Small Fiber Neuropathy due to Isolated Vasculitis of the Peripheral Nervous System

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Peripheral neuropathy is a prevalent disorder with diverse etiologies. Most peripheral neuropathies affect all fiber sizes. A relatively small subset of patients present with pure or predominant small fiber involvement, which is characterized by autonomic dysfunction and abnormal thermal and pain sensations, with normal proprioception, tendon reflexes and motor strength [1]. Mild involvement of large nerve fibers can coexist in many patients with small fiber neuropathy. We present a patient suffering from intractable painful peripheral neuropathy, refractory to combined analgesic therapy including narcotics. Clinical and diagnostic findings supported the diagnosis of SFN due to small vessel vasculitis of the peripheral nervous system, most probably of non-systemic origin, an etiology rarely reported with SFN. Cyclophosphamide treatment resulted in a marked response.

Patient Description

A 24 year old woman was admitted to the Department of Internal Medicine with attacks of burning pain in her palms and soles that had begun 3 months earlier at the end of her second pregnancy. Her medical history was unremarkable except for third-trimester hypertension in both pregnancies. After labor the pain increased, followed by deterioration in her daily functional state. Ambulatory orthopedic and neurologic examinations were unrevealing. A therapeutic trial with carbamazepine, amitriptyline, oxycodone and aspirin brought no relief. On the night of admission, she was suffering from burning pain in her feet and was writhing and crying in pain. Acute therapy with morphine was initiated parallel to combined therapy with clonazepam, carbamazepine, amitriptyline and fentanyl patches. Partial relief of pain occurred under treatment, but only 2 days later acute intense pain returned, without cessation until epidural anesthesia was accomplished.

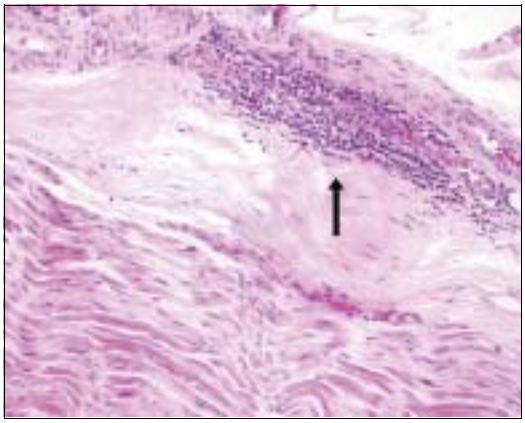
Physical and neurologic examinations on admission were normal without focal findings, with good motor and sensory functioning and intact cerebellar tests. Blood pressure was 150/109 and body temperature was normal. Initial laboratory tests included complete blood count, fasting glucose, erythrocyte sedimentation rate, serum electrolytes, and renal, thyroid and liver function tests – all within normal limits.

Further diagnostic workup was performed to clarify the etiology of peripheral neuropathic pain. Her medical history was negative for trauma, surgery, metabolic and hereditary diseases. No toxic materials, drugs or alcohol were consumed. Vitamin B12 and folic acid levels were normal. Urine and stool samples for porphyrines and serologic tests for hepatitis viruses were negative. No risk factors for human immunodeficiency virus were present. Tumor markers were not elevated. Electromyography was normal without evidence of peripheral nerve injury. Skin biopsy from the heel was taken; there was no evidence of vasculitis or amyloid deposits. Psychiatric consultation revealed no signs of addiction, weaning symptoms or any psychiatric disorder. Evaluation for the cause of hypertension, including ultrasound and Doppler of renal blood vessels, urine collection for cathecholamines and electrolytes, electrocardiogram and echocardiographic examinations were negative.

