Joint and muscle pain with mononeuritis multiplex, tetraparesis, and myocardial infarction in a previously healthy adult

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Case report
A 49 year old man presented with a three months' history of symmetrical joint and muscle pain, starting in the elbow region with further extension to the whole body, and weight loss of 11 kg within four months. Laboratory investigation showed an erythrocyte sedimentation rate (ESR) of 100 mm/1st h, leucocytosis of 20.6×10⁹/l, and a massively raised rheumatoid factor. Creatine kinase (CK) and antineutrophil cytoplasmic antibodies (ANCA) were normal. The patient had pain in elbow, wrist, knee, and ankle regions, though no joint swelling was seen. Rheumatoid arthritis was suspected and treatment with steroids and methotrexate was started. Four weeks later, an ascending numbness of the extremities occurred, starting in the left foot and subsequently spreading to both lower legs and forearms. This was accompanied by a progressive muscle weakness. The patient was then referred to our institution.

On admission, the patient presented with a temperature of 38.6°C, severely reduced general condition, blood pressure of 120/95 mm Hg, and a heart rate of 120 beats/min. He had gastric cramps after food intake and could not control bowel movements and urination owing to generalised weakness. Neurological examination showed severe pain on palpation of the proximal extremities and marked impairment of sensibility of the distal extremities as well as generalised hypo/areflexia. In addition, a distally accentuated, almost complete paralysis rendered the patient unable to lift his arms, legs, or head against gravity.

Laboratory investigation at that time showed an ESR of 120 mm/1st h, CK of 1425 IU/l (normal <80 IU/l) with a muscle-brain isoenzyme (CK-MB) of 31 IU/l (normal <10 IU/l or less than 6% of total CK), rheumatoid factor of 719 IU/l, leucocytosis of 21.6×10⁹/l with normal eosinophils, and a C reactive protein (CRP) of 306.3 mg/l. Complement levels were normal. Hepatitis B and C antibodies and HIV testing were negative. ANCA were negative in the beginning and twice during the course of the disease. Urine analysis showed a proteinuria of 120 mm/1st h, with 5–15 leucocytes per high power field without erythrocytes or cellular casts. An ECG and echocardiography were normal. An angiography of the mesenteric arteries showed no aneurysms or vascular occlusions. An EMG of the tibial anterior muscle was equivalent with complete denervation. Sural nerve biopsy (fig 1) showed a necrotising vasculitis of the vasa nervorum as the cause of the acute and further progressive neuropathy; muscle biopsy detected a necrotising myositis (fig 2); immunohistology was not performed. Livedo racemosa of the legs appeared a few days after admission.

Treatment was started with intravenous methylprednisolone, 1000 mg/day for three...
days, with continuous dose reduction to 50 mg on day 10. Intravenous cyclophosphamide, 700 mg/m² body surface every 28 days, was added and prednisolone was tapered to 25 mg one week later. Clinical amelioration of the symptoms occurred rapidly. Increased muscle strength became clinically evident about 10 days after starting the steroid treatment. Gastric cramps also resolved rapidly. The patient regained control over bowel function and urination. CK was back to normal two weeks, and CRP and white blood cell count four weeks, after admission, respectively.

Six weeks after admission, a routinely performed ECG in the asymptomatic patient showed elevations of the ST segment in the anterior leads. Troponin I was markedly raised while CK remained normal. Acute coronarography (fig 3) showed a 90% stenosis of the left anterior descendant artery that could not be discerned from an arteriosclerotic process and was treated by stenting. In addition, multiple distal occlusions of its final branches were seen at the left coronary artery, which had to be interpreted as manifestations of the vasculitic process. Ventriculography showed a reduction of the ejection fraction to 29%.

The acute coronary syndrome was preceded by an otherwise unexplained rise in leucocytes and CRP. Anti-inflammatory treatment was intensified again by giving 100 mg of intravenous prednisolone each day for three days, which was reduced to 75 mg given over eight days. This was followed by 50 mg for four days, 40 mg for another four days, and continued at 30 mg for 15 days until a maintenance dose of 25 mg was given orally. Aspirin, ticlopidine for prophylaxis of stent occlusion, an angiotensin converting enzyme inhibitor, and a β blocker as regular treatment for the acute coronary syndrome were added. Intravenous cyclophosphamide bolus treatment was continued. Under this regimen, the condition of the patient stabilised during the next five months. The control ECG did not reveal a full thickness myocardial infarction rather than a negative T in the thoracic leads V5 and V6 without a Q wave and without R reduction. The patient was able to stand up and walk a few steps with assistance, and able to write some words. The renal function did not deteriorate and the blood pressure remained stable. The clinical picture and the chest x-ray examination showed no pulmonary disease. There was also no sign of hepatic manifestation. Apart from the initial episode of livedo racemosa, no further cutaneous manifestations of vasculitis occurred.

