Non-secretory immunoglobulin E myeloma associated with immunoglobulin G monoclonal gammopathy of undetermined significance

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Abstract

A 68-year old woman came to our hospital with a severe case of anemia. Serum immunoelectropheresis identified a monoclonal immunoglobulin (Ig) G and κ protein. The serum IgE level was within the nomal range and the amounts of remaining immunogloblins were low. On bone marrow aspirate, plasma cells made up 55.5% of nucleated cells and the plasma cells showed positive readings for IgE κ and IgG by immunohistochemistry. Serum immunofixation did not reveal the IgE monoclonal band. She was diagnosed as having non-secretory IgE myeloma with IgG monoclonal gammopathy of undetermined significance. The nature of this rare myeloma will be discussed.

Introduction

Non-secretory myeloma is a rare condition of multiple myeloma (MM) that accounts for 1.0-5.0% of all myeloma patients. IgE myeloma is a very rare type of MM. Here, we report on an IgE myeloma patient with IgG monoclonal gammopathy of undetermined significance with non-secretory IgE.

Case Report

A 68-year old woman presented with fever, palpitation and dyspnea. Upon physical examination, the patient was diagnosed with anemic conjunctiva. The patient did not present hepatosplenomegaly nor peripheral lymphadenopathy. On admission, hemoglobin was 49 g/L (reference ranges 120~160 g/L), albumin 47 g/L (reference ranges 37~52 g/L), Cr 7.6 mg/L (reference ranges 5~12 mg/L), Ca 9.4 mg/dL (reference ranges 8~10.5 mg/dL), and β2-microglobulin 2.2 mg/L (reference ranges 1~1.9 mg/L). No circulating plasma cells were detected in the blood film. Immunoglobulin (Ig) levels were IgE 9.38 IU/mL (reference ranges 0~173 IU/mL), IgG 4.68 g/L (reference ranges 8.7~17.0 g/L), IgA 0.25 g/L (reference ranges 1.1~4.1 g/L) and IgM 0.324 g/L (reference ranges 0.46~2.6 g/L), respectively. On Wright's stained smears of bone marrow aspirate, atypical plasma cells made up 55.5% of the nucleated cells (Figure 1). Chromosomal analysis of bone marrow cells showed a normal karyotype. Immunohistochemically, plasma cells had positive readings for CD138, IgE and κ, but the IgG bearing plasma cells were scattered (Figure 1). Immunofluorescence staining of IgG and IgE was performed on a paraffin section of bone marrow using fluorescein (FITC)-conjugated rabbit anti-human IgG antibodies for detecting IgG, and using both rabbit anti-human IgE polyclonal antibodies and Alexa Fluor594-labeled goat anti-rabbit IgG antibodies for detecting IgE. Dual staining of IgE and IgG showed that a part of the IgE and IgG positive cells was identical (Figure 2). The specificity of the anti-IgE antibodies was confirmed by an intensive control study (*data not shown*). Polymerase chain reaction (PCR) and capillary immunoelectrophoresis of the PCR products on the paraffin section of bone marrow revealed a rearrangement of the *IgH* gene in the VH (FR3) region. Bone X-ray showed a compression fracture and osteoporosis in L1 and L3. Magnetic resonance imaging showed an abnormal signal interpreted as a possible involvement of myeloma in the vertebrae, sacrum and coccyx. Immunoelectrophoresis showed an abnormal arc precipitating with anti-IgG and anti-κ sera in the serum and anti-κ in the urine sample, although the free light chain was not measured (Figure 3). Serum immunofixation test identified a faint IgG band and clear band of κ light chain but not IgE (Figure 4). The patient was diagnosed as having non-secretory IgE myeloma with IgG monoclonal gammopathy of undetermined significance (MGUS) based on the following findings: i) serum immunoelectropheresis identified a monoclonal IgG and κ protein; ii), atypical plasma cells made up 55.5% of the nucleated cells on bone marrow aspirate; iii) immunohistochemical staining showed most plasma cells were positive for IgE and κ, but a few for IgG; iv) there was no increase in serum IgE level; v) serum immunofixation did not show any IgE monoclonal band. The patient was at stage III A (Durie and Salmon staging system) or 1 (international staging system). The patient was started on two cycles of ROAD-IN chemotherapy: vincristine 1.2 mg/m^2 (day 1), ranimustine 40 mg/m^2 (day 1), melphalan 8 mg/m^2 (days 1-6), dexamethasone 40 mg (days 1-4, days 9-12, days 17-20), IFN-α 300×10^6 IU SC 3 times/week (days 22-43, every 6 weeks). Therapeutic response was judged as a partial response based on international response criteria for multiple myeloma.[1] Afterwards, she was treated with eight cycles of MP therapy: melphalan 10 mg/day for 4 days and prednisolon 60 mg/day for 4 days every 6 weeks. Unfortunately, the patient relapsed in November 2007. She received ROAD-IN chemotherapy again but relapsed after a transient remission. Bone marrow showed the proliferation of myeloma cells with cytoplasmic IgE and κ chain. Two color flow cytometric analyses of bone marrow plasma cells revealed 36.8% CD38$^+$ CD49e$^-$ and 7.8% CD38$^+$ CD49e$^+$. In June 2008, the patient was then started on five cycles of BTZ-DEX therapy: bortezomib 1.0 mg/m^2 (day 1, day 4, day 8, day 11), dexamethasone 20 mg (days 1, 2, days 4, 5, days 8, 9, days 11, 12, every 3 weeks) followed by three cycles of VAD therapy: vincristine 0.4 mg/day (day 1-4), doxorubicin 9 mg/m^2 (days 1-4), dexamethasone 40 mg/day (days 1-4). She died of tumor progression 42 months after the diagnosis. No autopsy was performed (Figure 5).

