



A Case Report of Hairy Cell Leukemia: An Unusual Presentation

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Abstract

Hairy cell leukemia is a rare B cell lymphoproliferative disorder. Patients typically present with peripheral cytopenias, circulating leukemia cells, marked splenomegaly and marrow infiltration. We describe a case of a 68 year old man who presented solely with psychiatric symptoms of delusions, without the classical features of cytopenias or splenomegaly. Initial imaging revealed involvement with lymphoma at multiple nodal and extranodal sites, including the base of skull, skeletal bone, bone marrow and pleura. Histology of the lesions from the base of skull, bone marrow and iliac bone revealed small B cells with the typical immunophenotype for hairy cell leukemia, but with aberrant expression of cyclin D1. Only rare cases of skeletal bone disease and neurological involvement have been previously reported in the literature. He achieved only partial response to initial treatment with cladribine, and subsequently achieved complete metabolic response following treatment with rituximab. He experienced no toxicities with treatment and remains in complete remission at 12 months following treatment. This case highlights that careful hematopathological assessment and clinical correlation is required for accurate diagnosis of unusual cases of hairy cell leukemia. In addition, this case also demonstrates that a combination of cladribine and rituximab therapy can be effective in deepening frontline response in patients with hairy cell leukemia without significant treatment-related toxicity.

Introduction

Hairy Cell Leukemia (HCL) is a rare B cell lymphoproliferative disorder, with patients typically presenting with cytopenias, marked splenomegaly and circulating leukemia cells. Leukemic cells classically have central nuclei, abundant cytoplasm with hairy-like projections, and express CD11c, CD25, CD103, CD123, CD20, CD22, CD52, and mild to moderate expression of cyclin D1 [1].

Rare cases of neurological and skeletal bone involvement have been reported in the literature [2-4]. We describe a case of a 68 year old man diagnosed with HCL involving base of skull, skeletal bone and bone marrow, but without classical features of cytopenias or splenomegaly.

Case Presentation

A 68 year old man with a longstanding history of paranoid personality disorder presented with acute delusional symptoms. His past history was significant for atrial fibrillation, type 2 diabetes mellitus, dyslipidemia and paranoid personality disorder. His medications included rivaroxaban, digoxin, perindopril and simvastatin. He did not have any B symptoms or other neurological symptoms or signs. On further questioning, there was no family history of dementia or malignancy.

Brain CT and MRI scans (Figure 1) showed a soft tissue mass in the right skull base involving the right occipital bone and petrous temporal bone with extension into the posterior fossa, with an enhancing component of the mass extending along the right glossopharyngeal nerve into the right jugular foramen and becoming contiguous with a large soft tissue mass within the suboccipital region, measuring 4.7 cm x 2.3 cm x 5.3 cm in size. A staging PET scan (Figure 2) showed moderate FDG avidity at the right base of skull, bony involvement at the pelvis and right humerus, pleural uptake, and nodal uptake within the anterior mediastinum and right internal mammary chain. Full blood count showed mild thrombocytopenia of $143 \times 10^9/L$ and a low monocyte count of $0.1 \times 10^9/L$. There were no circulating hairy cells seen on blood film. Peripheral blood flow cytometry did not detect any monoclonal B cell population. Cerebrospinal fluid analysis revealed elevated protein levels (0.91 g/L). Flow cytometry of CSF did not detect any monoclonal B cell population.

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Figure 1: MRI Brain.

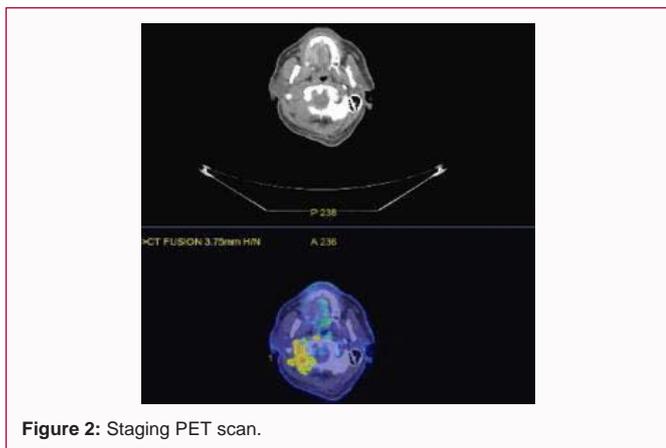


Figure 2: Staging PET scan.

