Case Report

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Hairy cell leukemia in a 51-year-old Syrian male: a case report

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Introduction: Hairy cell leukemia (HCL), a rare B-cell lymphoproliferative disorder, originates from the splenic marginal zone B cell. However, diagnosis can be particularly challenging in resource-limited settings where advanced tests are not readily available. Misclassification may result in non-selective chemotherapy exposure and increased toxicity. Reporting such cases is important to highlight diagnostic challenges in resource-limited countries.

Case presentation: A 51-year-old male presented with abdominal discomfort, weight loss, and fatigue. Examination revealed splenomegaly. Initial evaluation suggested lymphoplasmacytic lymphoma, and the patient received multi-agent chemotherapy (R-CHOP), which was complicated by severe cytopenias. Splenectomy was performed, yielding a spleen weighing 2216 g. Histopathology and immunophenotyping confirmed hairy cell leukemia. Molecular testing for BRAF V600E (the gold standard for diagnosis) was unavailable due to financial and infrastructural restrictions. Treatment was switched to single-agent cladribine, resulting in marked clinical improvement and a significant reduction in chemotherapy adverse effects. Follow-up imaging and blood work revealed that the patient was in complete remission.

Clinical discussion: In our case, we emphasize the diagnostic challenges of HCL in low-resource environments and clarify how the empirical administration of R-CHOP chemotherapy led to unnecessary toxicity and suboptimal outcomes. Splenectomy played a crucial diagnostic role when bone marrow tests were directional but not conclusive. We provide an extensive review of differential diagnoses, immunophenotypic hallmarks, what lies beyond the BRAF V600E mutation, and therapeutic approaches.

Conclusion: Early recognition of HCL is crucial to avoid delayed optimal therapy and to enhance patient outcomes. This case emphasizes the critical role of morphology and immunophenotyping in confirming HCL, especially in resource-limited countries.

Keywords: BRAF, case report, hairy cell leukemia, immunohistochemistry, lymphoma, resource-limited countries

Introduction

Hairy cell leukemia (HCL), a rare B-cell lymphoproliferative disorder first recognized in 1958 as leukemic reticuloendotheliosis, remains a compelling subject of clinical and molecular investigation due to its unique biological features and evolving therapeutic landscape. The cell of origin for HCL is thought to be the splenic marginal zone B cell. The characteristic "hairy" projections result from impaired BRAF activity, and this hair-like morphology enhances leukemic cells' interactions with their microenvironment[1,2].

The identification of the BRAF V600E mutation in 2011 marked a watershed moment, as this genetic alteration was detected in more than 95% of classic HCL cases, offering both diagnostic clarity and therapeutic targets[2].

Globally, HCL accounts for 2–3% of all leukemias. The annual incidence is 2.9–4.7 cases per million. It predominantly affects middle-aged Caucasian men, with a male-to-female ratio of 4:1[2,3].

Clinical hallmarks at diagnosis include pancytopenia and splenomegaly without lymphadenopathy. However, the disease's heterogeneity is increasingly apparent. An increased risk of infection is a very common complication. This is due to monocytopenia, neutropenia, and altered T-cell function[1,4].

Definitive diagnosis rests on a triad of morphologic identification of villous lymphocytes, a characteristic immunophenotype (CD20+, CD11c+, CD25+, CD103+, CD123+), and molecular confirmation of BRAF V600E, and is usually negative for CD5, CD23, CD10, and CD27[2,3].

Therapeutic strategies have undergone profound development, which has clearly improved patient outcomes. The

HIGHLIGHTS

- Diagnosis of hairy cell leukemia (HCL) confirmed by morphology/immunophenotype, overcoming the limits of BRAF testing.
- Initial misdiagnosis as splenic lymphoma led to an inappropriate R-CHOP regimen.
- Clinical utility of splenectomy confirmed in HCL diagnosis after failed chemotherapy.
- Patient achieved radiological remission and blood count recovery with first-line cladribine post-splenectomy.

