We report a case of hairy cell leukemia variant developing in a background of polycythemia vera in a 77-year-old man who presented with lymphocytosis and splenomegaly. Classic hairy cell leukemia in a patient with polycythemia vera has been reported previously, but hairy cell leukemia variant arising in a patient with polycythemia vera has never been described to the best of our knowledge. Initial testing of the peripheral blood showed circulating medium to large leukaemic cells with large, centrally placed nuclei, each containing a prominent nucleolus, and some cells showed cytoplasmatic projections. A bone marrow biopsy had marked myeloid and erythroid hyperplasia and interstitially distributed cells with a fried-egg appearance. We verified a monoclonal B-cell population by flow cytometric analysis, which revealed expression of bright CD11c, CD22, and CD103 expression, and a lack of CD25 expression. The patient received a 5-day course of cladribine and subsequently had a complete remission. Approximately 2 months later, he had a relapse and was treated with pentostatin; however, he had no clinical response and died.

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Polycythemia vera (PV) is a chronic myeloproliferative disorder characterized by an increased red blood cell mass independent of a secondary cause of erythropoiesis.

Polycythemia vera is associated with several other disorders, including acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, other myeloproliferative disorders, and multiple myeloma.

Among patients with PV, the risk of developing myelodysplastic syndrome or acute leukemia increases from 1% to 13% to 14% when they are treated with chlorambucil or radioactive phosphorus, but does not significantly increase with hydroxyurea therapy.

Most of the leukemias developing in patients with PV are acute myelogenous leukemias. Occasionally, patients develop lymphoid leukemias, including acute and chronic lymphocytic leukemia.

A single case of classic hairy cell leukemia (HCL) arising in a patient with PV has been previously described.

We describe a case of hairy cell leukemia variant (HCL-V) developing in a background of PV. HCL-V is a rare and more aggressive form of HCL accounting for 10% of HCL cases and 0.4% of chronic lymphoid malignancies. Affected patients are typically elderly men presenting with high white blood cell counts, variable cytopenias, and splenomegaly. Morphologically distinct B lymphocytes with centrally located nuclei containing a single prominent nucleolus and cytoplasmic projections infiltrate the blood, bone marrow, spleen, liver, and lymph nodes. Immunophenotypic analysis of the malignant lymphocytes reveals a monoclonal B-cell population with variable expression of tartrate-resistant acid phosphatase.

REPORT OF A CASE

A 77-year-old white man with a 25-year history of PV presented with marked lymphocytosis, anemia, thrombocytopenia, and dependent edema. The patient was in the spent phase of PV, having been treated with phlebotomy only to keep his hematocrit at 45% or lower. In July 2001, the patient received radiation to his spleen at a dose of 1000 Gy for the treatment of pain, dyspnea, and early satiety. Over the course of 6 weeks, he noted increased dyspnea on exertion, anorexia, and fatigue. He had lost 4.5 kg in the previous year. A complete blood cell count with differential analysis showed the following (reference ranges are given in parentheses): white blood cell count, 87,200/μL (4000–10000/μL); red blood cell count, 3.05 (4.5–6.0) × 10^12/μL; hemoglobin concentration, 7.0 (14.0–17.0) g/dL; hematocrit, 22.6% (40.0%–54.0%); mean corpuscular volume, 74.2 (85–95) μm^3; mean corpuscular hemoglobin, 22.8 (28.0–32.0) pg; mean corpuscular hemoglobin concentration, 30.8 (32.0–36.0) g/dL; red blood cell distribution width, 25.5% (11.0%–15.0%); platelet count, 56 (150–400) × 10^9/μL; segmented neutrophils, 11% (45%–70%); lymphocytes, 86% (20%–45%); basophils, 1% (0%–2%); and monocytes, 2% (0%–10%). Red blood cell morphology was characterized by the presence of teardrop cells, ovalocytes, schistocytes, polychromasia, and basophilic stippling. Oxygen saturation on room air was 93% and 65 mm Hg (74–108 mm Hg) by co-oximetry.

Physical examination showed a mildly cachectic man in no acute distress. Cardiopulmonary examination revealed a grade 3/6 systolic murmur at the left sternal border and crackles that were greater on the right. Abdominal examination was remarkable for a markedly enlarged spleen measuring 23 cm below the costal margin, and examination of the extremities revealed 1 to 2+ pitting edema that was greater on the right. The patient was given a transfusion of packed red blood cells. Based on the results of the peripheral blood smear and bone marrow biopsy evaluation, we rendered a diagnosis of HCL-V.

