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Letter to the Editor

Poor response to daratumumab and carfilzomib in newly diagnosed anaplastic multiple myeloma

Keywords: anaplastic multiple myeloma; daratumumab; carfilzomib

TO THE EDITOR

A 62-year-old woman presented to our hospital with fatigue and weight loss of 10 kg within a month. She had been previously healthy, and her serum creatinine level was almost normal (1.0 mg/dL) at a medical checkup two months earlier. Blood tests revealed anemia, thrombocytopenia, an increased serum creatinine level (9.58 mg/dL), hypercalcemia, and an increased serum LDH level (531 U/L). Serum albumin, IgG, IgA, and IgM levels were suppressed concurrently, and the beta-2-microglobulin level was increased to 82.9 mg/L. Large amounts of urine protein (20,902 mg/g•Cre) were detected. Urine protein electrophoresis demonstrated an M spike in the beta-fraction, M protein of the Bence-Jones protein (BJP)-κ type was found on urine immunoelectrophoresis, and the serum free-light chain ratio was 11,750 (κ 32,900 mg/dL; λ 2.8 mg/L). Punched out lesions of the skull and osteolytic lesions on the entire body were found on systemic screening by computed tomography (CT). Examination of bone marrow aspirate demonstrated increased plasma cells (22.6%) on May-Giemsa staining (Figure 1A). The plasma cells were mainly large, with a high nucleus-to-cytoplasm ratio and clear nucleoli, resembling large cell lymphoma. In the Greipp classification,[1] 58% of plasma cells were classified as plasmablastoid cells. A small but significant minority had pleomorphic nuclei such as multinucleated (Figure 1B, 1C), cleaved (Figure 1D), or irregular lobulated (Figure 1E) nuclei. On flow cytometry with CD38-gating analysis of the bone marrow, plasma cells were positive for CD138, CD56, and κ, and negative for CD19, CD20, MPC-1, CD45, CD49e, and λ. Immunohistochemically, plasma cells were positive for CD138 and κ, and negative for λ. In addition, the MIB-1 index for plasma cells was 80% (Figure 2). Chromosomal analysis by G-banding of the bone marrow demonstrated a hypodiploid complex karyotype, including monosomy 13 and 17 in nineteen-twentieths of the cells in the mitotic phase (Figure 3). On fluorescence in situ hybridization (FISH), del(17p) was positive in 39%, reflecting monosomy 17, and t(11;14)(q13;q32), t(4;14)(p16;q32), and t(14;16)(q32;q23) were negative. The serum LDH level increased rapidly from 531 U/L to 1234 U/L in the 10 days before chemotherapy. Anaplastic multiple myeloma (AMM) was diagnosed on the basis of the aggressive clinical manifestations, anaplastic morphology, and hypodiploid complex karyotype of plasma cells (BJP-κ type, ISS, and R-ISS stage III). The patient was treated using Vd (bortezomib and

