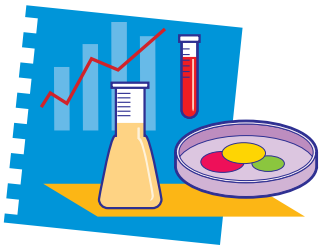

Vanlila K. Swami, MD
Lisa E. A. Dwyer-Joyce, MD

CLINICAL

PATHOLOGY ROUNDS

Diagnosing Plasma Cell Leukemia

From the Department of Pathology and Laboratory Medicine, Medical College of Pennsylvania Hospital, MCP Hahnemann University, Philadelphia.

Case Presentation

An 85-year-old woman was referred to the emergency department because a routine CBC count revealed a hemoglobin level of 5.4 g/dL (54 g/L). She was a nursing home resident with advanced Alzheimer disease. Her caregiver reported that during the preceding 2 weeks, the patient had been unusually weak and inactive and had had a poor appetite. The patient's hemoglobin levels 6 months and 12 months earlier were 11.9 g/dL (119 g/L) and 13.0 g/dL (130 g/L), respectively, according to the caregiver.

The patient's history included hypertension, degenerative joint disease, osteoporosis, pneumonia, and a hiatal hernia. She had been a nursing home resident for 4 years and had severe dementia. She was disoriented as to time, place, and person.

Physical examination showed that she was afebrile and comfortable with a pulse rate of 82. Her oropharyngeal mucosa was pale. No evidence of lymphadenopathy, abdominal tenderness, or organomegaly was present. The results of rectal examination were normal, and her stool was negative for hemoglobin. Initial laboratory results were as follows: hemoglobin level, 5.4 g/dL (54 g/L; reference range, 12.0-16.0 g/dL [120-160 g/L]); hematocrit, 16% (0.16; reference range, 36%-46% [0.36–0.46]); mean corpuscular volume, 110.3 cu μm (110.3 fL; reference range, 80-100 cu μm [80-100 fL]); platelet count, 106 × 10^3/μL (106 × 10^9/L; reference range, 150-400 × 10^9/L); WBC count, 10,000/μL (10.0 × 10^9/L; reference range, 4,800-10,800/μL [4.8-10.8 × 10^9/L]). The total protein concentration was elevated at 11.5 g/dL (115 g/L; reference range, 6.0-8.2 g/dL [60-82 g/L]), and the relative serum viscosity was high at 2.6 (reference range 1.5–1.8) × water. Her RBC folate, vitamin B_{12}, ferritin, and haptoglobin levels in serum were within the reference intervals. Peripheral blood smear examination with manual differential count revealed 26% plasma cells with numerous immature cells and RBC rouleaux (Fig 1).

Serum protein electrophoresis revealed a band in the gamma region. The band was shown by immunofixation (Fig 2) to be monoclonal IgG lambda. Urine electrophoresis and immunofixation revealed free lambda light chains (Bence Jones protein). Serum immunoglobulin quantification disclosed a markedly elevated serum IgG level at 7,160 mg/dL (71.6 g/L; reference range, 613-1,295 mg/dL) [6.1-13.0 g/L]); normal con-

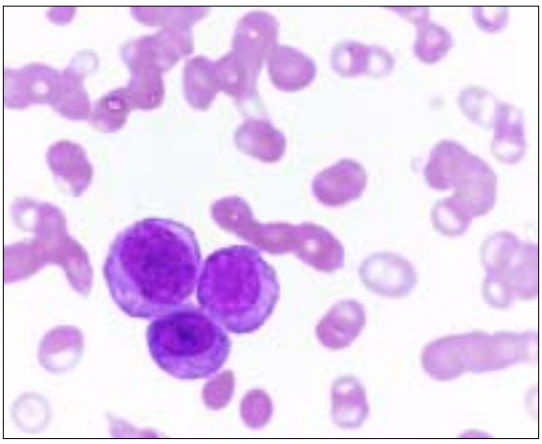

Fig 1. Peripheral blood smear showing 3 plasma cells and RBC rouleaux formation in a patient with plasma cell leukemia (Wright stain, original magnification × 1,000).

centration of IgA and IgE; and a low level of IgM at 20 mg/dL (0.2 g/L; reference range, 53-334 mg/dL [0.5-3.3 g/L]).

