

*Letter to the Editor*

## **Anaplastic multiple myeloma: possible limitations of conventional chemotherapy for long-term remission**

**Keywords:** anaplastic multiple myeloma, high-dose chemotherapy, autologous hematopoietic stem cell transplantation

### **TO THE EDITOR**

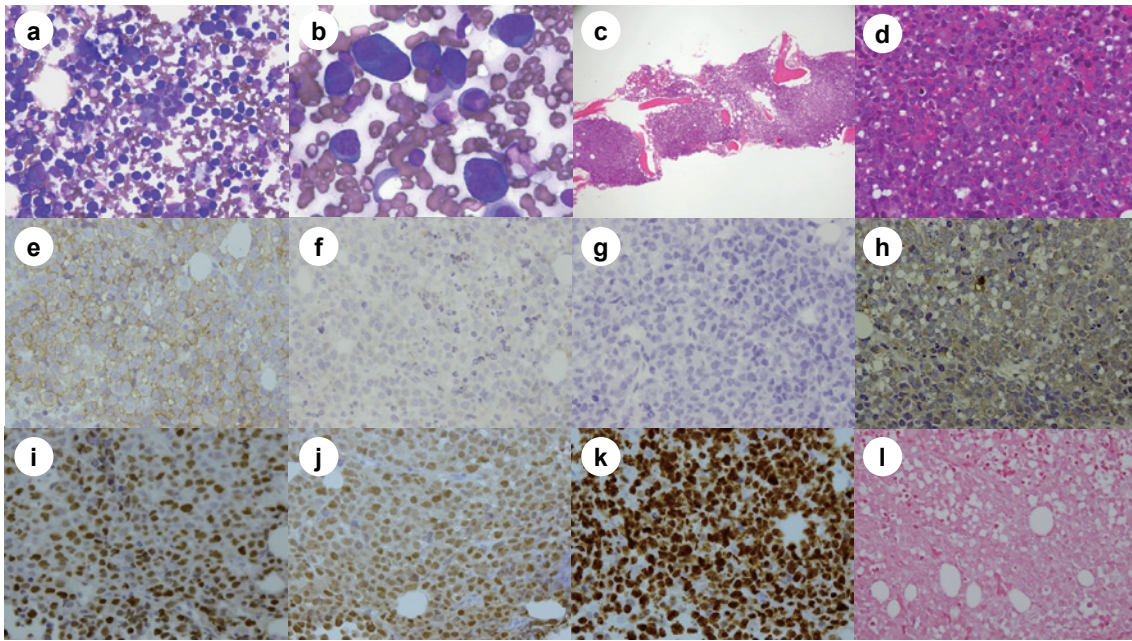
Anaplastic multiple myeloma (AMM) is a very rare morphological subtype of multiple myeloma, which has been reported only sporadically, mostly in case reports (1-3). The clinical course of AMM is highly aggressive and the disease has an extremely poor prognosis, which is considerably different from that of conventional myeloma. Some patients are diagnosed with AMM at disease onset, whereas others can develop anaplastic transformation during the course of conventional plasma cell myeloma. AMM can present as multiple extramedullary tumors (3). Pathologically, the pleomorphic multinucleated morphology of AMM can mimic multinucleated carcinoma (4). Due to its rarity, however, a therapeutic strategy for AMM remains to be established.

A 63-year-old woman with severe lumbago and right upper limb pain for longer than 1 week was referred to us because of thrombocytopenia, high serum lactic dehydrogenase (LDH) level, and a mass on the right brachial plexus found by magnetic resonance imaging (MRI). The patient's general condition was very poor, with severe pain and easy fatigability. She was afebrile and her vital signs were normal. There was no lymphadenopathy or hepatosplenomegaly. The complete blood count indicated thrombocytopenia (38000/ $\mu$ L) without anemia (hemoglobin, 12.2 g/dL). The white blood cell count (8600/ $\mu$ L) was normal, with a normal differentiation count (69% neutrophils, 18% lymphocytes, 9% monocytes, 3% eosinophils, and 1% metamyelocytes); there were no atypical lymphocytes, plasma cells, or blasts. Biochemical analysis revealed an extremely high serum LDH level (16200 IU/L) and mild elevation of the serum transaminase level (asparagine transaminase, 226 IU/L; alanine transaminase, 88 IU/L). The alkaline phosphatase level was within the normal range. LDH subclass analysis demonstrated the predominance of LDH<sub>2</sub> (39%) and LDH<sub>3</sub> (44%). Renal function was normal (serum creatinine, 0.74 mg/dL) with normal findings on urinalysis. Serum levels of uric acid (8.8 mg/dL) and inorganic phosphate (6.3 mg/dL) were elevated, but there were no abnormalities in other electrolytes. Serum total protein (6.6 g/dL) and albumin (4.5 g/dL) levels were normal. Coagulation tests revealed only slight elevation of fibrin degenerative products. Elevated levels of serum ferritin (3338 ng/mL), soluble interleukin-2 receptor (625 U/mL), and beta-2 microglobulin (2.5 mg/L) were also observed. Immunoelectrophoresis of serum and urine detected monoclonal IgD-lambda protein and Bence-Jones