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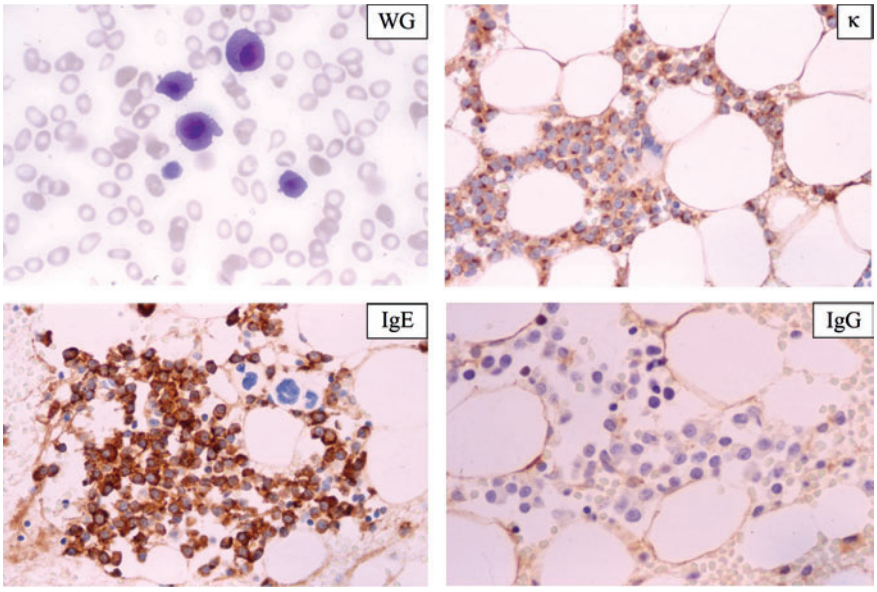

Figure 1. Bone marrow aspiration. Myeloma cells were detected at 55.5% (Wright-Giemsa stain ×100). Myeloma cells showed strong positivity for IgE and κ (immunostain ×60) but few cells were positive for IgG (immunostain ×80).

