

Localized Bone Disease as a Presentation of Hairy Cell Leukemia

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Hairy cell leukemia (HCL) is an indolent B-cell malignancy that typically presents with splenomegaly, pancytopenia, and bone-marrow involvement resulting in an inaspirable marrow—a “dry tap.” We describe an unusual case of HCL in a patient with localized skeletal disease and no bone marrow involvement or splenomegaly. To the best of our knowledge, there has been only one other report in the literature of a similar case.¹ We address the options for the management and follow-up of HCL patients presenting with localized bone disease.

Case Review

A 41-year-old man with no significant past medical history originally presented to his primary-care physician with several months of progressively worsening left-hip pain. He became debilitated and required a crutch for ambulation. Physical examination did not reveal any lymphadenopathy or hepatosplenomegaly. Other than left-hip pain on passive and active movement, the examination was unremarkable. The patient’s complete blood count (CBC) showed hemoglobin of 14.2 g/dL, a white blood cell (WBC) count of $5.08 \times 10^3/\mu\text{L}$, and a platelet count of $192 \times 10^3/\mu\text{L}$. A complete metabolic panel was unremarkable. Magnetic resonance imaging (MRI) showed a geographic area of signal alteration in the left hip involving the inferior half of the femoral head and neck curving around into the lesser trochanteric region. It was well demarcated and measured 8.9 cm in length. An additional focus of signal change was noted in the left ischium, measuring 2.4 cm in its largest axial dimension. There were no fractures or joint effusions, and the

surrounding musculature appeared symmetric. From a radiologic standpoint, the geographic nature of the left-hip abnormality made a neoplastic process less likely. Furthermore, these findings were consistent with polyostotic fibrous dysplasia. A bone scan showed multiple foci of increased uptake that corresponded to the areas seen on the MRI. A computed tomography (CT) scan of the chest, abdomen, and pelvis was unremarkable.

A bone biopsy of the hip revealed a mature B-cell lymphoproliferative disease consistent with HCL (Figure 1A). Flow cytometry on the bone specimen showed that the cells were CD20-positive, CD22-positive, and cyclin D-1-positive, but CD5-negative. DBA44 was positive and the tartrate-resistant acid phosphatase (TRAP) stain was positive by immunohistochemical stain (Figure 1B). Following the diagnosis of HCL, the patient had a bone-marrow biopsy and peripheral blood examination, both of which were negative for evidence of the disease. A positron emission tomography (PET) scan showed increased uptake in the same area that was abnormal on the MRI (Figures 2A, 2C). The patient was treated with a 5-day course of cladribine. At 1 month of follow-up, the patient’s clinical symptoms had subsided; he was once more fully active and did not require the aid of crutch. A 6-month follow-up PET scan showed resolution of the left-hip bone lesions (Figures 2B, 2D).

Discussion

Historical Evolution of HCL

The clinical/pathologic entity now called HCL was initially described as leukemic reticuloendotheliosis. Since 1923, there have been several references to leukemic reticuloendotheliosis, with variations in terminology. The first case of leukemia with reticuloendothelial hyperplasia and reticuloendothelial cells in peripheral blood was described by Edwald as leukämische reticuloendotheliose.

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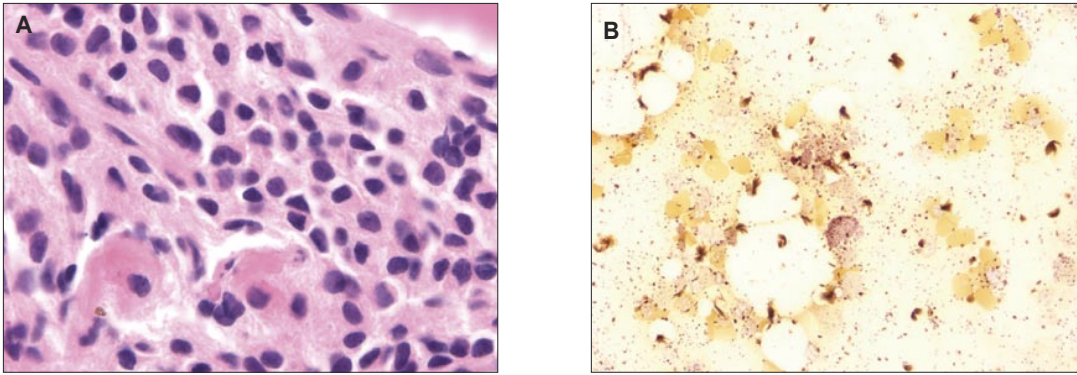


Figure 1. Histology of left-hip core bone biopsy. (A) Marrow infiltrate of large evenly spaced lymphoid cells with abundant clear cytoplasm and small- to medium-sized nuclei, imparting a "fried egg" appearance to the cells. No bone changes. (B) Tartrate-resistant acid phosphatase stain: strong, diffuse positivity in a variable proportion of the hairy cells (50× Oil).

