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K. J. A. Kairemo^a, M. Lindberg^a, M. Prytz^a

^a Department of Nuclear Medicine, Helsinki University, Central Hospital, P.O. Box 360, Finland.

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IgE myeloma: a case presentation and a review of the literature

K. J. A. KAIREMO, M. LINDBERG & M. PRYTZ

Department of Clinical Chemistry, Trondheim University Hospital, Norway

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In the literature, fewer than 40 cases of IgE myeloma have been described. We report the first Norwegian case, an 80-year-old man presenting with progressive weakness, dyspnea and dizziness. With the exception of hypersedimentation, routine chemistry values were within reference limits. Plasma cells were not observed in the peripheral blood. Serum protein electrophoresis showed a monoclonal protein in the gammaglobulin fraction. Immunofixation confirmed the presence of an IgE kappa monoclonal protein. A bone marrow biopsy revealed an interstitial and nodular infiltration of abnormal plasma cells comprising 40% of nucleated cells present. Skeletal roentgenograms of this patient showed osteolytic lesions in the skull and in the left pubic arc. The findings for this patient were compared with the previous reports of IgE myeloma.

Key words: electrophoresis; IgE; immunofixation; immunoglobulins; monoclonal gammopathy; multiple myeloma; plasma cells; proteins

K. J. A. Kairemo, Department of Nuclear Medicine, Helsinki University, Central Hospital, P.O. Box 360, FIN-00025 HYKS, Finland. Tel. +358 9471 72565, fax. +358 9470 76678, e-mail. Kalevi.Kairemo@huch.fi

INTRODUCTION

The first report of IgE myeloma was published in 1967 (1), and since then approximately 40 cases have been described in the literature (2–44). The prevalence of IgE myeloma is 0.01% in all plasmocytomas (44). Although signs and symptoms are similar, it is generally accepted that IgE myeloma has a more malignant clinical course than other forms of plasmocytoma with monoclonal gammopathy (43, 44). The disease has widely variable presentation. Most of the reported cases have been accompanied by complications that are rarely seen with other types of

myeloma. Also benign IgE monoclonal gammopathies have been reported (22, 31). Biclinal (7, 13, 24) and triclinal gammopathies (19, 24) have been described, where IgE is one component.

IgE levels in sera of patients with multiple myeloma have been found to be similar to those of patients with monoclonal gammopathy of unknown significance and to normal controls (45). This is in contrast to the significant depression in the level of the other polyclonal isotypes in patients with multiple myeloma (45). Here we report the first recorded IgE myeloma in Norway and review the known cases in the literature.

CASE HISTORY

The patient, an 80-year-old male, was admitted to hospital with progressive weakness, shortness of breath and intermittent dizziness. Cyanotic lips were observed upon exercise. Seven weeks prior to admittance, when he had a cerebral thrombosis, he was hospitalized for 3 days for investigations, and discharged with slightly reduced control of his left arm. Past medical history included operations for prostate hyperplasia in 1992 and hemorrhoids in 1976. He also had chronic pain in the neck/shoulder region for several months. A test for occult fecal blood was also positive and endoscopic investigations did not reveal any abnormal findings. Furthermore, the patient had a sedimentation rate of 75 mm/h.

Upon admittance, there was no abnormal bruising or bleeding. Blood pressure was 130/70 mmHg, heart rate 64 beats/min, regular without murmurs. No abdominal tenderness or mass was revealed and the size of the liver and spleen was normal. There were no signs of peripheral edema. He had paresthesia and reduced force in his left arm subsequent to a cerebral thrombosis verified 7 weeks earlier.

Routine laboratory evaluation gave the following: Hemoglobin 129 g/L, creatinine 110 $\mu\text{mol/L}$, calcium 2.34 mmol/L, total protein 88 g/L, leucocytes $6.4 \times 10^9/\text{L}$, and thrombocytes $276 \times 10^9/\text{L}$. Beta-2-microglobulin was 3.3 mg/L. Roentgenograms of the bones revealed osteolytic defects in the skull and in the inferior pubic arc. No lesions were found in the vertebral column nor in the extremities.

