Two Cases of Nonsecretory Multiple Myeloma Presenting as Primary Plasma Cell Leukemia

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Abstract

Plasma cell leukemia (PCL) is a rare variant of multiple myeloma (MM) with a poor prognosis. Nonsecretory myeloma is also a rare form of MM characterized by the absence of detectable M-protein in the serum and urine. This report describes two cases of nonsecretory PCL. The first patient was an 85-year-old man in whom the lack of monoclonal immunoglobulins made it difficult to make a diagnosis because the malignant cells showed an atypical morphology. He died of rapid disease progression before starting chemotherapy. The second patient was a 78-year-old woman whose tumor cells displayed a typical plasma cell morphology. She was successfully treated with bortezomib-containing chemotherapy.

Key words: nonsecretory, plasma cell leukemia, multiple myeloma

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Introduction

Plasma cell leukemia (PCL) is a rare variant of multiple myeloma (MM), accounting for approximately 1-2% of all plasma cell neoplasms (1). PCL is characterized by the presence of malignant plasma cells in the peripheral blood (more than 20% of white blood cells and/or an absolute number of greater than 2×10⁹/L) and has a poor outcome following both conventional therapy and autologous stem cell transplantation (2, 3). Nonsecretory myeloma is also a rare form of MM characterized by the absence of monoclonal immunoglobulins on either serum or urine electrophoresis and represents less than 1% of cases of MM (4). Only a few well-documented cases of nonsecretory MM presenting as primary PCL have been reported (5-9). We herein report two elderly cases of primary nonsecretory PCL.

Case Reports

Case 1

An 85-year-old man was admitted to the department of respiratory medicine in late November 2012 due to acute pneumonia associated with pleural effusion. He had been treated and followed elsewhere under a diagnosis of schizophrenia since 1949. He underwent colectomy due to colon cancer in 2000, at which time diabetes mellitus was also diagnosed. In addition, he had dehydration, hypercalcemia, hyperglycemia, and congestive heart failure. He was treated with antibiotics, diuretics, zoledronate, calcitonin, insulin, etc. and his condition stabilized. In late December, he was referred to the department of hematology due to the emergence of atypical cells in the peripheral blood. The white cell count was 13,620/μL, with 54.0% neutrophils, 17.5% lymphocytes, 4.5% monocytes, 2.0% eosinophils, 0.5% basophils and 20.5% atypical cells. The atypical cells exhibited a lymphoplasmacytoid cell morphology and were not recognized as malignant plasma cells. The hemoglobin concentration was 9.1 g/dL and the platelet count was 169,000/μL. Urinary protein was negative. Serum protein electrophoresis showed no M-spikes, and serum and urine immunofixation electrophoresis demonstrated no monoclonal proteins. A bone marrow aspiration disclosed that 38.6% of the marrow cells consisted of atypical cells with a mixture of lymphoplasmacytoid cells and bizarre lymphoid cells exhibiting

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extracellular projections (Fig. 1). A chromosome analysis of the marrow cells revealed a finding of 46, XY. In addition, a bone marrow biopsy showed massive infiltration of small round lymphoid cells (Fig. 2), and immunostaining of the biopsied specimen showed that the cells were positive for CD38 and CD138. Therefore, a diagnosis of nonsecretory PCL was made. A whole-body CT scan did not show any lytic bone lesions, extramedullary lesions, or hepatosplenomegaly.

The serum IgG, IgA and IgM levels were moderately low at 800 mg/dL, 77 mg/dL and 10 mg/dL respectively. A flow cytometric analysis of the peripheral lymphoid cells revealed that the cells were positive for CD38, CD138 and MPC-1, but negative for CD19, CD20, CD45 and CD56 (Fig. 3). The number of peripheral plasma cells gradually increased, and the patient died in early January 2013 due to the disease progression before starting chemotherapy (Fig. 4).

Case 2

A 78-year-old woman was admitted to another hospital due to severe lumbago in the middle of January 2013. Compression fractures of thoracic and lumbar vertebrae were diagnosed. She was transferred to our hospital in early February because abnormal cells were detected in her peripheral blood. She was apparently ill, with an Eastern Cooperative Oncology Group (ECOG) performance status of 4 at presentation. The white cell count was 11,900/μL, with 43.5% neutrophils, 30.5% lymphocytes, 4.0% monocytes, 2.0% eosinophils and 20.0% atypical cells. The atypical cells displayed plasma cell morphology (Fig. 5). The hemoglobin concentration was 10.1 g/dL and the platelet count was 112,000/μL. A bone marrow aspiration showed massive infiltration of myeloma cells. A flow cytometric analysis of the marrow cells revealed that the cells were positive for CD38, CD138, MPC-1 and CD56, but negative for CD19, CD20 and CD45 (Fig. 6). A chromosomal analysis of the marrow cells demonstrated finding of 46, XX. Fluorescent in situ hybridization analyses disclosed that 83 of 100 cells analyzed had IgH/CCND1 fusion signals, while 84 of 100 cells analyzed had an allelic deletion of 13q14.3. No fusion
signals of IgH/MAF or IgH/FGFR3 were observed. Serum IgG, IgA and IgM levels were suppressed at 349 mg/dL, less than 23 mg/dL and 12 mg/dL, respectively. The serum total protein level was 5.6 g/dL, the albumin level was 3.8 g/dL, the creatinine level was 1.21 mg/dL, the Ca level was 10.2 mg/dL and the beta 2-microglobulin level was 11.7 mg/L. Urinary protein was negative. The serum protein electroforesis showed no M-spike, while serum and urine immunofixation electrophoresis demonstrated no monoclonal proteins. Therefore, a diagnosis of primary nonsecretory PCL was made. The serum free kappa chain level was less than 0.3 mg/L (reference range: 0.26-1.65) and the free lambda chain level was 5.1 mg/L (5.7-26.3).

