Lymphoplasmacytic lymphoma associated with polyradiculoneuritis and cryoglobulinemia mimicking polyarteritis nodosa

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Introduction > Systemic vasculitis is sometimes associated with malignant blood disease.
Case > We describe the case of a 77-year-old woman who had extensive livedo racemosa, acute polyradiculoneuritis, and meningeal hemorrhage. The skin biopsy showed evidence of necrotizing angitis. This vascular involvement resembled polyarteritis nodosa (PAN). Despite corticosteroid and cyclophosphamide treatment, the polyradiculoneuritis worsened and the patient died of acute respiratory failure. Type II cryoglobulinemia was detected late, and the autopsy revealed lymphoplasmacytic lymphoma involving the spleen and infiltrating nerve roots, together with necrotizing angiitis involving small-sized arteries.
Conclusion > This case shows that necrotizing angiitis involving small arteries may occur with type II cryoglobulinemia.

Résumé

Lymphome lymphoplasmocytique associé à une polyradiculonévrite et à une cryoglobulinémie imitant une polyarthrite noueuse

Introduction > Les vascularites systémiques peuvent parfois révéler une hémopathie maligne.
Observation > Nous rapportons l’observation d’une patiente de 77 ans ayant un livédo racemosa, une polyradiculonévrite aiguë et une hémorragie méningée, en rapport avec une vasculite nécro-sante prouvée sur une biopsie cutanée. Malgré un traitement par corticoïdes et cyclophosphamide, on a assisté à une aggravation de la polyradiculonévrite, puis au décès de la patiente par détresse respiratoire aiguë. Une cryoglobulinémie de type II a été mise en évidence 2 jours avant le décès et l’autopsie a révélé un lymphome lymphoplasmocytique touchant la rate et infiltrant les racines nerveuses ainsi que des lésions de vascularites nécro-santes.
Conclusion > Cette observation montre que les vascularites nécro-santes touchant les vaisseaux de petit calibre peuvent être associées à une cryoglobulinémie de type II.
Polyarteritis nodosa (PAN) is characterized by fibrinoid necrosis of medium- and small-sized arteries [1]. Its cause is most often unknown, but it may follow immune-complex deposition, as observed in cases of hepatitis B virus (HBV) [2], or be associated with a solid tumor or malignant blood disease [3]. We report here the case of a 77-year-old woman who had livedo racemosa and polyradiculoneuritis, with histological evidence of necrotizing angiitis of dermal arteries. Despite intravenous methylprednisolone and cyclophosphamide, the polyradiculoneuritis worsened and the patient developed respiratory failure and died. Cryoglobulinemia was detected late. The autopsy found lymphoplasmacytic lymphoma in the spleen and infiltrating nerve roots.

Case report

A 77-year-old woman was hospitalized in our unit on May 1, 2000, for livedo racemosa and distal sensory and motor deficiencies of all 4 limbs, all of which had worsened over the preceding month. She had a history of hypertension, which had been treated with ramipril (5 mg/day). At admission, she was febrile, with blood pressure of 170/100 mm Hg and a pulse of 80 beats/min. Her abdomen was distended, without evidence of hepatomegaly or splenomegaly. Livedo racemosa covered all four limbs, the trunk, neck, and face. Deep tendon reflexes were absent, and predominantly distal severe motor and sensory deficits were noted in all 4 limbs. Chest radiographs showed a raised dome of the left diaphragm. Blood count findings included: 7600 leukocytes/mm³ with 6900 neutrophils/mm³ and 300 lymphocytes/mm³; hemoglobin 11.1 g/dL; normal mean corpuscular volume, reticulocytes and peripheral blood smear were normal; creatinine 1.58 mg/dL, C-reactive protein 113 mg/L (n < 6), and fibrinogen 4.5 g/L (n < 4); creatine phosphokinases 1440 IU/L (n < 230), ASAT 116 IU/L (n: 10-50), ALAT 105 IU/L (n: 8-37), alkaline phosphatase 143 IU/L (n: 28-93), gamma glutamine transferase 116 IU/L (n: 10-50), ALAT 105 IU/L (n: 8-37), alkaline phosphatase 143 IU/L (n: 28-93), gamma glutamine transferase 116 IU/L (n: 10-50), and lactate dehydrogenase 143 IU/L (n: 28-93), gamma glutamine transferase 116 IU/L (n: 10-50), ALAT 105 IU/L (n: 8-37), alkaline phosphatase 143 IU/L (n: 28-93), gamma glutamine transferase 116 IU/L (n: 10-50), and lactate dehydrogenase 143 IU/L (n: 28-93). Peripheral blood and urinary immuno fixation tests were negative as were serological tests for HBV, hepatitis C virus (HCV), human T lymphotropic virus (HTLV) 1 and 2, human immunodeficiency virus (HIV) 1 and 2, and polymerase chain reaction (PCR) for HCV. Lumbar puncture showed meningeal hemorrhage. Electromyography of all limbs showed reduced motor and sensory potentials and muscle involvement. Brain computed tomography was normal; magnetic resonance imaging detected a lacuna of the left lenticular nucleus and hyperintense (bright) cortical signals close to the vermis. A skin biopsy contained necrotizing vasculitis lesions involving dermal arteries, but immunofluorescence studies were negative.