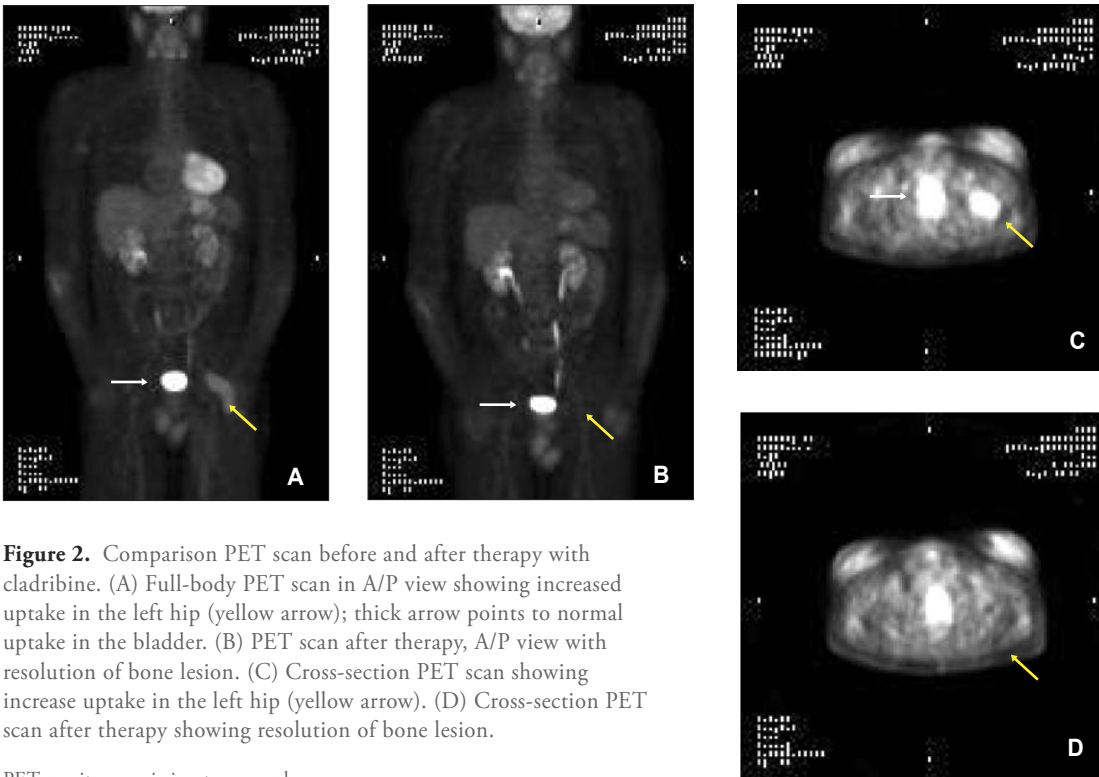


Figure 2. Comparison PET scan before and after therapy with cladribine. (A) Full-body PET scan in A/P view showing increased uptake in the left hip (yellow arrow); thick arrow points to normal uptake in the bladder. (B) PET scan after therapy, A/P view with resolution of bone lesion. (C) Cross-section PET scan showing increase uptake in the left hip (yellow arrow). (D) Cross-section PET scan after therapy showing resolution of bone lesion.

PET=positron emission tomography.

Terms such as malignant leukemic reticulohistiocytosis and aleukemic reticulosis followed.² However, leukemic reticuloendotheliosis was first established as a distinct hematologic entity by Bouroncle and colleagues in 1958.³ In 1966, Schrek and Donnelly named this entity hairy

cell leukemia based on the observation of atypical lymphocytes with cytoplasmic villous projections.⁴ Since the 1960s, there have been significant advances in defining the clinical presentation, diagnostic evaluation, and management of classic HCL.

