A Case of Aggressive Multiple Myeloma with Cleaved, Multilobated, and Monocytoid Nuclei, and No Serum Monoclonal Gammopathy

Y. Albert Yeh, Alex A. Pappas, James T. Flick, and Anthony W. Butch
Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, Arkansas
("Current address: Department of Pathology and Laboratory Medicine, UCLA Medical Center, Los Angeles, CA"

Abstract

Multiple myeloma is a B-cell malignancy characterized by proliferation of neoplastic plasma cells. A few cases have been reported identifying variant forms of neoplastic plasma cells with atypical nuclei that secrete myeloma protein. We report a highly unusual case of plasma cell myeloma that presented with cleaved, multilobated, and monocytoid nuclei, without detectable myeloma protein in the serum or urine. The bone marrow contained sheets of plasma cells exhibiting pleomorphic nuclei with cleaved, multilobated, and monocytoid features that were negative for myeloperoxidase and dual esterase. Flow cytometric analysis revealed CD38high/CD45low cells expressing cytoplasmic kappa light chain, without evidence of myeloid or lymphoid differentiation. Following chemotherapy, the patient developed secondary plasma cell leukemia. A high plasma cell labeling index was obtained from bone marrow and peripheral blood, indicating a poor prognosis. In addition to quantitative immunoglobulins, serum protein electrophoresis, and immunofixation electrophoresis of serum and urine, we recommend cytochemical and flow cytometric studies for evaluation of suspected plasma cell myeloma with atypical cellular features.

Keywords: multiple myeloma, plasma cell, cleaved, multilobated, monocytoid, non-secretory

Introduction

Plasma cell myeloma constitutes approximately 1% of all malignancies and 10% of all hematologic malignancies. Several classifications and grading schemes for plasma cell myeloma have been proposed [1,2]. Histologic classification is based on cellular size, cytoplasmic structure, and nuclear pattern, and is divided into six groups: Marschalko, small cell, cleaved, polymorphous, asynchronous, and blastic type [1]. The Marschalko type is a low-grade malignancy that accounts for 59% of all cases, and is characterized by normal-appearing mature plasma cells [1]. The small-cell type is also considered low-grade and accounts for 11% of all myeloma cases. The other groups individually account for <10% of the remaining cases, with the plasmablastic type being a high-grade malignancy (2% of all cases) associated with a poor prognosis [1]. In a small percentage of myeloma cases, the plasma cells exhibit unusual morphologic characteristics and the disease follows an aggressive clinical course. For instance, Buss et al [3] identified 10 multiple myeloma patients with neoplastic plasma cells containing multilobated nuclei while Zukerberg et al [4] reported 6 patients with cleaved, multilobated, and monocytoid plasma cell nuclei. In addition, a few isolated case reports of this morphologic variant of multiple myeloma have been described [5-8]. A monoclonal protein consisting of either an intact immunoglobulin (IgG, IgA, or IgD) or a free light chain (kappa or lambda) is normally detected in serum samples from patients presenting with this morphologic variant of multiple myeloma [3-8]. In this report, we...
describe an unusual case of plasma cell myeloma with cleaved, multilobated, and monocytoid nuclei that express cytoplasmic immunoglobulin in the absence of a corresponding serum monoclonal protein (ie, nonsecretory).

Case report

A 69-year-old man was seen at a community hospital in March 1997 for a complaint of back pain. Clinical imaging studies revealed multiple osteolytic lesions in the vertebrae involving the thoracolumbar region at levels T10, T11, T12, L1, and L2. Multiple expansile lytic lesions were also observed involving the right proximal ribs #4 and #5, and the left lateral rib #5. A bone marrow biopsy showed plasmacytic infiltrates comprising 80 to 90% of the nucleated marrow cell population. The bone marrow aspirate was markedly hypercellular, revealing sheets of plasma cells. Many plasma cells were atypical, showing bi- and tri-nucleation along with numerous monocytoid forms. The peripheral blood white count was normal and plasma cells were absent. Serum lactate dehydrogenase and beta2-microglobulin levels were within the normal ranges. A diagnosis of stage III plasma cell myeloma was made, based on the lytic bone lesions. The patient received two cycles of melphalan and prednisone, followed by three cycles of dexamethasone, all of which were well tolerated. A bone marrow biopsy in January 1998 revealed a decrease in the number of plasma cells to 4%, indicating that the patient was in clinical remission. The patient subsequently developed a fever of 38.5°C that was unresponsive to ciprofloxacin. The CBC revealed mild anemia and thrombocytopenia.
Atypical myeloma with no serum monoclonal protein

Table 1. Flow cytometric analysis of bone marrow and peripheral blood mononuclear cells

<table>
<thead>
<tr>
<th>Cytoplasmic immunoglobulin</th>
<th>Bone marrow aspirate</th>
<th>Peripheral blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% light chain</td>
<td>DNA index</td>
</tr>
<tr>
<td>Kappa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diploid</td>
<td>68</td>
<td>1.0</td>
</tr>
<tr>
<td>aneuploid</td>
<td>18</td>
<td>1.92</td>
</tr>
<tr>
<td>Lambda</td>
<td>&lt;1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bone marrow aspirate</th>
<th>Peripheral blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>% G0/G1</td>
<td>%G0/G1</td>
</tr>
<tr>
<td>%S+G2M</td>
<td>%S+G2M</td>
</tr>
</tbody>
</table>

DNA cell cycle

* Dual color fluorescent staining was performed using antibodies against either kappa or lambda light chains to identify plasma cells and propidium iodide to determine the DNA index and cell cycle distribution.