Bone marrow biopsy and aspiration showed that normal marrow elements had been replaced by sheets of immature plasma cells (Fig 3). A bone survey showed no lytic lesions.

In view of the patient's mental status and age, and after consultation with her family, supportive care and pulsed dexamethasone therapy were considered the best option for this patient.

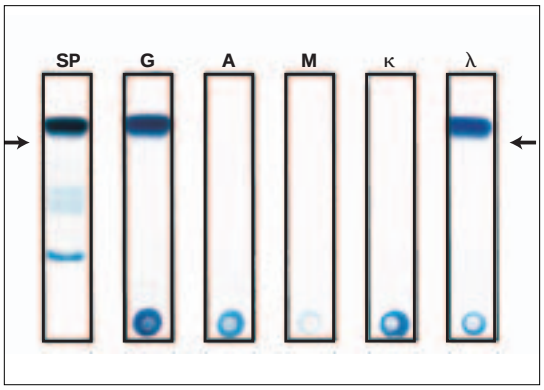

Fig 2. Immunofixation of serum showing IgG lambda monoclonal protein in a patient with plasma cell leukemia.

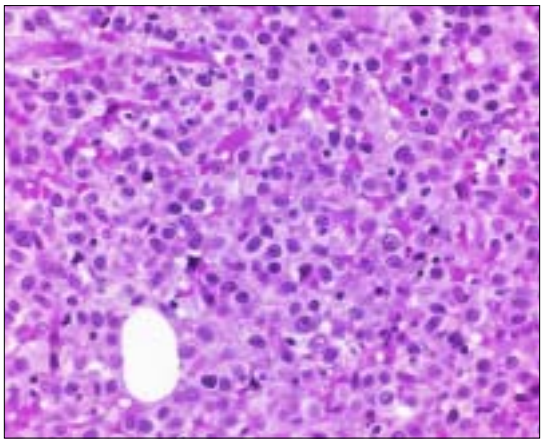

Fig 3. Bone marrow biopsy showing sheets of immature plasma cells in a patient with plasma cell leukemia (H&E stain, original magnification ×400).

Clinical Background

The diagnosis in this case was plasma cell leukemia (PCL), a rare manifestation of a plasma cell dyscrasia, which constitutes 1% to 2% of multiple myeloma (MM) cases. It may arise de novo (as the primary condition), or it may be a terminal complication of a preexisting MM. The malignant disorder involves proliferation of plasma cells in which plasma cells account for more than 20% of the differential WBC count; the concentration of plasma cells exceeds 2×10^9/L.[1,2]

After PCL was first described in 1904,[3] single case reports have appeared. The incidence of secondary PCL among cases of MM has a wide range of 2% to 9%.[4] The clinical presentation of PCL differs from MM and resembles that of acute leukemia. The disease manifests itself with weight loss, fatigue, anemia, and bleeding. Patients with PCL have a higher incidence of organ and tissue infiltration and less bone pain than patients with MM.

Extensive infiltration into visceral organs occurs, with hepatomegaly, splenomegaly, and lymphadenopathy in PCL.[5] The lung, pleura, testes, central nervous system, and skeletal muscle may also be infiltrated.[6-9] In MM, the extra osseous penetration occurs later in the disease and is often detected during autopsy.[10]

At initial diagnosis, a hemoglobin level of less than 9 g/dL (90 g/L) is more common in PCL (80% of cases) than in MM (35% of cases). Thrombocytopenia with platelet counts less than $100 \times 10^3/\mu L$ ($<100 \times 10^9$/L) have been reported with higher frequency in PCL (50%) than in MM (10%). Leukocytosis may occur, with WBC counts ranging from 20,000 to 100,000/μL (20 to $>100 \times 10^9$/L) and absolute plasmacytosis with plasma cells present at more than 2×10^9/L. Peripheral blood smear examination reveals rouleaux formation in most cases. Other laboratory abnormalities include hypercalcemia and elevated levels of creatinine, blood urea nitrogen, and total serum protein. Monoclonal serum protein, Bence Jones proteinuria, or both are present in most patients.

