

An unusual case of IgE-multiple myeloma presenting with systemic amyloidosis 2 years after cervical plasmacytoma resection

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Abstract A 69-year-old man suffered from a fractured cervical vertebra, and magnetic resonance imaging revealed a solitary mass occupying the injured lesion. Surgical resection of the mass was conducted, and the infiltration of plasma cells expressing IgE- λ monoclonal protein was shown on pathological investigation. Concurrently, a monoclonal band of IgE- λ was shown in the sera on immunoelectrophoresis, and the proliferation of plasma cells (more than 10%) was also detected in bone marrow aspirates. A rare IgE-multiple myeloma (MM) was diagnosed, and careful monthly follow-up was started. During this observation period, the level of IgE gradually increased and, at 2 years after the initial diagnosis, bilateral leg edema and ascites with marked hepatosplenomegaly appeared. Combination chemotherapy of melphalan and prednisolone (MP) was started, which resulted in the partial, transient resolution of symptoms. Additional treatment with bortezomib and dexamethasone could neither resolve these clinical symptoms nor decrease the serum IgE concentration. At 5 months after the start of chemotherapy, amyloid deposition was suggested based on typical echocardiographic findings, and the diagnosis of amyloidosis was confirmed based on the histopathology of a liver biopsy. In spite of MP plus thalidomide treatment, cardiac failure due to amyloidosis aggravated, and the patient died of multiple organ failure. This is the second reported case in which IgE-MM was complicated by systemic amyloidosis.

Keywords IgE · Multiple myeloma · Plasmacytoma · Amyloidosis

1 Introduction

Since the initial report by Johansson and Bennich in 1967 [1], only 47 IgE-multiple myeloma (MM) cases have been reported [2–9]. Unique clinical features such as a higher frequency of plasma cells in the peripheral blood, a high incidence of osteosclerotic (osteoblastic) change, and hepatosplenomegaly have been documented [10]. Possibly because of diagnostic delay, IgE-MM cases show more aggressive clinical courses, with a mean survival of 16 months, compared with an average of 30 months in other immunoglobulin types [11].

The present patient, showing few typical myeloma-related symptoms or laboratory findings, was primarily diagnosed with solitary plasmacytoma, which was then proven to be IgE-MM based on bone marrow findings and serum immunochemical analysis. After 2 years of stable disease without treatment, the patient displayed clinical signs of systemic amyloidosis that are rarely complicated with IgE-MM. Here, the quite unique clinical picture is presented, and the treatment of this rare type of myeloma is discussed.

2 Case report

A 69-year-old male visited our hospital because of cervical pain and paresthesia of the upper arm soon after falling off a chair. A fracture of the sixth cervical vertebra was noted on X-ray examination, and magnetic resonance imaging revealed a solitary mass occupying the injured lesion (Fig. 1). Surgical resection of the mass was performed, and the infiltration of plasma cells expressing IgE- λ monoclonal protein was shown on pathological investigation (Fig. 2). Laboratory evaluation disclosed a white blood cell

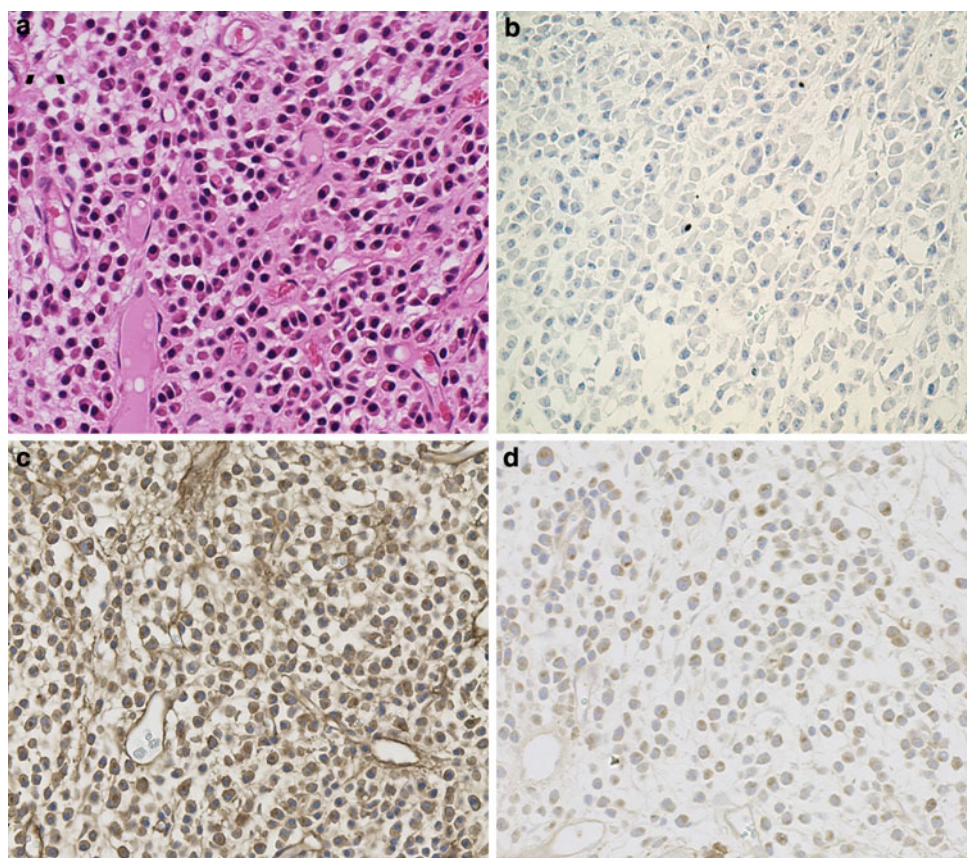
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Fig. 1 MRI findings at disease onset. A 6th vertebral fracture with a solitary mass can be seen (arrow)