Pathogenesis

The pathogenesis of HCL remains unclear. HCL possesses features suggestive of late stage B-cell development, such as post-germinal center (GC) memory B cells or preplasma cells. HCL cells express the pan-B cell surface antigens CD19, CD20, and CD22; the early plasma cell marker PCA-1; and clonally related heavy and light chains. Basso and associates found that the HCL genome-wide expression profile and mutated immunoglobulin genes are most similar to post-GC memory B cells.⁵ Of note, these gene-expression profiling data also brought to light the unique expression patterns in HCL cells, including the lack of CD27 and the upregulation of cyclin D-1 and annexin-1 genes, implicating them in cell-cycle regulation and molecular pathogenesis.^{2,5,6}

Clinical Presentation

HCL is an indolent lymphoproliferative disorder of B-cell origin that constitutes 2% of all leukemias in the United States. It is observed primarily in middle-aged men, with a median age of 50 years, and has a male:female incidence ratio of 4:1.^{2,7} HCL typically involves the bone marrow, peripheral blood, liver, and spleen without associated lymphadenopathy.⁷ Patients most often present with splenomegaly (80%) and pancytopenia (60–80%). Involvement of other organs, including lymph nodes, lung, skin, kidney, brain, and pancreas, has been reported but is less common.^{3,8} Skeletal involvement is infrequent, with reported incidences ranging from 0% to 13%,³ resulting in lytic or mixed lytic/blastic lesions. A predilection for the femoral head or neck or the thoracic or lumbar spine,⁸⁻¹⁰ aseptic necrosis,⁸ and diffuse osteosclerosis,⁹ have also been described. Lembersky and coworkers looked at HCL patients who had osseous involvement and found that all of them had bone-marrow involvement.¹¹ They concluded that bony involvement is typically associated with a high tumor burden.

Imaging Modalities in Diagnosis and Follow-up

Evaluation of the extent of bone marrow involvement is most accurately achieved with MRI. Additionally, MRI is helpful in evaluating focal areas of diseased bone in areas that appear normal on radiography.^{1,10} Other useful imaging modalities include bone, gallium scan, and PET scanning. Bone scans have the greatest utility in the setting of multiple bony lesions but lack specificity in the setting of fractures and infections, yielding false-positive results. PET relies on bone metabolic activity for uptake and therefore provide useful functional information, even in the presence of subtle abnormalities. Additionally, as demonstrated in studies involving metastatic disease of the lung, breast, and esophagus, PET detects bony metastases

and can be used to evaluate response to chemotherapy with higher sensitivity and specificity when compared to bone scans.¹²⁻¹⁴

Seemann and colleagues explored the role of PET and MRI in the assessment of bone involvement in metastatic gastrointestinal carcinoid tumors.¹⁵ MRI is a modality that looks at structural changes, whereas PET relies on metabolic changes for uptake and can detect bone disease before it manifests on anatomic imaging studies. Therefore, it is not surprising that PET was more sensitive than MRI (100% vs 66.7%) in detecting osseous metastases in the Seemann study.

PET and MRI have also been compared in the evaluation of response to chemotherapy in a small study involving 18 patients with primary lymphoma of the bone (PBL).¹⁶ All 18 patients had positive PET and MRI findings, with histologic verification of PBL with bone biopsy. Postchemotherapy, lesions appeared resolved on subsequent PET scans, despite unchanged MRI findings. These results suggest that MRI cannot reliably be used to distinguish between viable malignant tumor versus benign lesions or lesions of prolonged osseous recovery. In our patient's case, the utility of PET was extrapolated from these studies. PET was used after MRI for further evaluation of the extent of the patient's bony lesions and to follow-up the lesions posttreatment.

Treatment

HCL often has an indolent course, and patients may be asymptomatic for many months or even years. However, most patients will eventually require treatment. With purine analogs, patients can achieve a complete response (CR). In the past, interferon- α usually resulted in only a partial response. The purine analogs pentostatin and cladribine target DNA synthesis in resting and dividing lymphocytes but have different mechanisms of action. Cladribine has become the preferred purine analog because of lower toxicities and ease of administration; it is phosphorylated by deoxycytidine kinase to form a metabolite that cannot exit the malignant cell, inducing apoptosis.¹⁷ Although several groups have tried to shorten the cladribine regimen to a 5-day schedule,^{18,19} the standard regimen is still a continuous intravenous infusion for 7 days at a dose of 0.1 mg/kg/day. With this single course of therapy, CR rates have been reported at 76–91%, with minimal toxicities.^{20,21} As with pentostatin, immunosuppression may occur with cladribine treatment, leading to opportunistic infections. Long-term follow-up data from Else and associates using cladribine monotherapy showed overall response and CR rates of 100% and 82%, respectively.²² Five- and 10-year relapse rates were 33% and 48%, respectively.

