CASE REPORT

Renal Involvement in Multicentric Castleman Disease With Glomeruloid Hemangioma of Skin and Plasmacytoma

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• **A 47-year-old man presented with fever of unknown origin, generalized weakness, edema, and renal failure. He had left-sided pleural effusion, generalized lymphadenopathy, multiple nontender cutaneous nodules, hepatomegaly, renal failure, and hypergammaglobulinemia. Axillary lymph node biopsy showed findings consistent with Castleman disease of the hyaline vascular type associated with interfollicular plasmacytosis. A renal biopsy performed in view of proteinuria and acute renal failure showed hypercellular glomeruli with capillary loop thickening and double contours consistent with membranoproliferative glomerulonephritis. Skin nodule biopsy showed a glomeruloid hemangioma characterized by dermal proliferation of capillary loops in a nodular manner resembling a glomerulus. He experienced clinical and biochemical remission with steroids. Discontinuation of steroid therapy was associated with recurrence of renal failure, reappearance of nodules, lymphadenopathy, and appearance of bony lytic lesions. Biopsy of bony lytic lesions showed plasmacytoma. The patient achieved complete remission on treatment with steroids and cyclophosphamide and is free of symptoms at the end of 40 months of follow-up. To our knowledge, this is the first case report of the occurrence of membranoproliferative glomerulonephritis, glomeruloid hemangioma of the skin, and plasmacytoma in a patient with multicentric Castleman disease without human immunodeficiency virus infection. *Am J Kidney Dis* 48:E17-E24.**

INDEX WORDS: Multicentric Castleman disease; membranoproliferative glomerulonephritis; glomeruloid hemangioma of skin; plasmacytoma; nephrotic syndrome; interleukin 6 (IL-6); vascular endothelial growth factor (VEGF).

CASTLEMAN DISEASE, or angiofollicular lymph node hyperplasia, is a group of complex disorders causing nonmalignant proliferation of lymphoid tissue throughout the body. Clinically, Castleman disease may be unicentric or multicentric. Histologically, it is classified into the common hyaline vascular type seen in 90% of cases, the less common plasma cell type, and a mixed form. Localized disease can be divided into hyaline vascular type or plasma cell type. Multicentric Castleman disease (MCD) usually is associated with the plasma cell variant, but association with hyaline vascular and mixed types also are described. Most recently, an aggressive plasmablastic variant of MCD is described.[1]

MCD commonly is seen in patients with human immunodeficiency virus (HIV) infection, older individuals with Kaposi sarcoma, and also in HIV-negative individuals. Independent of HIV infection, MCD occurs in the setting of immunoregulatory dysfunction. MCD is considered an aggressive disorder characterized by a waxing and waning course over long periods.[2] In patients with MCD, renal involvement is an uncommon secondary phenomenon related to immune dysregulation. Renal manifestations include nephrotic syndrome, acute renal failure, thrombotic microangiopathy, amyloidosis, and renal lymphoma. We present a case of multicentric Castleman disease of the hyaline vascular type with interfollicular plasmacytosis associated with membranoproliferative glomerulonephritis (MPGN). This patient also had plasmacytoma in the ribs and skin nodules, with histological examination showing glomeruloid hemangioma. In this context, we also discuss clinical manifestations, pathogenesis, and treatment of MCD, with special emphasis on renal involvement and glomeruloid hemangioma of the skin.

CASE REPORT

In July 2001, a 47-year-old man was admitted to our hospital with low-grade fever, generalized weakness, cough, dyspnea, edema, and macrohematuria. He had experienced weight loss of 10 kg during 6 months, small-joint arthritis, bilateral tender gynecomastia, and painless swellings over

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the scalp, upper limbs, and left side of the chest. One month before admission, he had received antituberculous treatment in view of prolonged fever, night sweats, and left-sided pleural effusion. Because there was no improvement, he was admitted for further evaluation. Physical examination showed a well-built middle-aged man who was pale, with facial puffiness, bilateral pitting pedal edema, and bilateral tender gynecomastia. Blood pressure was 150/86 mm Hg. He had bilateral multiple firm rubbery nontender cervical, axillary, and inguinal lymph nodes and hepatomegaly. There were multiple nontender cutaneous nodules over the scalp and extensor surface of the upper limbs. A diffuse subcutaneous 6 × 4–cm swelling was present over the left sixth and seventh ribs in the midaxillary line, which was nontender, hard, and fixed to the bone. Cardiovascular and neurological examination showed no abnormalities.

