Case Report: Multiple myeloma, IgAκ type, accompanying crystal-storing myeloma cells and macrophages

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ABSTRACT

We report a 75-year-old male with multiple myeloma, IgAκ, accompanying crystal-storing myeloma cells and macrophages in the bone marrow. Bone marrow aspiration showed increased plasmacytoid cells (15.6%) with around 20 to 50 of pink-staining rod crystals in their cytoplasm. These inclusions were stained by May-Giemsa and acid phosphatase, but not by peroxidase, esterase, periodic acid Sciff, alkaline phosphatase, direct fast scarlet and thioflavine-T. Large macrophages containing numerous cytoplasmic crystalline rods were also found at 0.6%. Cytochemical findings of the inclusions were the same as those of myeloma cells. Immunohistochemical staining of the inclusions with anti-α and anti-κ antibodies was negative. Electron-microscopic studies demonstrated clear hexagonal crystalline structures in myeloma cells, part of which appeared to be bound by a single smooth membrane. These data suggest that the cytoplasmic inclusions may be related with lysosomal granules.

Key words: Multiple myeloma, IgAκ, Crystalline cytoplasmic inclusions, Crystal-storing macrophages

INTRODUCTION

Crystalline cytoplasmic inclusions in neoplastic lymphocytes and plasma cells have been described well[1-17]. It is of interest that similar inclusions have been so rarely found in macrophages of those diseases. When limited to multiple myeloma, only 8 cases have thus far been reported as far as we know[1, 10-16]. Here, we report a case of multiple myeloma, IgAκ, with crystal-storing myeloma cells and macrophage-like cells in the bone marrow.

