Hairy cell leukemia with CCND1/IGH fusion gene and BRAF V600E mutation

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A R T I C L E   I N F O

Keywords: Hairy cell CCND1 BRAF V600E t(11;14)

A B S T R A C T

A 75-year-old male evaluated for pancytopenia. Abnormal lymphocytes with hairy projections noted on peripheral blood. Bone marrow examination showed diffuse proliferation of CD20+ B-lymphocytes. Flowcytometry revealed monoclonal lambda-restricted B-cells expressing CD19, CD20, CD11c, CD103, CD25 and CD123, negative for CD5 and CD10. Additional staining showed positivity for cyclin-D1, Annexin-A1 and TRAP. FISH identified t(11;14). PCR was positive for BRAF V600E. Given the above findings, nonspecificity of t(11;14) and the presence of BRAF V600E, the diagnosis of HCL was favored. Patient achieved CR with infusional cladribine. Herein, we report the co-occurrence of CCND1/IGH and BRAF V600E in HCL, a rare scenario that could characterize a new subtype of HCL.

1. Introduction

Overlapping features between B-cell neoplasms are common, making differentiation and classification a challenging process. Hairy cell leukemia is an uncommon chronic B-cell lymphoproliferative disorder. It represents approximately less than 1% of lymphoid neoplasms. In the United States, the estimated incidence is three cases per million persons per year, which equates to 600 to 800 new cases each year [1]. Most cases are postulated to arise from an activated (post-germinal) memory B cell that acquires a BRAFV600E gene mutation [2]. The presence of t(11;14)(q13;q32) CCND1/IGH fusion gene is considered the hallmark of mantle cell lymphoma (MCL), however, it is not specific for MCL, as it can also be found in plasma cell disorders and rarely in other B-cell malignancies [3]. Here, we report a case of hairy cell leukemia with BRAF V600E mutation and CCND1/IGH fusion gene.

A 75-year-old male with a past medical history of hypertension, atrial fibrillation and dyslipidemia, who was evaluated for incidentally found pancytopenia: white blood cell count (2.2 × 10(9)/L; reference range 3.4 - 9.6 × 10(9)/L), absolute neutrophil count (0.87 × 10(9)/L; reference range 1.56 - 6.45 × 10(9)/L), absolute lymphocyte count (1.23 × 10(9)/L; reference range 0.95 - 3.07 × 10(9)/L), hemoglobin (11.2 g/dL; reference range 13.2 - 16.6 g/dL), platelets (73 × 10(9)/L; reference range 135 - 317 × 10(9)/L). Patient denied any fever or nights sweats but endorsed a 10 kg weight loss over the last 6 months.

He did not have any appreciable peripheral lymphadenopathy or splenomegaly on physical examination. Patient had no personal history of malignancy, chemotherapy or radiation exposure. No family history of a hematological malignancy was noted.

Examination of peripheral blood showed abnormal lymphocytes with hairy projections (Fig. 1A). Bone marrow examination showed a hypercellular marrow with approximate cellularity of 75%, with diffuse proliferation of CD20 positive B-lymphocytes (Fig. 1B).

Flow cytometry on bone marrow aspirate revealed a monoclonal lambda-restricted B-cell population expressing CD19, CD20, CD22, CD11c, CD103, CD25 and CD123; negative for CD5 and CD10. Additional immunohistochemical staining showed neoplastic B-lymphocytes positive for cyclin D1, tartrate-resistant acid phosphatase (TRAP) stain (Fig. 1C) and Annexin A1.

Chromosomal analysis was performed and his karyotype was 46 XY, t(11;14)(q13;q32.3)/46, XY[17]. Fluorescence in situ hybridization (FISH) analysis confirmed the presence of CCND1/IGH fusion gene (Fig. 2). Molecular analysis by PCR was positive for BRAFV600E mutation.

Patient was treated with a 7-day infusional cladribine course (0.1 mg/kg/day), followed by growth factor support with pegfilgrastim (6 mg subcutaneous injection) on day 8. Patient was also maintained on prophylactic antimicrobials against bacterial, fungal and viral infections. Supportive transfusions were provided as needed. After receiving cladribine, patient developed significant cytopenias post-chemotherapy as expected, requiring transfusions of leukoreduced and irradiated

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https://doi.org/10.1016/j.lrr.2020.100197
Received 24 December 2019; Received in revised form 11 March 2020; Accepted 13 March 2020
Available online 17 March 2020
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blood products. Four months after chemotherapy, his counts normalized and a bone marrow biopsy showed no morphologic evidence of a residual lymphoproliferative disorder.