The total white cell count was normal (3.3 x 10^9/L) with 82% plasma cells. At this point, the patient was transferred to the Arkansas Cancer Research Center at the University of Arkansas for Medical Sciences.

Laboratory results on admission in April 1998 were as follows: hemoglobin 86 g/L (reference range 135-175), and hematocrit 0.25 (reference range 0.40-0.72). The white blood count was 61 x 10^9/L (reference range 3-12 x 10^9/L) and consisted of 74% plasma cells, 15% segmented neutrophils, 6% lymphocytes, 3% monocytes, and 2% eosinophils. The platelet count was 24.6 x 10^9/L (reference range 150-500 x 10^9/L). Serum urea nitrogen, creatinine, calcium, and alkaline phosphatase levels were within normal limits. The serum total protein was decreased at 52 g/L (reference range 65-85) and beta2-microglobulin elevated at 6.3 mg/L (reference range <2). Serum immunoglobulin levels were decreased, with IgG 5.27 g/L (reference range 8.4-16.4), IgA <310 mg/L (reference range 1150-4250), IgM <280 mg/L (reference range 600-4100), kappa light chain 1430 mg/L (reference range 2300-4900), and lambda light chain 560 mg/L (reference range 1250-2300). Total urine protein was 1100 mg/day (reference range 50-100). Serum and urine protein electrophoresis were negative for a restricted peak; albumin was the major urinary protein. Immunofixation electrophoresis was negative for intact immunoglobulin and free immunoglobulin light chains when serum and urine were analyzed on numerous occasions.

Examination of a peripheral blood smear revealed moderate normochromic normocytic anemia with no rouleaux formation. Mild anisocytosis and occasional oval macrocytes were noted. The majority of nucleated blood cells were large with plasmacytoid features. The neoplastic plasmacytoid cells had pleomorphic nuclei with irregular contours, cloverleaf shapes, and monocytoid features (Fig. 1a). Occasional bi-nucleated cells were noted. Nuclei in these atypical cells were centrally located and contained clumped chromatin. Cytoplasmic granules were absent.

A smear of bone marrow aspirate showed sheets of plasma cells that accounted for 82% of the overall nucleated cell population. Large, bi-nucleate and trinucleate forms were noted. Many of these atypical plasma cells contained small, inconspicuous nucleoli. Other features of these plasma cells were the same as those in the peripheral blood smear. Cytochemical stains were negative for myeloperoxidase and dual esterase using both the chloroacetate esterase and the alpha-napthyl esterase techniques.

Bone marrow biopsy revealed a packed marrow with sheets of atypical plasma cells (Fig. 1b). Plasma cell nuclei showed mild to marked irregularity in contour, and many were monocytoid. Fine associated fibrosis was also noted.

Flow cytometric analysis of the bone marrow aspirate revealed an abnormal population of cells with a plasma cell phenotype (CD38^high/CD45^low) that was negative for myeloid (CD13, CD14, CD15, CD33)
and lymphoid (CD4, CD5, CD7, CD19, CD20) surface markers. Dual fluorescent staining using propidium iodide and antibodies against immunoglobulin light chain [9] demonstrated that 86% of the bone marrow cells were positive for cytoplasmic kappa light chain, and that 15% of these cells were in cell cycle (S/G2M phase). An aneuploid population of plasma cells comprising 18% was also present. When peripheral blood was examined, 78% of mononuclear cells were positive for cytoplasmic kappa light chain and 27% of these cells were in cell cycle (Table 1). An aneuploid population of 9% was also detected in the peripheral blood. A plasma cell labeling index was measured to determine the proliferative capacity of the myeloma plasma cells based on incorporation of the DNA analog bromodeoxyuridine, after a 1-hr pulse in culture [10]. Plasma cells were identified by morphology and cytoplasmic staining with anti-kappa light chain antisera, and the incorporation of bromodeoxyuridine was quantitated by immunocytochemistry. Approximately 3.2% of plasma cells in the bone marrow and 4.4% in peripheral blood were positive for the DNA label, indicating a high proliferative capacity. Taken together, these findings indicated a high-grade malignancy with a poor prognosis.