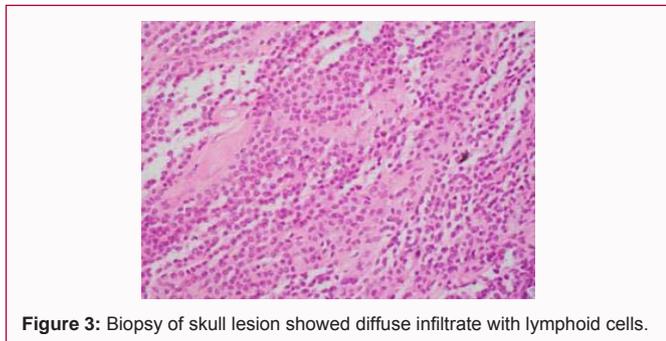


Figure 3: Biopsy of skull lesion showed diffuse infiltrate with lymphoid cells.

Initial biopsy of the right base of skull lesion (Figures 3-5) showed infiltration of small cells with regular round nuclei, which on immunohistochemistry were consistent with B cells that were CD5-, CD20+, CD138-, cyclin D1+ diffuse, CD10+, BCL2+ strong diffuse, BCL-6 weak, CD25+, DBA44+, MYC- and EBER-ISH-. Due to the high cyclin D1 expression, an initial diagnosis of mantle cell lymphoma was considered. However, the findings were inconsistent with classic mantle cell lymphoma given the negativity of CD5 expression on immunohistochemistry and the low Ki67 index. Further testing with FISH was negative for t(11;14).

A staging bone marrow biopsy from the right posterior superior iliac spine (Figures 6-9) showed a normocellular marrow with involvement with hairy cells morphologically and on flow cytometry. Flow cytometric analysis showed 15% of lymphocytes were B cells of hairy cell phenotype (CD5-, CD 10 -, CD11c+, CD 19+, CD20+, CD22+, CD23-, CD25+, CD103+), and monoclonality was demonstrated by light chain restriction. Bone marrow trephine showed diffuse effacement of the marrow space with sheets of small

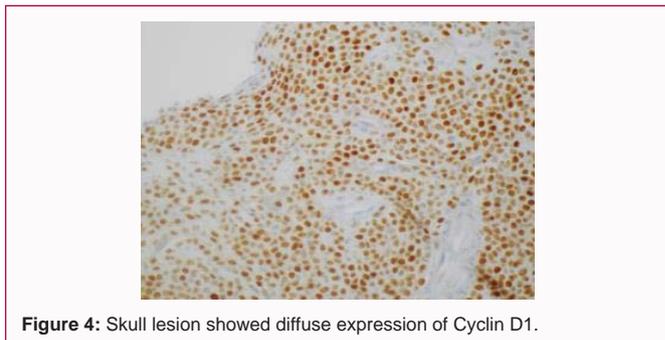


Figure 4: Skull lesion showed diffuse expression of Cyclin D1.

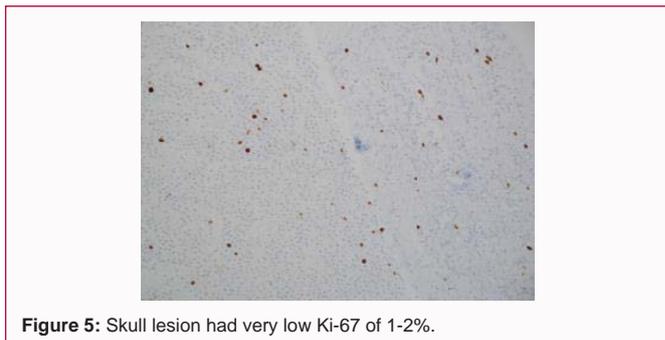


Figure 5: Skull lesion had very low Ki-67 of 1-2%.

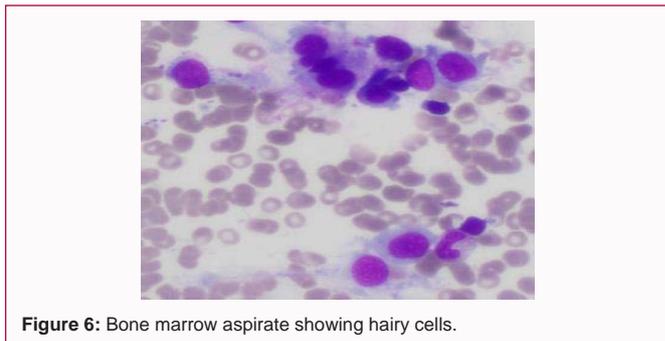


Figure 6: Bone marrow aspirate showing hairy cells.

