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Anaplastic Multiple Myeloma: An Aggressive Myeloma Variant with A Poor Response to Autologous Stem Cell Transplantation

Anaplastik Multiple Miyeloma: Otolog Kök Hücre Nakli Tedavisine Yanıtsız Agresif Miyeloma Varyantı

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Abstract

Anaplastic multiple myeloma is an aggressive, chemotherapy-resistant subtype of myeloma with a poor prognosis. Approximately 2% of plasma cell myelomas are pleomorphic, anaplastic, and resemble metastatic tumor cells. Morphological differentiation of anaplastic cells is difficult, and immunohistochemistry and flow cytometry should be performed for immunophenotyping. We shared our experience with peripheral stem cell transplantation in this rare malignancy.

Keywords: Anaplastic multiple myeloma, CD38, Autologous stem cell transplantation

Öz

Anaplastik multipl miyeloma agresif seyirli, kemoterapilere dirençli, kötü prognozlu miyeloma alt tipidir. Plazma hücreli miyelomun yaklaşık %2'si pleomorfik, anaplastik özellikte olup metastatik tümör hücrelerine benzer. Anaplastik hücrelerin morfolojik ayırımı güç olup, immunfenotipleme için immunhistokimya ve akım sitometrik inceleme yapılmalıdır. Nadir görülen bu malignitede otolog periferik kök hücre nakil deneyimimizi paylaştık.

Anahtar Kelimeler: Anaplastik multipl miyeloma, CD38, Otolog kök hücre nakli

Introduction

Anaplastic multiple myeloma (AMM) is a type of multiple myeloma that is exceptionally scarce and aggressive. The prognosis of most AMM patients is poor, and the disease has a resistance to current chemotherapies (1). In this report, we present a case of an AMM patient with widespread metastasis and involvement of the extramedullary space who had poor outcomes with new myeloma therapies and autologous stem cell transplantation (ASCT).

Case Presentation

A man of 45 years of age was admitted to the hospital with swelling of the right breast, widespread pain, unintentional weight loss, night sweats, and fatigue for two months. The patient's past medical and family history was unremarkable. Physical examination showed localized tenderness of palpable mass. The positron emission tomography-computed tomography scan demonstrated a 15x12 cm mass involving the right anterior chest wall, destructing the 4th and 5th costas with an standardized uptake value 20.7, and abnormal ^{18}Fluorine-fluorodeoxyglucose intake of the right axillary, internal mammary, parasternal,

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retrosternal, pericardiac, supradiaphragmatic lymph nodes, 5th and 8th costas. A trucut biopsy pathology revealed that large atypical cells with pleomorphic nuclei, a moderate amount of polarized cytoplasm, and common necrotic areas infiltrated the fibrous and muscular tissues. Immunohistochemical staining showed the tumor tissue was positively stained for CD138, multiple myeloma oncogene 1 (MUM-1), CD45 (LCA), CD117, vimentin, lambda light chain, and negatively stained for CD3, CD4, CD15, CD20, CD30, CD38 CD56, PAX5, TDT, desmin, actin. The in situ hybridization for the Epstein-Barr virus-encoded RNA was negative. The Ki-67 proliferation index was exceedingly high (100%) (Figure 1). Cytogenetic analysis demonstrated no abnormality for multiple myeloma. Bone marrow was not involved. From these findings, the patient was reported to have AMM.

The laboratory examination showed an average blood count with a hemoglobin of 14.8 g/dL. Biochemical tests demonstrated that albumin, 3.6 g/dL (normal range 3.5-5.2); total serum protein, 6.5 g/dL (normal range 6.6-8.3); mildly elevated beta-2 microglobulin, 2.82 mg/L (normal range 1.16-2.52), and lactic dehydrogenase, 272 U/L (normal range 0-248); serum renal and liver function tests were in the normal range. The results of the serological tests for Epstein-Barr virus, human immunodeficiency virus, hepatitis B, and hepatitis C were all negative. Serum and urine protein electrophoresis and immunofixation analysis revealed no monoclonal bands. There was an increase in the free lambda light chain level in the serum [39.1 mg/L (normal range 5.71-26.3)], but no change in the kappa/lambda ratio [0.24 (normal range 0.26-1.65)].

The patient received a VCD regimen of a 21-day cycle, including bortezomib 1,3 mg/m^2 per week, cyclophosphamide 300 mg/m^2 per week, and dexamethasone 40 mg/day (d) (on d1, d4, d8, d11). After three cycles of VCD, the disease progressed rapidly with right pleural effusion. Our patient underwent 3500 cGy of radiation therapy with the RD regimen (lenalidomide 5 mg/day for 21 days, dexamethasone 40 mg/week). After two cycles of the RD regimen, the patient achieved partial remission, and severe dyspnea improved. Because of the CD38 negativity, we did not offer daratumumab-based regimens. High-dose chemotherapy (cyclophosphamide, 60 mg/kg on d-5, d-6; total body irradiation, 2x2 Gy/day on d-3, d-2, d-1) with ASCT was sequentially performed and achieved very good partial remission (VGPR). Two months later, the disease progressed quite aggressively, and the patient died of infectious causes after surviving 11 months from the time of diagnosis.