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remarkable efficacy of purine analogs (PAs), such as cladribine and pentostatin, has led to 5-year overall survival rates exceeding 85%. Furthermore, the addition of rituximab to PAs in the latest chemoimmunotherapy regimens can deepen and prolong responses, while BRAF inhibitors have shown promise in the management of relapsed or refractory disease[4].

In our case, we present a patient with HCL diagnosed through the integration of morphological and immunophenotypic features. Although molecular testing for the BRAF mutation is considered the gold standard for diagnosis, in our setting, it was not available due to infrastructural and financial limitations. This case emphasizes the critical role of morphology and immunophenotyping in confirming HCL, especially in resource-limited countries.

This case report has been presented in line with the SCARE checklist[5].

Case presentation

A 51-year-old male with a 20-pack-year smoking history and no alcohol use presented with mild abdominal discomfort, weight loss, and fatigue. Past history included a hemorrhoidectomy 13 years prior. Examination revealed splenomegaly palpable below the left costal margin without hepatomegaly, generalized lymphadenopathy, or ascites. Mild left flank tenderness was noted.

Initial laboratory workup on 22 November 2023 demonstrated pancytopenia: WBC 2.3 × 10^9/L, hemoglobin 7 g/dL, and platelets 87 × 10^9/L. Lactate dehydrogenase levels were within normal limits. Protein electrophoresis revealed a polyclonal increase in gamma globulins with a low Albumin/Globulin (A/G) ratio, consistent with chronic inflammation but not monoclonal gammopathy. A CT scan showed massive splenomegaly (10.5 × 18 cm) and para-aortic lymphadenopathy (largest 17 mm), without hepatomegaly or osseous lesions.

Bone marrow biopsy on 7 December 2023 revealed CD20+, LCA+, CD3–, CD138 focally positive, supporting a diagnosis of lymphoplasmacytic lymphoma. Further studies confirmed pancytopenia with negative Coombs testing, normal renal and liver function, and mildly elevated CRP. The patient was diagnosed with splenic lymphoma and admitted for chemotherapy.

He initially received CVP (cyclophosphamide, vincristine, prednisone) but developed severe pancytopenia requiring transfusions. Subsequently, alternating follow-up CT revealed persistent splenomegaly (17 × 10 × 18 cm), mild hepatomegaly, and a small pulmonary scar nodule. Splenectomy was performed, yielding a spleen weighing 2216 g and measuring 7 × 14 × 21 cm (Fig. 1A). Histopathology and immunophenotyping confirmed HCL with CD20 and Bcl-2 positivity, CD103 positivity, CD5 negativity, and a low Ki-67 proliferation index of 10% (Fig. 1B–D, Fig. 2).

Cycles of CVP and R-CHOP were administered from January to April 2024, with supportive Neukin (300 mcg) at each cycle. Therapy was complicated by transient renal dysfunction, but six cycles of R-CHOP were completed by June 2024.

Postoperatively, the patient developed an infiltrative retroperitoneal mass with chronic portal vein thrombosis and a stable hepatic cavernous hemangioma. Weekly cladribine (10 mg) was initiated, with seven cycles completed by April 2025.

Follow-up imaging and blood work demonstrated near-complete regression of thoracic and abdominal lymphadenopathy, stable hepatic hemangioma, and no new lesions. Bone window evaluation showed no osseous involvement. These findings were