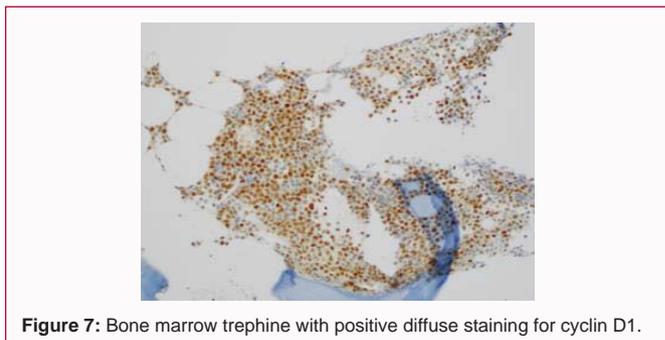


Figure 7: Bone marrow trephine with positive diffuse staining for cyclin D1.

lymphoid cells and scant pale cytoplasm. These cells were CD20+, BCL-2+, BCL-6+ weak, CD10+ patchy, and once again had diffuse cyclin D1 expression. FISH once again did not detect t(11;14). Subsequent repeat PET-guided iliac bone biopsy on the contralateral side (Figures 10,11) validated the same findings on the bone marrow biopsy.

Given classic morphological and immunophenotypic features of HCL along with negative FISH for t(11;14), he was diagnosed with HCL involving multiple nodal and extranodal sites, including base of skull, skeletal bone, bone marrow, and pleura. Following diagnosis of HCL, treatment was commenced with a standard course of intravenous cladribine. Restaging PET scan post cladribine showed

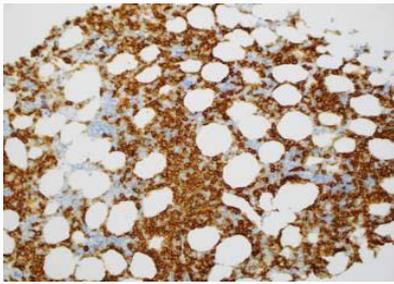


Figure 8: Bone marrow trephine with positive staining for CD20.

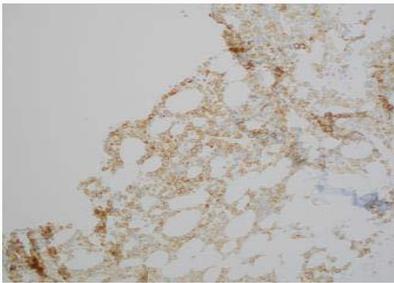


Figure 9: Bone marrow trephine with positive staining for CD25.

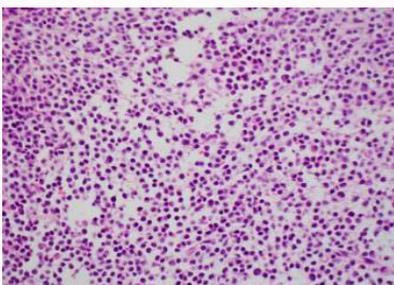


Figure 10: Contralateral iliac bone biopsy again showed infiltration by small lymphoid cells.

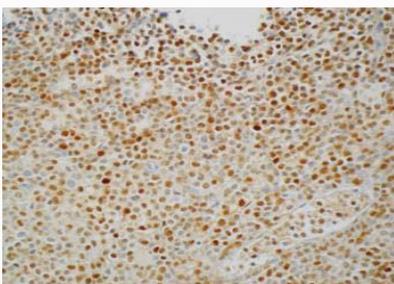


Figure 11: Contralateral iliac bone biopsy showed high levels of expression of cyclin D1.

persistent mild-moderate FDG avidity at nodal and extranodal sites consistent with partial metabolic response. Repeat bone marrow biopsy showed marked reduction of HCL with no hairy cells detected by flow cytometry and small amounts of DBA44+ B cells on the trephine. BRAF V600E mutation was not detected on this sample, which is likely due to low tumor burden from this site. Unfortunately, BRAF V600E mutation testing was not performed on the initial diagnostic sample. Given the lack of complete response post cladribine, he was commenced on four cycles of rituximab of 375 mg/m². There were no toxicities from treatment. Subsequently, his full blood count normalized and a further restaging PET scan was

consistent with complete metabolic response. Currently, he remains in complete remission at 12 months post treatment with resolution of delusions.