MATERIALS AND METHODS

Electrophoretic separation and quantification of serum and urine proteins were performed on agarose gel (Hydragel/Hydrasys, Sebia, Paris, France) and automatized densitometry (Hyrus Scanner, Sebia, Paris, France). Standard immunofixation was done on agarose gel with antisera against IgA, IgG, IgM, kappa, lambda and free light chains purchased from Sebia (Paris, France). A second immunofixation was performed in serum with antiserum against IgD from Dako AS (Glostrup, Denmark) and antiserum against IgE from Behringwerke AG

(Marburg, Germany). The immunofixation for IgE was done twice using different batches of antisera. For urine analysis, the urine was concentrated 100 times, and immunofixation was performed with antisera against IgA, IgG, IgM, IgD, IgE, kappa (bound and free), free kappa and lambda light chains.

RESULTS

The major results are shown in Figure 1. Serum protein electrophoresis confirmed the monoclonal immunoglobulin concentration of 25.6 g/L. The densitogram is shown in Figure 1D. Quantification of the other immunoglobulins gave IgA <0.3 g/L, IgG 2.7 g/L and IgM <0.2 g/L. On examination of bone marrow, plasma cells made up 40% of nucleated cells. Immunofixation demonstrated clearly that the clonality is caused by an IgE-kappa monoclonal protein (Fig. 1A, B).

Urine had a total protein concentration 0.15 g/L. Electrophoresis and immunofixation showed proteinuria of all serum proteins, but the major component was a broad band of polyclonal nature, about 0.06 g/L (Fig. 1C). In this band kappa light chains were dominant and staining probably represents aggregated kappa chains of variable size. The urine sample was negative with antisera to other heavy chains (G, M, A, D) besides E (Fig. 1C).

DISCUSSION

So far there are about 40 known cases in the literature, Alexander *et al.* (43) reported 28 cases in 1992 and Jako *et al.* (44) 38 cases in 1997. Of the known cases including ours, 20 have been females and 17 males. The youngest patient has been a 38-year-old woman (30) and our patient, an 80-year-old male, is the oldest. Our patient has been a very active athlete and veteran sportsman even in recent years. He presented with progressive weakness, shortage of breath and intermittent dizziness.

IgE myeloma has a wide variety of symptoms and they do not differ from those of more common forms of myelomatosis. There are no specific or typical symptoms and findings for IgE myelomatosis. However, among those most often reported are bone pain, weight loss,