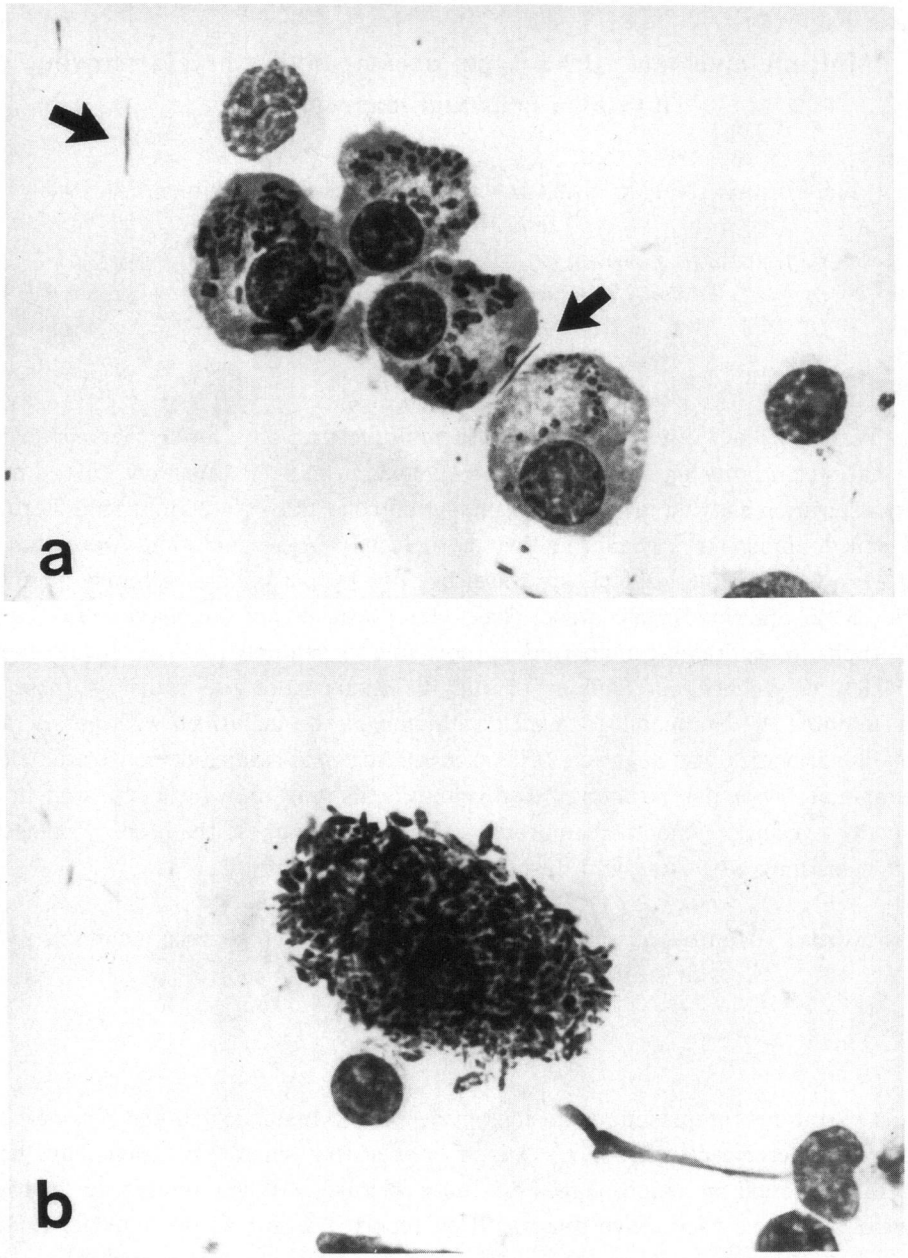

Fig. 1 Bone marrow smear stained with May-Giemsa showing plasmacytoid cells (a) and large macrophage-like cells with low N/C ratio (b) containing rod-shaped cytoplasmic inclusions (×1180). Some extracellular rods were seen scattered in the aspirate smear as indicated by arrows (a).

CASE REPORT

A 75-year-old male was admitted to our hospital on November 17, 1991 due to evidence of acute pneumonia. Physical examination revealed no remarkable findings except for moist rale auscultated in the right upper area of the chest. There were no remarkable past or familial histories. Laboratory investigation revealed that hemoglobin was 124 g/*l*, white blood cell (WBC) count was $3.8\times 10^9/l$ with 4% bands, 59% segmented neutrophils, 25% lymphocytes, 8% monocytes, 3% eosinophils and 1% basophils. Bone marrow aspiration showed normocellularity and a myeloid/erythroid ratio of 3.1 with 15.6% plasmacytoid cells whose cytoplasms contained around 20 to 50 pink crystalline rods per cell (Fig. 1). Many extracellular rods were seen scattered in the aspirate smear (Fig. 1). Large macrophage-like cells containing numerous crystalline rods were also observed at 0.6% (Fig. 2). The total serum protein level was 90 g/*l*, and serum immunoglobulin levels were as follows: IgG, 5.35 g/*l*; IgA, 43.2g/*l*; IgM, 0.7 g/*l*. Urinary protein was 30 mg/d*l* and Bence Jones protein was positive. The serum and urine β_2-microglobulin levels were 4.6 mg/*l* and 10.9 mg/*l*, respectively. Serum immunoelectrophoresis showed IgAκ paraprotein. Serum creatinine and electrolytes were within normal range. Radiographs of the bones disclosed changes consistent with mild osteomalasia but no lytic or sclerotic lesions.

The patient was diagnosed with multiple myeloma and treated with melpharan, prednisolone and antibiotics. After recovering from pneumonia, he had virtually no symptoms. Following 3 months chemotherapy, the serum IgA level remained stable at around 2.5 g/*l*. Melpharan and prednisolone were administered for further 9 months. The serum IgA and β_2-microglobulin levels have not progressed to date and a bone marrow aspiration performed on February 24, 1993, showed 6.8% plasmacytoid cells, most of them still containing crystalline rod-like inclusions.

Cytochemical, immunohistochemical and electron-microscopic analyses were performed to evaluate the crystalline inclusions in the cytoplasm of myeloma cells. They were positive for May-Giemsa and acid phosphatase (Fig. 2), but negative for α-naphthyl butyrate esterase, periodic acid Sciff, alkaline phosphatase, peroxidase, direct fast scarlet and thioflavine-T. The cytoplasm of macrophage-like cells was clearly stained with α-naphthyl butyrate esterase, suggesting that those cells could be macrophages. Immunohistochemical staining of acetone-fixed smears of bone marrow aspirate was carried out with anti-α and anti-κ antibodies. The inclusions were consequently negative for both antibodies. Electron-microscopic studies of glutaraldehyde/osmium tetraoxide-fixed

