Case report

Intravenous immunoglobulins in polyarteritis nodosa restricted to the limbs: case reports and review of the literature

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ABSTRACT

Polyarteritis nodosa (PAN) of the calf muscles is a rare form of vasculitis. We present two cases of PAN limited to the calf and a review of the literature, based on a MEDLINE (PubMed) search of the English literature from 1980 to 2005, using the key words "vasculitis restricted to limbs", "polyarteritis nodosa", and "intravenous immunoglobulin".

PAN limited to the calf muscles is a condition presenting with severe shin pain and walking difficulties. In contrast to classic PAN, there is no skin, joint, visceral or nerve system involvement in this form of the disease. The main clinical signs are tenderness and swelling of the calf. Inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, are usually elevated, and a perinuclear pattern of anti-neutrophil cytoplasm antibodies can be found. Electromyography of the calf is not contributory. Magnetic resonance imaging may be useful in recognizing the limb-restricted vasculopathy and selecting the muscle biopsy site, which is obligatory for diagnosis. Corticosteroids (CS) are the main treatment regimen, but CS-resistant cases have been reported. The patients presented here failed to respond to CS but were successfully treated with intravenous immunoglobulin therapy (IVIG). In the absence of vital organ involvement, the addition of cytotoxic drugs is controversial. IVIG seems to be an efficient alternative therapy in PAN limited to the calf muscles especially for patients with limitations to conventional cytotoxic treatment.

Introduction

Polyarteritis nodosa (PAN) is a necrotizing vasculitis of medium arteries with multi-system manifestations. Systemic PAN is treated with high-dose steroid and cytotoxic treatment (1). A rare form of the disease, limited to a single organ such as the uterus, testes, ovary, cecum or gallbladder, has been described (2-4). Most of these cases were found incidentally in surgically-obtained specimens. As there were no signs of systemic disease, the patients were followed for up to two years without any medication and without any manifestation of progression to systemic vasculitis.

Another rare variant of PAN is necrotizing vasculitis limited to the calf muscles, and prolonged high-dose corticocsteroids (CS) has been the main treatment regimen. Due to a relapse tendency in this form of vasculitis, cytotoxic drugs were added to the treatment of some of these patients (5-7).

Methods

We report two cases of PAN limited to the calf muscles, which were successfully treated with high-dose intravenous gammaglobulins (IVIG) and moderate steroid doses. The review is based on a MEDLINE (PubMed) search of the English literature from 1980 to 2005, using the key words "vasculitis restricted to limbs", "polyarteritis nodosa", and "intravenous immunoglobulin".

Case presentations

Patient 1

A 22-year old previously healthy man presented with a three month history of severe pain in the calves. The pain was aggravated by effort and he noted increasing difficulty on walking. On examination, temperature, blood pressure and peripheral pulses were normal, but the calves were very tender. The strength of the gastrocnemies muscles was moderately reduced. The rest of the physical examination was not contributory. Blood tests revealed

mild hemoglobin (Hb) reduction (10.4 gr%) and thrombocytosis (platelets = 560 x 10 mm^3). The erythrocyte sedimentation rate (ESR) was 80 mm/1st h and the C-reactive protein (CRP) was 200 mg/L (normal < 20 mg/L). Serum electrolytes, liver and kidney function tests, proteins, creatinekinase (CK), aldolase, and urine analysis were normal. Tests for hepatitis B and C, cryoglobulins, rheumatoid factor (RF) and antinuclear factor (ANA) were negative. Protein electrophoresis, levels of immunoglobulins and complement C3 and C4 were normal. The test for antineutrophil cytoplasm antibodies was positive in a perinuclear pattern (pANCA). Electromyography (EMG) of the calf muscles revealed no abnormalities. Biopsy from the left gastrocnemius muscle showed arterial fibrinoid necrosis and lymphocytic infiltration of the vascular walls compatible with PAN. Therapy with CS (prednisone 0.5 mg / kg/day) for one month gave only partial pain relief. After initiation of IVIG (25 g/day for five days), rapid resolution of the symptoms occurred. Steroid dosage was gradually reduced and tapered off after three months. During this period of time, ESR and CRP values returned to normal and pANCA become negative. Over five years of follow-up, no relapses occurred and the patient remained symptom free.

