

Hairy cell lymphoma: a potentially under-recognized entity

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Abstract

Hairy cell leukemia (HCL) is a low grade B-cell lymphoproliferative disorder that typically presents with splenomegaly, cytopenias, and diffuse bone marrow infiltration. There have been few cases in the literature of HCL presenting as lymphomas in extra-nodal locations, such as soft tissues and bones without circulating leukemic cells, splenomegaly, or iliac crest bone marrow involvement. We present an additional case presenting as a thoracic mass, and discuss potential diagnostic pitfalls and management of these rare cases.

Introduction

Hairy cell leukemia (HCL) is an indolent, mature B-cell lymphoproliferative disorder (B-CLPD) recognized by its near universal presentation of splenomegaly with splenic red pulp involvement, cytopenias with the frequent finding of monocytopenia, bone marrow infiltration with reticulin deposition, and identification of lymphocytes with non-polar, hair-like cytoplasmic projections in the peripheral blood.¹ There have been few previous reports of a lymphomatous variant of HCL, most frequently presenting as a marginal zone-like lymphoma without any other classic features, particularly a leukemic component. We report the fifth case in medical literature and discuss the potential diagnostic pitfalls of this rare entity.

Case Report

A 53-year-old white man developed left chest wall pain and a persistent cough. He had no associated B symptoms or shortness of breath. He had smoked one pack of cigarettes per day for 35 years. There was no family history of cancer. He had age appropriate recommended cancer screening and did not take any medications. A chest X-ray

showed a left anterior chest wall mass, so he was referred to an oncologist.

His physical exam was unremarkable, without any lymphadenopathy or organomegaly. Laboratory testing that included a complete blood count, full chemistry, and a hepatic panel were unremarkable. A computed tomography (CT) scan of the chest revealed two anterior mediastinal soft tissue masses involving the pleura with extension to the chest wall; the larger mass measured 8.7 cm x 4.7 cm. A core needle biopsy of one of the chest wall lesions showed sheets of small to medium sized plasmacytoid lymphoid cells that stained positive for CD20, CD45, cyclin D1, and BCL2 by immunohistochemistry (IHC). There was weak cytoplasmic staining for kappa light chain. IHC staining was negative for keratin AE1/AE3, TTF-1, chromogranin, synaptophysin, CD3, CD5, CD10, and CD23, and CD138.

Fluorescence in situ hybridization (FISH) for BCL2, BCL6, c-Myc, CCND1/IGH [(t(11;14)], and MALT1 showed no rearrangement. Traditional cytogenetics of 20 metaphases revealed a normal 46 XY karyotype without clonal aberrations. Subsequent positron emission tomography (PET) imaging demonstrated uptake only in the chest wall masses, with a maximum standardized uptake value (SUV max) of 11.7 and 14.1. Bone marrow biopsy was unremarkable with normal trilineage hematopoiesis. Serology for hepatitis and HTLV1/2, protein electrophoresis, and lactate dehydrogenase were normal.

He was initially diagnosed as having low-grade marginal zone lymphoma based on the morphologic appearance and non-specific staining pattern. He was treated with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP), but he had no response after 3 cycles; adriamycin was added (R-CHOP) for an additional 3 cycles. Subsequent PET-CT imaging showed no change in size or SUV of the lesions. This led to a repeat biopsy. The malignant cells were consistent with prior IHC staining, but they were also found to be diffusely positive for CD123 and CD200 (Figure 1 and Table 1), dimly positive for BCL-1, and negative for CD56, CD117, LEF1, SOX11, MUM-1, and BCL-6. The Ki-67 proliferation rate was 5%.

The patient was referred to our institution for a second opinion for primary refractory B-cell lymphoma. A comprehensive pathological review was performed. In terms of differential diagnosis, we considered marginal zone lymphoma and lymphoplasmacytic lymphoma on the basis of the lesions' morphology and immunophenotype (CD5-, CD10-, CD23-); we also considered

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Key words: Lymphoma; B-cell lymphoproliferative disorder; splenomegaly; cytopenias; diffuse bone marrow infiltration.