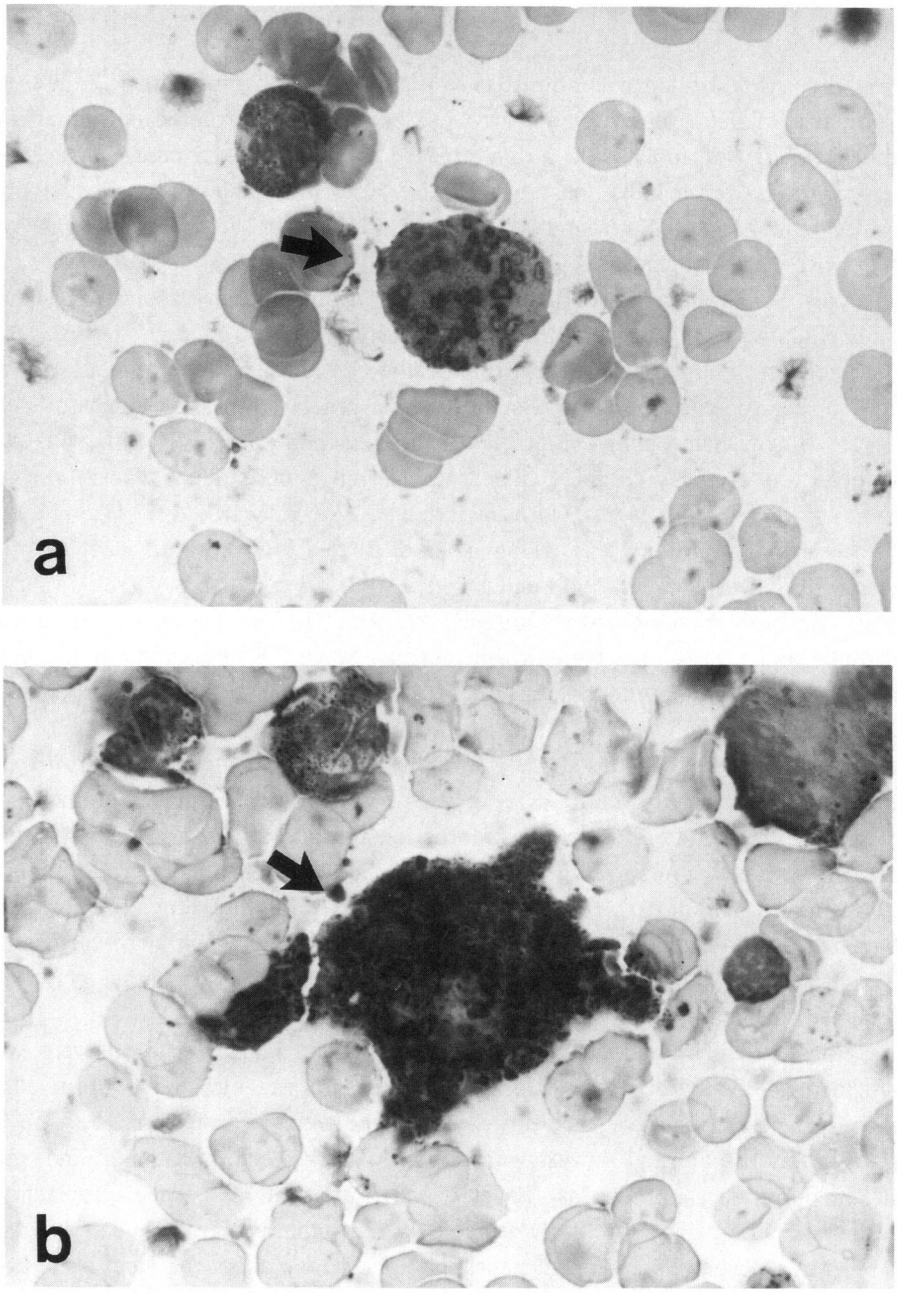

Fig. 2 Bone marrow smear stained with acid phosphatase showed plasmacytoid cells (a) and macrophage-like cells (b) containing cytoplasmic inclusions as indicated by arrows (×1180). The surrounding area of inclusions appeared to be positively stained.