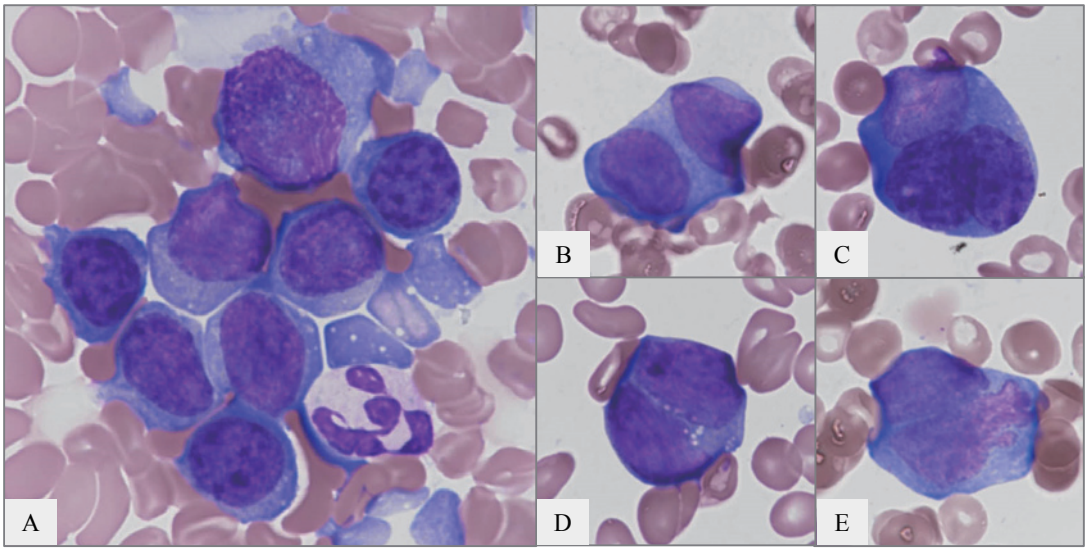

Fig. 1. Plasma cells of bone marrow on May-Giemsa staining (original magnification, ×1000).
Plasma cells are large with a high nucleus-to-cytoplasm ratio and clear nucleoli, classified as plasmablastoid cells (***A***). Some of them have pleomorphic nuclei such as multinucleated (***B***, ***C***), cleaved (***D***), or irregularly lobulated (***E***) nuclei.

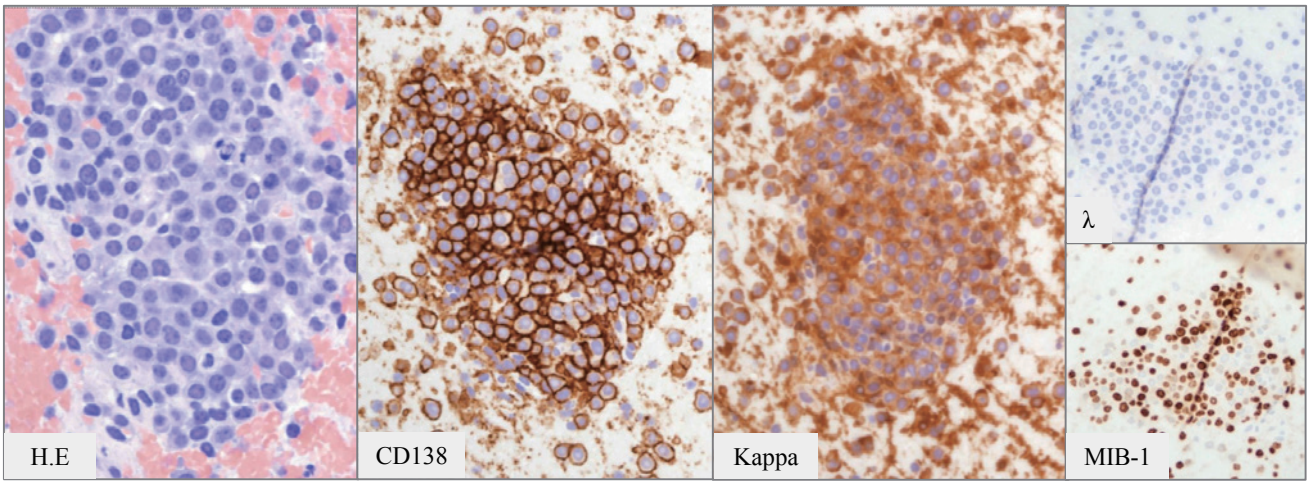

Fig. 2. Histological findings of bone marrow on hematoxylin-eosin staining and immunostaining.
Plasma cells form clusters. Immunohistochemically, the plasma cells are positive for CD138 and κ, but negative for λ, and the MIB-1 index for plasma cells is 80%.

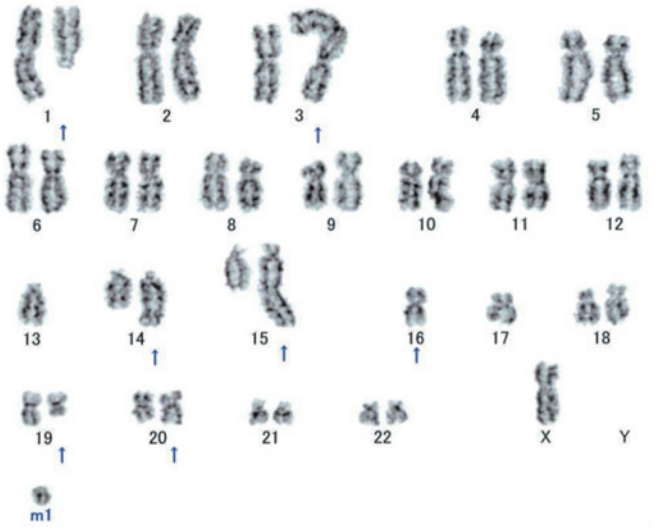

Fig. 3. Chromosomal analysis by G-banding of the bone marrow.
G-banding of the bone marrow shows 43, X, -X, add(1)(q11), add(3)(p21), -13, add(14)(q32), der(15)t(1;15)(q12;q26), -16, add(16)(q22), -17, add(19)(q11), add(20)(q11.2), +mar1 in nineteen-twentieths of the cells in the mitotic phase.