count of $8.3 \times 10^9/L$ with no atypical cells, a hemoglobin level of 97 g/L, and a platelet count of $512 \times 10^9/L$. Serum total protein was 69 g/L, albumin was 43 g/L, creatinine was 0.79 mg/dL, serum calcium was 9.3 mg/dL, and serum β_2 -microglobulin was 2.7 mg/L (normal <1.9). The concentrations of IgG, IgA, and IgM were 473, 30, and 7 mg/dL, respectively. The initial serum protein electrophoresis showed a small peak in the γ region; concurrently, a monoclonal band of IgE- λ was identified by immunoelectrophoresis and quantified as 2,540,000 IU/mL (normal <173). Bence Jones λ proteinuria was also positive. Bone marrow aspirates revealed a proliferation (at around 10% among all nucleated cells) of plasma cells with an abnormal morphology (data not shown), and the patient was diagnosed with MM. The cervical tumor was thought to be completely resected as there was no residual symptom or radiographical findings around the invaded lesion. A systemic bone survey revealed no other lesions, and there was no myeloma-related complaint. Therefore, we did not perform radiotherapy or chemotherapy and a careful monthly follow-up was started. Alfacalcidol and alendronate were administered to prevent osteoporotic change due to myeloma. In addition to IgE-MM, the patient also

Fig. 2 Immunohistological staining of a resected plasmacytoma. Sections were stained with hematoxylin–eosin (a), anti- κ (b), anti- λ (c), and anti-IgE (d), respectively



suffered from hypertension, chronic cardiac failure, and the temporal appearance of atrial fibrillation. He had been taking amlodipine, trichlormethiazide, telmisartan, carvedilol, digosin, and warfarin.

At 2 years after the diagnosis of IgE-MM, marked edema appeared in the bilateral legs and scrotum, with an increase in the body weight. Chest radiography revealed cardiomegaly with no pulmonary congestion, and abdominal computed tomography (CT) scans showed prominent hepatosplenomegaly with a moderate amount of ascites (data not shown). Echocardiography showed diffuse concentric hypertrophy of the left ventricular wall with a preserved left ventricular ejection fraction (LVEF: 73%). As the brain natriuretic peptide (BNP) level was elevated to 937 pg/ml (normal <18), the acceleration of diastolic heart failure was confirmed by a consultant cardiologist. However, the administration of furosemide and spironolactone was ineffective. On the other hand, during the 2-year observation period, although there were no myeloma-related clinical findings other than a moderate reduction of the hemoglobin level (90 g/L), the serum concentration of IgE gradually increased to 3,790,000 IU/mL (1.5 times the initial value), suggesting a worsening of IgE-MM. At this time, these symptoms were suspected to be caused by the MM-related amyloidosis; however, bone marrow and

upper gastric tract biopsies could not confirm this diagnosis.

The patient was then admitted to our hospital and started on melphalan (M: 6 mg/m²/day for 4 days) and prednisolone (P: 40 mg/m² for 4 days). At the beginning, partial resolution of the leg edema and ascites was observed, whereas, at around 3 weeks after treatment, the symptoms again aggravated with a slight decrease in the serum IgE value (from 4,500,000 to 3,500,000 IU/mL).

Therefore, bortezomib (1.3 mg/m²/day; biweekly for 2 weeks) was started and repeated for 4 cycles, and dexamethasone (20 mg/body on the same and the day following bortezomib infusion) was added to the regimen in the latter 2 cycles. As shown in Fig. 3, there was no significant improvement in the clinical findings even after a decrease of IgE (from 3,500,000 to 2,500,000 IU/mL). Furthermore, cardiovascular complications such as orthopnea and distress on exertion gradually progressed and echocardiography showed hypokinesis (43% of LVEF) of the left ventricular wall and concentric thickening with a granular sparkling appearance (Fig. 4). These observations suggested that cardiac failure had been accelerated by a progressive accumulation of amyloid, and all the above-mentioned symptoms were associated with systemic amyloidosis. Therefore, we conducted a liver biopsy to make a final diagnosis.