2. Discussion

The diagnosis of hairy cell leukemia is based on clinical, morphologic and characteristic immunophenotypic findings. The usual presenting features are fatigue, infections, splenomegaly and/or pancytopenia. Although our patient did not present with splenomegaly—a traditional hallmark of the disease—, the incidence and severity of splenomegaly is thought to be decreasing given the earlier recognition and diagnosis of cases [4]. The neoplastic B-lymphocytes in hairy cell leukemia have a characteristic immunophenotype as they express pan B-cell markers (CD20, CD19 and CD22), in addition to CD11c, CD103, CD25 and CD123. Tartrate-resistant acid phosphatase (TRAP) stain is sensitive, however it is technically challenging and not specific rendering it obsolete. Annexin-1 stain on the other hand is more specific and is preferred for diagnosis [5]. More recently, studies using sensitive molecular assays identified the BRAF V600E mutation in the entire tumor clone of the vast majority of cases of hairy cell leukemia and in no cases of other B cell lymphomas/leukemias [6] adding yet another useful tool for diagnosis.

Possible differential diagnoses that should be ruled out in patients with suspected hairy cell leukemia include; hairy cell leukemia-variant, which unlike hairy cell leukemia, does not express Annexin-1, CD25 and is usually dim or negative for CD123. Splenic marginal zone lymphoma is also a possible differential diagnosis; however, the neoplastic lymphocytes do not express CD103, CD11c, and CD25 in this entity. Chronic lymphocytic leukemia can also have a similar presentation but the neoplastic B-lymphocytes usually express CD5 and are CD103 negative.

The presence of CCND1/IGH fusion gene is the hallmark for mantle cell lymphoma; however, it is not specific and has been described in plasma cell disorders and other B-cell malignancies. Given the clinical presentation, morphologic, immunophenotypic findings in peripheral blood and bone marrow, the nonspecificity of CCND1/IGH fusion gene and the presence of BRAFV600E, the diagnosis of Hairy cell leukemia was favored in this case.

The CCND1/IGH fusion gene represents a translocation between the CCND1 locus on chromosome 14 and the immunoglobulin heavy chain (IgH) locus on chromosome 11 [7,8]. The fusion results in over-expression of Cyclin D1 (BCL1), a product that is not normally expressed in normal B-lymphocytes and is involved in regulation of the G1-S phase transition in cell cycle [9]. Several studies reported over-expression of Cyclin D1 in hairy cell leukemia at mRNA and protein levels without an underlying rearrangement in the CCND1 gene, suggesting the presence of alternative mechanisms for expression other than chromosomal rearrangement [10].

In summary, the diagnosis and initial evaluation of a patient with suspected hairy cell leukemia should take into consideration other lymphoproliferative disorders that can possibly mimic the disease. The initial recommended work-up includes complete history and physical examination, complete blood count with differential, peripheral smear evaluation using Wright's stain. Immunophenotypic analysis by flow cytometry is essential to demonstrate the characteristic immunophenotype for confirmation of diagnosis. Bone marrow aspiration and biopsy for diagnosis, confirmation and to determine the extent of involvement are also important. Initiating treatment should be considered if at least one of the following parameters is met: hemoglobin <11 g/dL, platelet count <100 000/μL, or absolute neutrophil count <1000/μL. Other clinical features that could prompt the clinician to start treatment include: symptomatic splenomegaly, progressive lymphocytosis or lymphadenopathy, unexplained weight loss (>10% within prior 6 months) and excessive fatigue.

3. Conclusion

The presence of CCND1/IGH fusion gene is the hallmark for mantle cell lymphoma; however, it is not specific and has been described in plasma cell disorders and other B-cell malignancies. We describe the first report of a case of hairy cell leukemia with t(11;14) and confirmation of diagnosis by BRAF V600E mutation testing, in what we believe is an exceedingly rare scenario that could characterize a new subtype of hairy cell leukemia.

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