Montelukast-Related Churg-Strauss Vasculitis Presenting with Peripheral Neuropathy

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Churg-Strauss syndrome is a systemic inflammatory disorder frequently associated with mononeuritis multiplex affecting both sensory and motor components of the peripheral nerves. We report an asthmatic patient treated with montelukast, a leukotriene receptor antagonist, who subsequently developed CSS presenting as peripheral neuropathy. Discontinuation of the medication and treatment with prednisone resulted in gradual improvement.

Patient Description

A 29 year old woman was admitted because of severe pain and a burning sensation in the lower limbs. Her past history included bronchial asthma for 11 years that worsened over the last 3 years. Intermittent eosinophilia was detected on repeated blood tests. She was treated with prednisone for the previous year intermittently, including 2 weeks prior to hospitalization. Medications received by the patient before admission were prednisone 40 mg/day for the preceding 4 days, montelukast 10 mg/day for the last year, inhalator of terbutaline, and budesonide as needed. More recent history included a burning sensation and pain in the right lateral shin for the last 8 months, followed by the same symptoms in the right foot. Later, severe burning of the left foot and in both calves developed over 3–4 months and low back pain and asymmetric pain in both hands ensued. In addition, a rash over her hands and elbows, and pain in the wrists and ankles were evident 2 weeks prior to admission.

Physical examination demonstrated a maculopapular rash over the hands and elbows. Tenderness without swelling of the wrists and ankles bilaterally was elicited. Cranial nerve and motor examination at admission were normal. There was evidence for bilateral pes cavus. Tendon reflexes were active and symmetric in both arms. Right ankle jerk was absent and decreased on the left side. Plantar responses were flexor bilaterally. There was decreased distal sensation for temperature and vibration in both legs. Vibration was absent below the ankles, and position sense was impaired for toe movements bilaterally. Sensation to touch and pain were decreased in the right leg as compared to the left and affected the dorsal plantar surface of the foot and lateral aspect of the leg. Gait and cerebellar functions were normal.

Nerve conduction studies were performed on admission and showed a severe predominantly axonal sensorimotor neuropathy affecting the legs with clear electrophysiologic asymmetry. The laboratory workup at admission included: erythrocyte sedimentation rate 50 mm/hour, white blood cells 18,030 cells/dl, hemoglobin 12.4 g/dl, platelets 298,000 cells/dl, eosinophils: 4.2–58%, creatinine 0.9 mg/dl and albumin 3.1 mg/dl. Serologic tests included: perinuclear antineutrophil cytoplasmic antibodies 93 EU/ml (normal < 15 EU/ml); antinuclear antibodies, anticardiolipin antibodies, rheumatoid factor and cytoplasmic-ANCA were all negative; C3 and C4 were normal; urinalysis showed WBC ++. Chest computed tomography was normal, and pulmonary function tests revealed an obstructive pattern. Echocardiography, abdominal ultrasound, magnetic resonance imaging of the spine, and gastroscopy were normal. The skin biopsy from the area with the rash revealed granulomatous dermatitis with necrobiosis and many neutrophils, nuclear dust and eosinophils. The features were compatible with palisaded granulomatous dermatitis associated with systemic disease.

This patient fulfilled the American College of Rheumatology criteria for the diagnosis of CSS based on the findings of asthma, polyneuropathy, rash, eosinophilia, and elevated titers of p-ANCA. The patient received treatment with intravenous hydrocortisone 100 mg x 3/day for 3 days, followed by prednisone 60 mg/day, omeprazole 20 mg twice a day, and amytriptyline 50 mg/day. Therapy with montelukast was discontinued.

Following initial therapy, there was a significant improvement in pain and paresthesia. Follow-up over 20 months showed incomplete neurologic recovery. The second NCV/electromyography examination 4 months later showed decreased motor and sensory amplitudes. It is important to note that the sural sensory responses obtained during the second test were in the normal range. Electrophysiologic testing was repeated a third time 2 years after the onset of the patient's initial symptoms

CSS = Churg-Strauss syndrome

c-ANCA = cytoplasmic antineutrophil cytoplasmic antibodies

WBC = white blood cells
p-ANCA = perinuclear antineutrophil cytoplasmic antibodies
NCV = nerve conduction studies

Table 1. Follow-up over a 20 month period

	Day 1, admission	2 weeks	6 weeks	10 weeks	22 weeks	12 months	20 months
Prednisone	60 mg/day	50 mg/day	40 mg/day	35 mg/day	10 mg/day	5/10 mg/day	5 mg/day
ESR (mm/hr)	50	32	20	10	14	ND	6
Eosinophils (%)	58%	2.9%	ND	ND	1.6%	11%	11.1%
p-ANCA (EU/ml)	93	ND	ND	NEG.	NEG.	NEG.	ND
Parasthesia and pain	++++	+++	++	++	++	++	++

ESR = erythrocyte sedimentation rate, ND = not determined, NEG = negative

and showed significant improvement in sensory and motor amplitudes that returned to the normal range but showed significant asymmetry. The EMG examination performed at this time showed mild chronic neurogenic changes in motor unit potential morphology and recruitment patterns. p-ANCA titers reverted to negative, and there was a substantial drop in the eosinophil count [Table 1]. However, a repeated NCV/EMG revealed persistent axonal sensory neuropathy.

Comment

CSS (allergic granulomatosis and angiitis) is a rare systemic vasculitis, more common in middle-aged men, occurring in patients with asthma or a history of allergy, and affects the lungs, kidneys, skin, gastrointestinal tract and peripheral nervous system (64–75%), in the presence of eosinophia. The clinical and electrophysiologic signs of neuropathy in CSS usually include asymmetric abnormal motor and sensory responses that are suggestive of mononeuritis multiplex. Lower limbs are more likely to be affected and the sciatic nerve is most commonly affected followed in frequency by the tibial, and peroneal nerves [1]. The present case is atypical because of the predominant motor dysfunction without definite sensory abnormalities on the patient's first examination. A follow-up examination suggested mild sensory involvement since sensory amplitudes improved over time. The electrophysiologic findings in this patient are probably better conceptualized as a predominantly motor neuropathy.

There are isolated reports of CSS patients with acute predominantly motor axonal polyneuropathy typical of Guillain-Barre syndrome [2]. Neuropathy as the initial manifestation of CSS following therapy with montelukast remains rare [3,4]. An asthmatic patient developed a severe neuropathy during long-term treatment with montelukast and continuous low doses of inhaled steroid, as the initial clinical feature of CSS. He developed an abnormal gait due to a sensory neuropathy of the lower limbs. Biopsy revealed an axonal sensorimotor neuropathy [3].

Potential mechanisms for the development of CSS following therapy with leukotriene receptor antagonist include an increase in the number of reported cases due to ascertainment bias, allergic drug reaction, or the development of leukotriene imbalance resulting from leukotriene receptor blockade. CSS develops primarily in patients who had an underlying eosinophilic disorder that was masked by corticosteroid treatment and later unmasked by novel asthma medication-mediated corticosteroid withdrawal [5]. Finally, since longstanding asthma is almost the rule in CSS, the cases related to montelukast may be coincidental.

In conclusion, this case is noteworthy because the time course of events strongly suggests a direct etiologic role for montelukast in the development of CSS. Peripheral neuropathy as the initial manifestation of the disease is rare and should be suspected if it develops upon tapering of prednisone therapy. To our knowledge, this is the first case reported in Israel of CSS occurring in a patient treated with montelukast presenting with isolated peripheral neuropathy.

EMG = electromyography

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