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mantle cell lymphoma on the basis of cyclin D1 expression or a lymphomatous presentation of HCL on the basis of cyclin D1 and CD200 expression in the absence of positive markers for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Mantle cell lymphoma was ruled out by negative FISH testing for t(11;14). As cyclin D1 and CD200 are characteristically expressed in HCL, we performed further stains for HCL. This diagnosis was confirmed by strong expression of annexin A1 and BRAFV600E. Polymerase chain reaction (PCR) identified a BRAFV600E mutation but no MYD88 mutation. The patient was initiated on cladribine therapy with a single 7-day continuous infusion.² Evaluation four weeks after treatment revealed that he had achieved a partial response with near resolution of the chest wall masses and a reduction in the SUV max from 11.7 and 14.1 to 2.0 and 5.6, respectively.

Discussion

Although rare, the diagnosis of classic

HCL (HCL-c) can reliably be made by recognizing a typical clinical and pathological presentation, but diagnosis can be challenging when presentation is atypical. HCL-c lymphoma cells tend to have a predictable pattern of immunohistochemical (IHC) staining, including bright staining for pan B-cell markers CD19, CD20, and CD22; positive staining for CD11c, CD25, CD103 and CD123; and negative staining for CD5, CD10, and CD23.¹ Recently, the near universal prevalence of *BRAFV600E* mutation, identified by IHC staining and/or PCR analysis, has been reported as a disease-defining feature³ and can be used as a confirmatory test. However, a variant form of HCL (HCL-v), accounting for approximately 10% of all cases, with similar morphologic features but a different IHC staining

pattern and a negative *BRAFV600E* mutation status has also been well described. This disease variant does not respond to cladribine therapy like HCL-c.^{4,5} Other unusual presentations of HCL-c involving non-lymphoid, non-reticuloendothelial tissue,⁶ including bones,⁷ soft tissues,⁸ and the brain,⁹ have also been reported; however, these have been in the setting of other classic clinical features of HCL. Occasionally, usually at advanced stages, HCL-c may involve lymph nodes, most often in the abdomen or retroperitoneum.¹⁰ There have been few cases reported so far in the medical literature where HCL presents as an extra-nodal mass (soft tissue or bone), without cytopenias, splenomegaly, bone marrow involvement, or circulating hairy cells,¹¹⁻¹⁶ as outlined in Table 2. As is the pattern with

HCL-c, five of six patients published have been middle-aged males.

The presentation of hairy cell lymphoma without leukemic phase, splenomegaly, or bone marrow involvement could morphologically mimic other non-specific small to moderate sized B-CLPDs. It could have been misdiagnosed as a mantle cell lymphoma given weak cyclin D1 staining, though the lack of CCND1/IGH translocation excluded this possibility. Morphologically, it may appear similar to a lymphoplasmacytic lymphoma, and rarely, it may even have associated paraprotein production; however negative results from *MYD88* mutation testing can help exclude this. It could also be misdiagnosed as an atypical small lymphocytic lymphoma (SLL) due to the strong CD200 staining;

Table 1. Diagnostic clues and confirmatory pathologic findings.

| Clinical clues | Pathologic clues | Confirmatory pathologic findings |
|--|--|---|
| A low-grade lymphoma in extranodal locations resistant to standard lymphoma regimens | Lymphoplasmacytic morphology | Expression of CD25, CD103, CD200, CD123, Annexin A1 |
| | Cyclin D1 expression with negative FISH for t(11;14) | Positive <i>BRAF</i> stain |
| | CD200 expression without CD5 and CD23 expression | Positive <i>BRAFV600E</i> mutation |

Table 2. Comparison of reported cases of lymphomatous presentation of Hairy cell leukemia without involvement of bone marrow, splenomegaly, or cytopenias.

