IgG Cryoglobulinemia Associated With Amyloidosis

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A patient with symptomatic primary cryoglobulinemia was followed for 9 yr and was found at autopsy to have generalized amyloidosis. There was a monoclonal serum protein spike of IgG kappa type that was cryoglobulin. The cryoglobulin was further characterized as IgG_2 kappa Gm (n—). This case constitutes, to our knowledge, the first example of amyloidosis associated with monoclonal IgG cryoglobulinemia, with characterization of the monoclonal serum cryoglobulin, and also the first reported case of successful symptomatic treatment of cryoglobulinemia by plasmapheresis.

Cryoglobulins are proteins that precipitate or form a gel at 0°C and redissolve on heating. Disorders in which significant amounts of circulating cryoglobulins are present are designated "cryoglobulinemias." Cryoglobulinemias are classified according to the immunologic type of the protein, which can be IgG, IgM, rarely IgA, or mixed IgG and IgM or IgG and IgA, and in clinical practice as primary ("idiopathic") or as secondary to an underlying disease.

Primary (idiopathic) isolated monoclonal IgG or IgM cryoglobulinemia is a condition characterized clinically by intolerance to cold (Raynaud's phenomenon, livedo reticularis, cutaneous ulcerations) and by purpura. The serum contains a large amount of cryoprecipitable protein; usually there is an underlying dyscrasia of the lymphoreticular system (plasmacytic myeloma, chronic lymphatic leukemia, lymphosarcoma). Such malignancy may become evident in the course of observation of a case previously considered to be idiopathic.

Mixed cryoglobulinemia (IgG plus IgM or IgG plus IgA) is most commonly associated with a syndrome that resembles lupus erythematosus, and it is occasionally seen in lymphoplasmacytic disorders. In mixed cryoglobulinemia the amount of cold-precipitable protein is usually small.

Systemic amyloidosis is seen in 10%–15% of patients with plasmacytic...
myeloma. Conversely, a plasmacytic dyscrasia is often uncovered in the marrow of patients with primary or systemic amyloidosis.

Our patient had monoclonal IgG cryoglobulinemia; at autopsy she was found to have generalized amyloidosis. For 2 yr her clinical symptoms were controlled dramatically by plasmapheresis. Examination of the bone marrow revealed abnormalities of the lymphoplasmacytic line consistent with a lymphoplasmacytic dyscrasia.

CASE REPORT

A 50-yr-old white woman first was seen at the Mayo Clinic in June 1959. Her main complaints were purpura present for 18 mo and painful ulcers of the lower extremities present for 10 mo and occurring after exposure to cold.

June 1959

She had a blotchy red rash and healed atrophic scars on both lower legs. Her hemoglobin concentration was 12.6 g/100 ml; the erythrocyte count was 4,180,000/cu mm, and the leukocyte count was 8800/cu mm with a normal differential. The sedimentation rate was 61 mm in 1 hr (Westergren). The urine had grade 1+ reaction for protein. Serum protein electrophoresis revealed normal values for all the fractions except the γ-globulin, which was 1.99 g/100 ml and homogeneous. A qualitative test for cryoglobulin was strongly positive. There were no bony lesions. Specimens of bone marrow showed an increase of lymphocytes, some with plasmacytoid features.

November 1959

When she returned 5 mo later, she reported having done well during the summer, but 1 mo before admission, pruritus had developed in the distal lower extremities. Several black areas had developed, and one of these had ulcerated.

Results of laboratory studies were essentially unchanged, but the serum γ-globulin was now 2.42 g/100 ml.

The patient did not return to the Mayo Clinic until August 1968. In the interim she had been continuously under medical care. (We are grateful to Evanston Hospital, Evanston, Ill.; Michael Reese Hospital, Chicago, Ill.; and the University of Chicago Hospital and Clinics, Chicago, Ill. for making their records available.) Throughout this period she continued to have recurrent painful ulcerations of the legs. In 1962, she noticed progressive numbness and tingling of the first three fingers of both hands. Mild, progressive, generalized weakness gradually developed.

