Short reports

Hypercalcaemia due to calcium binding IgM paraprotein in Waldenström's macroglobulinaemia

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Abstract

A case of Waldenström's macroglobulinaemia with asymptomatic hypercalcaemia is reported in which calcium binding to the paraprotein was found. This is the first report of this phenomenon in Waldenström's macroglobulinaemia and the first report of calcium binding to an IgM paraprotein.

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Case report

In 1986 a 57 year old woman complained of low back pain. On examination a possible mass was felt in the right iliac fossa but pelvic ultrasound showed no abnormality. Blood tests at this time showed a normal full blood count, total protein (77 g/l), and albumin (47 g/l), but slight hypercalcaemia (2·78 mmol/l). The erythrocyte sedimentation rate (ESR) was 68 mm/h. She was discharged to the care of her general practitioner.

In 1991 she attended the ear, nose and throat clinic with a right submandibular swelling which was ascribed to sialoadenitis. The full blood count was again normal but ESR was 98 mm/h, serum calcium 2·85 mmol/l, total protein 87 g/l, and albumin 42 g/l. The calculated globulin—45 g/l—prompted serum electrophoresis, which revealed a paraprotein subsequently identified as IgMK. She was referred to the haematology clinic where she complained of malaise and poor appetite, but examination revealed nothing of note. The haemoglobin was 12·1 g/dl, white cell count 9×10^9/l, platelets 328×10^9/l, serum urea 4·0 mmol/l, creatinine 84 μmol/l, IgG 5·7 g/l, and IgA <0·5 g/l. The concentration of the IgM paraprotein was 15 g/l. No free light chains were detected in the urine, and skeletal survey showed no lytic lesions. Bone marrow trephine showed increased lymphoplasmacytoid and plasma cells, and a diagnosis of Waldenström's macroglobulinaemia was made.

In June 1993 the patient remained well without treatment and with a normal full blood count and plasma urea and creatinine. However, the paraprotein concentration had risen to 30 g/l and the serum calcium to 3·01 mmol/l. Further investigation of the hypercalcaemia showed normal serum intact parathyroid hormone concentration of 24 pg/ml (reference range 10-50), normal fasting urine calcium excretion (Ca_E) of 0·03 mmol/l glomerular filtrate (reference range <0·045), and normal serum ionised calcium of 1·27 mmol/l (1·20–1·30). The increased serum total calcium with a normal ionised fraction indicated increased protein bound calcium and we therefore sought direct evidence of this.

Methods

We investigated the binding of calcium to protein fractions by the gel filtration method of Tofaletti *et al.*[1] Brief details are as follows: 2 ml serum from freshly collected blood was applied to the top of a gel filtration column (2 cm diameter, 39 cm height) of a Sephacryl S-300 (Pharmacia). The eluent contained (in mmol/l): sodium chloride 130, sodium hydroxide 6·8, sodium azide 3·0, magnesium chloride 0·5, calcium chloride 1·2, and tris(hydroxymethyl)methylamine 10, with pH adjusted to 7·43. The apparatus and eluent were maintained at 37°C during chromatography and 60 fractions of approximately 1·5 ml were collected at a flow rate of 30 ml/h. The fractions were analysed without delay using standard techniques for calcium (cresolphthalein complexone), total protein (biuret), and albumin (bromocresol green), and later for immunoglobulins (immunoturbidimetry) after storage at −20°C. Assays were carried out using a DAX 48 analyser (Bayer) and an Encore centrifugal analyser (Baker Instruments). We also examined the mobility of the IgM paraprotein on agarose gel electrophoresis in barbitone buffers containing 2 mmol/l calcium lactate or 2 mmol/l disodium EDTA.[2]

Results

The results of gel filtration chromatography of serum from a normal subject (figure, panel A) show a peak of calcium associated with albumin and a later peak probably representing complexed calcium (citrate, phosphate, bicar-