A diagnosis of non-secretory plasma cell myeloma with secondary plasma cell leukemia was made, and the patient received combination chemotherapy with dexamethasone, cyclophosphamide, etoposide, and cisplatinum (DCEP), followed by DCEP plus thalidomide. Although there was resolution of the plasmacytosis, the patient failed to respond to therapy. Subsequent bone marrow biopsies were extensively involved by plasma cell myeloma. In August 1998, the patient received high-dose chemotherapy with melphalan followed by peripheral stem cell rescue. The patient tolerated high-dose chemotherapy well and was discharged from the hospital, but he died 2 mo later.

Discussion

Circulating cells with cleaved, multilobated, or monocytoid nuclei can be present in a variety of non-hematologic and hematologic disorders such as reactive plasmacytosis associated with breast carcinoma, metastatic carcinoma, plasma cell leukemia, myelomonocytic leukemia, malignant lymphoma, and multiple myeloma [3-8,11,12]. In our case, the patient had multiple osteolytic lesions and bone marrow plasma cell infiltrates. Plasma cells were not detected in the peripheral blood on initial presentation. Although these findings are consistent with multiple myeloma, a final diagnosis could not have been made with certainty without flow cytometric studies, because of the unusual plasma cell morphology and the absence of a serum or urine monoclonal protein. The neoplastic cells in the bone marrow were CD38^{high}/CD45^{low}, cytoplasmic immunoglobulin positive, and negative for myeloid/lymphoid markers by flow cytometry, consistent with a diagnosis of multiple myeloma. The plasma cell morphology was similar before and after treatment, indicating that chemotherapy did not contribute significantly to the atypical nuclear features. Multiple myeloma with cleaved, multilobated, and monocytoid plasma cells carries a very poor prognosis [4,7]. Therefore, recognition of these atypical forms is important and should be reported so that appropriate chemotherapy can rapidly be instituted.

Non-secretory multiple myeloma is a rare form of multiple myeloma accounting for 1% of all cases [13]. The morphologic variant of multiple myeloma presented in this report is also uncommon, with fewer than 25 cases described in the literature [3-8]. Thus, the presence of these two variant forms of multiple myeloma in the same patient is exceedingly rare and of clinical interest, since it presents a diagnostic problem due to lack of a circulating monoclonal protein and unusual nuclear morphology.

The classification scheme proposed by Bartl et al [1] divides multiple myeloma into 6 histologic types that can be combined into 3 prognostic grades. Plasma cells with cleaved and polymorphous types were considered of intermediate clinical grade and had a median survival of 21 months and 27 months, respectively, from onset of symptoms [1]. In a study of 6 multiple myeloma patients with plasma cells exhibiting cleaved, multilobated, and monocytoid nuclei, the majority presented with stage III disease, advanced lytic bone lesions, and either a monoclonal immunoglobulinemia or Bence-Jones proteinuria [4]. These cases would be considered intermediate clinical grade (cleaved and polymorphous subtype) according to the Bartl classification [1]. However, all the patients had highly aggressive disease that was unresponsive to...
Atypical myeloma with no serum monoclonal protein

Three patients died within 1 month of diagnosis and 2 of the 3 remaining patients had rapidly progressive disease [4]. The aggressive nature of this variant of plasma cell myeloma has been confirmed by Buss et al [3], who reported 10 cases with a median survival of 16 months, and by individual case reports [5-8]. Although our patient had similar clinical manifestations, we were unable to detect the presence of a monoclonal protein or Bence-Jones protein in multiple samples of serum and urine. The atypical plasma cells in our case were CD10-(CALLA-), with CD10+ being associated with more aggressive forms of myeloma [14]. However, our patient had a plasma cell labeling index of 3.2%, indicating a high proliferative capacity. Plasma cell myeloma cases with a labeling index >1% are associated with a poor prognosis [15]. The elevated serum beta2-microglobulin level of 6.3 mg/L was also indicative of clinically aggressive disease and a shortened survival time [16].

There are two forms of plasma cell leukemia. The primary form occurs de novo in individuals without previously recognized multiple myeloma, while the secondary form develops in patients with pre-existing multiple myeloma. The diagnosis of plasma cell leukemia is made when the number of plasma cells in peripheral blood is greater than 2 x 10⁹/L and comprises 20% of the total leukocytes [17]. The incidence of secondary plasma cell leukemia is estimated to be approximately 2% during the course of multiple myeloma [17]. Secondary plasma cell leukemia may also occur in multiple myeloma patients who receive intensive chemotherapy with stem cell rescue [17]. Our patient had secondary plasma cell leukemia that was diagnosed 10 mo after combination chemotherapy with melphalan, prednisone, and dexamethasone. It has been postulated that intensive chemotherapy may select for a plasma cell clone that is highly aggressive. This may account for the dismal median survival rate of only a few months in patients with secondary plasma cell leukemia [18].

Acknowledgement

We thank Dr. Faramarz Naeim of the UCLA Medical Center for his critical review of this manuscript.

References