dexamethasone) and hemodialysis three times a week (Figure 4). After bortezomib was administered twice, only minimal reduction and a slight increase in the LDH level were observed. Vd was then changed to DVd (daratumumab, bortezomib, and dexamethasone). Daratumumab was administered weekly after hemodialysis on the same day without dose modification. This resulted in an increase in the serum LDH level from 937 U/L to 1819 U/L on the following day, probably due to tumor lysis. No additional hemodialysis was needed because pulmonary edema, anoxia, and hyperkalemia did not develop. The serum LDH level decreased to 1293 U/L transiently, but after daratumumab was administered twice, the serum LDH level increased rapidly to 2574 U/L, with exacerbation of urine protein, serum free-light chain, and beta-2-microglobulin levels. DVd was changed to Kd (carfilzomib and dexamethasone) without dose modification. However, this resulted in a slight reduction of the LDH level on the following day. Just after the second day of administration of carfilzomib, the patient suddenly complained of nausea and headache, with an acute increase in systolic blood pressure. Head CT revealed massive cerebellar hemorrhage, and the patient died due to respiratory arrest 10 minutes after CT evaluation.

AMM is a rare morphological subtype of multiple myeloma, and its clinical features have been unclear because of its rarity and the absence of a distinct definition for diagnosis. In 1990, Allen and Coleman reviewed 108 cases of AMM characterized by extramedullary disease, younger age at presentation, cytopenias, IgA isotope, and an aggressive clinical course.[2] However, this report contained some cases of end-stage or terminal-phase multiple myeloma. AMM is recently often diagnosed at the initial presentation by anaplastic morphology, unfavorable cytogenetics, and an aggressive clinical course with a high incidence of increased serum LDH levels and refractoriness to conventional chemotherapies in case series. Large-sized plasmablastic cells with pleomorphic nuclei, such as multilobation or multinucleation, were diagnostic morphologies,[3-8] and cytogenetic abnormalities of del(17p), t(4; 14) and 1q21 gain were detected with high frequencies in AMM.[9] The present patient exhibited positive FISH for del(17p), but additional analyses of cytogenetic abnormalities, such as FISH for 1q21 gain and MAFB translocation, SKY, or RT-PCR, were unable to be performed. The current prognostic factor for multiple myeloma is R-ISS containing cytogenetic abnormalities, and the morphology is not a poor prognostic factor, whereas R-ISS includes an increased LDH level, which reflects an aggressive clinical manifestation and is also important for the prognosis of multiple myeloma. Ichikawa *et al*. reported that use of the EPOCH regimen (etoposide, doxorubicin, vincristine, prednisolone, and cyclophosphamide) following high-dose chemotherapy with autologous stem cell transplantation resulted in short-term remission.[7] However, the outcomes of AMM