The patient was treated with cladribine. Three days later, he was readmitted because of mental status changes, fever, and a mild productive cough. During his hospital course, he was given a transfusion of 6 units of platelets because of continued thrombocytopenia. The patient had a partial remission. Approximately 2 months after his diagnosis of HCL-V, he had a relapse, and a course of pentostatin was administered, without evidence of re-
Peripheral blood smear with circulating leukemic cells. The cells have large, centrally located nuclei with a distinct nucleolus and moderately abundant, lightly basophilic cytoplasm with projections (May-Grünwald–Giemsa, original magnification ×1000). B, Cytochemical stain with tartrate-resistant acid phosphatase showing positive brick-colored cytoplasmic granules in peripheral blood (original magnification ×500). C, The bone marrow core biopsy is hypercellular with leukemic cells showing nuclei embedded in clear spaces, imparting a fried-egg appearance (hematoxylin-eosin, original magnification ×500). D, The results of an immunohistochemical stain for CD20 are strongly positive (original magnification ×400).

PATHOLOGIC FINDINGS

The peripheral blood contained circulating leukemic cells characterized by moderately abundant and slightly basophilic cytoplasm with projections, and oval to round nuclei with centrally placed nucleoli (Figure 1, A). Some of the leukemic cells also showed cytoplasmic, focally localized azurophilic granules. The bone marrow was hypercellular for the patient's age, with marked myeloid and erythroid hyperplasia. There was patchy interstitial infiltration by the leukemic cells, with nuclei embedded in clear spaces imparting a fried-egg appearance (Figure 1, C).

Immunohistochemical staining of the bone marrow biopsy showed both scattered and occasionally loosely localized lymphoid infiltrates with strong expression of CD20 (Figure 1, D). A cytochemical stain with tartrate-resistant acid phosphatase resulted in typical cytoplasmic brick-colored granular staining in the aspirate smear (Figure 1, B). The bone marrow core biopsy also revealed markedly increased reticulin fibrosis. Flow cytometric analysis of the lymphoid cells revealed a monoclonal B-cell population with strong expression of CD11c and CD20 as well as CD19, CD22, CD103, and FMC7 with κ light chain restriction; there was no expression of CD25 (Figure 2).

COMMENT

Patients with PV, if left untreated, survive for approximately 18 months after diagnosis, and their deaths are largely due to thrombotic events. Therefore, treatment has been aimed at reducing the risk of these thrombotic events with phlebotomy or chemotherapeutic agents. Chlorambucil and radioactive phosphorus therapy are no longer used because of the increased risk of leukemic transformation associated with these agents. To date, hydroxyurea is the agent of choice as it has not been found to increase this risk in a statistically significant manner.

The development of lymphoproliferative disorders in patients with myeloproliferative disorders is well known, but the underlying mechanisms are poorly understood. It is not possible to determine if radiation of the spleen was a factor in the development of HCL-V in this patient or if it altered the behavior of this disease. To our knowledge, this is the first reported case of the lymphoproliferative disorder HCL-V arising in a patient with a history of PV. In 1984, Lishner et al reported a case of HCL in a patient with PV. The patient received busulfan therapy, which may have contributed to the development of HCL.

First described by Cawley et al in 1980, HCL-V is an extremely rare chronic B-cell lymphoproliferative disorder, accounting for only 0.4% of these disorders; it is related to, but distinct from, HCL and is postulated to be a prolymphocytic variant of HCL. Patients with HCL-V are usually older men who have massive splenomegaly, marked lymphocytosis, and easily aspirable bone marrow without monocytopenia. In contrast, classical HCL usually presents with monocytopenia and neutropenia, a low white blood cell count, and fibrotic bone marrow leading to a dry tap. In this case, the patient's bone marrow showed marked reticulin fibrosis that was most likely secondary to PV-related myelofibrosis.

HCL and HCL-V can be distinguished morphologically and immunophenotypically: classic hairy cells have smaller, reniform nuclei lacking distinct nucleoli and are usually positive for CD25. Other chronic B-cell malignancies to be distinguished from HCL-V include B-cell prolymphocytic leukemia (B-PLL) and splenic marginal zone lymphoma (SMZL). In some cases, distinguishing B-PLL prolymphocytes from HCL-V lymphocytes based on morphologic examination can be difficult as both cell types contain large nuclei with a prominent nucleolus. The prolymphocytes of B-PLL, however, lack cytoplasmic projections. The leukemic cells of SMZL are smaller than those of HCL-V, with clumpy chromatin and inconspicuous nucleoli, and may show short, polar cytoplasmic projections. Demonstration of bright CD11c and CD22 expression, and expression of CD103 can further distinguish these entities from HCL and HCL-V.

Various treatment regimens that have been shown to be effective in patients with classic HCL have been less than...
successful in those with HCL-V, achieving mostly either a partial or an absent response to therapy. Patients with HCL-V have a variable clinical course, but the disease is usually aggressive, and survival is short. The most promising drug to elicit a partial or complete response has been cladribine. Similar to disease in the majority of patients with HCL-V, our patient’s disease had an aggressive clinical course, and he died only 3 months after his diagnosis despite treatment with cladribine.

References