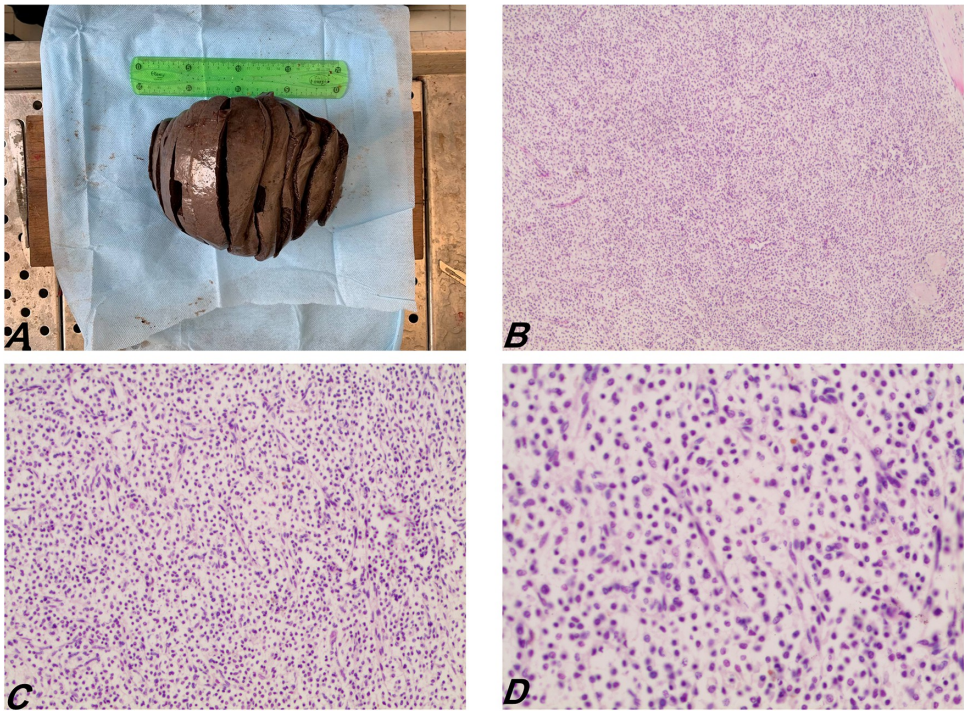

Figure 1. Gross appearance and histopathological findings of the resected spleen (H&E stain). (A) Gross appearance of the resected Spleen weighing 2216 g and measuring 7 × 14 × 21 cm, demonstrating massive splenomegaly. (B) 40× magnification. (C) 100× magnification. (D) 200× magnification. The H&E-stained microscopic images reveal atypical lymphocytes with round central nuclei and abundant clear cytoplasm.

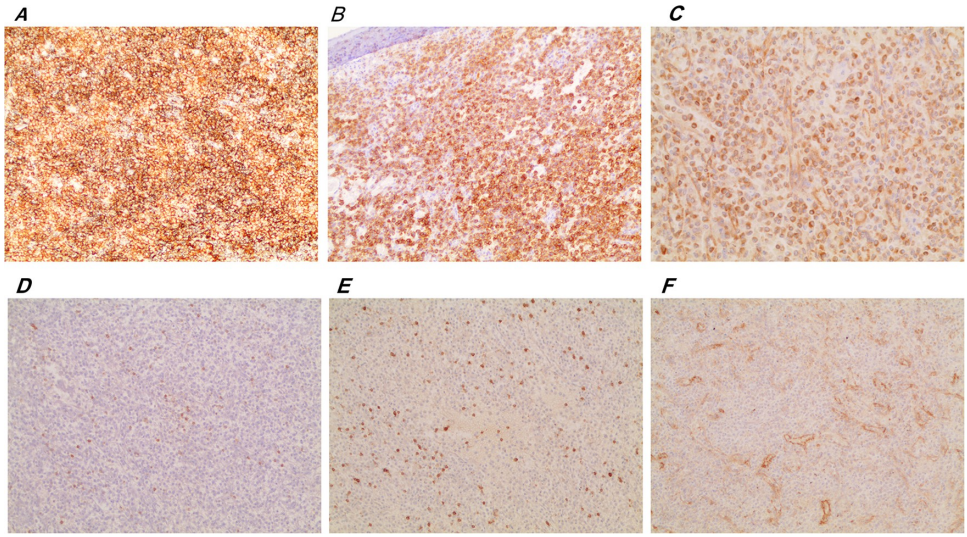

Figure 2. Immunohistochemical (IHC) profile of the splenic biopsy. (A) CD20 positivity. (B) Positivity for CD103 (the most specific marker for classic HCL). (C) BCL2 positivity. (D) CD5 negativity. (E) CD3 negativity. (F) CD10 negativity. This immunohistochemical profile supports the diagnosis and rules out other B-cell lymphomas.

consistent with radiological remission of HCL. The patient remains under surveillance with 3-monthly follow-ups.