A pathological investigation revealed amyloid deposition around hepatic arteries and the periportal infiltration of IgE-positive myeloma cells (Fig. 5). Systemic AL amyloidosis secondary to IgE-MM was diagnosed, and then an alternative salvage therapy of MP-T (melphalan and prednisone, the same as above-mentioned, plus thalidomide at 100 mg/day) was started. Peripheral edema and ascites completely disappeared with a decrease in the body weight after treatment. However, cardiac complications, manifested as an extremely low blood pressure due to the inability to sustain cardiac output, gradually worsened and, at around 2 months after the start of MP-T treatment, severe septic shock induced by *Pseudomonas aeruginosa* occurred: The patient died of multiple organ failure at

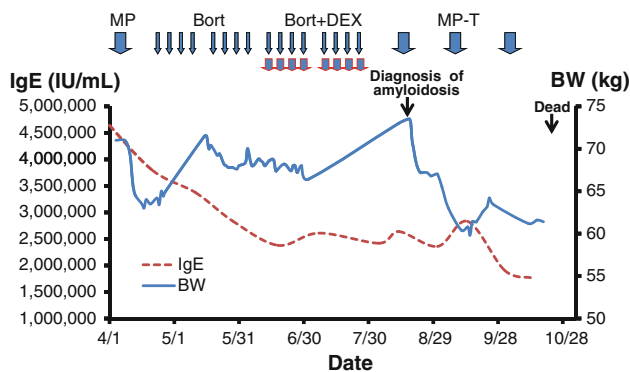


Fig. 3 Clinical course after disease progression. *Bor* bortezomib, *MP* melphalan and prednisolone, *T* thalidomide, *DEX* dexamethasone

Fig. 4 Echocardiography shows diffuse concentric hypertrophy of the left ventricular wall with a granular, sparkling appearance

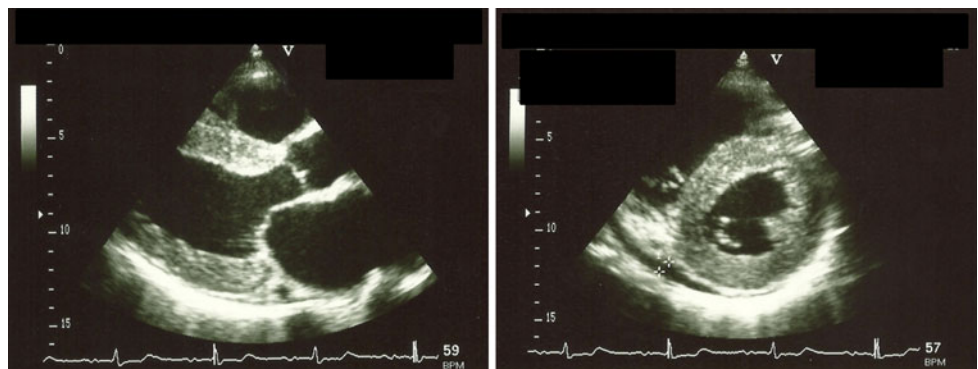
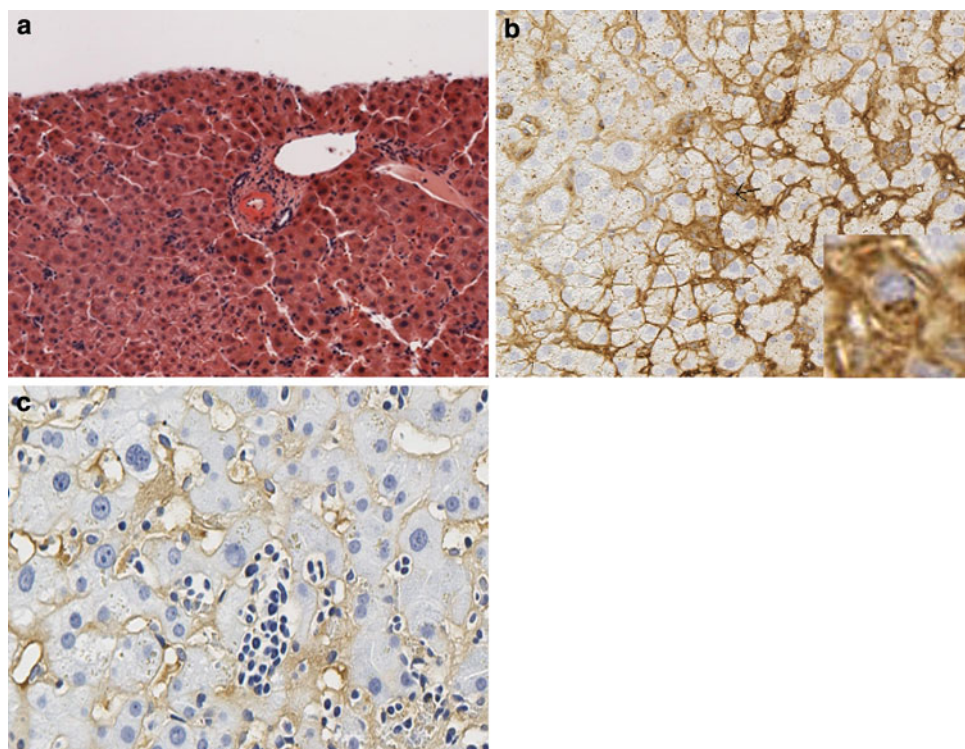


