

## Letter to the Editor

**A case of IgE-multiple myeloma presenting with a high serum Krebs von den Lungen-6 level****1. Introduction**

Since the first report of IgE-MM was published in 1967, fewer than 50 cases have been described in the literature [1]. As compared with other immunoglobulin types, IgE-MM cases showed more aggressive clinical courses, with unique clinical features including a higher frequency of plasma cells in the peripheral blood, a high incidence of osteosclerotic (osteoblastic) change, and hepatosplenomegaly [2].

Here we describe a case of IgE-MM (stage III) complicated by a high serum level of Krebs von den Lungen-6 (KL-6) [3]. An immunohistochemical study revealed that myeloma cells markedly expressed KL-6 in parallel with IgE. Bortezomib, a novel proteasome inhibitor, plus dexamethasone remarkably reduced both IgE and KL-6 levels in sera. Thus, it was assumed that in addition to IgE, KL-6 may be also a good parameter for predicting disease activity in this unique case.

**2. Case report**

A 65-year-old woman had visited an orthopedic clinic because of fractures in her lumbar vertebrae one year previously. The case was referred to the hematological department of our hospital when the bone fractures extended to include her thoracic vertebrae and ribs, accompanied by severe chest and back pains.

A laboratory evaluation disclosed a white blood cell count of  $2.8 \times 10^9/L$  with no atypical cells, a hemoglobin level of 10 g/L, and a platelet count of  $160 \times 10^9/L$ . The serum total protein level was 77 g/L, the albumin level was 44 g/L, the creatinine level was 0.56 mg/dL, the serum calcium level was 10 mg/dL, and the serum  $\beta_2$ -microglobulin (MG) level was 5.1 mg/L (normal < 1.9). The concentrations of IgG, IgA, and IgM were 190, 8 and 5 mg/dL, respectively. An initial serum protein electrophoresis analysis showed a small peak in the  $\gamma$  region; concurrently, a monoclonal band of IgE- $\lambda$  was identified using immunoelectrophoresis and was quantified as 2,540 IU/mL (normal < 173). Bence Jones  $\lambda$  proteinuria was also positive. Bone marrow aspirates revealed a proliferation of plasma cells (around 28% of all nucleated cells) with an abnormal morphology, and the patient was diagnosed as having IgE-MM.

After admission, the patient was treated with 4-day infusion of dexamethasone (40 mg/body), however, her serum IgE level markedly increased ( $442 \times 10^4$  IU/mL) at around 2 weeks after the start of treatment. Therefore, we decided to change the regimen to bortezomib (B: 1.3 mg/m<sup>2</sup> on days 1, 4, 8 and 11 of 21-day cycle) plus dexamethasone (D: 20 mg/body on the same day and the day after the bortezomib infusion).

Acute lung injury or interstitial pneumonitis (IP) is a serious potential adverse reaction of bortezomib treatment [4]. Although

the frequency of such pulmonary complications is quite low, a routine lung examination is mandatory before the infusion of bortezomib at our institute. In preliminary examinations, the serum KL-6 level was measured as a marker of IP [3]. A significantly elevated level (3800 U/mL) was observed; however, no abnormal findings were observed during a computed tomography examination of the chest, and no increases in other IP-associated biochemical markers, such as surfactant protein-D, were seen.

As shown in Fig. 1, an immunohistochemical study revealed that plasma cells in the bone marrow reacted positively with antibodies for anti-IgE, anti- $\lambda$  light chain and anti-KL-6. IgE and KL-6-producing MM was definitively diagnosed. As shown in Fig. 2, the two parameters, together with  $\beta_2$ -MG significantly decreased after 4 courses of BD treatment. At that point, a severe skin rash appeared, and the regimen was changed to lenalidomide plus dexamethasone. However, a similar skin reaction occurred 2 days after the start of therapy. Finally, although a classical melphalan plus prednisolone (MP) therapy was chosen, quite similar skin complication occurred on day 2 of treatment.

The patient transferred herself to another hospital to seek a second opinion.

**3. Discussion**

IgE-MM is very rare type of plasma cell disorders, presenting with a more aggressive clinical course, as compared with other immunoglobulin types [5]. The post-transplant survival in IgE-MM appears to be worse than that in other myelomas [6]. Recently, several novel therapies including bortezomib and lenalidomide have been extensively applied for treatment of myelomas, appearing to have a beneficial effect in common myelomas. However, the clinical benefits of these novel agents for IgE-MM remain uncertain. In our previous case, treatment with bortezomib plus dexamethasone or MP-thalidomide slightly reduced the serum concentration of IgE, although these treatments were insufficient to improve the clinical symptoms of systemic amyloidosis [1]. In contrast, the present case showed that bortezomib plus dexamethasone treatment significantly reduces the serum IgE level.