| | Waxman 1983 ¹¹ | Lal 2002 ¹⁴ | Osman 2012 ¹² | Morgan 2014 ¹⁵ | Yonal-Hindilerden, 2015 ¹⁶ | Liu 2015 - Case 2 ¹³ | Current Case |
|---------------------------|---------------------------|--|--|--|---|---|---|
| Age, gender | 39, male | 45, male | 39, male | 49, female | 55, male | 40, female | 53, male |
| Location of disease | Parotid mass | Bilateral femurs | Right sacral ala | Breast | Right femur, multiple other bony lesions | Right submandibular mass | Right chest pleural based masses |
| Initial diagnosis | Hairy cell leukemia | Hairy cell leukemia | Hairy cell leukemia | Hairy cell leukemia | Hairy cell leukemia | Mantle cell lymphoma | Marginal zone lymphoma |
| Treatment | Surgery, radiation | Cladribine | Cladribine | None ("watch and wait") | Radiation, cladribine | Cladribine - Diagnosis revised prior to treatment | 3 cycles R-CVP, 3 cycles R-CHOP → Cladribine |
| Positive markers, IHC | Not reported | CD20, CD45, TRAP | CD20, PAX5, BCL2, TRAP, CD72 (DBA44), CD25, cyclin D1, kappa | CD10, CD20, CD25, CD43, CD103 (subset), CD123, cyclin D1, LCA, annexin A1, TRAP, DBA.44, BRAFV600E | CD11c, CD20, CD68, CD79a, LCA, TRAP, annexin A1 | CD10, CD11c, CD20, CD25, BRAFV600E, annexin A1, cyclin D1, TRAP | CD11c, CD20, CD25, PAX-5, CD45, CD56, CD117, CD123, CD200, cyclin D1, BCL-2, kappa, annexin A1, BRAFV600E, TRAP, DBA.44 |
| Positive markers, flow | Not reported | CD11c, CD19, CD20, CD25, CD103, kappa, FMC-7 | Not performed | Not reported | Not reported | Not reported | Not performed |
| Negative markers, IHC | Not reported | CD3 | CD10, CD5, CD117, CD138, CD56, CD43, MPO, lambda | CD3, CD5, CD23, CD34, MPO, AE1/AE3, S100, ER, PR, HER2 | Not reported | CD5, CD123, SOX11 | CD3, CD5, CD10, CD23, CD138, LEF1, SOX11, MUM-1, BCL-6 |
| Negative markers, flow | Not reported | Not specified | Not performed | Not reported | Not reported | Not specified | Not performed |
| CD200 expression | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Positive |
| <i>BRAFV600E</i> mutation | Not reported | Not reported | Positive | Positive | Positive | Positive | Positive |

IHC: immunohistochemistry

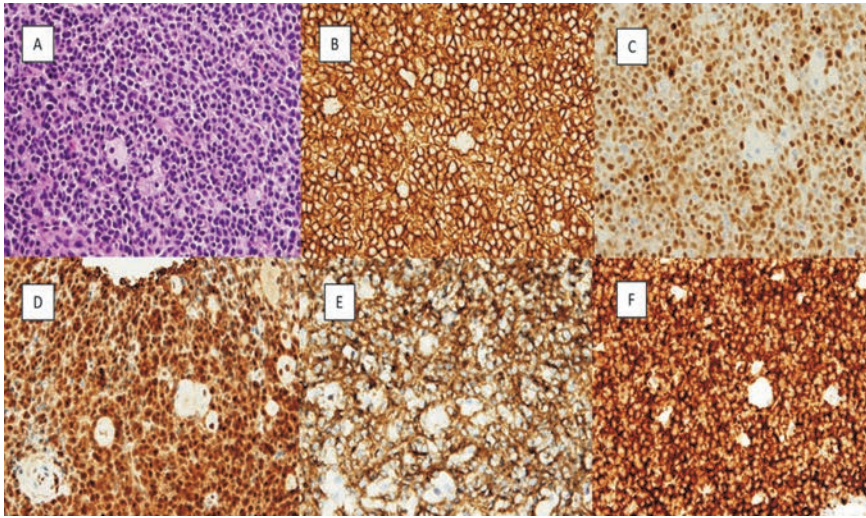


Figure 1. Diagnostic pathologic findings for lymphomatous presentation of hairy cell leukemia. All stains at 400× except *BRAFV600E* (F) at 600×. A. Hematoxylin & Eosin stain showing small to medium sized cells with interspersed histiocytes. Further positive stains including CD20 (B), cyclin D1 (C), annexin A1 (D), CD200 (E), and *BRAFV600E* (F). Diagnostic clues and confirmatory pathologic findings are listed in Table 1.

however the remainder of the IHC stains lean toward an HCL diagnosis. CD200 can be used to help distinguish between chronic B-CLPDs, as it is strongly expressed in CLL/SLL and HCL, but less so in splenic marginal zone lymphoma and follicular lymphoma and weak to negative in other lymphomas.¹⁷ Annexin A1 can also be used as a confirmatory test as it is highly specific to HCL, with specificity reported at 100%, although caution must be used in the interpretation of results because it can also stain myeloid and T cells.¹⁸ Confirmative testing for *BRAFV600E* (exon 15) secured a diagnosis in our case, leading to effective treatment. In the rare event that this mutation is negative, one could consider testing exon 11 for alternate *BRAF* mutations.¹⁹ Table 1 lists diagnostic clues and confirmatory tests.

