

Case Report

# A Unique Hairy Cell Leukemia Variant

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## Keywords

Hairy cell leukemia variant · B-cell lymphoid leukemia

## Abstract

A 65-year-old woman presented with easy bruising, left upper quadrant pain, decreased appetite, and weight loss. She had splenomegaly and lymphocytosis (lymphocyte count of  $11.6 \times 10^9/l$ ), with remarkably abnormal appearing morphology. Her hemoglobin and platelet counts were normal. Peripheral blood flow cytometry revealed a monoclonal B-cell population expressing CD11c, CD25, CD19, CD20, and CD103. An initial diagnosis of hairy cell leukemia (HCL) was made, and the patient was treated with a standard 5-day course of cladribine. However, her lymphocytosis improved transiently, with a relapse 4 months later. There was no improvement in her splenomegaly. An HCL variant (HCL-v) was considered based on her resistance to treatment with a purine nucleoside analog. A subsequent splenectomy improved symptoms. Two years after, the patient suffered a relapse and underwent 6 cycles of CHOP-R (cyclophosphamide, hydroxydaunomycin, oncovin, prednisone, and rituximab), achieving partial remission. While under observation, she progressed with lymphocytosis 6 months later and was treated with pentostatin. There was no significant improvement in her disease, and she died 8 weeks following treatment initiation. HCL-v is a clinically more aggressive mature B-cell lymphoma than HCL with worse splenomegaly, higher lymphocyte counts, and resistance to typical HCL therapy with purine nucleoside analogs. Early recognition of HCL-v in the history, physical examination, and investigations with morphology and flow cytometry is key to patient management. Further, as in our case of HCL-v, cell morphol-

ogy can be distinctly atypical, with large nucleoli and extremely convoluted nuclei. The distinction between HCL and HCL-v is important as HCL-v patients require more aggressive therapy and closer follow-up.

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## Introduction

Hairy cell leukemia (HCL) is a rare mature B-cell lymphoid leukemia with an indolent course [1]. It accounts for approximately 2% of all leukemias, has a male-to-female ratio of 4:1, and a median age at diagnosis of 58 years [2]. Clinically, patients typically present with pancytopenia, splenomegaly, and often absolute monocytopenia. Morphologically, HCL in peripheral blood is characterized by mature B cells with circumferential cytoplasmic projections resembling hairs. Histologically, HCL cells in bone marrow biopsies have abundant cytoplasm surrounding the nuclei, resembling a fried egg.

In comparison to HCL, patients with an HCL variant (HCL-v) are often older, present with lymphocytosis, and are resistant to common treatments using purine nucleoside analogs [3, 4]. Typically, patients with HCL-v are treated with more aggressive therapies often containing anthracycline and rituximab [5]. Morphologically, HCL-v presents similar to HCL, with small-to-medium cells with abundant cytoplasm showing fine or poorly defined hairy projections [6]. Further, in some cases of HCL-v, as in the patient describe here, morphology can be very striking and differ from that reported in the literature. This makes a differentiation between HCL and HCL-v difficult using morphology alone.

## Case Description

A 65-year-old Caucasian woman presented with occasional left upper quadrant pain, decreased appetite, and had lost approximately 10 pounds. The patient had several comorbidities, including chronic obstructive pulmonary disease with ongoing smoking, hypercholesterolemia, gastrointestinal reflux disease, and a history of cholecystitis. She also complained of chronic easy bruising on the extensor surface of her arms. Splenomegaly was noted on examination.

Initial bloodwork showed a leukocyte count of  $37.3 \times 10^9/l$ , a hemoglobin level of 148 g/l, a mean corpuscular volume of 93 fl, a platelet count of  $152 \times 10^9/l$ , with a neutrophil count of  $5.97 \times 10^9/l$ , a lymphocyte count of  $11.6 \times 10^9/l$ , and a monocyte count of  $19.4 \times 10^9/l$ . A peripheral blood film revealed abnormal large lymphocytes with abundant cytoplasm and hairy projections and nuclei that were extremely convoluted and contained large nucleoli. Peripheral blood flow cytometry demonstrated a monoclonal B-cell population positive for CD11c, CD19, bright CD20, CD25, and CD103, expressing kappa light chains. She was diagnosed with HCL and treated with cladribine over 5 days with very little response. The patient's lymphocytosis improved transiently and recurred 4 months later, and her spleen did not shrink significantly after treatment.

She was referred and investigated 4 months after treatment. The physical examination revealed no palpable adenopathy, with a palpable spleen 6 cm below the costal margin. Bloodwork revealed a hemoglobin level of 134 g/l, a leukocyte count of  $54.9 \times 10^9/l$ , and a platelet count of  $114 \times 10^9/l$ . A bone marrow cytogenetic examination revealed abnormalities in chromosomes 1 and 7. An HCL-v was considered based on this atypical presentation

(see discussion below). The patient underwent a splenectomy several months after this investigation, which improved the symptoms.

Two years after, the patient suffered a relapse and underwent 6 cycles of CHOP-R (cyclophosphamide, hydroxydaunomycin, oncovin, prednisone, and rituximab), achieving partial remission. While under observation, she again developed lymphocytosis 6 months later and was treated with several courses of pentostatin. There was no significant improvement in her disease, and she died 8 weeks following the initiation of this treatment.

## Discussion

This case represents an extremely rare hematological malignancy: a morphologically distinct case of HCL-v unresponsive to multiple therapies. The patient was unresponsive to cladribine, the typical first-line HCL therapy. A splenectomy is often performed in HCL-v, with two thirds of patients achieving clinical remission lasting 1–10 years, with a median of 4 years [7]. In our case, a relapse occurred 2 years later that was somewhat responsive to CHOP-R and unresponsive to pentostatin.

