

A Case Report of Hairy Cell Leukemia and Breast Cancer

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Introduction

Hairy cell leukemia (HCL) is a rare, chronic, B-cell lymphoproliferative disorder characterized by pancytopenia, splenomegaly, and constitutional symptoms.¹ Although HCL is an indolent disorder, most patients will require treatment at some point. Indications to initiate therapy include disease-related symptoms, signs of bone marrow failure, or frequent infections.^{2,3} Asymptomatic patients without cytopenias can be observed.² Therapeutic options usually include purine analogs, either alone or in combination with monoclonal antibodies, biological agents, and surgery.^{2,3} We report a case of a female who developed HCL years after receiving adjuvant chemotherapy and hormonal therapy for breast cancer.

Case Report

In August 2012, a 65-year-old white woman presented for evaluation of a 14-month history of leukopenia, neutropenia, and monocytopenia, which were initially noticed during a routine complete blood count (CBC) that revealed the following: white blood cell (WBC), 3,000/ μ L; hemoglobin (Hgb), 12.3 g/dL; hematocrit (Hct), 36.2%; mean corpuscular volume (MCV), 95.8 fL; platelets, 188,000/ μ L; absolute neutrophil count (ANC), 1,300/ μ L; and absolute monocyte count (AMC), 200/ μ L. In 1991, she was diagnosed with estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, human epidermal growth factor receptor 2 (HER2)-negative tubulolobular carcinoma of the left breast. The patient underwent left modified radical mastectomy with reconstruction using a saline implant followed by adjuvant therapy with 6 cycles

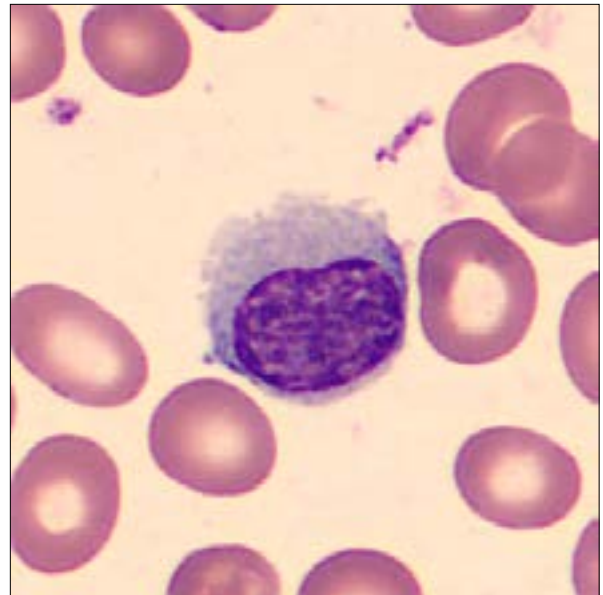


Figure 1. Peripheral blood smear revealed the presence of atypical lymphocytes, which had circumferential hairy projections with indented atypical nuclei.

of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) plus tamoxifen for 4 years. However, in 2010, she noted pain in the left reconstructed breast that was associated with a firm palpable mass, and biopsy proved positive for recurrent breast cancer. She underwent surgical excision followed by chemotherapy with paclitaxel and carboplatin for 4 cycles, and has since remained on the aromatase inhibitor exemestane (Aromasin, Pfizer).

On physical examination, the patient looked well, with no signs of cachexia, pallor, lymphadenopathy, or organomegaly. Blood studies revealed a WBC of 2,800/ μ L, Hgb and Hct of 12.0 g/dL and 34.5%, respectively, MCV of 94.0 fL, platelet count of 156,000/ μ L, ANC of 1,200/ μ , and AMC of 100/ μ L. Review of the peripheral blood smear was notable for the presence of atypical