Table 1. Analysis of MRD After Rituximab Maintenance Therapy (N=13)

	Post-cladribine, n/N (%)	1 month, n/N (%)	Post-rituximab maintenance therapy, n/N (%)
CR	13/13 (100)	13/13 (100)	13/13 (100)
MRD by flow cytometry	N/A	12/13 (92.3)	1/13 (7.6)
MRD by PCR	N/A	5/12 (41.6)	1/12 (7.6)

Data from Ravandi et al.²⁵

CR=complete remission, MRD=minimal residual disease.

CR defined as absence of hairy cells on bone marrow aspirate smears or the presence of less than 1% atypical cells, absolute neutrophil count $>1.5 \times 10^9/L$, hemoglobin >12 g/dL, and platelet count $>100 \times 10^9/L$.

CR-MRD defined as for CR but with persistence of 1–5% hairy cells in the marrow.

Recently, research in HCL has focused on the detection and treatment of minimal residual disease (MRD) in the hopes of reducing relapse rates. Newer targeted therapies are being used in all of the indolent lymphoproliferative disorders for this purpose. The most common targeted agent is rituximab (Rituxan, Genentech/Biogen Idec), a monoclonal anti-CD20 antibody.²³⁻²⁵ This agent has been shown to confer response rates of 73% when used alone in patients with low tumor burden.²³ Most B-cell lymphomas express the CD20 antigen on their cell surface to a varying degree. HCL is a non-Hodgkin lymphoma with extremely high expression of the CD20 antigen. Therefore, rituximab will probably be used alone or in combination with chemotherapy in the future to treat HCL.

To date, there have been several small studies demonstrating eradication of MRD with rituximab after the use of cladribine. Thomas and coworkers looked at the efficacy of rituximab in 15 patients treated with prior cladribine therapy with refractory (2/15) or relapsed (13/15) HCL.²⁴ Of these patients, 8 (53%) achieved CR after receiving 4–12 doses of rituximab at 375 mg/m², with 4 of 8 patients remaining positive for MRD. Similarly, Ravandi and colleagues evaluated the use of rituximab for the eradication of MRD in a group of 13 patients (11 newly diagnosed and 2 refractory cases).²⁵ Six women and 7 men with an average age of 55 years (range, 32–74 years) were treated with cladribine by intravenous infusion over 2 hours for 5 days followed by eight doses of weekly rituximab at 375 mg/m². This treatment resulted in a 100% CR and 92.3% MRD eradication in 13 of 13 and 12 of 13 patients, respectively, with a median follow-up at 14 months (Table 1). However, there are no randomized studies evaluating the role of rituximab in the treatment of MRD. Hence, observation

alone following treatment with cladribine remains the current standard of care.

Conclusion

As was seen in this case, HCL may have an unusual presentation, making the diagnosis more challenging. HCL should be included in the differential diagnosis of patients presenting with isolated bony abnormalities. In patients with localized bone involvement, PET is highly sensitive for detecting malignant lesions and has a higher specificity for the exclusion of malignant bone tumors than MRI. In addition, MRI may give a false-positive result after treatment because of the prolonged recovery phase of osseous abnormalities. In such cases, PET can be highly specific and useful for differentiating malignant and non-malignant disease before and after treatment.

Regardless of the initial presentation, patients with HCL can achieve a CR with the purine analog cladribine. Although small, nonrandomized studies have shown a reduction in MRD and relapse rates after treatment with rituximab, further investigation is needed to establish rituximab as the standard of care in treating HCL.

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Review

Isolated Skeletal Involvement in Hairy Cell Leukemia

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Karmali and colleagues have reported an interesting case of hairy cell leukemia (HCL) in a 41-year-old man presenting with progressive left-hip pain.¹ Functional imaging studies indicated hypermetabolic activity in the left hip. A bone biopsy established the diagnosis of HCL. No peripheral blood or bone marrow involvement was seen. The patient experienced complete radiologic response following treatment with cladribine.

HCL is a relatively rare hematologic malignancy with an estimated annual incidence of 0.3 cases per 100,000^{2,3} and a 4:1 male preponderance.⁴ Diagnosis is based on the distinctive hairy cell morphology, bone marrow histology, and immunologic profile. Hairy cells can be identified in Romanovsky-stained peripheral blood smear in the majority of the patients. The HCL cell is a mononuclear cell, usually 1–2 times the size of a small lymphocyte. The cytoplasmic outline is often indistinct, with varying numbers of projections, giving the cell a “hairy” appearance. The hairy projections are readily evident on electron microscopic examination.⁵ Hairy cells exhibit a mature B-cell phenotype and typically express one or more heavy chains⁶ and monotypic light chains. Hairy cells strongly express pan-B cell antigens including CD19, CD20, CD22, and CD25, and usually lack expression of CD5, CD10, and CD23.⁷ The mucosal lymphocyte antigen CD103 is a sensitive marker for HCL and when co-expressed with other pan-B cell markers is highly suggestive of HCL.⁸ Hairy cells also strongly express CD11c, a marker associated with myelomonocytic cells and CD25, the alpha chain of the interleukin-2 receptor.⁷ B cell-associated immunostains, including anti-CD20 (L26) and DBA44, react with hairy cells in fixed, routinely processed tissue sections. However, these antibodies are not