Conclusions

Given the rarity of this entity, an accurate diagnosis can be challenging and pathologists and clinicians must maintain a high index of suspicion when confronted with a B-CLPD with an atypical staining pattern, especially if the tumor does not respond to the initial treatment. Patients respond predictably to treatment with infusional cladribine. In cases of incomplete response, relapse, or no response to treatment, clinicians can now also consider using the *BRAF* inhibitor vemurafenib.²⁰ Our case highlights and also questions the under-recognition of hairy cell lymphoma,

which might masquerade as a refractory low-grade B-cell lymphoma and lead to ineffective treatment.

References

1. Swerdlow S, Campo E, Harris N, et al, eds. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: International Agency for Research on Cancer; 2008.
2. Saven A, Burian C, Koziol JA, Piro LD. Long-term follow-up of patients with hairy cell leukemia after cladribine treatment. *Blood* 1998;92:1918-26.
3. Tiacci E, Trifonov V, Schiavoni G, et al. *BRAF* mutations in hairy-cell leukemia. *N Engl J Med* 2011;364:2305-15.
4. Matutes E, Wotherspoon A, Catovsky D. The variant form of hairy-cell leukaemia. *Best Pract Res Clin Haematol* 2003;16:41-56.
5. Xi L, Arons E, Navarro W, et al. Both variant and IGHV4-34-expressing hairy cell leukemia lack the *BRAF* V600E mutation. *Blood* 2012;119:3330-32.
6. Tadmor T, Polliack A. Unusual clinical manifestations, rare sites of involvement, and the association of other disorders with hairy cell leukemia. *Leuk Lymphoma* 2011;52:57-61.
7. Herold CJ, Wittich GR, Schwarzinger I, et al. Skeletal involvement in hairy cell leukemia. *Skeletal Radiol* 1988;17:171-5.
8. Pilichowska M, Shariftabrizi A, Mukand-Cerro I, Miller K. Primary hairy cell leukemia/lymphoma of the breast: a case report and review of the literature. *Case Rep Pathol* 2014;2014:497027.
9. Chandana SR, Kotecha R, Al-Janadi A, et al. Rare case of hairy cell leukemia with brain parenchymal involvement: a diagnostic dilemma. *J Clin Oncol* 2013;31:e186-8.
10. Kraut EH. Clinical manifestations and infectious complications of hairy-cell leukaemia. *Best Pract Res Clin Haematol* 2003;16:33-40.
11. Waxman JH. Hairy cell sarcoma. *Postgrad Med J*. 1983;59:40-2.
12. Osman H, Roth T, Zhou J. Hairy cell lymphoma: a unique presentation of hairy cell leukaemia. *Br J Haematol* 2013;162:294.
13. Liu H, Wang W, Tang G, et al. Lymphomatous variant of hairy cell leukaemia: a distinctive presentation mimicking low-grade B-cell lymphoma. *Histopathology*. 2015;67:740-5.
14. Lal A, Tallman MS, Soble MB, et al. Hairy cell leukemia presenting as localized skeletal involvement. *Leuk Lymphoma* 2002;43:2207-11.
15. Morgan, EA, Katzman LE, Georgian-Smith D, et al. Hairy cell leukemia presenting as a palpable breast mass. *J Hematopathol* 2014;7:181-7.
16. Yonal-Hindilerden I, Hindilerden F, Bulut-Dereli S, et al. Hairy Cell leukemia presenting with isolated skeletal involvement successfully treated by radiation therapy and cladribine: a case report and review of the literature. *Case Rep Hematol* 2015;2015:803921.
17. Fan L, Miao Y, Wu YJ, et al. Expression patterns of CD200 and CD148 in leukemic B-cell chronic lymphoproliferative disorders and their potential value in differential diagnosis. *Leuk Lymphoma* 2015:1-7.
18. Toth-Liptak J, Piukovics K, Borbenyi Z, et al. A comprehensive immunophenotypic marker analysis of hairy cell leukemia in paraffin-embedded bone marrow trephine biopsies—a tissue microarray study. *Pathol Oncol Res* 2015;21:203-11.
19. Tschernitz S, Flossbach L, Bonengel M, et al. Alternative *BRAF* mutations in *BRAF* V600E-negative hairy cell leukaemias. *Br J Haematol* 2014;165:529-33.
20. Tiacci E, Park JH, De Carolis L, et al. Targeting mutant *BRAF* in relapsed or refractory hairy-cell leukemia. *N Engl J Med*. *N Engl J Med* 2015;373:1733-47.