Patient 2

A 27-year old previously healthy woman was referred to our department for severe calf myalgia and difficulty on walking of two months' duration. Her general clinical examination, temperature, blood pressure, and peripheral pulses were normal, but there was severe tenderness and swelling of both calves. Her ESR was 90 m/1st h, CRP was 150 mg/L and Hb was 10.9 gr/%. The rest of the blood count and biochemistry, including muscle enzymes and serum proteins, were within normal range. ANA, RF, ANCA, and cryoglobulins were negative. No signs of deep vein thrombosis were found on Doppler ultrasound. A Techneciu-99m bone scan did not reveal signs of periositis. EMG of the gastrocnemies muscles was normal. Muscle biopsy revealed acute necrotizing arteritis. Her condition improved rapidly after starting on prednisone (1 mg/kg/day). After one month, a slow-rate reduction in CS dosage was started and three months later the patient was pain-free. Her Hb, ESR and CRP tests returned to normal levels, and CS treatment was tapered off to 5 mg daily. A further reduction in CS dose was accompanied by a clinical relapse with appearance of severe leg pain aggravated on walking and standing. On examination, the calf muscles were tender and mildly weak. In the laboratory tests, ESR (65 mm/1st h) and CRP (80 mg/L) were abnormal. EMG did not reveal any abnormalities. Steroid pulse therapy (methylprednisolone 1 g/d for three days) followed by prednisone (30 mg/day for 4 weeks with further reduction) induced only partial relief. Rapid improvement in all clinical aspects (pain, muscle power and walking ability) and inflammatory markers (ESR, CRP) was achieved with a course of IVIG infusions (total 125 g). Six months later, while on prednisone 5 mg/d, another episode of effort pain and weakness in the calf muscles developed. A brief increase of prednisone dose (20 mg/d for 4 weeks) and the addition of weekly 15 mg methotrexate injections led to a slow resolution of effort calf pain.

Discussion

PAN limited to the calf muscles is extremely uncommon (5-10). Clinical features are few: progressive calf pain, tenderness and swelling, inability to walk and, rarely, low-grade fever. Blood tests show only non-specific signs of inflammation: elevated levels of ESR and CRP. While positive cytoplasmic ANCA rule out PAN diagnosis, pANCA against myeloperoxidase may be positive in some of PAN patients (11). Positive pANCA were found in about 25% of PAN cases in Guillevin *et al.* study (12). Recently, the complementary usefulness of skeletal magnetic resonance imaging (MRI) in recognition of the limb-restricted vasculopathy has been demonstrated (8, 13). The technique of MRI contributes to selecting the muscle biopsy site. In some patients concomitant fasciitis of the gastrocnemius muscle has been recognized (9, 10). The precise sensitivity of MRI in this setting has not been established yet; therefore, muscle biopsy and histological confirmation of vasculitis (necrotizing arteritis) are crucial. In all previously documented cases, PAN of the calf muscle was effectively treated with prolonged and high-dose corticosteroids, but sometime the disease was resistant to therapy or had a tendency to relapse (6, 8).

Calf muscle vasculitis might be similar to other forms of limited PAN. It is not clear if limited forms of PAN are a separate entity or only an early and limited presentation of imminent, more severe progressive systemic inflammation. The demonstration of silent kidney aneurysms on selective kidney angiography in a patient with the cutaneous form of PAN, as well as the presence of signs of systemic disease in cases with isolated organ involvement, might add weight to the latter possibility (14-16). Such an approach justifies the addition of cytotoxic drugs in cases of apparently isolated or single organ disease. In view of the side effects of cytotoxic drugs, the use of alternative drug regimens should be considered in cases without vital organ involvement.

For more than two decades, IVIG has been an efficient therapy for various autoimmune disorders: inflammatory neuropathies and myopathies, myasthenia gravis, autoimmune thrombocytopenia, systemic lupus erythematosus, Kawasaki's disease and other systemic vasculitides (17-22). Several mechanisms may explain the action of IVIG: Fc receptor blockade; control of T-cell function; regulation of antibody production by B-cells; interference with cytokines production; regulation of idiotypic-anti-idiotypic reactions (17, 18). Unlike cytotoxic drugs, the side effects of IVIG treatment are relatively rare and in most cases benign. The most common is migraine-like headaches. Sporadic cases of aseptic meningitis, myocardial ischemia and infarction, hemolytic anemia, renal dysfunction, skin rashes, retinal symptoms, and anaphylactic reaction have been reported (23-27).

We present two patients with PAN lim-

ited to the calf muscles. Both patients had no signs of systemic involvement but elevated inflammatory markers. CK and EMG were not contributory. One of the patients had positivity to pANCA. Both our patients failed to respond completely to moderate doses of CS. Cyclophosphamide could be a reasonable choice for treatment of PAN resistant to treatment with steroids (28). In the light of their young age and known effect of cyclophosphamide on fertility, and in order to control the disease earlier, we choose the addition of IVIG to ongoing CS treatment. In the first patient IVIG allowed to achieve and maintain the remission for more then five years. In the second case, the IVIG treatment was effective in controlling the acute disease, but its effect on maintaining PAN remission was insufficient, as the patient needed methotrexate supplementation.

We suggest that, in PAN limited to calf muscles resistant to CS, complementary IVIG treatment might enable the rapid achievement of clinical and laboratory remission and reduction of the CS dosage. IVIG could be an alternative for patients with limitations to conventional aggressive cytotoxic therapy.

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