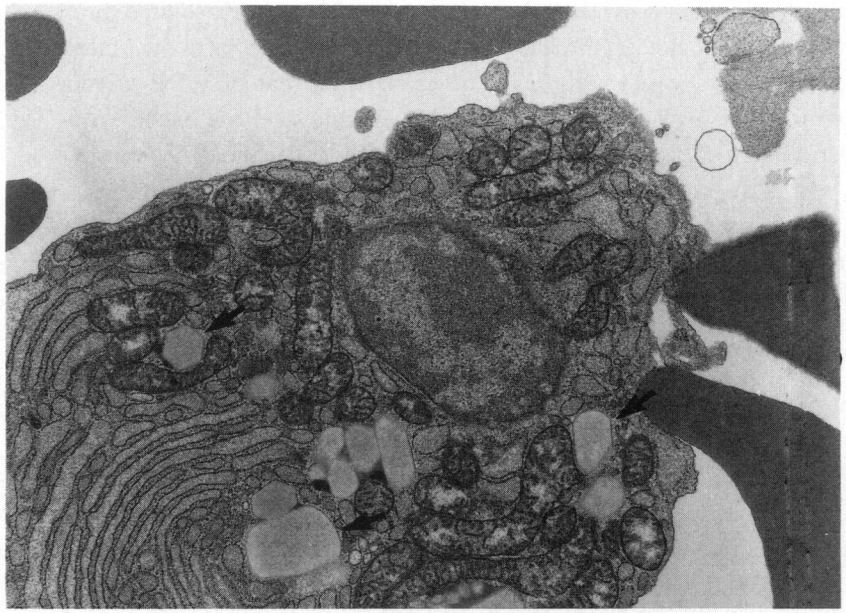

Fig. 3 Electron-micrograph of a myeloma cell containing crystalline inclusions (×10000). Some inclusions appeared to be bound by a single smooth membrane as indicated by arrows.

bone marrow aspirate showed clear hexagonal crystalline in myeloma cells, part of which appeared to be bound by a single smooth membrane (Fig. 3). Macrophages could not be identified, probably due to the small percentage of those cells (0.6%) in the bone marrow.

DISCUSSION

Although the cytoplasmic inclusions found in neoplastic lymphocytes and plasma cells have not been fully characterized, Kanoh *et al.*[4] classified them into 4 groups, i. e., immunoglobulins, amyloid fibrils, lysosomal granules and unknown substances. The inclusions of myeloma cells in our case were stained with May-Giemsa and acid phosphatase, but not with thioflavine-T. In addition, they were negative for immunostaining with anti-α and anti-$\varkappa$ antibodies. Ultrastructurally some of the crystals appeared to be surrounded by a single smooth membrane. These findings were almost consistent with those in the cases described by Sundara *et al.*[5] and Shioya *et al.* [7], suggesting that they may be of lysosomal origin. Furthermore, Yasuda *et al.* reported that all vacuoles, probably originating from the lysosomal system, found in plasma cells from a

patient with primary macroglobulinemia or with κ-chain Bence Jones multiple myeloma showed acid phosphatase activity on the demarcating membrane[18]. This fact also coincided with our findings showing that only the surrounding area of the inclusions was positively stained by acid phosphatase as shown in Fig. 2.

Morphological, cytochemical and immunohistochemical findings of the inclusions of macrophages were similar to those of myeloma cells in our case. Also, the staining pattern of acid phosphatase was similar to that of myeloma cells as indicated by arrows in Fig. 2. The inclusions in macrophages have been shown positive for anti-immunoglobulin antibodies in most reported cases where the immunohistochemical evaluations could be performed, suggesting that they are mostly immunoglobulins or light-chains. However, Padmalatha *et al.*[17] demonstrated the crystal-storing peseudo-Gaucher cells in lgMκ plasmacytoid lymphoma, only a few of which were focally stained by anti-μ and anti-κ antibodies. They conjectured that this could be explained by the dense packing and exclusion of antigenic sites of immunoglobulins in macrophages. Alternatively, immunoglobulins may have lost antigenicity as has been reported by Preud' Homme *et al*[19]. Thus, it is possible that the inclusions in the macrophages had originated from immunoglobulins. Although the mechanism of their ingestion remains unknown at the present time, it is not plausible that it is merely a non-specific phagocytic process for overproduced immunoglobulins, since crystal -storing macrophages were not found in a case of IgAκ multiple myeloma reported by Sundara *et al.*[5] in spite of the fact that bone marrow aspiration demonstrated many extracellular rods as observed in our case. There may be a structural abnormality in immunoglobulins as previously reported, [19] making it possible for macrophages to recognize them.

The clinical course of multiple myeloma patients with crystal-storing myeloma cells and macrophages is rather variable. This case has showed a non-progressive clinical course for these 2.5 years without any extramedullary organ dysfunction. The survival periods of reported three long- and two short-cases were 3.9 to 5.5 years[14-16], and 5.5 and 7 months[12, 13], respectively. The most distinct clinical findings distinguishing these two groups may be the amount of tumor cells infiltrating into the bone marrow. In the former, the invasion of myeloma cells was less than 20%, whereas it was more than 80%[13] or "predominant"[12] in the latter. Our case appears to belong to the former group, but is different from all those 5 cases[12-16] in the point that they showed systemic distribution of macrophages or their marked infiltration into the bone marrow. Further accumulation of data on cases of multiple myeloma with crystal-storing macrophages will be required to clarify whether this difference reflects different biochemical properties of abnormal immunoglobulins, different clinical

stages of the same disease or different disease states.

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