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CASE REPORT

Peripheral Neuropathy as Initial Manifestation of Churg-Strauss Syndrome

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Introduction

Peripheral neuropathies are well-known complications of primary systemic vasculitides. Antineutrophil cytoplasmic antibody (ANCA)-associated small vessel systemic vasculitides and medium-sized vessel vasculitis are known to frequently damage the peripheral nervous system [1-5]. In some cases, peripheral neuropathy is one of the first symptoms of systemic vasculitis [1,2,5-7]. Churg-Strauss syndrome is a systemic disorder characterized by asthma, hypereosinophilia, and systemic vasculitis and frequently involves peripheral nerves and skin. Some cases of this syndrome presented without history of asthma indicate that asthma is not the requisite condition for the diagnosis.

We describe a case of Churg-Strauss syndrome in a young man (without asthma) having signs of rapidly evolving peripheral neuropathy.

Case Report

A 47-year-old man had a fifteen day history of pain in his lower and upper limbs associated to paresthesias and hypostenia. His medical history revealed no history of asthma, but in the last year some episodes of obstructive-congestive rhinitis were described.

His physical examination revealed 130/70 mmHg blood pressure, 74/min pulses, normal respiratory rate and oxygen saturation and no fever. He suffered for pain (Numeric Rating Scale = 8). His neurological examination showed: Left eyelid ptosis, less power in left deltoid and triceps, difficulty in tightening the fist bilaterally, dysesthesia with hypoesthesia from the forearm to the hand, bilaterally. The right stylus-radial, achilles and medioplant osteo-tendon reflexes were absent. Mild deficit of proximal strength in the lower limbs. Not sensory levels. He was able to walk on points and heels.

Laboratory examination revealed white blood count 28.5×10^9 (eosinophils 61%); C-reactive protein level was 62 mg/dL (normally 0.0-5.0 mg/dL); creatine kinase and transaminase levels was increased, respectively 62 mg/dL and 93 mg/dL.

Chest x-ray and head computed tomography scan were normal.

The patient was admitted in the neurological ward. Blood exams confirmed leukocytosis with hypereosinophilia. Serum tests were positive for ANCA. Nerve conduction studies showed a neurogenic suffering of the investigated muscles, compatible with axonal motor nerve distress with blocks of motor conduction and sensory axonal suffering with asymmetric distribution; these findings were suggestive of multiplex mononeuritis.

Nerve biopsy showed features of axonopathy. Muscle biopsy showed a picture with features of eosinophilic vasculitis. Spirometry was normal, with a FEV1/FVC rate of 77% of predicted.

He was treated with intravenous methyl-prednisolone and Cyclophosphamide, followed by maintenance with azathioprine.

After some days of therapy a blood exam control showed: White blood count 20.5×10^9 (eosinophils 5%); C-reactive protein level 5 mg/dL; creatine kinase levels 51 mg/dL, and transaminase levels 30 mg/dL.

Patient improved and there was no recurrence of symptoms since about two years of follow-up.

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Discussions and Conclusions

The ANCA-associated vasculitides are a collection of relatively rare autoimmune diseases of unknown cause, characterized by inflammatory cell infiltration causing necrosis of blood vessels [8]. The association between ANCA and vasculitis was first described in 1982 [9]. The ANCA-associated vasculitides include granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg-Strauss syndrome) [8].

Named Churg-Strauss syndrome for many years, this entity has now been recognized by the 2012 revised nomenclature for vasculitides as eosinophilic granulomatosis with polyangiitis (EGPA) [10].

There are no commonly accepted diagnostic criteria for EGPA. In 1990, the American College of Rheumatology defined the classification criteria to discriminate the different vasculitides and identified six criteria for EGPA:

1. Asthma
2. Eosinophilia > 10%
3. Neuropathy
4. Non fixed lung infiltrates
5. Paranasal sinus abnormalities
6. Extravascular eosinophils on biopsy

With four or more of these criteria, vasculitis can be classified as EGPA with a sensitivity of 85% and a specificity of 99.7% [11].

EGPA have annual incidence rates of 0.5-3.7 per million in Europe [12]. The relative rarity and non-specific presentation of the ANCA-associated vasculitides pose diagnostic challenges and often result in a significant diagnostic delay of more than 6 months in a third of patients [8].

EGPA mainly affects patients with asthma, sinusitis, allergic rhinitis, and nasal polyposis. In Table 1 the main clinical features and their prevalence are reported [13].

Table 1: Main clinical features in EGPA and their prevalence (modified by 13).