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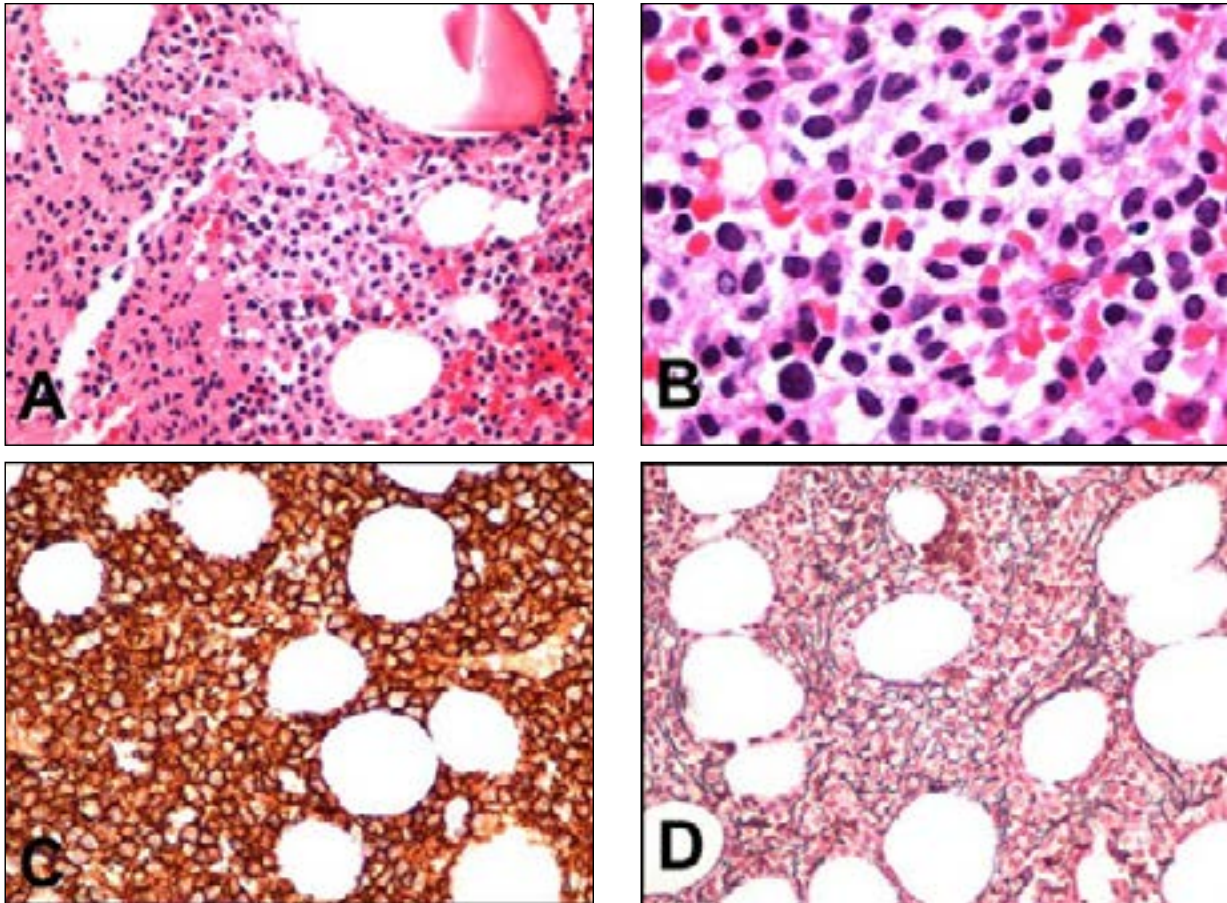


Figure 2. Bone marrow trephine biopsy. Hematoxylin and eosin [H&E] stain demonstrating infiltrate of small, mature-appearing lymphocytes, many with clear cytoplasm (A, B). The atypical lymphocytes were diffusely positive for CD20 (C), and were associated with grade 2 reticulin fibrosis using the modified Bauermeister scale (D).

A, C, and D are $\times 400$ (original magnification) and B is $\times 1,000$ (original magnification).

lymphocytes, which had circumferential hairy projections with indented atypical nuclei (Figure 1).