June 1963

She experienced pain in the metacarpophalangeal joints, wrists, shoulders, feet, ankles, and knees and had morning stiffness of 1-2-hr duration. A skin eruption with a butterfly distribution occurred. Marked intermittent claudication appeared (walking a distance of 100 m induced severe pain).

A bone marrow aspirate revealed 16.5% lymphocytes and 2.0% plasma cells. Many of the lymphocytes had plasmacytoid features and contained Russell bodies.

April 1965

The patient was seen by one of us (H.H.F.) in consultation. He suggested that the disease was a lymphoproliferative disorder other than myeloma or macroglobulinemia and advised plasmapheresis for control of symptoms of intermittent claudication, on the assumption that these were due to cryoglobulinemia. Protein studies revealed that the cryoglobulin was IgG. Therapeutic plasmapheresis, 1 U of blood twice weekly, was begun. For about 1½ yr she had dramatic relief from pain, and her ulcers healed. Symptoms were minimal as long as the cryocrit value was 6 or less and as long as the patient was on plasmapheresis once or twice weekly.
March 1967

An erythematous rash appeared on her face, arms, chest, and back.

August 1967

Treatment with prednisone (40 mg daily) was begun and was continued at 10 mg daily. Chlorambucil (4 mg daily) and furosemide (40 mg daily) were added to the program, and the rash disappeared.

December 1967

Symptoms and signs of hypothyroidism became evident. Antithyroglobulin antibodies were found at a titer of 1:640 (Welicome sheep red cells coated with human thyroglobulin), and L-triiodothyronine (Cytomel) was prescribed.

January 1968

Thrombophlebitis of the left femoral vein led to hospitalization. Mild normocytic and normochromic anemia (hemoglobin, 10.7 g/100 ml) was present with features suggestive of hemolysis. A nonspecific cold autoagglutinin was detected in the serum (before the cryoglobulin was precipitated out).

In the summer of 1968, anorexia, nausea and occasional vomiting, and abdominal discomfort began, and the patient lost 5 lb.

September 1968

The patient was readmitted to the Mayo Clinic. During the preceding year, plasmapheresis had not been as effective as during the first 2 yr of this treatment, but it had not been done as often and her cryocrit value increased.

She appeared mildly dyspneic on exertion, and rales were present in the bases of both lungs. Synovium was slightly thickened in the hands, wrists, and knees. She had severe distal loss of all sensory modalities and a symmetric decrease of deep tendon reflexes. The return of the biceps tendon reflex was slowed.

Results of laboratory studies on this admission were as follows: hemoglobin, 9.8 g/100 ml; leukocytes, 6800/cu mm with lymphocytes 1.5%, neutrophils 79.5%, monocytes 4.5%, metamyelocytes 1.5%, and myelocytes 2.0%; and platelets, 108,000/cu mm. The sedimentation rate was 110 mm in 1 hr. The lupus erythematosus (LE) clot, rheumatoid factor, antinuclear antibody (anti-DNP), and VDRL (for syphilis) tests were negative. A direct Coombs' test was positive. The urine was positive for Bence Jones protein. A 24-hr specimen of urine contained 0.6 g of protein, with 64% of the total protein migrating as a homogeneous \( \beta \) peak. Serum protein electrophoresis showed hypoalbuminemia (1.99 g/100 ml) and a \( \gamma \)-globulin value of 2.15 g/100 ml. The serum M-component was an IgG kappa monoclonal protein; on ultracentrifugation, it sedimented as 7S. The cryoglobulin test remained positive. The thyroglobulin antibody titer was 1:25,000, and serum thyroxine was 0.3 \( \mu g/100 \) ml. She had destructive changes in the fingers of both hands and wrists, which were compatible with rheumatoid arthritis.