A summary of the patient's clinical journey is presented in the timeline (Fig. 3).

Discussion

HCL accounts for about 2% of all new leukemia cases. It predominantly affects middle-aged Caucasian men, with a male-to-female ratio of 4:1[2,3].

Classic HCL presentation is characterized by splenomegaly (80–90% of cases) and pancytopenia, with a near-universal monocytopenia. Common symptoms include fatigue, frequent infections, and mild bleeding. There can also be rare but crucial presentations, such as spontaneous splenic rupture and rheumatic symptoms (such as transient polyarthritis), which may lead to misdiagnoses[6,7].

While the detection of the BRAF V600E mutation remains the diagnostic gold standard for confirming HCL and differentiating it from its morphological mimics[2], its clinical utility is often constrained by economic barriers. In resource-limited settings, the high cost of molecular profiling and immunohistochemical assays – typically borne as out-of-pocket expenses – poses a significant challenge to achieving a definitive diagnosis and implementing precision management[8].

In this case, financial barriers directly restricted the scope of the initial diagnostic workup, leading to a misclassification of the malignancy and the subsequent initiation of an inappropriate treatment protocol. This case centerpieces a critical diagnostic pitfall, highlighting the persistent difficulties of accurately categorizing splenic B-cell neoplasms in settings where resources are limited. It underscores a harsh clinical reality: when advanced diagnostics are inaccessible, even the most standard of care decisions can be compromised by the lack of definitive molecular data.

During the initial workup, the bone marrow biopsy demonstrated positivity for CD20 and LCA, along with focal expression of CD138. This focal CD138 staining, being a hallmark of plasmacytic differentiation, strongly skewed the diagnostic impression toward lymphoplasmacytic lymphoma (LPL)[9].

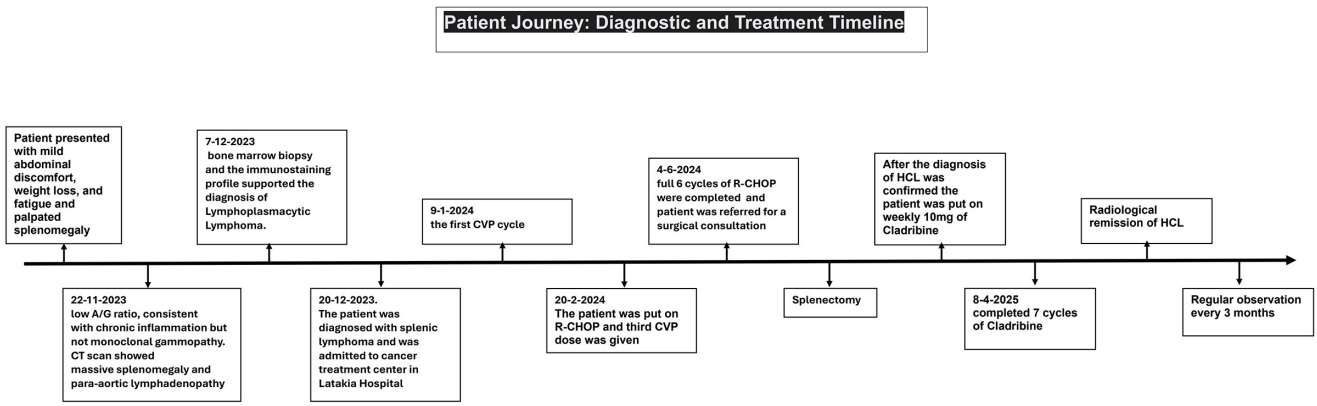

Figure 3. Time line of the patient's clinical journey from admission to complete remission.