Bone marrow biopsy performed in November 2012 demonstrated an infiltrate of atypical small B-lymphocytes (CD20+, CD79a+, and CD5-, by immunohistochemical stains) comprising approximately 60% of overall cellularity, which were associated with grade 2 reticulin fibrosis (modified Bauermeister scale). The aspirate was hemodilute and aspicular. Flow cytometry revealed a small, aberrant monoclonal B-cell population with expression of CD19 (bright), CD20, CD22 (bright), CD25, FMC7 (bright), CD103 (bright), and lambda (bright). Additionally, there was no expression of CD5, CD10, and kappa, which is consistent with HCL. Cytogenetic analysis revealed a normal female karyotype.

Discussion

HCL accounts for 2% of all adult leukemia cases in the United States.^{4,5} There are approximately 600 patients

diagnosed annually.⁶ The incidence is 4 times higher in men than in women, and whites are affected more frequently than African Americans.^{7,8} The median age at the time of diagnosis is 56 years.⁸ The exact cause is still unknown.

The clinical presentation of HCL can vary. Approximately 25% of patients are asymptomatic. However, the majority of patients complain of generalized fatigue and weakness. They may also have left upper quadrant (LUQ) abdominal pain, frequent infections, bruising, and weight loss. Physical examination may reveal splenomegaly, with or without hepatomegaly and lymphadenopathy. In addition, patients may present with cutaneous manifestations, such as herpes zoster, cellulitis, abscess, pyoderma, dermatophytosis, leukemia cutis, ecchymosis, and purpura.⁷

Laboratory findings may reveal leukopenia, neutropenia, monocytopenia, anemia, thrombocytopenia, and hypocholesterolemia. Autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia purpura (ITP) can also be observed.⁷

Indicators to initiate therapy include fatigue and weakness that interfere with quality of life, symptomatic organomegaly, frequent infections, and signs of bone marrow failure (eg, hemoglobin <10 g/dL, platelets <100,000/ μ L, and ANC <1,000/ μ L).² Symptomatic disease is initially treated with purine analogs, such as cladribine or pentostatin.^{2,3} Cladribine is considered to be the treatment of choice, as it produces durable overall response rates ranging from 97–100%, with a 4-year disease-free survival rate of over 80%.^{6,9} Other therapeutic options may include combination therapy with rituximab (Rituxan, Genentech/Bio-gen Idec), interferon α , and splenectomy.^{2,3} Complications associated with HCL include increased risk of infections and splenic rupture, with infections being the most common cause of death.⁷ We plan to observe our patient without therapeutic intervention until she develops symptoms or worsening cytopenias.

Conclusion

The incidence of HCL in breast cancer patients treated with chemotherapy and hormonal therapy has not been well described in the literature. Alkylating agents, antimetabolites, taxanes, and topoisomerase II inhibitors are known to cause secondary myelodysplastic syndromes (MDS) and acute leukemia, but an association with HCL has not been reported.¹⁰⁻¹⁶ As such, the possibilities for the etiology of this patient's HCL are either de novo or related to prior treatment.^{17,18} In conclusion, we report the first case of HCL in a patient treated with chemotherapy and hormonal therapy for breast cancer. We raise the possibility of prior therapy-related HCL in this individual.

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Review

Hairy Cell Leukemia Following a Diagnosis of Breast Cancer: Is There a Relationship?

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Hairy cell leukemia (HCL) is a rare, indolent, B-cell lymphoproliferative disorder that is characterized by pancytopenia, absolute monocytopenia, splenomegaly, and recurrent infections. Bouroncle¹ first described this clinical entity, which she termed *leukemic reticuloendotheliosis*, in 1958. Schrek and associates² further defined the morphology of HCL by describing abnormal mononuclear cells with their elongated, thin cytoplasmic projections, which they termed *hairy* cells. There is a strong male predominance of 3.44 to 1.³ Jewish men have a significantly increased risk of HCL compared to Protestant men, although no increased risk was seen for Jewish women.⁴ More recently, whole-exome gene sequencing has identified the *BRAF V600E* mutation in most HCL patients, suggesting disease-specific oncogene dependence.⁵