The bone marrow contained 20.5% plasmacytoid lymphocytes.

An electromyogram was consistent with widespread peripheral neuropathy. A skin biopsy revealed stasis dermatitis plus a thrombosed vessel.

The patient exhibited increasing symptoms and signs of congestive heart failure and died in September 1968.

Autopsy

The main finding was widespread amyloidosis, particularly involving the vascular walls. The pulmonary arteries were thick, on both gross and microscopic examinations, with the walls infiltrated by an acidophilic hyalinlike material (Fig. 1) with the appearance and histochemical characteristics of amyloid. A similar material involved the alveolar walls and septa.

The heart weighed 425 g. There was a firm induration around the entire aorta and its
Fig. 1. Section of lung, showing thickness of vessels with some instances of complete replacement of wall and occlusion of lumen by amyloid. Hematoxylin and eosin × 30.

Fig. 2. Section of atrium, showing thickening of endocardium by amyloid deposits. Hematoxylin and eosin × 50.

Fig. 3. Section of thyroid, showing extensive replacement of gland by fibrous tissue. Only few acini, surrounded by lymphocytes and lined by disintegrating epithelial cells, remain. Hematoxylin and eosin × 40.

Fig. 4. Section of sternal bone marrow, showing area of lymphocytic infiltration. Russell bodies are seen (arrows). Hematoxylin and eosin × 210.
bifurcation by a semicircular sheath of gray, translucent, waxy-like material. Patches of translucent granules were noted on the mural atrial endocardium. The material in the periaortic connective tissue had the same characteristics as that in the lungs. The amyloid had predominantly a perivascular distribution but extended beyond the vascular walls into the surrounding connective and adipose tissue. Embedded in the amyloid material were tiny islet-like collections of lymphocytes, histiocytes, and plasma cells. Amyloid deposition was responsible for thickening of the parietal and visceral pericardium and the atrial endocardium (Fig. 2).

The antrum of the stomach had four ulcers; the largest was 1 cm in diameter. Amyloid was found in the vessels and perivascular tissue in the adjacent submucosa.

The liver weighed 2050 g and had a number of yellow-gray nodules, ranging from 1 to 7 mm in diameter, from an extensive but benign proliferation of periportal hepatocytes. Amyloid deposition in the liver was limited to the arteries.

The kidneys weighed 295 g. Small deposits of amyloid were found in the arteries only. Vascular amyloid infiltration was also noted in the spleen, adrenals, and submucosa of the small and large intestines. The thyroid gland weighed only 5.07 g and was composed largely of dense fibrous tissue (Fig. 3). Some of the vessel walls had deposits of amyloid.

The bone marrow contained focal collections of medium-sized lymphocytes with slight to moderate amounts of pale cytoplasm and Russell bodies (Fig. 4).

Special Studies

The serum protein electrophoresis γ-spike, absent in the supernatant fraction obtained after precipitation in the cold, was identified as IgG. Further studies revealed that the cryoglobulin was IgG₂ kappa Gm (n—). 15

DISCUSSION

In the past several years, the emphasis and interest regarding the cryoglobulins have been in regard to their occurrence in patients with infectious diseases and in some patients with a variety of connective tissue disorders, primarily systemic lupus erythematosus. As a rule, in these disorders, cryoglobulins occur in smaller quantities, are not associated with monoclonal electrophoretic peaks, tend to be transient (infectious mononucleosis, cytomegalic virus disease) or to parallel the activity of the underlying illness and are usually of mixed type, most often an IgM-IgG combination. It has been proposed that mixed cryoglobulins may represent immune complexes. 16

