



Cladribine-Induced Remission in BRAF V600E–Negative Hairy Cell Leukemia: A Rare Case Report

Emad Dadgar^{1*}, Somayeh Sadat Shariatmaghan², Mostafa Eslami mahmoudabadi³, Amirhosein Nourbakhsh⁴

¹Students Research Committee, Baqiyatallah University of Medical Sciences.

²Division of Hematology and Oncology, Department of Internal Medicine, Faculty of Medicine, Baqiyatallah University of Medical Sciences.

³Students Research Committee, Baqiyatallah University of Medical Sciences.

⁴Students Research Committee, Baqiyatallah University of Medical Sciences.

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***Corresponding author:** Emad Dadgar, Medical Student, Department of Medicine, Baqiyatallah University of Medical Sciences.

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Abstract

Background: Hairy cell leukemia (HCL) is a rare indolent B-cell malignancy classically characterized by the presence of the BRAF V600E mutation, which has important diagnostic and therapeutic implications. BRAF V600E–negative HCL is uncommon, often poses diagnostic challenges, and is generally considered less responsive to standard purine nucleoside analog therapy.

Case Presentation: We report the case of a 42-year-old man who was incidentally found to have pancytopenia during routine blood donation. Initial evaluations suggested chronic lymphocytic leukemia, and the patient was treated with rituximab, corticosteroids, and subsequently ibrutinib, without clinical or hematologic improvement. Progressive cytopenia and splenomegaly prompted reevaluation. Repeat bone marrow examination and immunophenotyping were consistent with hairy cell leukemia. Molecular analysis for the BRAF V600E mutation was negative. Despite the reported lower sensitivity of BRAF-negative HCL to purine analogs, the patient was treated with cladribine in a 21-day regimen along with appropriate antimicrobial prophylaxis. Following therapy, the patient demonstrated gradual and sustained recovery of blood counts, achieving complete hematologic remission. on 5th month follow-up; the patient’s blood counts were normal and sustained remission was achieved.

Conclusion: This case highlights the importance of considering hairy cell leukemia in patients with atypical or treatment-refractory chronic lymphoproliferative disorders. It also demonstrates that selected cases of BRAF V600E–negative HCL may respond favorably to cladribine. Further studies are needed to better define the optimal management strategies for this rare HCL subset.

Keywords: Hairy cell leukemia; BRAF V600E–negative; Cladribine; Pancytopenia; Purine analogs; Case report

Introduction

Hairy cell leukemia (HCL) was first described in 1958 by Bouroncle and associates as a slow-growing tumor linked to pancytopenia and splenomegaly, representing 2% of all leukemias.¹

Hairy cell leukemia (HCL) is an indolent B-cell malignancy, with long-term responses to purine analogs, but with decreasing efficacy and increasing toxicity with repeated courses. Leukemic cells express CD22, CD20, CD25, tartrate-resistant acid phosphatase (TRAP), annexin 1A (Anxa1), and BRAF V600E mutation.²

HCL variant doesn't have CD25, Anxa1, TRAP, and BRAF V600E, and is more aggressive and less purine analog-sensitive.³ Since the BRAF V600E mutation was first identified in hairy cell leukemia (HCL)⁴, it has been extensively studied in various patient groups. Most of these studies have confirmed that the BRAF V600E mutation is present in classical HCL but absent in HCL variant and other mature B-cell cancers. This finding has established a strong basis for the use of targeted therapies in treating classical HCL. Since new therapies of this disease target BRAF, treatment of BRAF negative cases is a challenge.⁵

This case study aims to highlight the clinical challenges and treatment approaches used in a rare instance of BRAF V600E-negative hairy cell leukemia (HCL). It emphasizes the importance of considering HCL in patients with chronic lymphoproliferative disorders that don't respond to treatment, especially when the usual BRAF V600E mutation isn't present. In addition, this report shows the unexpected effectiveness of cladribine in achieving complete remission in a patient with BRAF-negative HCL, a result not often seen in similar cases.