Clinical features	Prevalence (%)
Asthma	91-100
Ear, noise, and throat involvement	48-75
Neuropathy	55-72
Pulmonary involvement	65-91
Cutaneous involvement	40-52
Renal involvement	27
Cardiac involvement	27-35
Gastrointestinal involvement	23-32
Central nervous system involvement	5-9
ANCA positivity	38

Neurological symptoms can be seen in 60-70% of patients with EGPA, secondary only to pulmonary manifestations in the overall frequency of organ involvement [14]. Some of the neurological manifestations in EGPA include cranial neuropathy, extremity mononeuropathy, multiplex mononeuropathy, symmetrical length-dependent polyneuropathy, and rarely manifestation of central nervous system dysfunction [15,16]. In a portion of cases, neurological dysfunction may precede the involvement of other organs or be part of the presenting constellation [5]. An early recognition of this entity is the key in leading to timely treatment and positive outcome [16].

Churg and Strauss reported three primary histopathological alterations: Eosinophilic tissue infiltration, necrotizing vasculitis and extravascular granulomas. The inflammatory process in Churg-Strauss syndrome tends to affect smaller epineural arterioles than those in systemic vasculitis [17].

The underlying pathogenic mechanisms of vasculitic neuropathy are still not fully understood. Presumably, the interplay of humoral antibodies (ANCA), activated neutrophil granulocytes, the complement system, and endothelial cells could lead to inflammation and luminal narrowing of the vessel wall of small epineural arteries, resulting in ischemic lesions of the peripheral nerve [5,18].

Therefore, the neuropathy is caused mainly by nerve ischemia due to occlusion of *vasa nervorum*. The result of this infarction is a loss of sensory and motor axons [17].

EGPA is traditionally described to evolve through a prodromic, allergic phase characterized by asthma and rhino-sinusitis, a eosinophilic phase hallmarked by peripheral eosinophilia and organ involvement, and a vasculitic phase with clinical manifestations due to small-vessel vasculitis [19]. These phases partially overlap and may not appear in such a defined order, although asthma and rhino-sinusitis only rarely arise after the vasculitic manifestations [20,21]. Asthma is found in 95-100% of patients and may precede the systemic disease manifestations of many years [19].

The vasculitic phase is heralded by constitutional symptoms (e.g., fever, weight loss, fatigue) and often by an apparently paradoxical improvement of asthma. Peripheral neuropathy is a cardinal feature of this phase, affecting 70% of the patients [2,19,22]. It is characterized by axonal damage on electrophysiological studies and frequently affects the peroneal, tibial, ulnar, and median nerves; the most common pattern is multiplex mononeuritis; sensory deficits and neuropathic pain are also frequent [2,19].

The diagnosis of polyneuropathy is based on clinical

and electrophysiologic studies, but precise histology, immunohistochemistry and morphometric studies of the peripheral nerve biopsy may be decisive to make diagnosis [17,23].

Nerve recovery is very slow, and only partial, thus early treatment is essential in preventing extensive damage and reduced quality of life [24].

In rare cases, vasculitis is confined to peripheral nerves without evidence of vasculitis in other organ systems [5].

In this case, the diagnosis of EGPA was established based on the hypereosinophilia, noise poliposis, the biopsy and ANCA positivity. This case indicates that the hypereosinophilia is the main risk factor for EGPA without the history of asthma. Several investigators reported that EGPA might occur in patients without asthma [25-32]. Therefore, the absence of asthma should be not an absolute criteria to exclude the diagnosis of EGPA.

These cases, which did not fulfill the criteria of classic EGPA, were also termed variant forms or incomplete forms ("formes frustes") of EGPA [30].

Although Churg-Strauss syndrome is rare, clinicians can ill afford to misdiagnose it, since it is easily diagnosable and treatable and potentially fatal in the absence of treatment.

Identification of cause is one of the important goals of clinician's approach to a patient with newly diagnosed peripheral neuropathy. Evaluating a patient of neuropathy by thorough history taking, clinical examination, and relevant laboratory investigations for presence of any associated medical conditions, which may serve as a clue to the diagnosis, is an important tool to accomplish this goal [31]. A structured approach based on a careful clinical and electrodiagnostic assessment with attention to the pattern of nerve involvement can help narrow the differential diagnosis and rationalise laboratory evaluation [31].

Churg-Strauss syndrome frequently presents polyneuropathy as a complication; since its remission depends on immunosuppression therapy, it is important to recognize it at an early stage.

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