Table 1

Differential diagnostic features of classic HCL and its mimickers[2].

Diagnostic feature	Classic HCL	HCL-V/SBLPN	SDRPL	SMZL
Clinical presentation	Pancytopenia, splenomegaly	Leukocytosis, splenomegaly	Leukocytosis, splenomegaly	Leukocytosis, splenomegaly
Cytological features	Circumferential «hairy» projections, inconspicuous nucleoli	Circumferential but shorter projections, prominent nucleoli	Broad-based polar projections, inconspicuous nucleoli	Shorter polar projections, inconspicuous nucleoli
Distinctive immunomarkers	CD11c+, CD103+, CD123+, CD25+	CD11c+, CD103+, CD123–, CD25–	CD11c+, CD103±, CD123–, CD25–	CD11c +, CD103–, CD123–, CD25±
Distinctive genetic mutation	BRAF V600E (90_100%)	MAP2K1 (30-40%)	BCOR, CCND3	KLF2, NOTCH2
Treatment response	Very good to purine analogs	Poor or primarily refractory to purine analogs	Good to splenectomy	Good to splenectomy
Prognosis	Excellent, long-term survival	Aggressive, median survival 9 years	Good, long-term survival	Good, long-term survival

However, the patient's clinical presentation – marked by massive splenomegaly and polyclonal gammopathy – necessitated a broader differential within the spectrum of "splenic lymphomas."

As outlined in Table 1, the most common diagnostic mimics of classic HCL include splenic marginal zone lymphoma (SMZL), splenic b-cell lymphoma/leukemia with prominent nucleoli (SBLPN, previously known as HCL-V), and splenic diffuse red pulp small b-cell lymphoma (SDRPL)[2].

The distinction between these entities is based on the careful integration of morphological and immunophenotypic features, as they present with similar clinical features but have different biological behaviors.

Regrettably, due to the prohibitive lack of access to confirmatory molecular diagnostics – specifically the MYD88 L265P and BRAF V600E mutations – a definitive distinction between LPL and HCL could not be established. Consequently, the patient was initiated on an empirical R-CHOP regimen. While such intensified multi-agent chemotherapy was historically the mainstay for bulky or unclassified B-cell lymphomas, it is increasingly regarded as suboptimal and excessively toxic in the modern era. Had a definitive diagnosis of LPL been feasible, clinical guidelines would have favored transition toward targeted, low-toxicity interventions, such as Bruton tyrosine kinase (BTK) inhibitors (e.g., ibrutinib) or the bendamustine–rituximab backbone. These contemporary regimens offer superior efficacy and a more favorable safety profile, circumventing the profound, transfusion-dependent cytopenias typically secondary to conventional R-CHOP therapy[10].

The diagnostic dilemma in our case was ultimately resolved through a therapeutic splenectomy. Histopathological examination of the splenic tissue revealed diffuse involvement of the red pulp, a distinct infiltration pattern that definitively excluded SMZL, which characteristically originates in the white pulp[1]. Furthermore, subsequent comprehensive immunophenotyping demonstrated robust expression of CD103 and CD20, coupled with the absence of CD5. These findings solidified the diagnosis of classic HCL, while effectively ruling out LPL and other morphological mimics. Establishing this definitive diagnosis facilitated the timely administration of cladribine, a highly specific and potent purine analog for HCL. This targeted intervention resulted in a rapid clinical recovery and significantly minimized the patient's morbidity[8].

A summary of the diverse therapeutic strategies for HCL is presented in Table 2, highlighting the molecular targets and clinical indications for both established and emerging drugs, to provide a clearer perspective on modern disease management.

