Dear Sir,

We describe a patient with cryoglobulinemia (CG) type II and secondary glomerulonephritis who had chronic severe neutropenia since his childhood. Treatment of the CG with prednisone, plasmapheresis, and cyclophosphamide progressively improved both conditions. A 24-year-old man was found to have neutropenia when admitted to the hospital with acute appendicitis. Over the next 3 years the patient suffered from aphthous ulcerations of the mouth. He was again admitted to hospital, at the age of 27, for treatment of leg ulcers. The biopsy specimen revealed a necrotizing vasculitis. Hepatosplenomegaly was noted.

Leukopenia and neutropenia persisted (white blood cell count 2,400/mm³, 7% neutrophils, 3% band forms). Repeated hemograms ruled out a cyclic neutropenia. The bone marrow aspirate was normocellular, with 58% granulopietic cells of different stages and normal morphology. Some plasma cells, macrophages, and myelocytes were found. No polymorphonuclear cells were detected. Hypocomplementemia was present: low C3, C4, and CH50 levels. The immunoglobulin levels were higher than normal. Kappa light chains were detected in urine samples. No monoclonal fraction was found. At this stage the patient was diagnosed as having idiopathic neutropenia, and a splenectomy was performed. No improvement in the granulocyte count was obtained. Over the next 12 years he presented occasional aphthous lesions of the mouth without any other manifestation.

At the age of 39 years he was again admitted to hospital because of retrosternal pain, intermittent low-grade fever, asthenia, and arthralgia in both hands with no evidence of arthritis or radiological articular affection. The clinical and electrocardiographical changes pointed to an acute pericarditis, so the patient received nonsteroidal anti-inflammatory drugs. Laboratory tests disclosed an erythrocyte sedimentation rate of 86 mm during the 1st h, leukocyte count 3,030 cells/mm³ (7% neutrophils, 1% band forms), hypocomplementemia, hypergammaglobulinemia with an elevated index of IgM, a positive latex test (titer 1/320), a positive Rose-Waaler test (titer 1/80), and antinuclear antibodies (titer 1/50). A renal test disclosed proteinuria of 1.2 g/24 h, microhematuria, and a serum creatinine level of 88.4 μmol/l (1 mg/dl).

Although therapy with cortisone at a dose of 1 mg/kg/day (70 mg/day) was begun, the patient developed a nephrotic syndrome with proteinuria of 12 g/24 h, arterial hypertension, and a purpuric maculopapular eruption, and the serum creatinine level raised to 177 μmol/l (2
(mg/dl). A skin biopsy was performed, showing necrotic vasculitis. The renal biopsy disclosed an endocapillary proliferative glomerulonephritis, accentuated lobulation, peripheral basement membrane duplication, and an occupation of the capillary lumen by eosinophilic hyaline material. Immunological study showed the presence of C3 and IgG in an intense granular diffuse subendothelial distribution. This type of glomerular involvement raised the suspicion of a cryoglobulinemic affection of the kidney. Specific tests to diagnose this entity were performed: cryoglobulins were positive (cryocrit 66.6%), and immunoelectrophoresis demonstrated a monoclonal IgM kappa in serum and urine, with rheumatoid factor activity, and a polyclonal IgG. The patient was diagnosed as having mixed CG with secondary mesangiocapillary glomerulonephritis. Plasmapheresis and immunosuppressive therapy with cyclophosphamide were instituted because of ineffectiveness of cortico-steroid alone. The patient received twelve sessions of plasmapheresis and a daily dose of 50 mg of cyclophosphamide. The white blood cell count after twelve plasmapheresis sessions was 5,000/mm³, creatinine 90 µmol/l (1.5 mg/dl), and the 24-hour proteinuria was 10 g. Two years after beginning of the therapy, with a daily dose of 50 mg cyclophosphamide, the proteinuria decreased to 0.9 g/24 h, the cryocrit was less than 10%, and the leukocyte count reached 9,930 leukocytes/mm³ with 77.8% granulocytes (fig. 1). X-rays of the joints did not reveal erosions.
The most perplexing feature of this case is the complete reversal of the chronic neutropenia after treatment of the CG (fig. 1). This is against the normal experience, as usually an improvement of the clinical picture of CG is seen with a control of polymorpho-nuclear cells during immunsuppressive or cytostatic treatment. The CG was of type II, with a monoclonal IgM kappa with rheumatoid factor activity and a polyclonal IgG. The patient had many of the clinical features that characterize this entity, such as necrotizing vasculitis, arthralgia, and mesangiocapillary glomerulonephritis [1,2]. Most of the laboratory findings were also consistent with this diagnosis: positive rheumatoid factor, elevated erythrocyte sedimentation rate, elevated transaminase levels, low positive antinuclear antibody levels, and hypocomplementemia. Type II CG can be essential or secondary to infectious, autoimmune, or lymphoproliferative diseases. The patient did not have any known disease that could be related to CG. It

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Fig. 1. Evolution of leukocyte count and cryocrit level.

is difficult to establish a linkage between neutropenia, splenomegaly, and CG. Some authors favor the diagnosis of Felty’s syndrome when neutropenia and splenomegaly are present and bone erosions appear later [3-6]. But to our knowledge there has not been diagnosed any patient with Felty’s syndrome in the absence of joint affection during a period of 30 years. Schifferli et al. [7] presented a case of rapid reversal of neutropenia by plasmapheresis in a patient with essential CG type I, splenomegaly, and arthralgia. In this case it was speculated that plasmapheresis had a quick and transitory effect, increasing the release of

References


Chronic Neutropenia and Cryoglobulinemic