protein (BJP) subtypes. Serum IgG, IgA, IgM, and IgD levels were 395, 16, 7, and 197.3 mg/dL, respectively. Serum free light chain analysis indicated deviation of the kappa/lambda ratio (kappa-chain, 1.4 mg/L; lambda-chain, 2150 mg/L). The patient was negative for anti-human immunodeficiency virus (HIV) antibody. Elevation of the Epstein-Barr virus DNA titer in peripheral blood was not observed.

Bone marrow aspiration resulted in dry tap. However, biopsy revealed nodular aggregation of atypical large cells that had basophilic cytoplasm and euchromatic nuclei (Figure 1); on flow cytometry and immunohistochemical analysis, they were CD3<sup>-</sup>, CD4<sup>-</sup>, CD7<sup>+</sup>, CD10<sup>-</sup>, CD13<sup>+</sup>, CD20<sup>-</sup>, CD30<sup>-</sup>, CD33<sup>+</sup>, CD56<sup>-</sup>, CD79a<sup>-</sup>, IgG<sup>-</sup>, IgM<sup>-</sup>, IgA<sup>-</sup>, Igk<sup>-</sup>, Igl<sup>+</sup>, c-myc<sup>+</sup>, MPO<sup>+</sup>, and MUM1<sup>+</sup> (Figure 1). CD38 was weakly positive and CD138 was negative. The Ki-67 labeling index was very high (95%). Epstein-Barr virus-encoded RNA was not detected by in situ hybridization. G-banding analysis revealed a complex karyotype, including duplication of the 14q32 locus (Table 1). Fluorescence in situ hybridization demonstrated no fusion signals of IgG/Myc, IgH/MAF, IgH/FGFR3, or IgH/CCND1, and no split signal of Myc. Strong uptake of fluorodeoxyglucose (FDG) in systemic bones without bone destruction and around the right brachial plexus was observed on positron emission tomography combined with computed tomography (PET/CT) (Figure 2). There was no lymphadenopathy or hepatosplenomegaly. Magnetic resonance imaging detected infiltrating lesions around the right brachial plexus.

The clinicopathological findings described above indicated atypical plasma cell dyscrasia with extreme clinical aggressiveness, features markedly different from those of conventional plasma cell myeloma, and considered to be included within the concept of AMM. We initially administered high-dose dexamethasone, which resulted in partial relief of pain, improvement of general status, and reduction of serum LDH to some extent. Thereafter, the anti-lymphoma EPOCH regimen (etoposide, doxorubicin hydrochloride, vincristine, prednisolone, and cyclophosphamide) was started. Further transient elevation of LDH was observed, but there were no signs of tumor lysis syndrome or disseminated intravascular coagulopathy. After 3 weeks, serum LDH and IgD levels had significantly decreased and abnormal cells were not detected in the bone marrow, suggesting that the EPOCH regimen was highly effective. After a total of four courses of EPOCH, a significant reduction in systemic bone FDG uptake was noted on PET/CT. Thereafter,



**Fig. 1.** Pathological findings of bone marrow at diagnosis. May–Giemsa staining of stamp preparation (*a, b*) demonstrated marked infiltration of extremely large aberrant plasmacytoid cells with frequent nuclear atypia and basophilic cytoplasm. Hematoxylin and eosin staining (*c, d*) showed nodular aggregation of atypical large cells, which had basophilic cytoplasm and euchromatic nuclei. Immunohistochemical examination indicated that the neoplastic cells were CD38+ (*e*), CD138+ (*f*), CD20- (*g*), MPO+ (weak) (*h*), MYC+ (*i*), and MUM1+ (*j*). The Ki-67 labeling index of the lymphoma cells was judged to be > 95% (*k*). EBER was negative (*l*).

