Atypical neuropathy in MPO-ANCA small vessel vasculitis

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ANCA-positive small vessel vasculitis is a rare condition, with a reported incidence that is variable according to the subtype of disease: Churg-Strauss syndrome (CSS), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). One study reported divergences on incidences between two populations located on different latitudes: 3.1 and 0.9 per million-person/year for CSS, 10.6 and 4.9 per million-person/year for GPA and 8.4 and 11.6 per million-person/year for MPA, respectively [1].

These are systemic diseases, usually with multi-organ damage. Peripheral nervous system symptoms are common on the course of the disease, with a reported frequency of 41-42% [2]. Furthermore, they are not unusually present at its onset [3].

Despite differences in methodology among studies, the most common type of neuropathy associated with ANCA-positive small vessel vasculitis is multiple mononeuropathy, followed by distal symmetrical polyneuropathy [2,3]. Cranial neuropathy and central nervous system symptoms are also possible, but much rarer [4].

We present the case of a 54-year-old male with history of a healed pulmonary tuberculosis at 37-year-old. His parents died old-aged and he could not precise the cause of death. He had 10 siblings, two of them deceased, one on a car accident and the other from an undetermined pulmonary problem.

He developed overt constitutional symptoms such as malaise, anorexia, asthenia and weight loss four months before being admitted. Fever 37.5-38.2 °C and nocturnal sweating were more recent features. A couple weeks after the beginning of the clinical picture, he began having paroxysms of dysesthesias on both legs, worse on feet, described as similar to 'electric shocks' and triggered by light touch. He had pins-and-needles sensation below L1 level and allodynia on the dorsum of both feet, so intense that having a bed sheet over them became too painful. He had also complaints of short episodes of lightheadedness, intense paroxysms of productive cough with white sputum and two brief episodes of epistaxis. These symptoms progressively worsened along four months.

When he was observed on the Emergency Department by a neurologist his general status was visibly deteriorated. He had lost 16% of his body weight and was unable to stand up because of the excruciating pain on both soles. He looked pale and was febrile. He had palpable infracentimetric lymph nodes on the axilla and inguinal region. His feet were very pale, cold, with light edema and pulses hard to examine because of the excruciating pain caused by light touch. The mental status, cranial nerves and upper limbs examination were unremarkable. Below L1 level, he had allodynia on light touch, worse on both feet. Light touch sometimes triggered an intense 'electric shock' sensation starting on the feet and going upward through the lateral face of the limb. Pinprick, temperature, vibration and joint position sense were intact. He had normal motor and deep tendon reflexes exam. Flexor plantar response was difficult to access due to pain. Coordination was normal. Gait testing was impossible.

In summary, our patient described a sort of complaints most likely caused by a peripheral nervous system disorder that affects small fibers, thus causing exuberant sensory symptoms in spite of an almost unremarkable sensory system examination. The pattern of injury was consistent with a distal symmetric polyneuropathy, exclusively of the lower limbs. Of note, he had subtle complaints of lightheadedness, which could mean a mild damage of autonomic nervous fibers.

The marked constitutional symptoms and the painful features helped to narrow down the differential diagnosis. Auto-immune, metabolic, neoplastic and infectious causes were considered: diabetes was promptly excluded because fasting glucose and glycosylated hemoglobin were both normal and HIV infection and crioglobulinemia or vasculitis secondary to HCV infection were also ruled out. The clinical features did not resemble stereotypical paraneoplastic peripheral nerve disorders, which typically afflict dorsal root ganglions causing sensory ataxia, and thus a paraneoplastic cause seemed unlikely. MGUS were in consideration, although the neuropathies associated with this condition occur by a predominantly demyelinating process, and serum protein level was normal. The patient's age and the absence of angiokeratoma on inspection were against Fabry's disease. Amyloidosis (hereditary or acquired) was at this point a major differential diagnosis as well as an auto-immune process such as a systemic vasculitis.

A basic analytic study revealed a normocytic and normochromic anemia, an elevated ESR of 59 mm, and an elevated creatinine value of 1.4 mg/dL. Urinalysis and 24-h urine collection demonstrated hematuria and excretion of 1044 mg of proteins/day. A thoraco-abdomino-pelvic CT revealed only fibrotic changes on both lung apexes. Tumor markers, serum and urine protein electrophoresis, auto-antibodies assay and electromyography with nerve conduction velocity study were also requested, but the result would be delayed by a few days.

A new through systematic examination revealed an erythema with a reticulated aspect in the dorsum of both feet. Since a nerve biopsy was just possible after two or three weeks, and considering the new physical examination finding, a biopsy of the skin on that region was performed.

Meanwhile, on the day 2 after admission, our patient continued to have excruciating pain despite analgesic therapy with paracetamol 1 g tid, tramadol 100 mg tid and gabapentine 100 mg tid. Neoplastic and auto-immune diseases were not yet excluded, as well as amyloidosis. We decided to start the patient on methylprednisolone EV 1 g/day during three days considering the high probability of an auto-immune disease and given that steroids would not be particularly deleterious if the patient had a neoplastic disease or an amyloidosis. After this cycle, we switched to oral prednisolone 1 mg/kg/day. On the day after beginning corticotherapy the patient was much better, and, two days later, initiated autonomous ambulation. He also referred

an increase of appetite. Given this impressive improvement, the primary suspicion became an auto-immune disease.