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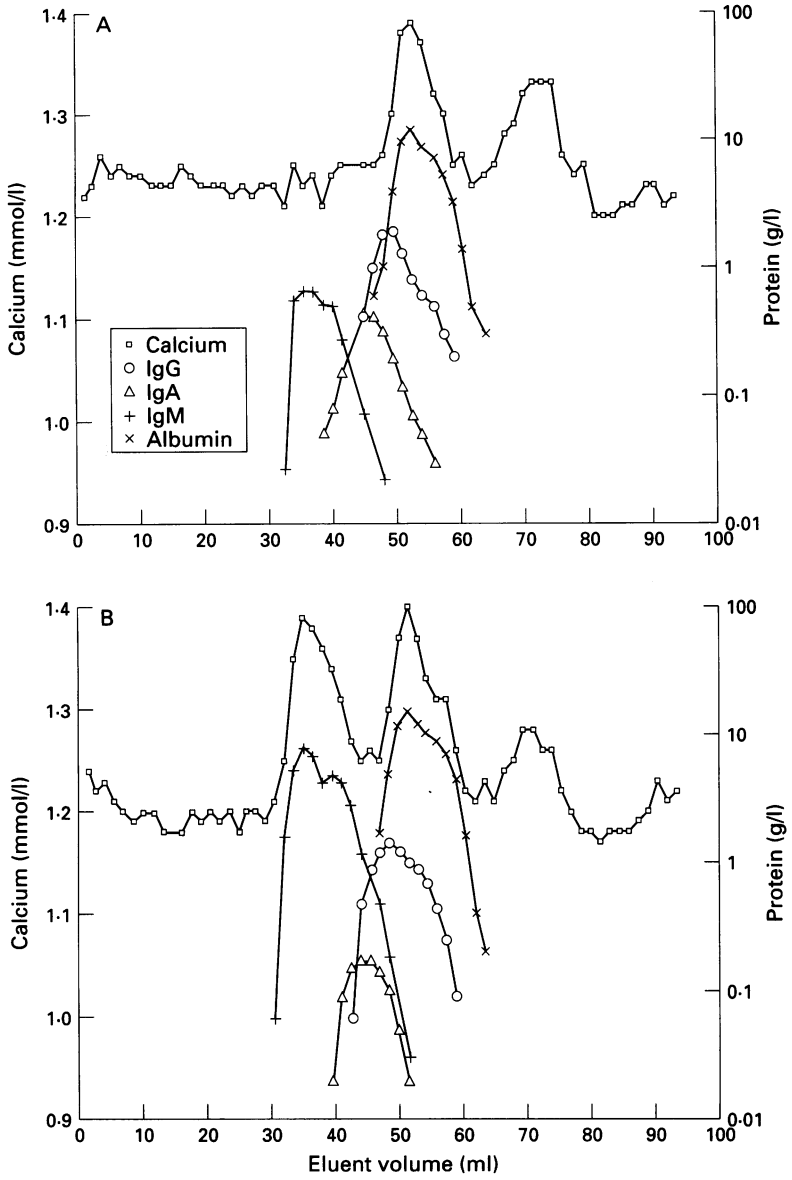

Gel filtration chromatography of serum from a normal control (A) and the case of Waldenström's macroglobulinaemia (B) showing the association of calcium with the fractions containing the macroglobulin.

bonate).[1] The corresponding experiment with serum from the case of macroglobulinaemia shows a further early peak of calcium associated with IgM (figure, panel B).

There was a statistically significant correlation ($p = 0{\cdot}05$) between serum IgM paraprotein concentration and serum calcium adjusted for serum albumin measured at various times over a period of 20 months.

The electrophoretic mobility of the IgM paraprotein from our patient was clearly increased by the presence of calcium in the buffer. Three other IgM paraproteins from subjects with normal serum calcium showed no difference in mobility.

Discussion

Myeloma is frequently associated with hypercalcaemia; approximately 30% of patients develop this complication during the course of their disease[3] as a result of increased bone resorption and decreased glomerular filtration.[4]

Rarely the hypercalcaemia has been found to be due to calcium binding to the serum paraprotein with no change in the serum ionised calcium.[4] Studies of calcium binding IgG[5,6] and IgA[7] paraproteins have shown binding of calcium by purified protein preparations,[2,6,7] *Fab* fragments,[2,6] and reconstituted IgG,[6] but not by free heavy or light chains.[2] The presence of 1·5–2·2 binding sites per molecule[2,5] suggests that calcium is binding to the variable domain.[2] It is important to identify this phenomenon to avoid inappropriate treatment to lower the serum calcium.[2,8]

IgM paraproteins are most frequently associated with Waldenström's macroglobulinaemia and in this condition hypercalcaemia is unusual except in a subgroup with the clinical characteristics of myeloma, sometimes termed IgM myeloma. In the case presented here there was no evidence of skeletal lesions and there were no symptoms attributable to the hypercalcaemia. The relationship between serum calcium and paraprotein concentrations suggested calcium binding to the paraprotein, and direct evidence for this was obtained by gel filtration chromatography. Normal serum ionised calcium and hence increased protein bound calcium was suggested by normal serum parathyroid hormone and urine calcium excretion, and ultimately confirmed by direct measurement. The value of urine calcium excretion in this regard is noteworthy, since it is a readily available measurement and is consistently raised in myelomatosis when hypercalcaemia is caused by increased bone resorption.[3]

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