Fig. 5 Immunohistological staining of the liver. Amyloid deposition around hepatic arteries shown by Congo-red staining (**a**), and the infiltration of myeloma cells shown by anti-IgE (**b**) and anti- λ (**c**) antibodies



30 months after the diagnosis of IgE-MM. Autopsy was not performed.

3 Discussion

The present case is considered to be quite unique in terms of the clinical manifestation. Firstly, the progression in our patient is considered to be quite slow, which is rather unusual compared with the majority of the other published cases. In general, a smoldering or indolent myeloma can be followed carefully without treatment. In our study, because of the absence of myeloma-related clinical findings except for moderate anemia, the patient was followed for 2 years until the appearance of amyloidosis-related symptoms. In the previous reports, 8 out of 30 patients survived for longer than 2 years. Hayes et al. reported a patient showing 20-year survival, the longest in our reviewed literature [5]. Even though the present patient was free of specific symptoms at the time of diagnosis, he had been started on combination chemotherapy (doxorubicin, cyclophosphamide, melphalan, and prednisone) and received intermittent treatment of MP for several years. Therefore, sustained high IgE levels may be a sufficient indication to start treatment. To devise criteria for the indication of treatment, more cases should be accumulated and analyzed in the future, as Durie–Salmon’s clinical staging [12] is not useful for this purpose in rare types of IgE- or IgD-MM.

Secondly, the patient was complicated with systemic (liver, heart, and possibly spleen) amyloidosis. The prevalence of amyloidosis among all myeloma patients is around 10% [13], whereas only one case of IgE-MM accompanied with amyloidosis has been reported [2]. Within the stable, long-term clinical course of IgE-MM, the sustained, quite high level of IgE-protein might be associated with promoting free light chain deposition in various organs. Besides the quantification of M-proteins, a serum-free light chain assay should have been conducted, being essential for the management of patients with AL amyloidosis [14, 15].

The standard primary induction therapy for elderly patients is MP [16], while VAD (vincristine, doxorubicin, and dexamethasone) with or without autologous stem cell transplantation (ASCT) is employed for patients aged <65 years old [17]. Several IgE-MM patients have been successfully treated employing conventional regimens such as MP, VAD, or interferon- α [3, 18]. As our patient was much older than 65 years and also had cardiac complications, MP therapy was selected as a first line, but it had only partial, transient effects on the clinical symptoms (edema and ascites) and the reduction in serum IgE.

Novel agents including bortezomib and thalidomide have been applied to refractory MM [19, 20] and also to AL amyloidosis [21–24]. Wozney et al. reported a 71-year-old IgE-MM patient in whom 1-year remission was achieved employing a thalidomide-containing regimen or bortezomib [3]. Jian et al. reported a 40-year-old patient

who was successfully treated with VAD and thalidomide, and subsequently received ASCT [7]. Furthermore, in some cases of primary amyloidosis, many convincing results have been demonstrated using bortezomib- [21, 22] or thalidomide- [23, 24] containing regimens. Moreover, Palladini et al. reported that 4 out of 22 patients with advanced cardiac amyloidosis achieved sustained improvement on MP-T treatment [25], and Choi et al. reported a single patient in whom marked improvement of the cardiac function was shown employing thalidomide and dexamethasone [23], although, in general, cardiac amyloidosis occurs in more than 50% of AL amyloidosis and the prognosis is quite poor, being as short as 6–9 months for the median survival time when heart failure is present [26]. In our patient, treatment with bortezomib plus dexamethasone or MP-T could reduce the level of IgE, possibly due to effects on the proliferation of myeloma cells, although these treatments were insufficient or too late to improve the clinical symptoms of systemic amyloidosis, which rapidly progressed to the terminal stage. Therefore, the early diagnosis of AL amyloidosis is important, and novel strategies including the optimal selection or combination of drugs are warranted to rescue such difficult cases.

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