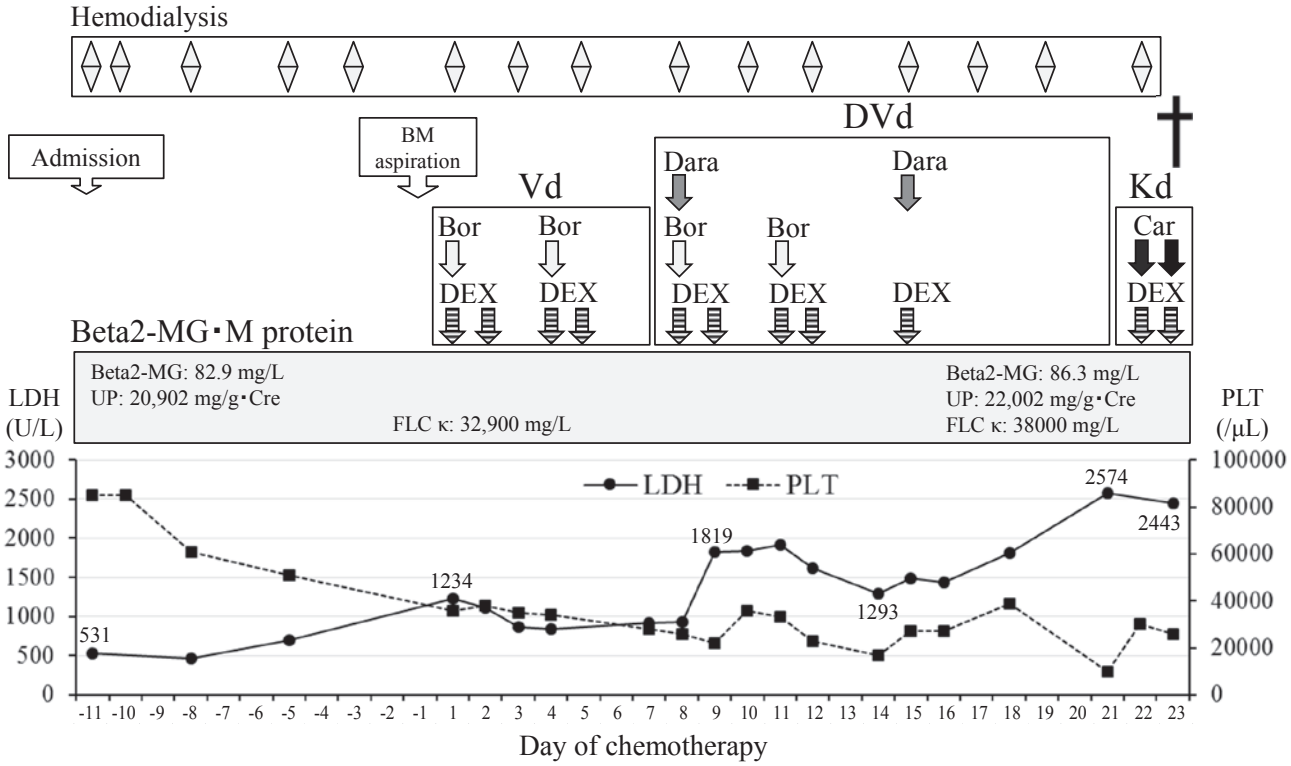

Fig. 4. The patient's clinical course from admission to death.
PLT: platelet count, beta2-MG: beta-2-microglobulin, UP: urine protein, FLC: free-light chain, BM: bone marrow, Bor: bortezomib, DEX: dexamethasone, Dara: daratumumab, Car: carfilzomib, Vd: bortezomib/dexamethasone, DVd: daratumumab/bortezomib/dexamethasone, Kd: carfilzomib/dexamethasone.

treated by the novel agents have remained incompletely understood. Ammannagari *et al*. reported two cases of AMM treated by iPAD (bortezomib, liposomal doxorubicin, and dexamethasone) and RVD (lenalidomide, bortezomib, and dexamethasone), and they were insufficient against fulminant disease progression.[8] To the best of our knowledge, this is the first reported case of a patient with AMM who was treated by DVd and Kd. Daratumumab is a first-in-class human IgG1 monoclonal antibody with high affinity to CD38, a cell surface glycoprotein.[10] Carfilzomib is a second-generation proteasome inhibitor (PI) with greater proteasome inhibition than bortezomib.[11] The efficacy and safety of daratumumab and carfilzomib, either alone or combined with other novel agents, have been explored in several phase I-III studies.[10-13] Daratumumab and carfilzomib improved the progression-free survival (PFS) of high-risk patients in relapsed/refractory multiple myeloma in several clinical trials.[14-17] In addition, PI and monoclonal antibodies have been reported to not require dose modification due to renal dysfunction or dialysis-dependent renal failure.[18-20] Therefore, they can be used for the induction regimen at the point of maintenance for the dose intensity required against aggressive disease progression with hemodialysis. However, even the next-generation novel agents were insufficient for AMM. The CASTOR trial demonstrated that DVd therapy is effective even in patients with del(17p)-positive multiple myeloma.[14] AMM represents an inclusive morphological subtype for unfavorable cytogenetics and aggressive clinical course. The clinical course of the present patient suggests that daratumumab-combined therapy cannot overcome the poor prognosis of patients with AMM, but further observation is needed. The present patient died due to intracranial hemorrhage after receiving carfilzomib therapy. Although the incidence of intracranial hemorrhage was not high in clinical trials using carfilzomib (0.3% in the ASPIRE trial[21] and 0% in the ENDEAVOR trial[11]), patients with thrombocytopenia, disseminated intravascular coagulation, and hemodialysis will have an increased risk for bleeding due to hypertension associated with carfilzomib therapy. The clinical course of the present patient suggests that carfilzomib should be administered cautiously to patients with risk factors for bleeding. In conclusion, the present patient developed AMM, and the tumor progressed rapidly despite DVd and Kd therapy. The prognosis of AMM remains poor in the novel agent era.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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