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"Benign" monoclonal IgE gammopathy

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Summary and conclusions

So far IgE monoclonal paraproteins have been found only in patients with malignant diseases, though there are benign monoclonal paraproteins of other immunoglobulin classes. A patient with osteoporosis first seen in Paris in 1965 was found to have a paraprotein type λ. In 1977 immunoelectrophoresis identified this as IgE λ paraprotein, and immunodiffusion studies showed precipitin bands identical with those in patients with IgE myeloma.

This patient seemed to have a benign monoclonal IgE gammopathy which had existed for 14 years. Though the possibility of transition into multiple myeloma cannot be excluded, this case suggests that a monoclonal expansion of IgE lymphocytes need not produce malignant change.

Introduction

"Benign" monoclonal paraproteins can be found in about 1% of the population over 25 years of age. With increasing age the incidence of paraprotein rises to more than 2·5% in individuals over 70. Thus benign paraproteinaemia of the IgG, IgA, IgM class or of light-chain type is relatively common and only rarely followed by multiple myeloma or Waldenström's macroglobulinaemia. For IgE, however, the immunoglobulin class with normally only trace serum concentrations, no benign monoclonal IgE gammopathy has been reported so far, although 13 cases of IgE myeloma[1-4] and two patients with lymphoproliferative disorders[5 6] and IgE paraproteinaemia have been described up to now.

Case report

A 71-year old woman was referred in 1977 for evaluation of occasional discomfort in her lumbar spine. She had suffered from malnutrition and anaemia from 1939 to 1946. In 1963 she had complained of pain in the thoracolumbar region. Calcium injections were given, but no radiographs taken until December 1965, when severe pain and almost complete immobilisation led to her admission to hospital in Paris, where osteoporosis with collapse of several vertebrae was found. Haemoglobin was 8·2 g/dl, leucocyte count $6·2 \times 10^9$/l with 35% lymphocytes (half atypical). The erythrocyte sedimentation rate was 40 mm in 1 h, while serum calcium, phosphate, and serum protein concentrations were normal. Serum electrophoresis disclosed a minimal spike in the gamma region. Proteinuria was 250 mg/24 h with no Bence Jones protein. Calcium excretion was 60 mg/24 h on an unrestricted diet and 150 mg/24 h after intravenous calcium. In January 1966 immunoelectrophoresis (Professor M Seligmann) showed a paraprotein type λ, which was not detected in unconcen-

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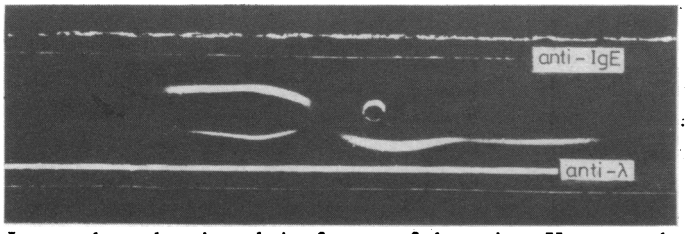
trated urine. The bone marrow showed 11% plasma cells with small clusters of atypical cells. Iliac crest biopsy showed massive thinning of the cortical and trabecular bone. Osteoid borders were very narrow with no osteoblastic activity and no resorption lacunes.

The patient was treated with 250 mg liver extract twice daily, which led to complete normalisation of her red cell count. Melphalan 10 mg/day was discontinued after two days because of adverse reactions. Subsequently she received intravenous calcium and anti-rheumatic drugs but no further cytostatic treatment.

When we saw her in 1977 she appeared to be healthy with no hepatosplenomegaly or lymphadenopathy. Haemoglobin was 11 g/dl, packed cell volume 40%, white cell count 4×10^9/l with 63% neutrophiles, 1% band forms, 3% monocytes, 3% eosinophiles and 30% lymphocytes (17% atypical), platelet count 152×10^9/l, and sedimentation rate 35 mm in 1 h. Serum calcium, creatinine, alkaline phosphatase, and lactic dehydrogenase were normal. The total protein was 65 g/l; serum electrophoresis showed a small spike in the gamma region, which was identified by immunoelectrophoresis as IgE λ paraprotein (see figure).



Immunoelectrophoresis analysis of serum of the patient. Upper trough: anti-IgE; lower trough: anti-λ.