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specific for HCL.⁹ Due to the implications for treatment, it is critical to differentiate HCL from other CD20-positive B-cell lymphoproliferative disorders that may share some immunophenotypic and morphologic features with HCL. Along similar lines, it is important to consider the possibility of HCL variant, in which patients typically have an elevated white blood cell count, easy-to-aspirate bone marrow, and infrequent tartrate-resistant acid phosphatase (TRAP)-positive staining in the neoplastic cells.⁴ Unlike in typical HCL, the cells in HCL variant are CD25- and HC2-negative,¹⁰ and may not respond as well to purine nucleosides.⁴

In the current case, the authors report that the B cells in the bone biopsy specimen were positive for CD20, CD22, cyclin D-1, DBA44, and TRAP. The authors, however, have not provided any information about presence or absence of CD11c, CD25, CD103, or HC2. Based on the most common phenotype of typical HCL—CD11c-, CD25-, HC2-, and B-ly-7-positive—Matutes and colleagues proposed a scoring system that considers the reactivity with each of these four markers and gives 1 point if positive and 0 points if negative. Scores range from 4 (typical of HCL) to 0 (atypical of HCL). In the study by Matutes, 98% of HCL patients had high scores (3 or 4).¹¹ Positive staining for cyclin D-1 in this case is also atypical. However conflicting reports about cyclin D-1 staining in HCL have been published,¹²⁻¹⁴ ranging from no to rare to occasional detection with immunohistochemistry,¹² flow cytometry¹⁴ and reverse-transcriptase polymerase chain reaction,¹³ respectively.

Isolated skeletal involvement with acute and chronic lymphoid and myeloid malignancies (granulocytic sarcomas) is well documented in the literature.¹⁵ Such extramedullary leukemic involvement can be seen before, with and after the diagnosis of systemic disease. Isolated skeletal involvement with HCL is uncommon. Although Karmali and colleagues label theirs the second reported case of isolated skeletal involvement with HCL, this rare presentation has been the subject of at least four reports in the past.¹⁶⁻¹⁹ Management of skeletal involvement with HCL is largely based on anecdotal experience and includes observation, external-beam radiation therapy, splenectomy, interferon- α , surgical excision, and systemic chemotherapy.¹⁹ Isolated extramedullary presentation of acute or chronic leukemia generally heralds systemic disease. In fact, such presentations when treated with localized radiation therapy or surgical excision invariably lead to systemic relapse.¹⁵ Based on the experience from extramedullary presentations of other hematologic malignancies, treatment of isolated extramedullary HCL with systemic chemotherapy is appropriate, as suggested by this case. Evidence of complete response to therapy was documented by resolution of radiographic abnormalities

in the current case. Other measures of response assessment in HCL have been proposed, including serum-soluble interleukin-2 receptor levels, which have shown utility in not only documenting response to therapy but also in predicting early disease relapse.^{20,21}

Treatment of HCL has been recently reviewed elsewhere.⁴ The authors mention cladribine as the preferred therapy of HCL because of ease of administration and lower toxicities. It is also important to mention the remarkable activity of pentostatin in HCL. A number of large prospective studies have consistently shown high rates of complete response and excellent long-term overall and disease-free survival with pentostatin.²²⁻²⁵ No prospective, randomized studies comparing cladribine and pentostatin have been or are likely to be conducted. Recently, Else and coauthors have reported equivalent complete response rates and 10-year survival with pentostatin and cladribine in 219 patients with HCL, with no difference in toxicities.²⁶ Novel therapies are currently evolving for HCL. Immunotherapy with rituximab is effective in relapsed or refractory HCL as well as HCL-variant. Clinical trials employing agents specifically targeting antigens on hairy cells for example CD22 (with recombinant immunotoxin BL22) are ongoing.²⁷

In conclusion, skeletal involvement with HCL is uncommon. Complete immunohistochemical assessment of suspected cases of HCL is critical, with careful documentation of typical HCL associated cell-surface markers. Symptomatic isolated extramedullary presentations should be treated with systemic therapy. The advances in treatment in HCL over the last two decades and the exciting new therapies have dramatically altered the prognosis of patients with HCL.

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