Laboratory evaluation showed a hemoglobin level of 10 g/dL (100 g/L) and white blood cell count of 9,800/μL, with 6,860 neutrophils/μL. Platelet count was 250,000/μL, and erythrocyte sedimentation rate was 110 mm/h. There was macrohematuria with red blood cell casts and proteinuria of 2 g/d. Results of biochemical investigations showed the following values: blood urea nitrogen, 26 mg/dL (9.28 mmol/L); serum creatinine, 3.5 mg/dL (309 μmol/L); serum calcium, 8.6 mg/dL (2.15 mmol/L); phosphorus, 3.5 mg/dL (1.13 mmol/L); and uric acid, 16.1 mg/dL (958 μmol/L). Results of liver function tests were as follows: alanine aminotransferase, 23 IU/L; aspartate aminotransferase, 20 IU/L; serum alkaline phosphatase, 273 IU/L; total protein, 6 g/dL (60 g/L); albumin, 2.7 g/dL (27 g/L); serum bilirubin, 0.8 mg/dL (14 μmol/L); and serum cholesterol, 104 mg/dL (2.6 mmol/L). Serum protein electrophoresis showed hypergammaglobulinemia with no monoclonal band and hypoalbuminemia.

Chest radiograph showed interstitial infiltrates and left-sided pleural effusion. Ultrasound scanning of the abdomen showed hepatomegaly; normal-sized echogenic kidneys, and left pleural effusion. Pleural fluid studies showed 4 g/dL (40 g/L) of protein and 55 cells/μL: 46% polymorphs, 54% lymphocytes, numerous red blood cells, and scanty macrophages. There were no malignant cells. Bacterial cultures were sterile. Autoantibodies, including antinuclear and antineutrophil cytoplasmic antibodies, were negative. Hepatitis B, hepatitis C, syphilis, and HIV screening were negative. CD4 and CD8 counts were normal. Collagen vascular disease workup also was negative.

Bone marrow examination, performed in view of anemia, hypergammaglobulinemia, and hyperuricemia, showed mild erythroid hyperplasia with normoblastic and micronormoblastic maturation. Myeloid series was mildly proliferative with predominant mature forms and 15% plasma cells. Megakaryocytes were normal. Histological examination of the axillary lymph node showed angiofollicular lymphoid hyperplasia with interfollicular plasmacytosis. Lymphoid aggregates contained varying degrees of hyalinization and were interspersed with capillaries suggestive of the hyaline vascular type of Castleman disease. However, the interfollicular plasmacytosis was a feature frequently seen in patients with the plasma cell type of Castleman disease (Fig 1).

Biopsy of the cutaneous nodule from the hand showed glomeruloid hemangioma, a neoplasm composed of proliferating vascular channels. Ectatic vascular channels with intravascular growth of papillary tufts of capillaries were noted (Fig 2).

Renal biopsy (light microscopy with hematoxylin and eosin) showed glomeruli with diffuse proliferation, fibrillary mesangial change, capillary loop thickening, and double contours. There were 3 to 4 glomeruli with segmental ectatic capillary loops and mesangiolysis. One artery showed focal mild intimal thickening. There was mild diffuse interstitial inflammation consisting of lymphocytes, plasma cells, and occasional neutrophils. Marked interstitial edema was present, separating the tubules. Mild interstitial fibrosis affecting less

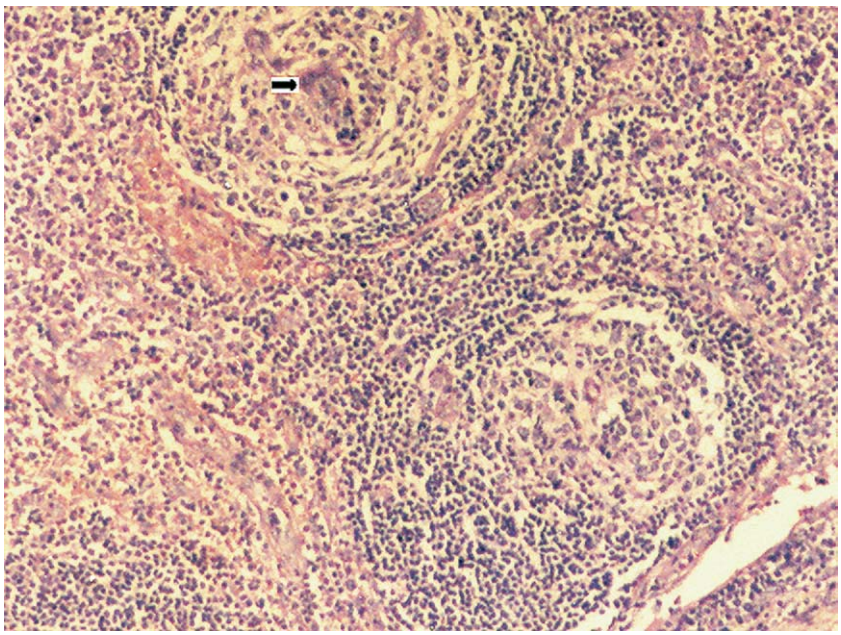

Fig 1. Light micrograph of lymph node biopsy specimen from the axilla (10 μm) shows follicle-like lymphoid structures interspersed with capillaries showing hyalinization, interfollicular vascular proliferation, and sheets of plasma cells. (Hematoxylin and eosin stain.)