Additional neurologic examination found high sensory thresholds for heat and cold in the lower limbs, which together with the patient's symptoms supported the diagnosis of SFN. Signs of accompanying minor damage to larger fibers were also evident on sural conduction tests. Further evaluation for the etiology of small fiber neuropathy included antibodies associated with Sjögren's disease, fasting lipid panel, protein electrophoresis, quantitative immunoglobulins, rheumatic factor, antinuclear antibodies, cytoplasmic antineutrophil cytoplasmic antibodies, perinuclear antineutrophil cytoplasmic antibodies and complement levels, and all were normal. Lumbar puncture revealed normal cerebrospinal fluid. Sural nerve biopsy was then performed, showing slight deficiency in nerve fibers, mainly in small myelinated and unmyelinated fibers. A dense mononuclear, mainly lymphocytic, perivascular infiltration was seen around some of the epineural blood vessels [Figure]. The infiltration invades the wall of the blood vessels. Leukocytoclasia, fibrinoid necrosis or amyloid deposits were not seen. Histopathologic diagnosis was consistent with moderately severe active axonopathy and non-specific small vessel vasculitis, a finding that could explain the apparent clinical findings. No signs of accompanying systemic vasculitis were observed during evaluation and follow-up.

High dose oral prednisone therapy was initiated, but was discontinued gradually due to lack of improvement. A therapeutic trial with oral cyclophosphamide 100 mg

SFN = small fiber neuropathy



Sural nerve biopsy demonstrating a dense mononuclear, mainly lymphocytic, perivascular infiltration around epineural blood vessel (arrow). The infiltration invades the wall of the blood vessel (shown in tangential section).

once daily was then applied, with dramatic effect on the patient's condition after 2 months of treatment.

Comment

SFN comprises a broad differential diagnosis. Idiopathic sensory neuropathy is the largest group of SFNs, especially at an older age. Secondary etiologies include metabolic diseases, mainly diabetes mellitus which is the most common identifiable cause of this type of neuropathy, and hypertriglyceridemia. Sjögren's syndrome, alcoholic polyneuropathy, HIV, hepatitis C, drugs and toxins such as metronidazole, monoclonal gammopathy, vasculitis and amyloidosis are additional causes. Hereditary conditions such as hereditary sensory autonomic neuropathies, Fabry's disease (alpha-galactosidase A deficiency) and Tangier disease (high density lipoprotein deficiency) are less common etiologies [1,2].

Diagnostic testing for peripheral neuropathy includes conduction and electromyographic tests, which may be normal in patients with SFN. Specialized electrodiagnostic tests of small fiber function, such as quantitative sensory testing and autonomic studies, are in use but are beyond the scope of this report and are not accessible in many institutions [2]. Pathologic tests include intraepidermal nerve fiber analysis from skin biopsy and sensory nerve biopsies of, e.g., the sural nerve. They are especially productive when amyloidosis, or an autoimmune or inflammatory process is suspected [3].

As mentioned above, SFN can be present in various systemic vasculitic syndromes. It can also appear as a non-systemic vasculitic neuropathy restricted to peripheral nerves without any constitutional symptoms or laboratory or serologic abnormalities, as described in the current case. However, this presentation is quite rare [1,4]. Rare paraneoplastic syndromes, such as in small cell lung cancer and lymphoma, can be characterized by non-systemic subacute vasculitic neuropathy.

Treatment of SFN is generally symptomatic, limited to the management of pain. Drug therapy for neuropathic pain includes anticonvulsants, tricyclic antidepressants, opiates and antiglutaminergic drugs [2]. Treatment with steroids and immunosuppressive therapy can be effective in autoimmune conditions. The most commonly used immunosuppressive agent in severe systemic as well as non-systemic necrotizing vasculitis that does not respond to corticosteroids is cyclophosphamide, although azathioprine and immunoglobulins have also been used in non-systemic vasculitic neuropathies [5]. The response to treatment of vasculitis restricted to peripheral nervous system is often good, with a substantially better prognosis than in systemic vasculitis.

In conclusion, SFN is an important clinical disorder that can cause much distress to patients. This entity and its etiologic basis are not well known to the general medical personnel. The case presented demonstrates an uncommon cause of sensory predominant painful neuropathy due to vasculitis, most probably of non-systemic origin, which was presented with peripheral neuropathy as the sole clinical feature. It is suggested that patients with SFN for which no other cause has been identified should be evaluated for the presence of non-systemic vasculitis. Follow-up of the patients may lead to the diagnosis of possible transition to systemic vasculitis. Our patient, who suffered excruciating pain and failed to respond to various drugs including large doses of corticosteroids, showed remarkable response to treatment with cyclophosphamide.

HIV = human immunodeficiency virus

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