Proteinuria was 436 mg/24 h. Electrophoresis of tenfold concentrated urine showed a minimal spike in the gamma region and a larger amount of albumin and β-globulins. There were no free light chains in the urine or serum. Serum IgE concentration was $2{\cdot}19 \times 10^6$ U/ml, urinary excretion $0{\cdot}45 \times 10^6$ U/24 h. Immunodiffusion studies showed precipitin bands identical with isolated paraprotein of the first recognised patient with IgE myeloma (reported by SGO Johansson and H Bennich, 1967) and with serum of the second IgE myeloma case. Twenty-four per cent of the peripheral blood lymphocytes were B lymphocytes and 4% IgE positive. The hypocellular bone marrow showed 12% plasma cells, often abnormally enlarged and sometimes multinucleated. They often had 2-5 nucleoli and signs of nuclear cytoplasmic disparity. The IgE synthesis rate of isolated bone marrow-cells was about 33×10^3 IgE molecules/lymphoplasmacytoid or plasma cell/min. Serum interferon concentrations varied from 4 to 16 U/ml in different blood samples; 1024 U interferon were produced spontaneously by 3×10^9 bone marrow cells during 18 hours' culture. Mitogen-induced (phytohaemagglutinin, ConA, and pokeweed mitogen) lymphocyte transformation was normal, whereas the activity of ConA-pre-stimulated suppressor cells (84% suppression of blastogenesis) was significantly increased.

Radiographs of the long bones and scull as well as body scans were unremarkable. Urinary excretion of calcium and hydroxyproline were normal. By July 1980 the patient showed no signs of myelomatosis and no increase of the paraprotein since July 1977.

Discussion

The main feature indicating a benign form of IgE paraproteinaemia in this patient was the length of the course of gammopathy, which virtually excludes multiple myeloma. Proof of a paraprotein dates back to January 1966, when only the light chain could be identified because IgE had not yet been discovered. The production of monoclonal light chains only at the time of diagnosis with subsequent switch to IgE is unlikely. Therefore the IgE gammopathy seems to have existed for at least 14 years. Other facts supporting the benign course are the constant rather than increasing M-component, the absence of free light chains in serum and urine, the lack of osteolytic bone lesions, the normocalcemia, and the normal blood count. There was no significant progression of osteoporosis, which we attributed to postmenopausal osteopenia rather than an underlying myeloma. Modification of IgE myeloma by treatment can be excluded since prolonged remission has never been achieved with 20 mg melphalan. The diagnosis of a benign monoclonal gammopathy seems therefore well established, although the possibility of eventual transition into multiple myeloma can at no time be definitely excluded in patients with idiopathic paraproteinaemia.

Our patient's serum paraprotein concentration ($2{\cdot}19 \times 10^6$ U IgE/ml) exceeded those observed in rare cases with allergic disease and IgE hypergammaglobulinaemia,[7] but ranged below that found in 11 of the 13 reported patients with IgE myeloma. Immunodiffusion analysis showed immunological identity between the paraprotein of our patient and the isolated M-component and serum paraprotein of two others with IgE myeloma.

This case thus suggests that a monoclonal expansion of IgE lymphocytes does not necessarily produce rapid malignant proliferation as suggested by the histories of the 13 IgE myeloma patients described so far.

We thank Professor Dr S G O Johansson (Uppsala) for providing isolated IgE paraprotein from his patient and Professor Dr T Waldmann (Bethesda) for supplying serum of another patient with IgE myeloma. The kind support of Professor M Kahn (Hôpital Bichat, Paris), who gave us the opportunity to review the patients' files, is gratefully acknowledged. This work was supported in part by the Austrian Research Council, Grant Number 3397.

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ONE HUNDRED YEARS AGO The power possessed by so-called uncertificated midwives to give certificates for burial in cases of still-born children was shown, at an inquest held by Mr Humphreys, to have been seriously abused. It appears that on Friday last a single woman, living at a common lodging-house in the East End of London, was delivered of a female child, which lived an hour and a half. A medical man was called in to see the child after death, but being unable to certify, as he had never attended it alive, he communicated with the coroner, who in due course issued his warrant for an inquest. It turned out, however, that the child had been buried by the parish authorities, who had received from the midwife in attendance on the mother a certificate to the effect that it was still-born. The coroner "strongly commented" on the course taken by the midwife. She was, however, "not present to explain the matter," and "the proposed inquiry fell through." A more singular parody of the forms of inquiry was rarely reported. It is lamentable to reflect how often the evils connected with the present unregulated system of midwifery have been exposed, and how universally and unanimously they have been condemned, but how vigorous and undisturbed a vitality they still display. (*British Medical Journal*, 1880.)