This case underscores a pivotal clinical lesson: in settings where economic constraints limit access to molecular technologies, meticulous morphological analysis coupled with robust immunophenotyping remains indispensable. Such diagnostic rigor is critical to preventing the pitfalls of misclassification and ensuring patients are shielded from the unnecessary toxicity of suboptimal empirical therapies.

Applying the prognostic criteria summarized in Table 3 to the present case, the patient exhibited a nuanced profile of clinical markers. Although certain features, specifically his male gender and the presence of massive splenomegaly (18 cm), are traditionally

Table 2

Overview of current and emerging therapeutic strategies for HCL[8].

Treatment type	Drug(s)	Target(s)	Clinical setting
Purine analogs	Cladribine, pentostatin	Nucleotide analogs	First-line, late relapse
Immunochemotherapy	Cladribine + rituximab	Nucleotide analogs & CD20	First-line, late relapse
BRAF/MEK inhibitors	Vemurafenib + rituximab, Dabrafenib + trametinib	BRAF V600E, MEK	Early relapse, first-line eligible patients
Immunotoxins	Moxetumomab pasudotox	CD22	Multiple relapse
BTK inhibitors	Ibrutinib	BTK	Relapse, HCL-V
Bcl-2 inhibitors	Venetoclax	Bcl-2	Under investigation (especially in HCL-V)
Emerging therapies	CAR T-cells, ROR1/2 antibodies	CD22, ROR1/2	Under clinical investigation
Bridging therapy	Interferon alpha	Anti-proliferative	Contraindications to purine analogs

Table 3

Key prognostic factors and their clinical impact in HCL[4,11].

Factor	Feature	Clinical impact
Clinical	Significant splenomegaly	Worse prognosis, shorter relapse-free survival
Clinical	Elevated LDH	Worse prognosis, shorter relapse-free survival
Gender	Male	Shorter time to next treatment compared to females
Immunophenotype	CD38+	Poor prognosis, shorter time to next treatment
Molecular	Unmutated IGHV	Poor prognosis, cladribine resistance, shorter overall survival
Molecular	Mutated TP53	Very poor prognosis, resistance to purine analogs
Molecular	MAP2K1 mutation	Poor prognosis, shorter relapse-free survival

indicative of an aggressive clinical course and a shorter interval to subsequent treatment, other indicators point toward a more promising trajectory. Notably, the maintenance of normal LDH levels and the attainment of a complete clinical remission following Cladribine therapy suggest a favorable long-term prognosis. However, a notable diagnostic constraint remained: the inability to assess key molecular prognosticators, such as IGHV mutation status or the presence of TP53 and MAP2K1 mutations[4,11].

Conclusion

This case underscores the significant diagnostic challenges of splenic B-cell lymphomas in resource-limited settings, where the lack of advanced molecular testing can lead to misclassification and the use of toxic empirical therapies. Our findings highlight that a definitive diagnosis remains achievable through the strategic use of accessible tools. Specifically, the combination of thorough histopathological evaluation – centered on the pivotal role of diagnostic splenectomy – and detailed immunophenotyping is essential to distinguish classic HCL from its mimics. Ultimately, leveraging these robust, conventional methods is critical to avoiding unnecessary treatment-related toxicity and ensuring the timely administration of targeted therapies like cladribine, which yield excellent clinical outcomes even when molecular profiling is out of reach.

Ethical approval

Ethical approval was not required for this case report in accordance with the policies of our institution and national/local guidelines.

Consent

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request. No identifiable patient information is included in this manuscript.

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Author contributions

Z.D.: Conceptualization; investigation; data curation; writing – original draft. M.R.: Conceptualization; investigation; project administration; writing – original draft. I.A.: Investigation; data curation; writing – original draft. I.A.: Resources; supervision; validation; writing – review & editing. K.A.-T.: Supervision; validation.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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Data availability statement

All data relevant to the case have been uploaded.

Methods

This case has been reported in line with the SCARE criteria.

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