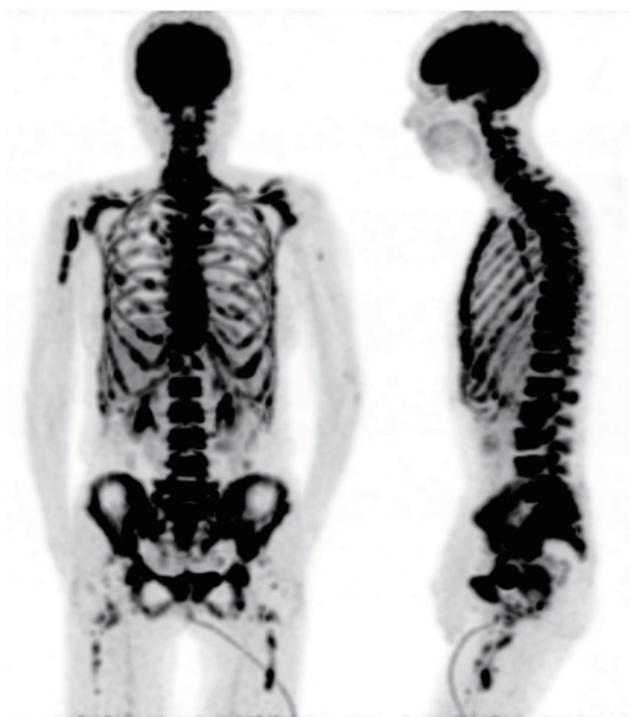
**Table 1.** Karyotype at diagnosis.

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| 77,X,-X,-X,add(1)(p13),add(1)(q25),dup(1)(q21q32),-4,add(5)(p15),-6,-6,-6,+9,add(9)(p22)x2,-10,+11,-13,add(14)(q32)x3,-17,+19,+20,+21,+22,+mar1x2,+mar2x2,+mar3,+mar4,+5mar [1]/       |
| 77,X,-X,-X,add(1)(p13),add(1)(q25),dup(1)(q21q32),-4,add(5)(p15),-6,-6,-6,+9,add(9)(p22)x2,-10,+11,-13,add(14)(q32)x3,+16,-17,+19,+20,+21,+mar1x2,+mar2x2,+mar3,+mar4,+mar5,+5mar [1]/ |
| 78,X,-X,-X,add(1)(p13),add(1)(q25),dup(1)(q21q32),-4,add(5)(p15),-6,-6,-6,+9,add(9)(p22)x2,-10,+11,-13,add(14)(q32)x3,+16,-17,+19,+20,+22,+mar1x2,+mar2x2,+mar3,+mar4,+mar5,+5mar [1]/ |
| 78,X,-X,-X,add(1)(p13),add(1)(q25),dup(1)(q21q32),-4,add(5)(p15),-6,-6,-6,+9,add(9)(p22)x2,-10,+11,-13,add(14)(q32)x3,+16,-17,+19,+21,+22,+mar1x2,+mar2x2,+mar3,+mar4,+mar5,+5mar [1]/ |
| 46,XX [3]  |

we performed high-dose therapy with the MEAM regimen (ranimustine, etoposide, cytarabine, and melphalan) followed by autologous peripheral blood stem cell transplantation. Complete remission was confirmed 1 month after transplantation based on the following findings: no abnormal cell population in bone marrow, no abnormal FDG uptake on PET/CT, and disappearance of monoclonal paraprotein by immunofixation of serum and urine. Thereafter, she was followed-up with administration of lenalidomide as maintenance therapy for several months. However, abrupt disease relapse occurred with right pleural effusion and an extramedullary tumor along the right pleura 5 months after transplantation. The patient received additional courses of the EPOCH regimen and bortezomib-containing chemotherapy, which resulted in only a marginal response. Intensive salvage chemotherapy was not applicable because of her general status and her own decision. She elected for palliative management, and died 4 months after relapse.

