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# A rare breed: Wild-type braf and ighv expression in a 29 year old lady with classical hairy cell leukemia



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## A B S T R A C T

The V600 BRAF mutation has been described as a key mutation in the pathogenesis of classical hairy cell leukemia (c-HCL) cases without expression of a mutant immunoglobulin heavy chain (IgHV). Here we present a rare case of c-HCL with neither V600 BRAF mutation nor the aforementioned IgHV variant successfully treated with cladribine and review the current literature on its use in women of childbearing age/pregnancy.

## 1. Introduction

Classical hairy cell leukemia is a rare, chronic mature B-cell lymphoproliferative disorder that exhibits specific morphologic, immunohistochemical and immunophenotypic features – expressing CD20, CD22, CD25, CD11c, CD103, CD123 and annexin A1. In 2011, Tiacci et al. proposed a genetic lesion that accounted for all studied cases of classical hairy cell leukemia—the V600E BRAF mutation, which serves in the RAS signaling cascade to propagate cell survival and division [1]. This mutation has been heralded as a key mutation in the pathogenesis of classical hairy cell leukemia, with BRAF-inhibitors being investigated in clinical trials for relapsed c-HCL [2]. Here we present a rare case of wild type BRAF c-HCL in a newly diagnosed woman of childbearing age.

### 1.1. Case presentation

A 29-year old woman is referred to the hematologist for pancytopenia. She denied any symptoms with an unremarkable physical exam. Her complete blood count was significant for leukopenia with severe-moderate neutropenia (ANC of 540), mild macrocytic anemia and mild thrombocytopenia. Initial rheumatologic and nutritional work up for pancytopenia was negative. Bone marrow flow cytometry revealed extensive involvement by monotypic B cells whose morphology and immunophenotype was consistent with c-HCL, expressing most characteristic markers (Fig. 1). Cytogenetics were unable to be performed due to inadequate initial sample and CT scan of the chest, abdomen, and pelvis showed mild splenomegaly. She was V600 BRAF mutation

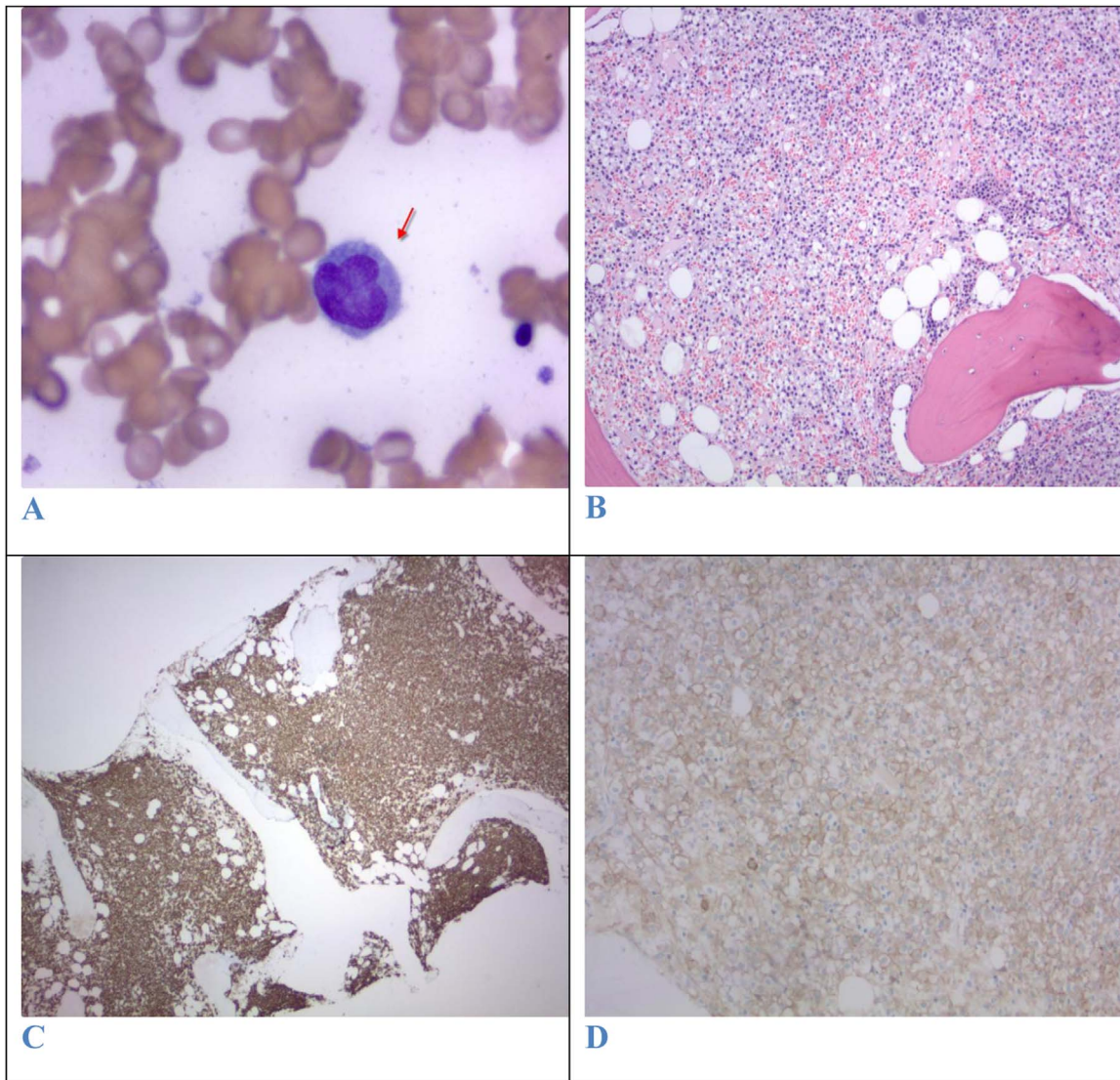
negative with unmutated, wild-type IgHV on PCR. She was referred for oocyte cryopreservation prior to completing one cycle of cladribine, which resulted in myelosuppression requiring transfusion, G-CSF and was complicated by neutropenic fever. No infectious source was found and repeat labs with bone marrow biopsy demonstrated complete remission (CR) with persistent minimal residual disease (MRD) of 5%. Although flow cytometry on hemodiluted bone marrow biopsy post cladribine induction revealed no B-cell clonality, morphologic evaluation showed focal B-cell infiltrate with increased size co-expressing CD25, consistent with c-HCL and estimated at ~5% MRD. PCR was not used to assess disease response since the PCR for BRAF was negative on diagnosis. After 6 rounds of weekly rituximab, the patient remained in complete remission with no evidence of disease on bone marrow biopsy to date.