HCL remains a largely incurable, though highly treatable, disease.⁶ Generally, treatment is started in symptomatic patients or those with significant cytopenias, including hemoglobin less than 10 g/dL, platelet count less than $100 \times 10^9/L$, and/or neutrophils less

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than $1.0 \times 10^9/L$.⁷ Splenectomy was the treatment of choice until the mid 1980s. Quesada and colleagues were the first to describe responses induced by interferon α in HCL patients, although further studies revealed a disappointingly low incidence of complete response, as well as a brief response duration.^{8,9} Subsequently, 2 nucleoside analogues, 2'-deoxycoformycin (pentostatin) and 2-chlorodeoxyadenosine (cladribine), were both found to induce long-lasting complete remissions in the majority of HCL patients.⁹⁻¹¹

Mikler and coworkers report the diagnosis of HCL in a 65-year-old woman more than 2 decades after an initial diagnosis of invasive breast cancer.¹² She was originally treated with 2 anti-metabolites and an alkylator, followed by a platinum and taxane at disease recurrence approximately 2 years predating her HCL diagnosis. The risk of second malignancies in patients with HCL has been published with widely varying results. The majority of studies have focused on second malignancies following the diagnosis of HCL. Au and associates reported on second cancers in as many as 31% of HCL patients followed for 20 years in British Columbia.¹³ Three reports^{11,13,14} have suggested an increased incidence of second malignancy, while 2 other studies do not corroborate these findings.^{15,16} Risk factors for developing a second malignancy following the diagnosis of HCL are thought to include a lower median age at diagnosis, coupled with longer survival rates with contemporary treatment.⁴ The oncogenic effect of systemic therapy has been questioned as well.¹⁷ Chronic lymphocytic leukemia, a much more common lymphoproliferative disorder, has also been associated with an increased incidence of secondary neoplasms.¹⁸ However, these explanations do not account for patients diagnosed with primary cancers prior to their HCL diagnosis.

Three studies suggest a greater risk of a different primary cancer predating the diagnosis of HCL. In an epidemiologic study of HCL in Los Angeles County, 27% of patients had another primary malignancy diagnosed at least 1 year prior to their HCL diagnosis, including 4 female patients diagnosed with breast cancer. HCL patients were more than twice as likely as other cancer patients to have an additional malignancy.⁴ A population-based study of HCL in Israel identified 6% of patients with a cancer diagnosed before their HCL. In the 2 female patients with a cancer antecedent to their HCL, both were diagnosed with breast cancer.¹⁹ In the Scripps Clinic experience, 11% of patients were diagnosed with an antecedent malignancy predating cladribine treatment for HCL. In this single-institution series, 3 women had a prior diagnosis of breast cancer.¹⁷ Of note, those patients with a malignancy predating their HCL diagnosis had a 3.7-fold increased risk of developing an additional malignancy compared with those who did not.¹¹ There is no

information regarding what these breast cancer patients received in terms of systemic therapy. Bernstein and associates proposed that patients who develop HCL may have an underlying, impaired immune function, which may be partly responsible for malignancies predating HCL.⁴ It has been postulated that impaired T-cell function and deficient natural killer cell activity may compromise immune surveillance and thereby predispose patients to second malignancies.^{20,21}

The report by Mikler and colleagues¹² correctly specifies that no causal association has been directly identified between the systemic agents this patient received for her invasive breast cancer and the subsequent development of HCL, though studies have clearly linked breast cancer therapy with treatment-related acute leukemia and myelodysplastic syndromes.^{22,23} While it is impossible to rule out her prior systemic therapy being the etiology predisposing her to HCL, it seems more probable that this reflects a de novo HCL diagnosis. We agree with their decision to withhold therapy and instead perform active surveillance in this HCL patient without current treatment indications.

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