

Systemic vasculitis with bilateral perirenal haemorrhage in chronic myelomonocytic leukaemia

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Abstract

The cases of two patients with chronic myelomonocytic leukaemia associated with periarteritis nodosa-like, antineutrophil cytoplasmic antibody negative, systemic vasculitis, are reported.

A 61 year old man was admitted with fever, diffuse myalgia, and abdominal pain. Blood and bone marrow examination showed chronic myelomonocytic leukaemia. Vasculitis of the gall bladder was responsible for acalculous cholecystitis. A massive spontaneous bilateral perirenal haemorrhage occurred. A 73 year old woman with chronic myelomonocytic leukaemia had been followed up for one year when unexplained fever occurred. Two months after the onset of fever, sudden abdominal pain was ascribed to spontaneous bilateral renal haematoma related to bilateral renal arterial aneurysms. Neuromuscular biopsy showed non-necrotising periarteriolar inflammation.

To our knowledge, systemic vasculitis has never been reported in chronic myelomonocytic leukaemia. In our two cases a non-random association is suggested because (a) chronic myelomonocytic leukaemia is a rare myelodysplastic syndrome, (b) spontaneous bilateral perirenal haematoma is not a usual feature of periarteritis nodosa.

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Chronic myelomonocytic leukaemia is a rare myelodysplastic syndrome.¹ Some authors also classify chronic myelomonocytic leukaemia in the myeloproliferative syndrome group rather than the myelodysplastic syndrome group, as proliferative symptoms, such as splenomegaly or polyadenopathy, can dominate the clinical picture.¹

Extrahaematological features associated with the myelodysplastic syndrome mainly include cutaneous and rheumatological manifestations. Other reports suggest a non-random association of refractory anaemia with autoimmune disorders or vasculitis.²

We report on two patients with chronic myelomonocytic leukaemia associated with periarteritis nodosa-like systemic vasculitis.

Case reports

PATIENT 1

A 61 year old man was admitted with high grade fever (40°C), weight loss, and diffuse polymyalgia, which he had had for three weeks. Physical examination was otherwise normal. Blood examination showed a white blood cell count of $29 \times 10^9/l$ and the differential was $9.2 \times 10^9/l$ neutrophils, $1.75 \times 10^9/l$ lymphocytes, $0.58 \times 10^9/l$ eosinophils, and $7.54 \times 10^9/l$ monocytes. Haemoglobin was 83 g/l and the platelet count $101 \times 10^9/l$. C reactive protein was 339 mg/l (normal <6 mg/l). A peripheral smear showed less than 5% of blasts and no dysplastic monocyte. The bone marrow specimen was hypercellular with normal erythroid activity, dystrophic megakaryocytes, increased number of monocytes, and blasts evaluated at 20%, suggestive of chronic myelomonocytic leukaemia. No infection could be elicited and treatment with wide spectrum antibiotics was prescribed, but had no effect on the fever.

Ten days later, pain occurred in the right upper quadrant. An abdomen ultrasound study showed increased thickness of the gall bladder. Because of acalculous cholecystitis, a cholecystectomy was performed. Histological analysis of the gall bladder showed vasculitis affecting medium sized arteries of the gallbladder wall (fig 1). Four weeks after surgery, the patient had a sudden haemorrhagic shock, caused by bilateral massive renal haematoma (fig 2). Angiography of the renal arteries was considered normal. Viral serologies (hepatitis A, B, and C viruses, Epstein-Barr virus, and human immunovirus), cryoglobulins, rheumatoid factor, lupus anticoagulant, antibodies to nuclear antigens, cardiolipin, and neutrophil cytoplasmic antigen were absent or non-reactive. Serum complement levels were normal. No monoclonal protein was detected by serum immunoelectrophoresis. Four episodes of haematochezia occurred. Gastroduodenoscopy was normal.

Treatment with corticosteroids was given (methylprednisolone 500 mg/d for three days, then oral prednisone 1 mg/kg/d). Within 10 days, fever, asthenia, and weight loss disappeared. C reactive protein blood levels decreased. Three weeks after the start of treatment, a colonoscopy was performed because of recurrent haematochezia. Colonoscopy was complicated by intestinal perforation. During surgery, ischaemic segments 5-10 cm long were disclosed on the small bowel. The patient died from peritonitis and septic shock.