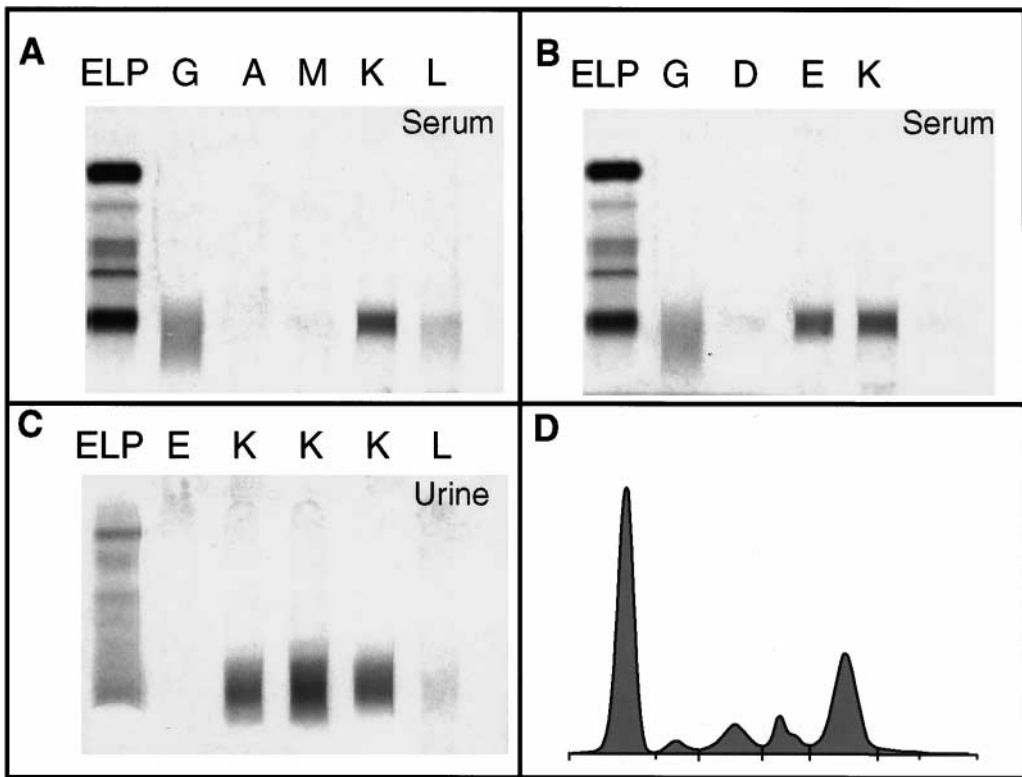


FIG. 1. Serum electrophoresis on the left (panels A, B). Immunofixation with antisera against IgG (G), IgA (A), IgM (M), kappa (K), and lambda (L) (panel A) and immunofixation with antisera against IgG (G), IgD (D), IgE (E), and kappa (K) (panel B). A strong monoclonal band, typed IgE can be seen. Urine electrophoresis (concentrated 100:1) on the left (panel C). Immunofixation demonstrates mainly a weak urinary excretion of polyclonal light chains, polyclonal kappa is dominant (panel C). Densitogram of serum electrophoresis demonstrates a moderate M-component, 25.6 g/L in the gamma region (panel D).

fatigue, dyspnea and anemia. Hepatosplenomegaly has been reported in 11 out of 38 cases. A sedimentation rate (ESR) >20 mm/h was present in 17 of 20 cases, with a mean value of 100 mm/h (44). The patient in this report presented with an ESR of 75 mm/h. A normal ESR cannot be used to rule out the diagnosis of myeloma.

Anemia is present in about half of the patients with multiple myeloma. Three of four patients with IgE myeloma had hemoglobin less than 119 g/L. Our patient had 129 g/L. Anemia does not affect the prognosis for the patient with multiple myeloma (44). Both leukopenia (leukocytes $<4 \times 10^9/L$) and leukocytosis (leukocytes $>10 \times 10^9/L$) have been reported in patients with IgE myeloma (1, 4, 5, 18, 35). Likewise, thrombocytopenia and thrombocytosis may both occur (3–5, 17, 18, 25, 26, 32, 33,

39). This is in concordance with the findings in other types of myeloma.

IgE myeloma has been associated with hematologic malignancies, chronic lymphatic leukemia (6, 13) and plasma cell leukemia (5, 11). It may also be associated with lung carcinoma (23). Some other specific features have been amyloidosis (44) and renal insufficiency (8, 18). Renal insufficiency is common and renal failure upon presentation indicates a poor prognosis. Survival time for 5 patients was 1–13 months. The mean survival time was 19 months for 23 patients who were not in renal failure (43). One-fourth of patients with multiple myeloma will present with symptoms of hypercalcemia as a result of bone destructions and renal dysfunction. Alexander et al. reported hypercalcemia in 5 out of 28 cases (43). Although hypercalcemia is the most important

disturbance, hypocalcemia has been reported (24).

Skeletal involvement has often been described, including osteoblastic lesions (14). Bone roentgenograms of our patient revealed osteolytic defects in the skull and in the inferior pubic arc. Bone lesions were reported in 19 out of 38 cases (44). Osteosclerosis has been reported in IgE myeloma (5, 14). Osteolytic lesions are common (80%) in patients with multiple myeloma from other immunoglobulins than IgE.

It has also been associated with infections (22) and specifically with Herpes zoster (25). Immunosuppression renders these patients liable to viral and bacterial infections. One-fifth of patients with IgE myeloma were reported to have respiratory tract infections on admission or later in the course of the disease (3, 11, 23, 33–35). Our patient did not have any infection.

Zavazal *et al.* (46) described a woman suffering from IgE myeloma, hay fever and polyvalent respiratory and skin allergy. The IgE monoclonal protein VL was isolated and investigated with respect to structural and functional properties, and they showed that changes in the IgE glycosylation contributed to IgE-mediated pictures of clinical allergy by the non-immunological pathway.

It is of importance to characterize rare IgE myeloma patients, because their cells may be suitable for the production of human monoclonal antibodies (28, 37).

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