment. At last evaluation, after three years, neurological examination was unchanged.

DISCUSSION

CSS is characterized by bronchial asthma, eosinophilia and systemic necrotizing vasculitis involving medium- and small-sized vessels with or without granulomas[1,2]. Diagnostic criteria for CSS have been established by an American College of Rheumatology subcommittee[3]. About a third of cases with CSS presents a nerve involvement that is characterized in two third of patients by a multineuropathy and in the remaining one by a polyneuropathy[4].

Pathological findings on nerve biopsy show in about half of cases a necrotizing vasculitis with inflammatory infiltrate while eosinophilic infiltration or granuloma are less frequently observed[2,5].

Our case presented with a multiple mononeuropathy associated with hypereosinophilia, asthma and pulmonary non cavitating micronodules, so suggesting a clinical diagnosis of CSS[6]. Interestingly our patient was ANCA-negative. Generally, compared to ANCA-positive patients, ANCA-negative patients less frequently had clinical vasculitis manifestations, such as peripheral neuropathy or renal involvement, but more frequently had cardiomyopathy; furthermore their mortality rate

was higher, but the risk of relapse appeared to be slightly lower[1].

Sural nerve biopsy, performed to confirm our diagnosis, revealed a prominent perineural thickening with microfasciculation. This so called "microfasciculation" results from focal proliferation and endoneural invasion of nerve fascicles by perineural cells. This pathological alteration is a nonspecific response to injury and has been described in different neuropathies, as leprosy or diabetic, including vasculitic forms, but has never been associated with CSS[7].

Clinical improvement after steroid therapy supported our diagnosis of CSS-related neuropathy. Indeed in some ANCA-negative patients, an overlap between some forms of EGPA and not classified systemic eosinophilic disorders cannot be totally excluded[8,9]. However, in practice, response to treatment is usually achieved better and faster in EGPA than in primary systemic eosinophilic disorders[1].

In conclusion we report a case of CSS with uncommon pathological findings on sural nerve and we underline the importance of clinical evaluation for this diagnosis.

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