In 1966, Meltzer and Franklin 1 reported that, of 36 cryoglobulins, 12 were of the mixed IgM-IgG type and 9 of these were from patients who had a characteristic clinical syndrome consisting of arthralgias, purpura, weakness, and hepatic, splenic, and lymph node enlargement. None of these 12 patients had an otherwise definable underlying disease ("essential mixed cryoglobulinemia"), and all had rheumatoid factor. Three patients had typical Sjögren's syndrome, three had thyroiditis, and three died of acute renal failure with findings of acute diffuse glomerulonephritis on renal biopsy. Four of eight had antinuclear antibodies, and all eight patients investigated for serum complement had low whole-complement levels. Subsequently, it was shown that patients with this syndrome have monoclonal IgM (almost always type kappa) and polyclonal IgG. 17

Monoclonal cryoglobulinemias are characteristically persistent and most commonly of IgG or IgM type 1,3 and only rarely IgA. 18 They usually are associated with lymphoplasmacytic proliferative diseases. 1,3,8 Farmer et al. 8 reported that 8 of 12 patients with serum cryoglobulin levels of 300 mg/100
ml or more had a diagnosable lymphoplasmacytic dyscrasia and that two others had marked increase of lymphoid cells in their bone marrow.

Our patient had symptomatic monoclonal cryoglobulinemia and was observed for 9 yr. During this period she had purpura and cutaneous ulcerations. In the bone marrow specimens obtained during the patient’s life and at autopsy, there were abnormalities suggestive, but not diagnostic, of a lymphoplasmacytic dyscrasia. Furthermore, during the final phase of her illness, Bence Jones proteinuria was demonstrated. The autopsy revealed widespread amyloidosis.

The case reported here had features resembling mixed IgC-IgM cryoglobulinemia and systemic lupus erythematosus. On the other hand, the presence of monoclonal IgG serum (cryoglobulin) and urinary (Bence Jones) protein suggests a neoplastic disorder of the lymphoplasmacytic line. The serum and urinary protein abnormalities were of the myeloma type, and the systemic amyloidosis and cellular abnormalities are consistent with a lymphoplasmacytic dyscrasia. The duration of the disease in our patient is entirely consistent with the data presented by Hobbs in regard to the long evolution times of plasmacytic myeloma. In addition, our patient had had a peripheral neuropathy and muscular weakness. Polyneuropathy has been associated with amyloidosis and with plasmacytic myeloma in the absence of amyloidosis.

A form of cryoglobulinemic neuropathy has also been described. In our patient, the amyloidosis could either reflect a primary plasmacytic disorder or result from a poorly understood repetitive or chronic stimulation of the immunocompetent cells. Barth et al. proposed a hypothesis to encompass multiple myeloma, primary amyloidosis, and “limited” production of an M-component; they suggested a relationship at the stem cell level.

Several human proteins found in myeloma and Waldenström’s macroglobulinemia possess specific antibody activity. Our patient had symptoms of autoimmunity (primarily thyroiditis); she had a high thyroglobulin antibody titer, a positive Coombs’ test, and arthritis. The association of monoclonal serum (cryoglobulin) and urinary (Bence Jones) protein (probably related to a plasmacytic dyscrasia, generalized amyloidosis, and autoantibodies) is compatible with the hypothesis of a “bridge” or connection between autoimmunity and lymphoreticular malignancies that has been suggested.

Myeloma presenting as cryoglobulinemia has been previously reported, but the association with amyloidosis has not. Our serum protein studies constitute the first analysis of a monoclonal cryoglobulin occurring in a patient with generalized amyloidosis. They also demonstrate the success of plasmapheresis in controlling symptoms related to cryoglobulinemia.

In a recent paper Virella and Hobbs reported the heavy-chain typing in 121 IgG monoclonal gammopathies; this group included 14 cryoglobulins. Although, in the whole group, IgG was the most common subtype (75%), 6 of the 14 cryoglobulins were IgGs and 4 of these 6 cryoglobulins had kappa light chain, as did our patient. Thus, our patient’s cryoglobulin is of the most common IgG monoclonal cryoglobulin subtype (IgG3K), if the results of the small series of Virella and Hobbs are confirmed in larger series.
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