After zolendronate was administered, the patient was treated with melphalan (9 mg/m², on days 1-4), prednisolone (60 mg/m², on days 1-4) and bortezomib (1.3 mg/m² on days 1, 8, 15, 22). The peripheral myeloma cells completely disappeared after the first course of chemotherapy. In April 2013, a bone marrow aspiration showed no detectable myeloma cells in the marrow after the second course of therapy. Following the completion of the third course of treatment, the patient suffered from acute pyelonephritis followed by septic shock. Although she completely recovered from the infection within two weeks, she declined to receive further courses of therapy. Only maintenance therapy (biweekly administration of bortezomib and dexamethasone) was continued thereafter. As of March 2014, the patient was in good health, and laboratory data, including the beta 2-microglobulin level, were normal, except for suppressed levels of immunoglobulins.
Primary PCL occurs in individuals without a preceding diagnosis of MM (10), whereas secondary PCL arises in patients with a history of MM who have progressed to a leukemic phase. Primary PCL accounts for 60% of all PCL cases (2). The present patients were considered to have primary PCL since they had no previous history of MM. Primary PCL has a more aggressive clinical presentation than MM, with a higher frequency of extramedullary involvement, as well as anemia, thrombocytopenia, hypercalcemia, and renal failure. On the other hand, the presenting features of nonsecretory myeloma are similar to those observed in patients with a detectable level of M-protein, with the exception of the absence of renal function impairment (2). The response to therapy and survival of patients with nonsecretory myeloma are similar to those of patients with measurable M-protein (2).

The coexistence of nonsecretory MM and primary PCL in the same patient is of clinical interest. However, clinical information regarding nonsecretory primary PCL cases is limited (5-9). Four of the seven previously reported patients (including our patients) were women, with a median age of 74 (60-85). Bone pain was present as the initial clinical symptom in five of the seven patients, whereas hepatosplenomegaly was not specifically indicated in these cases. The response to treatment was generally poor, although complete remission was achieved in one case (5). These features are not distinct from those of primary PCL with a detectable M-component. The simultaneous occurrence of the two rare forms of MM may be coincidental.

Morphological heterogeneity in atypical PCL lesions sometimes makes it difficult to diagnose PCL. PCLs without a plasma cell morphology may be indistinguishable from other lymphoproliferative tumors or other types of acute leukemia (11, 12). Immunohistochemistry, flow cytometric analyses and/or electron microscopic examination may be required to establish a definitive diagnosis. The diagnosis may be made with further difficulty in cases with a nonsecretory nature (7, 9). Indeed, we did not initially suspect a diagnosis of PCL in patient 1 because most of the cells exhibited an atypical morphology, and no monoclonal proteins were detected in either the serum or urine. In patient 2, it was not difficult to diagnose PCL since the peripheral malignant cells had a typical plasma cell morphology.

CD56 (NCAM) is a neural cell adhesion molecule. Malignant plasma cells express CD56 in the majority of MM cases (67-79%), whereas normal plasma cells do not (13). Pellat-Deceunynck et al. reported that malignant plasma cells derived from patients with either primary (n=12) or secondary (n=15) PCL do not express CD56, in either the bone marrow or peripheral blood in 81% of cases (14). The authors concluded that lack or weak expression of CD56 is a characteristic feature of PCL and suggested that a weak expression of CD56 is associated with a significantly less aggressive osteolytic potential. Indeed, in patient 1, CD56 was not expressed on plasma cells, and he had no apparent osteolytic lesions. On the other hand, CD56 was definitively expressed on the malignant plasma cells of patient 2, and she suffered from a compression fractures of the vertebrae. Further studies concerning the expression of CD56 in PCLs are necessary.

The prognosis of PCL patients who are treated with standard chemotherapy is usually poor, with the median survival being measured in months (15, 16). Stem cell transplantation may be more effective in some, but not all, PCL patients. Therefore, the best therapeutic approach for primary PCL remains unknown. A retrospective study of Gruppo Italiano Malattie Ematologiche dell’ Adulto (GIMEMA) with 29 primary PCL patients treated with a bortezomib-containing regimen showed promising results (17). In that study, bortezomib was administered in combination with other drugs, including dexamethasone, thalidomide, doxorubicin, melphalan, prednisone, vincristine and cyclophosphamide. The overall response rate was 79%, with 38% of patients exhibiting at least very good partial remission. Bortezomib, used as initial therapy, may produce a significant improvement in survival. The efficacy of single-agent thalidomide is limited in patients with primary PCL compared with the activity of this agent in those with MM (18). Lenalidomide is less toxic and more potent than thalidomide. The combination of lenalidomide and dexamethasone has been reported to be effective in cases of newly diagnosed primary PCL (19). In addition, combination chemotherapy with bortezomib, lenalidomide and dexamethasone is also promising (20). These novel agents may be used to overcome the poor prognosis of primary PCL.

We herein reported two cases of primary nonsecretory PCLs. In one case, the lack of monoclonal immunoglobulins made it difficult to arrive at a conclusive diagnosis because the malignant peripheral plasma cells showed an atypical morphology. Therefore, this case proved to be diagnostic challenge. In the other case, the patient was successfully treated with bortezomib-containing chemotherapy.

The authors state that they have no Conflict of Interest (COI).

References


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