Skin eruption is a common adverse reaction during bortezomib treatment. The frequency of such reactions is reportedly 18%; however, the incidence of severe reactions (grade 3/4) is quite low [7]. Generally, such reactions can be cured with the transient use of anti-allergic drugs or steroids. In our case, after the withdrawal of bortezomib nearly a one-month period was required for resolution of the skin lesions using these drugs. This event was considered to be a grade 3 adverse reaction according to the Common Terminology Criteria for Adverse Events (version 4.0) of the National Cancer Institute of the United States of America, which precludes the further BD treatment. Thereafter, both lenalidomide plus dexamethasone and MP therapies induced similar skin

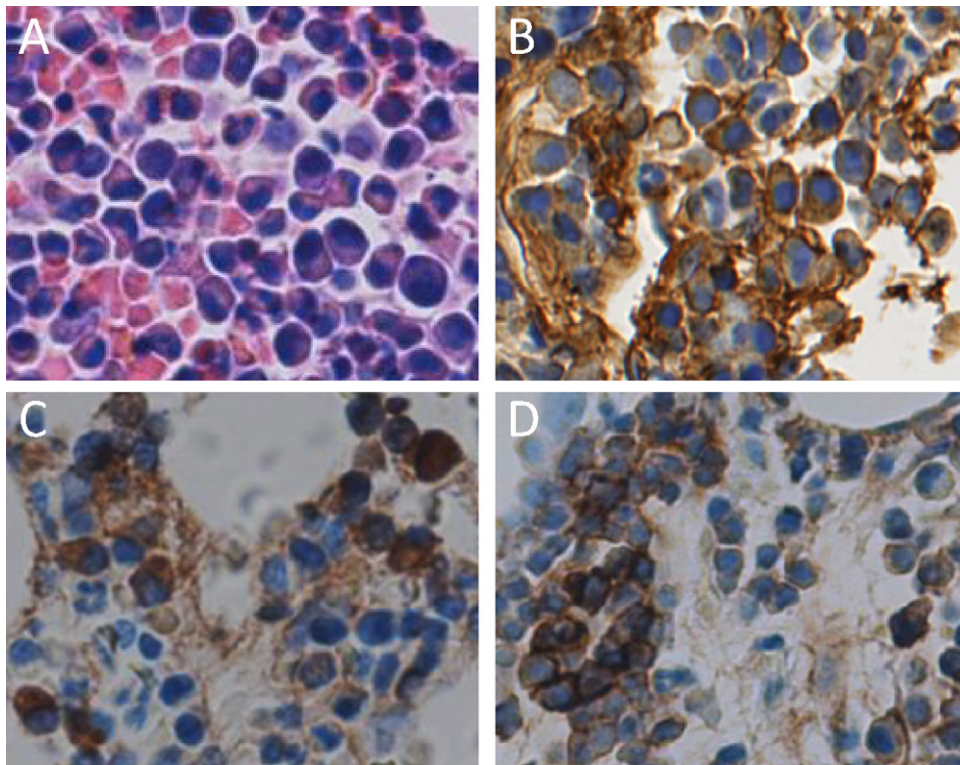


**Fig. 1.** Immunohistochemical staining of bone marrow. The plasma cells were positively stained using hematoxylin-eosin (A), anti-IgE antibody (B), anti- $\lambda$  antibody (C) and anti-KL-6 antibody (D). Original magnification 100 $\times$ .

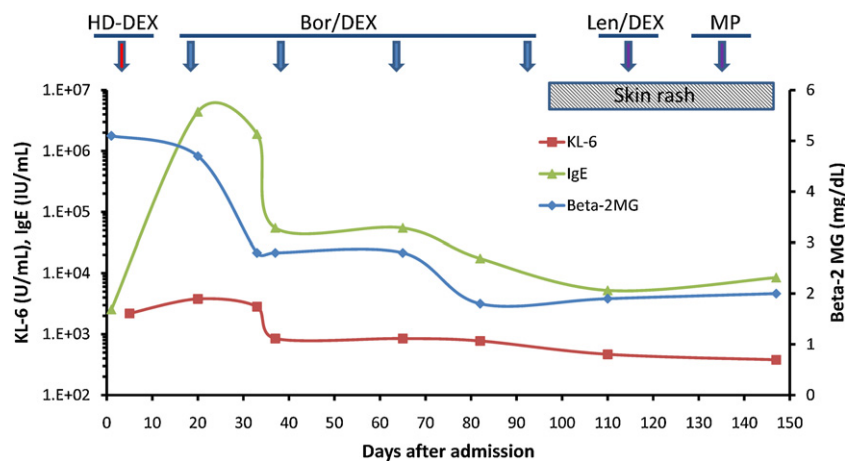


**Fig. 2.** Clinical course after disease onset. Bor: bortezomib; DEX: dexamethasone; HD-DEX: high dose dexamethasone; Len: lenalidomide; and MP: melphalan plus prednisolone. The KL-6 and IgE levels are shown using a logarithmic scale.

eruptions, although the grade was not as severe as that produced by bortezomib.

KL-6 is well known as a sensitive marker of IP [3]. The expression of KL-6 was recently shown to be increased in adenocarcinomas of the lung, breast, pancreas, ovary, colon and liver [8]. Because a relationship between KL-6 and the growth or survival of cancer cells has been suggested, KL-6 has been used as an indicator for predicting the clinical outcomes of such cancer patients. Recently, elevated circulating KL-6 levels were observed in patients with acute non-lymphoid leukemia, adult T cell leukemia/lymphoma and chronic myeloproliferative disorder [9]. Furthermore, KL-6 has also been shown to be produced from some myelogenous leukemic cells. However, an elevated level of KL-6 has not been previously reported in patients with MM. Therefore, the present case may be the first

report of the aberrant production of KL-6 by myeloma cells and its potential utility as a marker to evaluate disease activity of MM, similar to M-protein and  $\beta_2$ -MG.

Recently, KL-6 has also been shown to be a chemotactic factor for human fibroblasts and contribute to their proliferation [10]. Similarly, in some myeloma cells, KL-6 might play a role in tumor survival or progression. The mechanisms and biological functions of the overproduction of KL-6 in MM should be elucidated in the future.

#### Conflict of interest statement

All the authors have no conflicts of interest to report.

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