Five months after the acute coronary event, while the patient continued to receive 25 mg methylprednisolone a day, a ptosis of the right eyelid, double vision, and a motor dysphasia appeared, together with an increased temperature of 38°C and another rise in CRP, ESR, and leucocytosis. Examination showed the cerebrospinal fluid was normal. Cerebral magnetic resonance imaging identified multifocal hypointensive lesions in the deep white matter, and a single lesion in the oculomotor region of the midbrain (fig 4), indicating a cerebral manifestation of the vasculitic process. Treatment was started with intravenous immunoglobulin (20 g/day over five days), followed by intravenous prednisolone, 100 mg for five days with decreasing doses thereafter. Afterwards, the above described intravenous cyclophosphamide regimen was changed to the oral administration of 150 mg cyclophosphamide a day, with subsequent reduction to 100 mg/day. With this treatment, together with a stable dose of 25 mg prednisolone, the general condition, motor function, and the left ventricular ejection fraction recovered again. The patient was transferred to a rehabilitation centre. Over the next six months, the patient regained, in part, muscular strength and peripheral sensitivity of his arms and legs. The dose of cyclophosphamide was reduced to 50 mg/day by mouth without relapses.
Discussion
Polyarteritis nodosa (PAN) is a rare disease. Estimates of the annual incidence of PAN-type systemic vasculitis in a general population range from 4.6/1 000 000 in England to 77/1 000 000 in a hepatitis B hyperendemic Alaskan Eskimo population.3 Owing to the variability of the clinical presentation, diagnosis is often difficult and delayed. Presenting symptoms such as joint and muscle pain, weight loss, and malaise are non-characteristic.

In our patient the association of symmetrical joint pain with an increase of rheumatoid factor initially led to the diagnosis of rheumatoid arthritis, though there was no joint swelling and the small joints were not affected. Progression of the disease with development of myositis, mononeuritis multiplex with involvement of visceral nerves, and livedo reticularis made systemic vasculitis probable. The diagnosis was confirmed by muscle and nerve biopsy. The full-blown disease in our patient fulfilled six of 10 criteria for the classification of classical PAN,4 whereas only three are required for the diagnosis.

Clinically asymptomatic involvement of coronary arteries—in addition to a possibly pre-existing arteriosclerosis—resulted in myocardial infarction and severe impairment of the left ventricular ejection fraction. At necropsy, evidence of either active or healed coronary arteritis is found in 50% of patients.5 Congestive heart failure is the main clinical feature of myocardial disease. Reports of coronary angiography in patients with PAN are limited. Spontaneous dissection and aneurysm formation,6 as well as occluded vessels, intimal irregularities,7 and normal findings at coronaryography, have been reported. To our best knowledge, multiple distal occlusions of final branches, as seen in our patient, have not been observed so far. Our treatment of this event was to increase the dose of prednisolone. Another possible option in this situation might have been to switch from intravenous to oral cyclophosphamide. The rapid improvement of the cardiac situation of the patient and the stabilization of his condition over the next five months seemed to justify our procedure at first sight. However, one might argue that the cerebral disease later on might have been avoided by more aggressive treatment. This issue is controversial. Whereas some authors suggest that an oral and intravenous regimen has equal potential in the treatment of systemic vasculitides,8 others report the success of oral cyclophosphamide after the failure of the bolus treatment,9 a finding that is supported by the course of our patient.

After recovering from the first episode of the disease, our patient relapsed with central nervous system (CNS) disease. According to the five factor score of Lhote and Guillemin10 this could be seen as another negative prognostic factor, in addition to the cardiac involvement. The presence of two of the following five factors (proteinuria of more than 1 g/24 h, gastrointestinal tract involvement, renal insufficiency with a creatinine level exceeding 140 µmol/l, CNS disease, and cardiomyopathy) has been shown to be associated with a five year mortality of 46%.

Patients with relapses of PAN while receiving immunosuppressive treatment often present as a diagnostic dilemma because infections may mimic a flare of the vasculitis. In the case presented here, a central nervous infection—namely, cerebral toxoplasmosis, was considered; but imaging studies, as well as an analysis of the cerebrospinal fluid, did not support this hypothesis.

Fortunately, the occurrence of a cerebral vasculitis in PAN is rare. It has been reported to occur in 3–28% of patients with PAN. Palsies of the cranial nerves are present in less than 2% of cases.9 In contrast, peripheral neuropathy is one of the most common symptoms and often occurs early in the course of the disease. Mononeuritis multiplex, which was seen in our patient, is the classical form, but other neuropathies, such as polyneuropathy and extensive mononeuropathy, are reported as well. The time point at which CNS disease occurred in our patient confirms other reports, which describe the occurrence of CNS abnormalities preferentially after the disease is established.10

Except for a mild and transient mixed proteinuria, our patient had no renal disease. The absence of glomerulonephritis distinguishes PAN from microscopic polyangiitis.11

Involvement of the mesenteric arteries can result in bowel infarction and is often one of the most severe manifestations of PAN. Although the abdominal cramps were suggestive of bowel ischaemia in our patient, the respective angiography was normal. However, occlusions of smaller arteries might have remained undetected.

The initial treatment of PAN with methylprednisolone and cyclophosphamide bolus therapy in our patient was effective in reducing the severe flare of the disease on admission. However, it did not prevent the coronary involvement and the CNS manifestation of the disease. In contrast, oral cyclophosphamide has been effective in preventing further relapses up to the present day. Responses to intravenous immunoglobulins (IVIg) have been reported.12 In our patient, IVIg were applied for the acute treatment of CNS disease, in order not to over-suppress the immune system until CNS infection was ruled out. Because steroids and oral cyclophosphamide were applied shortly after IVIg, the contribution of the immunoglobulins to the clinical response cannot be defined with clarity.

Lessons
• Mononeuritis multiplex is a common symptom of PAN.
• Involvement of peripheral nerves precedes involvement of the CNS.
• Myocardial infarction in PAN is often clinically asymptomatic.
• Immunosuppressive treatment with steroids and cyclophosphamide bolus therapy does not always prevent relapses of the disease.


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