The monoclonal protein in patients with PCL may be IgG (50% of cases), IgA (15%), or, in rare cases, IgD or IgE. Bence Jones proteinuria occurs in 80% of cases.[5] Although rare, nonsecretory PCL has been reported.[4,11] Hyperviscosity of serum is also rare.

The bone marrow shows diffuse plasma cell infiltration of 50% to 100% (50%-100% of bone marrow cells are replaced by plasma cells). The bone marrow plasmacytosis usually exceeds that of peripheral blood; plasma cells are well differentiated and have eccentrically placed nuclei, a paranuclear halo, and abundant basophilic cytoplasm. Binucleated plasma cells may be present, as well as cells with immature nuclei and large prominent nucleoli.

Immunophenotypic analysis in PCL shows plasma cells to be immunologically heterogeneous and less mature than plasma cells in MM.[12,13] Studies of DNA content of MM plasma cells[14,15] report a high percentage of hyperdiploid cells (70%), with 20% diploid and 10% hypodiploid.[14,15] Patients with hypodiploid MM have a poor prognosis.[16,17]

One study of DNA content in plasma cells reported hypodiploidy in 50% of PCL cases.[13] This increased incidence may explain the reduced survival rate in PCL.[13] Most cytogenetic studies have been unsuccessful because the malignant plasma cells undergo cell division infrequently and, hence, the cytogenetic abnormalities are not easily discovered.[18,19]

Although the prognosis in PCL is generally poor, single case reports indicate good response to chemotherapy.[5] Patients with primary PCL respond better to chemotherapy than patients with secondary PCL; the latter have reduced bone marrow function and decreased performance status.[5] Various treatment protocols, including single-drug or combination chemotherapy, radiation,[20] and radioactive phosphorus 32,[2] have been reported. In 1 patient,[21] high-dose melphalan and autologous bone marrow transplantation resulted in a 30-month remission.[21]

Role of the Laboratory

The WBC flow cytometric histogram of the patient is shown in Figure 4A. The results revealed increased numbers of cells in the monocyte region, as well as cells spreading above the monocyte and neutrophil zones and to the upper border. A blast flag was seen on the printed report (not shown). These results met our criteria for manual differential count and review by a pathologist.

The peripheral blood smear revealed macrocytic RBCs with occasional ovalocytes; slight rouleaux formation was also noted. The WBC count was within the reference interval, although plasma cells represented 26% of the differential count. Most plasma cells were immature and had clumped nuclear chromatin, a relatively large nucleus, a single large nucleolus, and a moderate amount of blue cytoplasm. Our automated WBC differential count system did not recognize these plasma cells; instead, the system included them with monocytes.

The differential diagnosis clearly pointed to a plasma cell dyscrasia owing to large numbers of easily recognizable but immature plasma cells. Less likely conditions (ruled out by morphology alone) included acute monoblastic leukemia, acute prolymphocytic leukemia, leukemic phase of large cell lymphoma, and Waldenström macroglobulinemia. The abundant amount of blue cytoplasm and eccentric placement of the nucleus were not consistent with acute leukemia, in which one would expect blast morphology. Although the neoplastic cells in both acute prolymphocytic leukemia and circulating large cell lymphoma have nucleoli, they do not have plasmacytoid morphology or basophilic cytoplasm; the cells are generally recognized by automated hematology analyzers as lymphocytes. In Waldenström macroglobulinemia, cells have more mature nuclei and lymphoplasmacytoid or lymphocytic morphology.

Benign reactive plasmacytosis as seen in viral infections and autoimmune disorders was also considered as a diagnosis. However, in reactive conditions, plasma cells are more mature and usually present in smaller numbers except in AIDS, in which plasma cell proliferation may be prominent.