## 2. Discussion

The differential diagnosis for pancytopenia and splenomegaly in the context of a hypercellular bone marrow and marrow fibrosis, as indicated by the moderate to marked diffuse increase in reticulin fibers (grade 2–3 on a scale of 0–3) includes hairy cell leukemia, myeloid disorders such as myelodysplastic syndromes, myeloproliferative neoplasms, primary myelofibrosis, acute myeloid leukemia and systemic mast cell disease [3]. Based on the morphology of the cells, classical hairy cell leukemia (c-HCL), hairy cell leukemia variant (vHCL) and splenic marginal zone lymphoma (SMZL) should be the main diagnostic considerations. The morphology of the atypical lymphocyte in the bone marrow touch imprint (Fig. 1, A), diffuse infiltrate of the

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**Fig. 1.** A. Touch imprint (romanowsky stain) of the bone marrow core shows a oval lymphocyte with slightly dispersed chromatin, and pale blue moderately abundant cytoplasm with a ill-defined ruffled border. B. Bone Marrow core (hematoxylin & eosin stain) is hyper-cellular for age with diffuse sheets of hairy cell infiltrates. C. Immunohistochemical stain CD20 (B-cell marker) highlights the increased diffuse infiltrate of B-cells in the Bone Marrow core. D. Immunohistochemical stain Annexin-1 (lipocortin 1) highlights the hairy cell infiltrate.

CD20 positive atypical B-cells (Fig. 1, B & C) in the bone marrow and Annexin-1 (Fig. 1, D) positivity of these atypical B-cells confirms the diagnosis of classical hairy cell leukemia. The BRAF V600E mutation is considered key to the pathophysiology and diagnosis of c-HCL. In an attempt to confirm Tiacci, Xi et al. found that 11% of the tested population with c-HCL, without IgHV4-34, expressed wild-type BRAF, alluding to an alternate mechanism of action behind the pathophysiology of c-HCL in these patients. However, patients in this study were seeking treatment for relapsed HCL and had completed at least one cycle of cladribine, unlike our patient. While related wild-type BRAF processes like variant Hairy Cell Leukemia (vHCL) and IgHV4-34+ hairy cell leukemia confer poorer prognoses, the prognosis of wild-type BRAF in c-HCL is unknown; nonetheless, with 85–90% rates of CR after one cycle of cladribine, our patient has responded similarly [4,5]. While BRAF inhibitors, like vemurafenib, have exhibited 30–40% CR and 60% partial response rate in refractory c-HCL, in BRAF wild-type cells, vemurafenib paradoxically increases gene transcription by stimulating the kinase activity of BRAF dimers [6]. Therefore, with case reports documenting BRAF V600 negative c-HCL, we may recommend BRAF screening in exon 15 (v600) and 11 [7]. In addition to this, this case highlights the dilemma surrounding cladribine exposure in a

woman of childbearing age attempting to conceive, for which minimal data exists. Cladribine is a purine analog that inhibits the enzyme adenosine deaminase, interfering with the cell's ability to transcribe DNA. It is characterized as a FDA pregnancy category D where safety and efficacy in children has not been established. The median age of onset at 52 years and c-HCL shares a 4.2 to 1 male to female predilection, indicating the low prevalence of c-HCL in women of childbearing age [6]. In a PubMed literature search for “cladribine, pregnancy”, there is only one case report of successful pregnancy POST cladribine exposure [8]. Further literature search has shown successful splenectomy in a pregnant patient with c-HCL followed by one cycle of cladribine post 6 months breastfeeding, resulting in CR [9].

### 3. Conclusion

This is a rare case of BRAF V600 mutation negative c-HCL with wild-type IgHV that we know of documented in the literature. Though the long-term prognosis is unknown, initial response to cladribine is similar to V600 BRAF c-HCL.

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