Meantime, pending results arrived. Tumor markers were all negative and serum protein electrophoresis was normal. However, the auto-immune panel revealed positivity for ANCA anti-MPO autoantibodies. The skin biopsy revealed a necrotizing angiitis with visible destruction of small vessels wall. Therefore, our patient had a small-vessel ANCA-MPO positive vasculitis, which explained the marked improvement to corticotherapy.

Surprisingly, the nerve conduction study revealed a purely sensory axonal neuropathy, with reduced amplitude/absence of sensory responses on all the nerves tested on both legs, but with normal conduction velocities. Compound muscle action potentials on both legs and compound sensory action potentials on both arms were normal.

The patient was discharged 10 days after admission on oral prednisolone 60 mg/day, amytriptiline 50 mg/day and gabapentine 200 mg/day.

A renal biopsy was scheduled and it demonstrated a necrotizing glomerulonephritis 'pauci-imune', with 33% crescents. Thereafter, he was started on immunosuppressive therapy with cyclophosphamide 100 mg/day and prednisolone dosage was progressively reduced.

A month after being discharged the patient was reevaluated and, although much better, he maintained bilateral feet pain, triggered by touch, particularly at night. The constitutional symptoms were markedly improved. He gained about 6 kg, had more appetite and was less asthenic.

He continued to improve, and three months after discharge he denied any constitutional symptoms and had only complaints of discrete paresthesias on both legs.

The combination of constitutional symptoms and a subacute axonal sensory polyneuropathy raised several differential diagnosis with systemic vasculitis on top of the list as soon as the *livedo reticularis* was noticed. A tissue biopsy was crucial for the diagnosis of a small vessel vasculitis and positive ANCA-MPO antibodies helped to further classify the vasculitis. Renal impairment was a major concern thus a renal biopsy was considered fundamental in order to stratify the severity of the illness and help plan an adequate immunosuppressive treatment.

The association of peripheral neuropathy with systemic vasculitis, and the presumed pathogenic role of ANCAs is reported since early 90s [5,6]. Nervous system involvement in patients with small vessel vasculitis is not uncommon [7,8]. In a large cohort of 502 patients with biopsy proven and ANCA-positive small vessel vasculitis, the rate of peripheral nervous system involvement was 12% [9]. One of the most common types of peripheral nervous system disorder associated with systemic vasculitis is sensorymotor distal symmetric polyneuropathy [2,3]. On a report of 106 cases of vasculitic neuropathy collected over 30 years, only 17 had purely sensory symptoms. Moreover, only 3 of the 17 patients had only sensory electromyographic involvement [10]. An additional study reported 40 patients with MPA associated neuropathy, all with nerve conduction and EMG studies, and none of them had a pure sensory involvement [11]. Another study reported a pure sensory neuropathy on 5 of 269 cases of GPA and on none of 237 cases of MPA [4]. However, EMG tests were not made. No case of pure sensory neuropathy was reported on a study of 89 patients with primary systemic vasculitis [3]. The inconsistency on the description of the neuropathies and the lack of evaluation by a neurologist, electromyographic tests and immunologic study in many of the reported patients makes the comparison with other similar cases very difficult. Furthermore, the classification of systemic vasculitis is still non-consensual, thus authors uses different classification systems [9,12, 13], making this task even harder. Pure sensory axonal involvement such as described in our case is indeed rare.

Immunosuppressive treatment should be started as precocious as possible. First of all, vasculitis is a potentially fatal disease, because of the frequently severe multi-organic damage. Our patient presented with a necrotizing crescentic glomerulonephritis with high level of activity. Additionally, it seems that delaying the onset of immunosuppressive therapy increases the likelihood of resistance to therapy [9]. Even though peripheral nervous system affection is not life-threatening, it is associated with a poorer quality of life, when compared with patients without those symptoms [3], particularly on physical functioning, social functioning and pain [14]. When observed by a neurologist for the first time, our patient was almost confined to the bed because of the impressive neuropathic symptoms. After starting immunosuppressive therapy, his quality of life gradually improved, allowing him to restart ambulation and other daily activities. Like it was observed on our patient, it is reported that peripheral nervous system symptoms improves rapidly and remits almost completely in almost all patients after the onset of immunosuppressive therapy [2-4].

In conclusion, in a patient with subacute or chronic peripheral nervous system symptoms associated with overt systemic symptoms, a detailed general and neurological exam and an extensive laboratory panel, including ANCA test, is crucial to raise a diagnosis suspicion and to determine its etiology. ANCA-positive small vessel vasculitis is a rare but potentially disabling or fatal disease and, due to its multi-organic nature, a multidisciplinary approach is needed to diagnose and treat all the associated conditions. Neurological involvement is not rare, and clinical findings are variable. A detailed neurological examination by a neurologist and nerve conduction velocities/EMG studies may be valuable to accurately characterize and eventually expand the spectrum of neurological impairment associated with ANCA-positive and also other vasculitic neuropathies. Furthermore, immunosuppressive treatment should be started as early as possible to prevent serious complications of the disease, namely the development of multi-organic failure and long-term disabling chronic neuropathy, and to reduce the likelihood of resistance to therapy.

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