The peripheral blood findings, though suggestive, do not establish a diagnosis of neoplastic plasma cell disorder. Serum and urine protein electrophoresis with immunofixation are essential because these tests reveal the clonal nature of the plasma cells. In our patient, a monoclonal IgG lambda band in serum and lambda Bence Jones protein in the urine were identified. The sheets of neoplastic plasma cells (>70%) revealed by bone marrow biopsy confirmed the diagnosis. The macrocytic anemia was probably secondary to bone marrow replacement by MM cells. Macrocytosis is also seen in megaloblastic anemia, liver disease, hypothyroidism, and replacement of bone marrow by neoplastic cells.

Although criteria for MM diagnosis vary slightly, they usually include the following: bone marrow plasmacytosis with nuclear atypia of plasma cells, plasmacytoma with monoclonal gammopathy in serum or urine, or lytic bone lesion images on radiographs.

Although plasma cells may be numerous in the peripheral blood of patients in the terminal or leukemic phase of advanced MM or in PCL, this is not a common finding in MM. In our patient,

plasma cells constituted 26% of the differential WBC count, and radiologic studies revealed no osteolytic lesions. Her presentation was acute and involved an initial complaint of anemia.

The differential diagnosis involved primary PCL and the leukemic phase of advanced MM. The diagnosis of primary PCL was based on the patient's acute presentation with anemia and borderline thrombocytopenia, her lack of symptoms or history of MM, and, most important, the absence of radiologic evidence of lytic bone lesions.

Increased expression of CD38 is a consistent feature of MM. Also, the expression of adhesion molecule CD56 is useful in differentiating MM (CD56+) from reactive plasma cells and monoclonal gammopathy of uncertain significance (CD56–).[22]

Conclusion

Plasma cell leukemia constitutes only 1% to 2% of MM cases. Because automated hematology analyzers do not recognize plasma cells, peripheral blood films must be manually reviewed to ensure identification of plasma cells on the basis of morphology. Flow cytometric analysis may be required in difficult cases. Serum and urine protein electrophoresis, bone marrow biopsy, and bone survey data are necessary to establish a diagnosis of PCL.

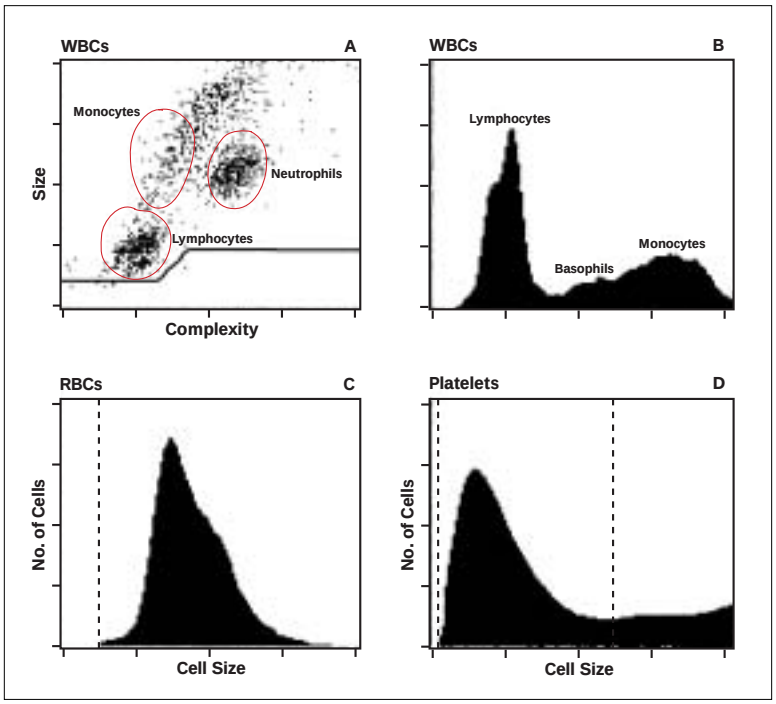

Fig 4. WBC scattergram (A) and histogram (B), RBC histogram (C), and platelet histogram (D) in a patient with plasma cell leukemia (Cell Dyn 3500 flow cytometer, Abbott Diagnostics, Abbott Park, IL).

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