Case report

Systemic lupus erythematosus preceded by long-term cryoglobulinaemia

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SUMMARY A patient with cryoglobulinaemia who developed systemic lupus erythematosus (SLE) 10 years later on is described. The relationship between these 2 conditions and the possibility that cryoglobulinaemia was the early presentation of SLE are discussed.

Cryoglobulinaemia is a condition characterised by the presence of circulating globulins, which precipitate on exposure to cold. The disease presents with various clinical symptoms, such as arthralgia, purpura, and multiple organ involvement. Cryoglobulinaemia may appear as a primary or secondary disease, or as an early presentation of an infectious, collagen, or lymphoproliferative disorder.

In the present report we describe a patient in whom cryoglobulinaemia was an early presenting symptom which preceded the expression of systemic lupus erythematosus (SLE) by 10 years.

Case report

A 50-year-old woman, born in Iraq, mother of 2, was admitted to our department 10 years before because of purpura and splenomegaly. During her childhood she suffered from infectious hepatitis. In 1959, while she was pregnant, a routine blood test showed a positive VDRL reaction, which later was proved to be false positive.

On physical examination she looked pale but in a good general condition. Her temperature was 37°C, the pulse 80/min and regular, and her blood pressure 90/60 mmHg. The spleen and liver were palpable 3 cm and 1 cm respectively below the costal margin, both hard and not tender.

The laboratory data showed: Westergren erythrocyte sedimentation rate (ESR) of 70/90 mm 1 h, haemoglobin 10.4 g/dl, haematocrit 30%, reticulocytes 1.6%, white blood cell count 4700/mm³ ($4.7 \times$

10^9 /l), platelet count 155 000/mm³ (155×10^9 /l). Albumin was 4.33 g/dl (43 g/l), globulins 3.4 g/dl (34 g/l), gammaglobulin 33%, IgM 500 mg/dl (5 g/l), antinuclear factor 1/40. Cryoglobulins and VDRL tests were positive. Normal or negative tests included: lupus erythematosus (LE) cell test, Nelson, Rose-Waaler, Coombs, and urine analysis. The latex test was 1/40 and complement 40%.

In June 1978 she was readmitted for evaluation of weakness, weight loss, arthralgia, and pruritic rash on the lower limbs. On physical examination, in addition to the hepatosplenomegaly, a macular, brown discoloration was seen on both her legs.

Laboratory data showed again increased ESR, elevated level of IgM (500 mg/dl (5 g/l)), mixed polyclonal cryoglobulin (IgG, IgM), and negative tests for LE cells and antinuclear factor. Liver needle biopsy showed hyperplasia of the Kupffer cells, and dilated sinusoids with mononuclear infiltration of the portal spaces. Skin biopsy showed blood vessels surrounded by numerous histiocytes, with amorphous material inside the endothelium. Congo red staining for amyloid was negative. Immunofluorescent staining gave a positive result for IgM in the vessel walls.

In January 1982 the patient developed anaemia, severe Raynaud's phenomenon with acrocyanosis, and skin necrosis of the second and third fingers of her right hand. Laboratory tests showed a positive LE cell test, antinuclear factor 1/10 240, proteinuria, granular white and red blood cells, and hyaline casts in urinary sediment.

The development of anaemia, Raynaud's phenomenon, renal involvement, and the laboratory results were compatible with the diagnosis of SLE. The patient was treated with azathioprine (Imuran)

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100 mg/day, without steroids because of her emotional instability. Two months later her general condition improved, the LE cells disappeared, and the titre of the antinuclear factor decreased to 1:330.

Discussion

Most of the globulins responsible for the symptoms and signs of cryoglobulinaemia are immunoglobulins. Immunochemical analysis of these molecules has led to their classification into 3 categories.^{1,2} Type 1 consists of a single monoclonal cryoglobulin, found most frequently in multiple myeloma and Waldenström's macroglobulinaemia. Type 2, represented by mixed cryoglobulins with one monoclonal and one or more polyclonal immunoglobulins, is found most frequently in rheumatoid arthritis, Sjögren's syndrome, and lymphoproliferative disorders, and Type 3, mixed polyclonal cryoglobulins, is associated most frequently with infections and autoimmune, lymphoproliferative, renal, and hepatic disorders and with most cases of the essential form of cryoglobulinaemia.

The relationship between cryoglobulinaemia and SLE is well established, and the presence of cryoglobulins in patients with lupus ranges between 20% and 80%.^{1,3-7} Almost all workers agree that the presence of cryoglobulins is related to the disease activity, and it has been suggested that mixed cryoglobulins are immune complexes.⁸

The question whether cryoglobulinaemia may precede the development of SLE by 10 years, as suggested in our patient, is of special interest. Brouet *et al.*¹ in a long-term follow-up (mean 9 years) have found that the initial diagnosis of essential cryoglobulinaemia in 10 patients had to be dismissed 2 to 10 years later on, when autoimmune diseases or malignancies of the haematopoietic system became apparent, but in the 4 SLE patients described in their series the cryoglobulins were found during the active phase of the disease.

Invernizzi *et al.*⁹ in their long-term follow-up of 35 patients with essential cryoglobulinaemia found that 18 of them remained asymptomatic or without complications, 13 patients developed renal disease, 2 had hepatic cirrhosis, 1 developed chronic lymphatic leukaemia, and 1 patient non-Hodgkin's lymphoma. None of the patients with the initial diagnosis of essential cryoglobulinaemia developed SLE. Although the chance association between cryoglobulinaemia and SLE in our patient cannot be excluded, the present report demonstrates the necessity of extensive evaluation and long-term follow-up in each case of essential cryoglobulinaemia, since cryoglobulinaemia may precede autoimmune and haematological abnormalities.

References

- 1 Brouet J-C, Clauvel J-P, Danon F, Klein M, Seligmann M. Biologic and clinical significance of cryoglobulins. A report of 86 cases. *Am J Med* 1974; **57**: 775-88.
- 2 Gorevic PD, Kassab H J, Levo Y, *et al.* Mixed cryoglobulinemia: clinical aspects and long-term follow-up of 40 patients. *Am J Med* 1980; **69**: 287-308.
- 3 Barr D P, Reader G G, Wheeler C H. Cryoglobulinemia. I. Report of two cases with discussion of clinical manifestations, incidence and significance. *Ann Intern Med* 1950; **32**: 6-29.
- 4 Christian C L, Hatfield W B, Chase P H. Systemic lupus erythematosus. Cryoprecipitation of serum. *J Clin Invest* 1963; **42**: 823-9.
- 5 Lee S L, Rivero I. Cryoglobulins in systemic lupus erythematosus (SLE) as circulating immune complexes. *Arthritis Rheum* 1964; **7**: 321 (abstr).
- 6 Barnett E V, Kantor G, Bickel Y B, Forsen R, Gonick H C. Systemic lupus erythematosus. *Calif Med* 1969; **111**: 467-81.
- 7 Stasny P, Ziff M. Cold insoluble complexes and complement levels in SLE. *N Engl J Med* 1969; **280**: 1376-81.
- 8 Winfield J B, Koffler D, Kunkel H G. Specific concentration of polynucleotide immune complexes in the cryoprecipitates of patients with systemic lupus erythematosus. *J Clin Invest* 1975; **56**: 563-70.
- 9 Invernizzi F, Pioltelli P, Cattaneo R, *et al.* A long-term follow-up study in essential cryoglobulinemia. *Acta Haematol* 1979; **61**: 93-9.