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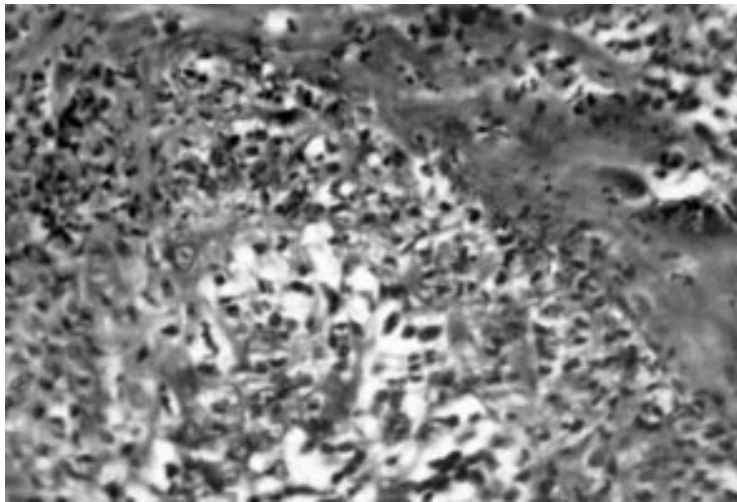


Figure 1 Gallbladder specimen. Arteriolar wall infiltration with polymorphonuclear neutrophils (haematoxylin and eosin $\times 250$).



Figure 2 Abdomen computed tomographic scan showing massive bilateral perirenal blood collection.

A postmortem histological study of the kidneys did not show vasculitis. The digestive tract was not analysed.

PATIENT 2

A 73 year old woman was admitted with high grade fever and polymyalgia, which she had had for almost two months. She had a one year history of uncomplicated and untreated chronic myelomonocytic leukaemia. Laboratory tests showed an increased white blood cell count up to $22.5 \times 10^9/l$ and the differential was $8.775 \times 10^9/l$ neutrophils, $8.1 \times 10^9/l$ monocytes, and $5.125 \times 10^9/l$ lymphocytes. Haemoglobin was 88 g/l and the platelet count was $101 \times 10^9/l$. The peripheral blasts count was below 5%. The C reactive protein level was 287 mg/l (normal <6 mg/l). Bone marrow examination showed normal cellularity, with increased monocytosis and medullar blasts rate at 16%. No cytogenetic abnormality was detected. Temporal arteritis was first suspected because of headache and scalp pain. A temporal artery biopsy was performed, but histological findings were negative.

One month later, a calf deep vein thrombosis was diagnosed by Doppler study of the leg. A chest angioscan was performed to exclude a



Figure 3 Selective renal angiography showing intraparenchymatous microaneurysms.

pulmonary embolism and showed distal aortic dissection, type III of de Bakey classification. The patient was then treated with low molecular weight heparin.

One month later, she was admitted to the intensive care unit, because of haemorrhagic shock due to massive spontaneous bilateral renal haematomas. The renal arteriography showed intraparenchymal microaneurysms in both kidneys (fig 3). No antibodies to hepatitis A, B, C viruses or human immunovirus were detected. Testing for antinuclear antibodies, cryoglobulins, or antineutrophil cytoplasmic antibodies was negative or normal. Serum rheumatoid factor was positive—latex was at 87.5 IU/ml (normal <20), but the Rose-Waaler test was negative. A direct Coombs test was negative. The total serum immunoglobulin concentration was high at 35.9 g/l, but no monoclonal component was detected by serum and urine immunoelectrophoresis. Electromyography of the arms and legs showed an axonal peripheral neuropathy in both sural nerves. Sural neuromuscular biopsy showed a vasculitis of small arteries, with non-necrotising periarteriolar inflammation.

Corticosteroid treatment was given daily with oral prednisone 1 mg/kg in association with intravenous cyclophosphamide treatment. Fever, asthenia, and diffuse polymyalgia improved in a few weeks. CRP was normal after the first month of treatment. The patient had a sudden digestive haemorrhage and died at home, two months after the start of treatment.