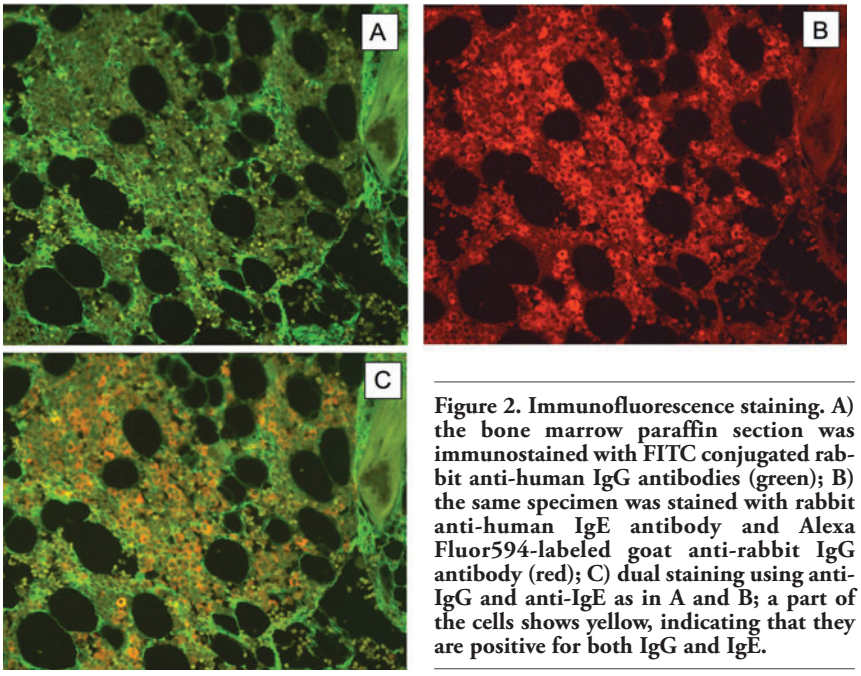

Figure 2. Immunofluorescence staining. A) the bone marrow paraffin section was immunostained with FITC conjugated rabbit anti-human IgG antibodies (green); B) the same specimen was stained with rabbit anti-human IgE antibody and Alexa Fluor594-labeled goat anti-rabbit IgG antibody (red); C) dual staining using anti-IgG and anti-IgE as in A and B; a part of the cells shows yellow, indicating that they are positive for both IgG and IgE.

Discussion

IgE myeloma is the rarest type of multiple myelomas. Forty-six cases have been reported since the first description in 1976.[2-9] Clinical manifestations are similar to other types of myeloma.[3] In contrast to our patient, in most reported cases the IgE serum level is extremely high (1000~200,000-fold increase). It is generally accepted that IgE myeloma takes a more aggressive clinical course and has a poorer rate of survival (median 16 months).[5] Our patient survived for a considerably long time (42 months) compared to the other patients with typical IgE myelomas.

In the present case, we detected the serum M-components of IgG and BJP-κ but not IgE by either immunoelectropheresis or immunofixation. However, cytoplasmic immunoglobulins mainly produced by bone marrow plasma cells (myeloma cells) were IgE and κ light chain, suggesting the non-secretory IgE heavy chain with two M-components (IgE, IgG) in our case.

MM with two M-components, which include an IgE, are rare.[10] Only 2 cases with IgE as a component of biclonal gammopathy (IgA/κ+IgE/κ or IgG/λ+IgE/κ) have been reported.[11,12] Due to the low serum M-component of IgG and few plasma cells that produce IgG, it appears that IgG-producing plasma cells are not subjective myeloma clones, suggesting IgG MGUS. The question is whether myeloma cells produce these two M-components (IgG and IgE) from the same parental clone or two unrelated clones. The dual staining of IgG and IgE by immunofluoresence revealed that identical myeloma cells produced both IgE and IgG despite most myeloma cells producing only IgE. Thus, myeloma cells producing IgE or IgG M-components may originate from the same parental clone. In fact, Bakkus *et al.* reported that myeloma cells that produce IgA/κ and IgE/κ double M-component share a common clonal origin and undergo a

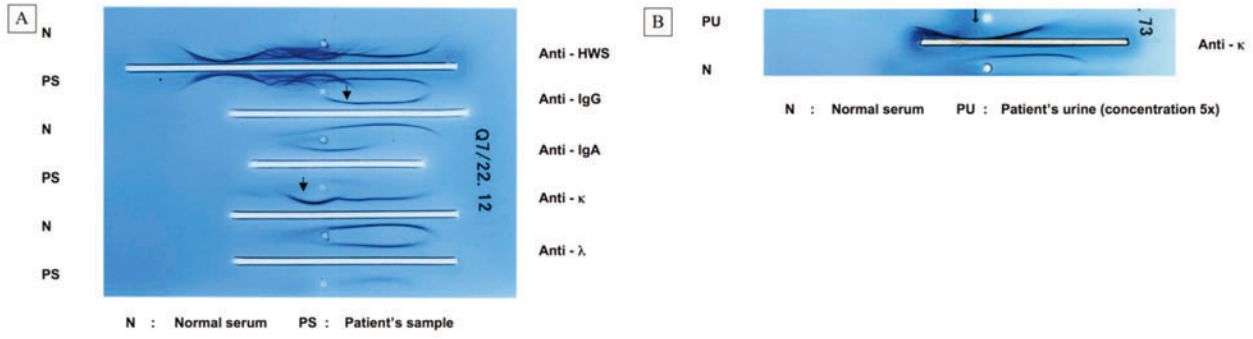

Figure 3. Immunoelectrophoresis: A) IgG and κ monoclonal bands were seen in serum (arrow); B) BJP (κ) were seen in urine (arrow).

different class switch,[11] suggesting the possible development of biclonal gammopathy, as in our case.