Discussion

AMM usually presents in young patients and is commonly characterized by an extramedullary involvement and immunoglobulin A isotype (2). AMM cells are usually positively stained for CD38, CD138, MUM1 and negatively stained for CD3, CD19, and CD20, which is consistent with our patient, except CD38 negativity. AMM and the CD38 negativity have been documented at diagnosis in several cases (4-6). This very rare CD38 negativity delays diagnosis and blocks the anti-CD38 therapy, so CD38 negative AMM are even more aggressive than CD38+ ones, and the absence of CD38 expression is linked to relapsed/refractory conditions (4-6). A patient with CD38 negative and (4;14) translocation died before initiating treatment (5).

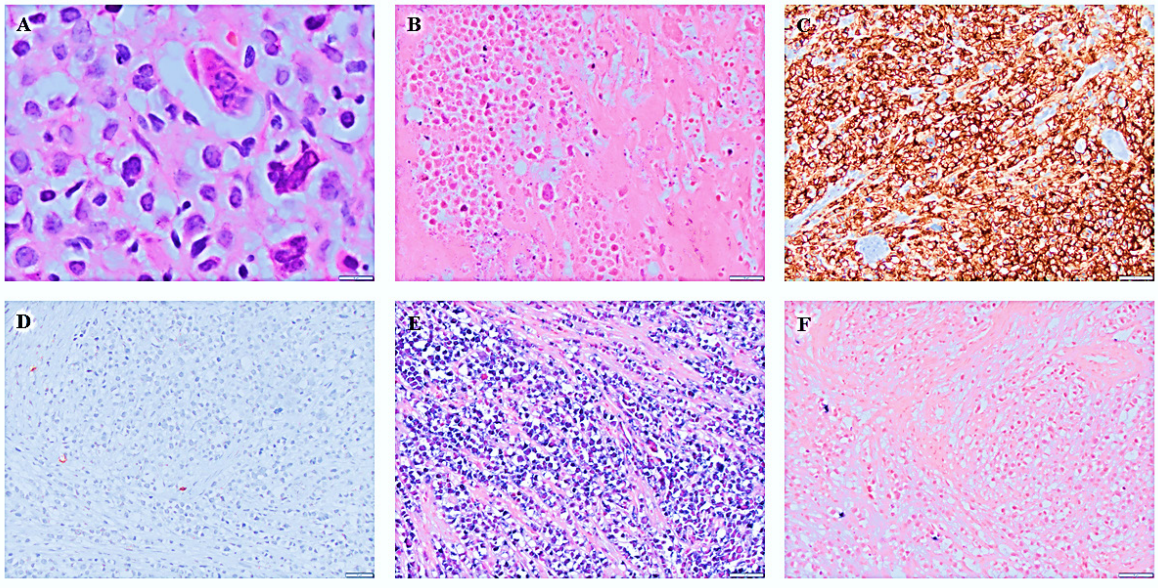

Figure 1: Pathological findings. **(A)** Tumour hematoxylin and eosin staining showed large atypical anaplastic cells (1000×). **(B)** Diffuse and severe coagulative necrosis in neoplastic infiltration (400×). Immunohistochemistry showed that the tumor cells were **(C)** CD138+, **(D)** CD 38-, **(E)** Lambda light chain+, and **(F)** Kappa light chain- (200×).

AMM demonstrates resistance to conventional chemotherapy, radiotherapy, and novel myeloma therapies (e.g., daratumumab, carfilzomib); in contrast, some reported cases had a relatively long-term outcome (1,3,7-10). In the study by Huang et al. (3), a patient treated with a combination of bortezomib and conventional chemotherapy survived for nine months. Another AMM patient with hepatic dysfunction was monitored for thirty months with RD maintenance therapy after VCD treatment, achieving a VGPR (9). A 70-year-old patient achieved a complete response after four cycles of VRD and was followed in remission for four months (10). Conversely, in the case report by Saburi et al. (8), a patient with AMM, 17p deletion, and CD38 positivity did not respond to treatments based on daratumumab and carfilzomib.

ASCT has been planned in which patients had a response to previous therapy, but they could not proceed because of rapid clinical deterioration (7,11). Ichikawa et al. (1) reported a case who received the four cycles of *etoposide, doxorubicin, vincristine, prednisolone, and cyclophosphamide*-EPOCH regimen with a VGPR response followed by ASCT resulted in six months remission. Our case received radiotherapy, bortezomib, and lenalidomide-based therapies followed by ASCT, which resulted in a VGPR response. However, the disease relapsed within two months after transplantation.

The remission status of the patient with AMM is the key to success. Using novel agents, cellular immunotherapies, and bispecific antibodies to reach this goal is a mission in progress, and the disease pathophysiology and genomic pathways need to be understood.

Ethics

Informed Consent: The Ankara University Human Research Ethics Committee approved this article (date: 10.12.2021, approval no.: İ11-690-21).

Authorship Contributions

Surgical and Medical Practices: D.K., İ.Ö.D., I.K., S.K.T., T.D., Concept: D.K., M.O., Design: D.K., Data Collection: D.K., Literature Search: D.K., M.O., Writing: D.K.

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