Discussion

Systemic vasculitis could be defined in both our patients. In patient 1 the association of histologically proved arteriolar vasculitis of the

gall bladder and spontaneous bilateral renal haematomas was suggestive of periarteritis nodosa. In patient 2 the association of microvasculopathy on the nerve biopsy specimen and spontaneous renal haematomas related to arteriolar microaneurysms in both kidneys was also highly evocative of periarteritis nodosa. Other causes of spontaneous renal haematoma, such as renal tumour, vasculopathy, infection, or renal cystic disease, were reasonably excluded. Interestingly, although only a few cases of bilateral renal haematoma have been reported in periarteritis nodosa, another case was recently described in association with refractory anaemia with excess blasts in transformation.^{3,4}

An increased incidence of immunological abnormalities has been reported in patients with the myelodysplastic syndrome, including a raised level of serum polyclonal immunoglobulins, monoclonal gammopathy, and various organ-specific or non-organ-specific autoantibodies.^{2,5} Clinical extrahaematological manifestations associated with myelodysplasia mostly include cutaneous and rheumatic features. In a retrospective study 16 of 162 patients with myelodysplasia (10%) had systemic findings, with a sex ratio of men to women of 3:1. Most patients with extrahaematological findings had refractory anaemia with excess blasts class.⁶

In 1981 Dreyfus *et al* reported the first six cases of the myelodysplastic syndrome associated with leucocytoclastic vasculitis.⁷ Since then, about 20 other cases have been reported, mostly in men over 65 years old. Histologically, cutaneous vasculitis affects small vessels and is characterised by both perivascular inflammatory infiltrates and vessel wall damage.⁸ Of note, chronic myelomonocytic leukaemia-associated cutaneous periarteritis nodosa has also been reported.⁹ Cutaneous features usually improve with corticosteroid treatment. In patients with the myelodysplastic syndrome, rheumatic manifestations occur mostly as acute peripheral seronegative polyarthritis affecting the wrist, metacarpophalangeal, proximal interphalangeal, shoulder, and knee joints. The other common clinical presentation is an asymmetrical migrating oligoarthritis limited to the large joints.⁶ Radiological studies show no erosive disease. Most often, the clinical course is not altered by non-steroidal anti-inflammatory agents, whereas corticosteroids bring about dramatic improvement.

Systemic features, such as pleuritis, pericarditis, mononeuritis multiplex, myositis, glomerulonephritis, episcleritis, or inflammatory colitis, have also been reported in the myelodysplastic syndrome, related to a vasculitic process. Indeed, a bilateral pulmonary vasculitis and an epididymic vasculitis have been reported in two men with refractory anaemia.¹⁰ Moreover, as in our patients, systemic vasculitis shown by spontaneous bilateral renal haemorrhage has also been reported in a 63 year old woman with a refractory anaemia with excess blasts in transformation.⁴

On the other hand, defined "classic" systemic diseases have also been reported in association with the myelodysplastic syndrome, including systemic vasculopathies (temporal arteritis and polymyalgia rheumatica, Henoch-Schönlein-type purpura, Behçet's disease, periarteritis nodosa), autoimmune diseases (lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, mixed connective tissue disease, systemic sclerosis), or "inflammatory diseases" (Crohn's disease, Shulman fasciitis).^{2,4,11,12} In all cases, mostly presented as single reports, a fortuitous association could be postulated. In contrast, a strong association appears to exist between the myelodysplastic syndrome and relapsing polychondritis. Actually, the reported prevalence of myelodysplastic features in relapsing polychondritis is 10–28%, affecting predominantly older men and often accompanied by cutaneous vasculitis.^{2,13}

The mechanisms causing vasculitis in the myelodysplastic syndrome are unknown. Quantitative or qualitative abnormalities of antibodies have been ascribed to immune dysregulation or clonal involvement, or both, of the B lymphocyte lineage. One possible explanation might be abnormal stimulation of T and B lymphocytes by antigenic dysplastic bone marrow stem cells. Besides the involvement of T or B cells, macrophage clearance of antigens may be greatly reduced, leading to enhanced levels of circulating immune complexes. In chronic myelomonocytic leukaemia, a high number of circulating monocytes might also contribute to vessel inflammation.¹⁴ Interestingly, numerous and complex karyotype abnormalities in the myelodysplastic syndrome seem to be associated with extrahaematological manifestations and carry a worse prognosis.¹⁵

In conclusion, a non-fortuitous association seems to exist between chronic myelomonocytic leukaemia, which is a rare myelodysplastic syndrome, and systemic vasculitis with bilateral spontaneous renal haematoma, which is not a common feature in periarteritis nodosa. More generally and practically, when unexplained systemic findings occur in patients older than 55, bone marrow or, at least a blood smear careful examination, should be performed in search of an underlying myelodysplastic syndrome.

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