It is essential to distinguish HCL from HCL-v and other indolent B-cell lymphomas due to the difference in management. Typically, purine nucleoside analogs such as cladribine and pentostatin have an excellent effect on HCL, with high complete remission rates with long-term progression-free survival. Diagnosis of HCL and HCL-v requires a thorough clinical history, physical examination, and investigations including the use of peripheral blood and bone marrow morphology, peripheral blood flow cytometry, and newer molecular diagnostics. HCL-v makes up 10% of all these cases and presents in older patients with more severe disease and higher lymphocytosis.

Peripheral blood morphology of HCL and HCL-v typically demonstrates mature small-to-medium lymphocytes and circumferential cytoplasmic projections. Splenic marginal zone lymphoma with villous lymphocytes is another indolent B-cell lymphoma that may be mistaken for HCL as it also has cytoplasmic projections. However, in splenic marginal zone lymphoma with villous lymphocytes, there are often unipolar or bipolar projections rather than an arrangement in a circumferential pattern [8]. In both HCL and HCL-v, the nucleus is often regular, taking up the majority of the cell. A prominent nucleolus can be seen in many cases of HCL-v [6] but is absent in other reported cases [9]. The shape of the nucleus in 'typical' HCL-v is regular or bilobed, but our case presented with extremely convoluted nuclei (fig. 1). This variability makes the differentiation between HCL and HCL-v difficult using morphology alone.

Due to marrow fibrosis associated with HCL, peripheral blood flow cytometry is the key to diagnosis and distinguishes it from other variants and indolent B-cell lymphomas. The typical immunophenotype of HCL cells show mature B-cell markers CD19 and CD20 with coexpression of CD11c, CD25, CD103, and CD123. In contrast, HCL-v often expresses CD11c and CD103, but is negative for CD25 and CD123 [6, 9]. Our case had a variant of this HCL-v immunophenotype in that CD25 was positively expressed. Another modality, although no longer available in most centers, is tartrate-resistant acid phosphatase on bone marrow immunohistochemistry. Tartrate-resistant acid phosphatase is positive in HCL but negative in HCL-v. Further, molecular diagnostic analysis, if available, for the *BRAF* V600E mutation is present in essentially all cases of HCL but not in HCL-v [10]. An accurate diagnosis of HCL-v will require a combination of all these assessments where available.

Currently, the front-line management of HCL and HCL-v, as mentioned above, is treatment with a single-agent purine nucleoside analog. Cladribine can be given as a single 5-day course of daily 2-hour intravenous infusions with excellent response rates. Relapses after several years may again be treated successfully, with a course of cladribine. Due to the rarity of this disease and the limited number of studies, no clear second or subsequent lines of therapy are superior to retreatment with cladribine or any other choice. Further options for relapsed disease include other purine nucleoside analogs such as pentostatin, monoclonal antibody against CD20, rituximab, monoclonal antibody against CD52, alemtuzumab, and combination chemotherapies such as CHOP or CHOP-R [11]. Newer therapies may include treatment with a recombinant immunotoxin with an anti-CD22 variable domain fused to a truncated *Pseudomonas* endotoxin, moxetumomab pasudotox [12]; a Bruton's tyrosine kinase inhibitor, ibrutinib [13], or even molecular targeting of the *BRAF* V600E mutation, vemurafenib [14].

### Conclusion

HCL-v is a clinically more aggressive mature B-cell lymphoma than HCL, with worse symptoms of splenomegaly, higher lymphocyte counts, and lacking the response to typical HCL therapy with purine nucleoside analogs. Early recognition of this variant in the history, physical examination, and investigations with morphology and peripheral blood flow cytometry is the key to patient management. Further, as in our case of HCL-v, the peripheral blood morphology can be distinctly abnormal, with large nucleoli and extremely convoluted nuclei. The distinction of HCL-v is important, as these patients often require a more aggressive therapy and a closer follow-up.

### Statement of Ethics

Written informed consent was obtained at the time of initial bone marrow investigation and therapy. IRB approval was not required for the described case. No human or animal experiment was performed.

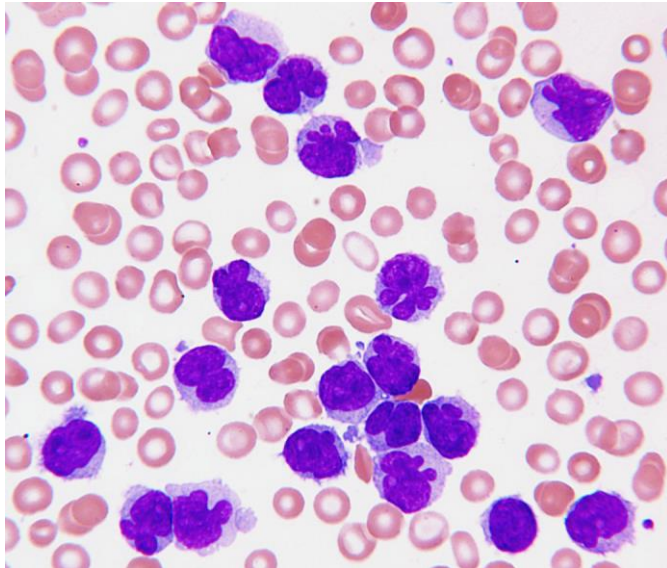
### Disclosure Statement

The authors have no financial or other conflicts of interest to declare. There was no funding source.

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**Fig. 1.** Peripheral blood demonstrating numerous lymphoid cells with extremely convoluted nuclei with prominent nucleoli and cytoplasmic irregular circumferential projections.