There have been no randomized controlled trials to outline the optimum approach of combined chemoimmunotherapy in HCL. Most guidelines for frontline treatment of HCL recommend use of purine analogues, in particular cladribine or pentostatin, and rituximab is not routinely incorporated into this regimen. However, failure to achieve complete remission to purine analogue therapy has now been recognized as a poor prognostic factor in classical hairy cell leukemia [5]; and some studies have demonstrated the efficacy of rituximab therapy in HCL, both in patients with incomplete response in frontline therapy, and in relapsed or refractory settings [6-8].

Discussion

This is an unusual case of HCL due to several reasons. Firstly, HCL rarely involves skeletal bone, lung pleura and the central nervous system. While bone marrow is involved in almost all cases of HCL, bone involvement with radiographic evidence of osteolytic lesions is rare. Reports of skeletal bone involvement have been found in 3% of cases [3,9]. Reported cases show that bony lesions can affect multiple sites, but most commonly proximal long bones, and is almost always associated with pain and extensive involvement of the bone marrow [10]. These lesions are often lytic, but cases of diffuse osteosclerosis, mixed sclerotic and lytic pattern, and osteoporosis have also been reported [9]. Our patient differs to these cases due to the predominant location of the lesions at the skull base, and without symptoms from bone pain. Secondly, it is very unusual for HCL to involve the central nervous system. Descriptions of nervous system involvement in HCL are largely limited to case reports, which have documented a range of neurological symptoms. These include isolated radicular infiltration, intracerebral hemorrhage secondary to leukostasis, intraparenchymal brain involvement, and tumor invasion of the cord with compression resulting from tumor infiltration of vertebrae [2,11]. A review of 108 patients in the Mayo Clinic with HCL found only 5 patients who had neurological symptoms. Of these, one had leukemic compression of neural structures, three had central nervous system infections and one had polyradiculopathy [12]. None were reported to have enhancing lesions within the cranial nerve distribution, or to have presented with personality change or paranoid delusions, as was the case with our patient. Thirdly, HCL frequently presents with peripheral cytopenias and splenomegaly, which was not seen in this case. In a recent review, the incidence of HCL without splenomegaly is thought to be between 0-40%, and the incidence of HCL without cytopenias is thought to be less than 25% [13,14]. In a recent analysis of over 500 patients, anemia defined as a hemoglobin level less than 120 g/L was seen in 75-84% of patients at presentation, platelets less than 100 000/ml were seen in 57-79% of patients at presentation, and leucopenia was seen in 60% of patients [14,15].

Lastly, the diffuse expression of Cyclin D1 as seen in the biopsies of the base of skull lesion, bone marrow biopsy and iliac bone biopsy, is unusual for HCL. Cyclin D1 is a cell cycle protein that is overexpressed most frequently in mantle cell lymphoma due to t(11;14)(q13;q32), which involves translocation of the immunoglobulin heavy chain gene on chromosome 14 and the bcl-1 region on chromosome 11. While many cases of HCL can have cyclin D1 overexpression, the level of expression is usually mild to moderate and usually involves a subset of the lymphoma cells, as compared to the high and diffuse level of expression typically seen in mantle cell lymphoma [16]. Cyclin

D1 overexpression has also been reported in head and neck, breast and lung carcinomas, as well as other lymphoproliferative disorders, including rare cases of CLL, lymphoplasmacytic lymphoma and multiple myeloma [16].

Conclusion

This case illustrates an unusual presentation of HCL, involving multiple atypical sites, with over expression of cyclin D1, and without the classical involvement of peripheral blood or spleen. In this patient, due to the unusual clinical presentation, disease distribution and aberrant immunohistochemistry staining, an initial diagnosis of mantle cell lymphoma was considered. Subsequent testing with FISH and further biopsies were required to confirm the diagnosis of hairy cell leukemia. This case highlights that accurate diagnoses often require careful assessment of morphology, immunophenotypic and cytogenetic findings in order to deliver appropriate treatment and prognostication. In this case, the patient failed to achieve complete response to initial treatment with cladribine, but went into complete remission with further administration of rituximab. As such, this case also demonstrates that rituximab therapy can be effective in deepening frontline response to cladribine in HCL which may be important in optimizing progression-free survival in patients with HCL without the addition of significant treatment-related toxicity.

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