The monoclonality of the IgE-producing myeloma cells was confirmed by PCR analysis. These cells, as predominant populations, do not secrete the IgE M-component, indicating non-secretory IgE myeloma. Non-secretory myeloma is also a rare condition of MM accounting for 1.0~5.0% in all myeloma patients.[13-15] To the best of our knowledge, the case described here is the first non-secretory IgE myeloma. The positivity for both IgE and κ in most myeloma cells suggests that our case is non-secretory IgE heavy chain (HC) with BJP-κ secretion. There are no reports of myeloma cases with non-secretory HC and secretory light chain (LC) so far. In general, it is presumed that immunoglobulin HC and LC are synthesized by polyribosome in the endoplasmic reticulum and then folded in the presence of a chaperon protein such as Bip. Both chains are constructed as a complete immunoglobulin after the formation of intrachain/interchain disulfide bonds. Complete immunogulobulins are transferred to a Golgi apparatus and secreted afterwards.[16] Therefore, when the assembly between HC and Bip is not achieved, a complete immunoglobulin cannot be assembled and both chains are degraded by proteasomes. Furthermore, it has been reported that mutations at Cys194 and Cys214 in LC result in the impairment of intrachain/interchain disulfide bond formation, causing non-secretory myeloma.[17,18] It is unknown whether the above mechanisms were involved in the non-secretion of IgE in the present case. Further investigations are needed to clarify the pathogenesis in cases like this.

Although IgE myeloma is thought to be very rare, it could be overlooked because the IgE M-protein cannot always be detected by standard immunoelectrophoresis, and the IgE value is low in some cases of IgE myeloma.[6,9] Therefore, it might be important for the diagnosis of IgE myeloma to perform not only a serum immunofixation test, but also immunohistochemistry using IgE antibodies in the bone marrow.

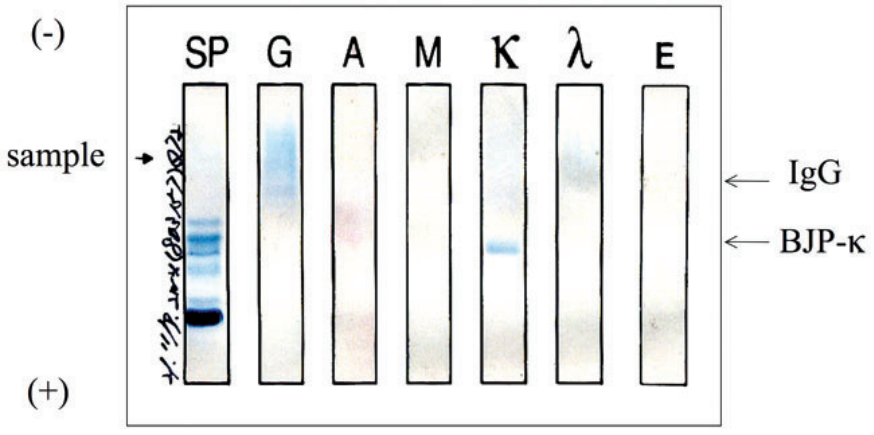

Figure 4. Serum immunofixation electrophoresis revealed a faint IgG band and a clear band of BJP (κ) (arrow).

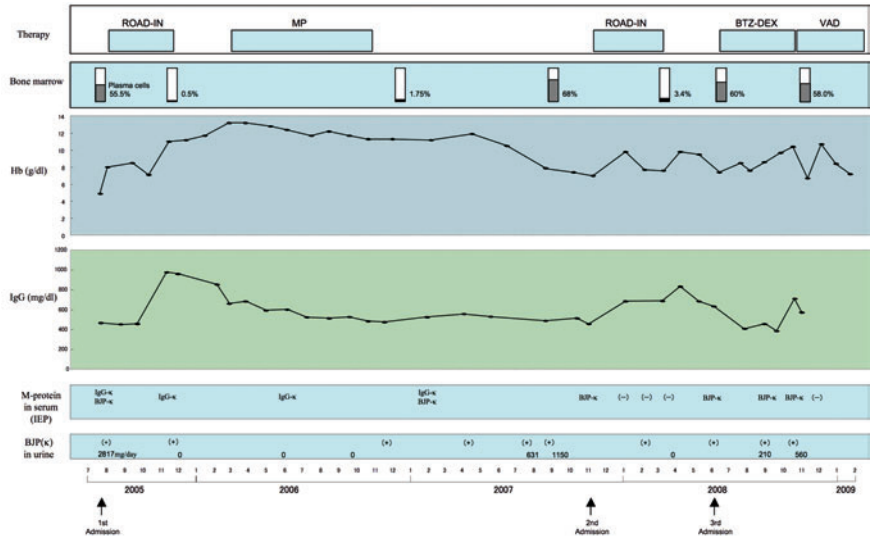

Figure 5. Patient's clinical course.

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