Anaplastic multiple myeloma (AMM), also known as plasmablastic plasma cell myeloma, is an extremely rare disease

with an aggressive clinical course and poor prognosis. It is considered to be a morphological variant of multiple myeloma and is often accompanied by extramedullary infiltration with large and immature aberrant plasma cells.<sup>1</sup> Aggressive transformation of myeloma is observed not only during the course of multiple myeloma, but also at the onset of the disease.<sup>1,2</sup> The cellular origin of AMM is considered to be an immature plasma cell;<sup>5</sup> therefore, differential diagnosis between AMM and plasmablastic lymphoma (PBL) is difficult. PBL is also a rare subtype of B-lymphoid malignancy, which has pathological features that can overlap with aggressive mature B-cell lymphomas and plasma cell neoplasms.<sup>6,7</sup> There are a number of clinicopathological features that support a diagnosis of AMM, i.e., renal dysfunction, significant paraprotein level, osteolytic lesions, hypercalcemia, and diffuse bone marrow involvement.<sup>7,8</sup> In contrast, EBV positivity in the neoplastic cells, association with HIV infection, and high Ki-67 proliferation index support a diagnosis of PBL.<sup>7</sup> In the present case, the diagnosis of AMM was considered appropriate because there was significant



**Fig. 2.** FDG-PET finding at diagnosis. Diffuse and strong uptake of FDG was observed in systemic bone marrow.

paraprotein and bone marrow infiltration without EBV positivity of the neoplastic cells.

The clinical and pathological features of AMM have yet to be fully elucidated because of the rarity of the disease and ambiguity in its definition. Bahmanyar *et al.*<sup>9</sup> reported that AMM was associated with a significantly higher prevalence of CKS1B amplification compared with non-anaplastic MM (91% vs. 34%, respectively). Deletion of 17p (p53) is also observed more frequently in the former (45% vs. 11%, respectively). The CKS1B gene has been mapped to the chromosomal locus 1q21, and was previously reported to be associated with aggressive disease progression and poor clinical outcome.<sup>10</sup> A recent report also indicated that gain of chromosome 1q is associated with poor prognosis in myeloma even with novel agent-based chemotherapy and high-dose therapy followed by autologous transplantation.<sup>11</sup> Overexpression of CKS1B was also found to result in an increase in multidrug resistance in neoplastic plasma cells.<sup>12</sup> In addition, Maslovsky *et al.*<sup>13</sup> reported a case of AMM with the presence of multiple chromosomal aberrations with hyperploidy (77 chromosomes). A similar case with a complex karyotype and hyperploidy was also reported.<sup>2</sup> In this case, duplication of the 1q21 locus, deletion of chromosome 17, and multiple chromosomal aberrations with hyperploidy were also observed, which support the diagnosis of AMM and may have been associated with the poor outcome. To our knowledge, this is the first report of AMM accompanying aberrant expression of myeloid lineage cell-surface markers, for which the biological and pathological significance is not clear.

AMM was reported to be refractory to chemotherapy with or without novel agents,<sup>2,13,14</sup> and the optimal therapeutic strategy for AMM has yet to be established. There has been only a single case report describing successful treatment with high-dose cyclophosphamide, bortezomib, and dexamethasone, which resulted in long-term remission for 30 months.<sup>3</sup> On the other hand, another recent report of two cases of AMM described a poor clinical course over a short period regardless of active treatment with novel agents, i.e., bortezomib and lenalidomide.<sup>2</sup> In this case, we administered an anti-lymphoma EPOCH regimen considering the immature phenotype and aggressive clinical course to be partially homologous with aggressive lymphoma such as PBL. As first-line treatment for PBL, dose-adjusted EPOCH and consolidative high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HDC+ASCT) during the first remission for appropriate candidates may be recommended.<sup>15,16</sup> In the present case, the EPOCH regimen followed by high-dose chemotherapy and autologous hematopoietic stem cell transplantation resulted in complete remission. However, disease relapsed within 6 months after transplantation. This suggests that there may be limitations of conventional chemotherapy for curing AMM.

In summary, we presented a case of AMM for which the EPOCH regimen followed by HDC+ASCT resulted in short-term disease remission, but failed to cure the disease. Another treatment strategy may be necessary to cure AMM such as allogeneic hematopoietic stem cell transplantation. Accumulation of additional clinical experience is needed to better understand the pathophysiology, develop treatment strategies, and improve the prognosis of AMM.

## CONFLICT OF INTEREST

The authors declare no conflict of interest in this study.

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