On May 3, treatment began: 3 boluses of methylprednisolone (15 mg/kg/d) followed by prednisone (1 mg/kg/day) and one intravenous infusion of cyclophosphamide (0.5 g/m²). One week later, the peripheral motor deficiency worsened and the patient developed respiratory insufficiency. Insulin-dependent diabetes mellitus occurred, together with urinary infection by Proteus mirabilis and Staphylococcus aureus septicemia. Despite appropriate antibiotic treatment, the patient developed acute respiratory failure and died on May 16, 2000. Two days earlier, blood samples had shown type II cryoglobulinemia, detected with monoclonal kappa IgM and polyclonal IgG components measured at 1.15 g/L.

At autopsy, macroscopic examination confirmed the meningeal hemorrhage and found splenomegaly (640 g). Histological examinations showed vasculitis with fibrinoid necrosis lesions of the small (diameter of 100 μm) arteries of the psoas, kidneys and liver (figure 1). The splenic parenchyma showed lymphoid infiltration predominantly at the marginal zone of white pulp with small aggregates in the red pulp (figure 2). This neoplastic infiltrate was composed of occasional immunoblasts, small lymphocytes, and lymphoplasmacytic cells with frequent Dutcher bodies (intranuclear periodic acid-Schiff-positive pseudoinclusions). Lymphoplasmacytic infiltrates were also seen in mediastinal lymph nodes and connective tissues close to the nerve trunk (figure 3), several distal nerves and the subserosa of the colon and bladder.

Figure 1
Sample of muscle with a necrotizing vasculitis image of a small artery
Hematoxylin-eosin; original magnification x 400.
Immunohistochemistry on paraffin sections showed tumor cells to be CD20+, CD5- and CD23- with cytoplasmic IgM. Unfortunately, labeling with anti-light chain antibodies was not specific, probably due to postmortem artefacts. Neither vasculitis nor lymphoid proliferation was found in the brain.

Discussion

Our patient presented with extensive livedo, severe peripheral neuropathy, renal insufficiency and histological evidence of necrotizing angiitis. These signs resembled PAN. Although the spleen was not palpable because of abdominal distension, the hypogammaglobulinemia and lymphopenia, together with mixed cryoglobulinemia, were suggestive of malignant lymphoma. In this patient, mixed cryoglobulinemia might have been due to lymphoplasmacytic lymphoma. Unfortunately, light chains from the cryoprecipitate and lymphoplasmacytic infiltrate could not be compared for technical reasons.

Cryoglobulinemia associated with B-cell lymphoproliferation may lead to systemic vasculitis [4], which usually corresponds to leukocytoclastic infiltration of small vessels. However, few reports mention necrotizing vasculitis [5, 6].

In the absence of cryoglobulinemia, vasculitides of the PAN group have been reported to be associated with hairy-cell leukemia, acute myeloblastic leukemia, multiple myeloma, Waldenström’s macroglobulinemia, Hodgkin’s disease, and non-Hodgkin’s lymphoma. The clinical presentation usually involves microscopic polyangiitis, but antineutrophil cytoplasmic antibodies (ANCA) are usually absent [3]. In hairy-cell leukemia, tumor cells infiltrate the artery wall [7] and antibody molecular mimicry has been reported [8].

We were not able to identify the cause of our patient’s meningeal hemorrhage. Subarachnoid hemorrhage secondary to necrotizing vasculitis involving the anterior spinal artery has been reported in a patient with mixed cryoglobulinemia [5]. Peripheral neuropathy represents one of the major clinical features of PAN [9] and cryoglobulinemia-associated vasculitis [3], but to the best of our knowledge, polyradiculoneuropathies has not been described in association with these diseases. Peripheral nervous system abnormalities occur in 5% of the patients with lymphoma, due to one of the following causes: direct meningeal propagation or neurotoxicity from chemotherapy, direct propagation of malignant cells into the peripheral nerves, monoclonal IgM with anti-myelin activity, Guillain-Barré syndrome or chronic demyelinating polyneuropathy, or other unidentified paraneoplastic mechanisms [10]. We think that lymphoplasmacytic infiltration of nerve roots is likely the mechanism at play in our patient.

In conclusion, necrotizing angiitis involving small arteries may be observed with cryoglobulinemia.
References