Presentation:

A 42-year-old male who had an incidental finding of pancytopenia during a routine blood donation was presented to the hematology clinic in November 2023. The patient had been donating blood for 15 years. In the summer of 2023, he contracted COVID-19, although he received three doses of Sinopharm vaccine. His infection lasted for about 2 weeks. He reported intense hunger, weakness, cough, malaise, and fever during the disease. No chills, vomiting, or nausea were reported. Notably, the patient experienced an insatiable appetite during the COVID-19 infection. Initial laboratory investigations in November 2023 revealed pancytopenia. Bone marrow aspiration was performed for further investigations. The cellularity was about 60% and a patchy lymphoid infiltration was noted. In immunostains CD20 was

positive and CD3, Annexin A1, DBA44 were negative. Before the final diagnosis, the patient developed clinical symptoms. He reports a palpable mass in his left upper quadrant of the abdomen and pain in the same location. Abdominal CT scan was performed for further investigation. Several lymph nodes with SAD up to 7 mm were seen in pericardial and peritracheal regions and 167*82 mm spleen were reported. Initial diagnosis of chronic lymphocytic leukemia (CLL) was made in the hospital. Treatment with Rituximab (Mabthera/Remptra) was initiated in February 2024. The patient used these drugs for three weeks along with Prednisolone (10 mg/day) Despite this treatment, his blood counts continued to decline.

In May 2024, a new drug regimen was started. He started taking Ibrutinib (420 mg PO qDay). Within ten days of initiating this new treatment, the patient developed petechiae and purpura. His platelet count decreased from 50,000/ μ L to approximately 28,000/ μ L, and his hemoglobin level decreased to 6.9 g/dL.

Due to the lack of response to initial therapies and the development of new symptoms, the patient met another doctor. A repeat bone marrow aspiration and biopsy, along with a few blood tests prescribes by Dr. Shariat suspecting misdiagnosis which led to a diagnosis of hairy cell leukemia (HCL) not CLL. The initial medications were discontinued. The patient underwent a 21-day period of isolation in June 2024, receiving Cladribine (0.1 mg/kg/day), Fluconazole (400mg/day), and Acyclovir (200 mg PO q4hr). In the meanwhile, testing for the BRAF V600E mutation was done showing negative results a week later, despite the clinical suspicion of HCL. Although BRAF negative HCLs typically have limited response to Cladribine, treatment continued because of good response and toleration of this specific patient. The patient experienced weakness and fatigue during treatment but remained ambulatory Following completion of chemotherapy and isolation, the patient's blood counts began to improve. Serial blood tests performed every two weeks showed continued improvement, and by November 2024, all blood counts had normalized indicating sustained remission. Blood counts and their clinical course is shown in **Table-1**.

Table-1: Patient's Blood counts and their clinical course

Date	WBC (x10 ⁹ /L)	Hb (g/dL)	RBC (million/ μ L)	Platelets (x10 ⁹ /L)	Timeline	Comments
14-Jun	1	7.2	2.36	61	Admission	Low WBC, low RBC, low Hb, low platelets
16-Jun	1	7.3	2.38	51	Beginning of chemotherapy	Continued low counts, pre-chemotherapy stage
18-Jun	0.9	8.3	2.64	61	While chemotherapy +Packed cell transfusion	Packed cell transfusion for anemia, low platelets
20-Jun	0.6	9	2.94	69	While chemotherapy	Progression with improvement in Hb and

						RBC
24-Jun	0.5	8.5	2.88	43	While chemotherapy	Platelets low, need for monitoring
27-Jun	1.7	8	2.64	47	End of chemotherapy +after GCSF administration	Post-chemotherapy recovery with GCSF
04-Jul	1.9	8.9	2.63	101	Week after chemo	Improvement in blood counts post-chemo
11-Nov	3.9	11.1	3.45	157	5 months follow-up	Complete recovery of blood counts, normal levels

Normal Ranges:

WBC (White Blood Cells): $3.5\text{--}10.0 \times 10^9/\text{L}$

Hb (Hemoglobin): Men: $13.3\text{--}17.2 \text{ g/dL}$, Women: $11.5\text{--}15.1 \text{ g/dL}$

RBC (Red Blood Cells): Men: $4.2\text{--}6.1 \text{ million cells}/\mu\text{L}$, Women: $4.2\text{--}5.4 \text{ million cells}/\mu\text{L}$

Platelets (plt): $150\text{--}450 \times 10^9/\text{L}$

Discussion:

The description of hairy cell leukemia as a specific clinical entity was published 50 years ago. The clinical outcome for patients was hampered by ineffective chemotherapy, and splenectomy was the major therapeutic approach to improve peripheral blood counts. The median survival after diagnosis was 4 years. The use of α -interferon in 1984 and using it for HCL in 1986 led to significant improvements in patient outcomes⁶. Following this, the development of purine nucleoside analogs turned hairy cell leukemia (HCL) into a highly manageable form of leukemia.⁷ Today, patients with the classic form of this rare leukemia can expect a nearly normal lifespan.⁸ However, accurate diagnosis is crucial because other conditions that resemble HCL do not respond to these treatments.⁷ In classic HCL, Leukemic cells express CD22, CD20, CD25, tartrate-resistant acid phosphatase (TRAP), annexin 1A (Anxa1), and BRAF V600E mutation. HCL variations that do not have CD25, Anxa1, TRAP, and BRAF V600E, are more aggressive and less purine analog-sensitive.⁹

BRAF is a serine/threonine kinase with a regulatory role in the mitogen-activated protein kinase (MAPK) signaling pathway. A mutation in the *RAF* gene, especially in BRAF protein, leads to an increased stimulation of this cascade. This causes uncontrolled cell division and development of malignancy. BRAF V600E mutation is present in almost all classic HCL patients.¹⁰ This mutation is not found in HCL-variant (HCL-v) or IGHV4-34 variants of HCL¹¹. These findings solidify the BRAF V600E mutation as a molecular hallmark of classic HCL. In BRAF V600E-negative HCL cases, two novel mutations in exon 11 of the BRAF gene have been identified¹², prompting recommendations to screen exon 11 in such cases. Additionally, the BRAF mutation has been detected in hematopoietic stem cells of patients with HCL¹³.

The treatment of BRAF-negative HCL can be more challenging compared to BRAF V600E-positive classic HCL. These cases often do not respond to BRAF inhibitors like vemurafenib which have shown good efficacy in treating relapsing diseases¹⁴. The

purine analogs pentostatin (2'-deoxycoformycin, 2'-DCF) and cladribine (2-chlorodeoxyadenosine, 2-CdA) are naturally targeted to lymphocytes and are cytotoxic to both resting and dividing cells. Both drugs induce durable complete remissions (CR) in the overwhelming majority of patients with HCL¹⁵ but the BRAF negative HCLs have shown poor sensitivity to these agents.¹⁶ However, several therapeutic options are available for managing BRAF-negative HCL :

- Rituximab, either alone or in combination with purine analogs, has shown efficacy in BRAF-negative HCL, particularly in relapsed or refractory cases¹⁷.
- While Vemurafenib and BRAF Inhibitors are not effective in BRAF-negative HCL, some cases with alternative BRAF mutations (e.g., in exon 11) may still benefit from targeted therapy. Screening for non-V600E BRAF mutations is recommended in these cases.¹⁸
- Moxetumomab Pasudotox is an anti-CD22 immunotoxin that has been approved for relapsed or refractory HCL, including BRAF-negative cases. It has shown promising results in achieving durable responses.¹⁹
- For refractory or difficult-to-treat cases, participation in clinical trials exploring novel agents, such as BTK inhibitors or MEK inhibitors, may be considered.²⁰
- In rare cases where systemic therapy is not feasible, splenectomy may be considered to alleviate symptoms related to splenomegaly a report has shown that Splenectomy followed by administration of rituximab is useful to treat a patient with hairy cell leukemia-variant.²¹
- There is Support for cladribine plus rituximab comes from small prospective studies that report

complete remission rates (CR) of at least 90 percent in HCLv.²² The favorable response of some cases of BRAF-negative HCL to Cladribine may be attributed to its mechanism of action. Cladribine incorporates into DNA, causing strand breaks and apoptosis, regardless of BRAF mutation status.²³ Cladribine's selective cytotoxicity targets malignant B-cells by interfering with DNA replication and repair, and it also depletes CD4+ T-cells, which may alter the tumor microenvironment. These explain the observed efficacy in some BRAF-negative cases.²⁴

In this instance, we suspected HCL due to the lack of response to standard chemotherapy regimens for CLL. The diagnosis of hairy cell leukemia (HCL) was established through the identification of LCA, CD20, CD25, and CD103 in bone marrow samples. Additionally, testing for the BRAF V600E mutation yielded negative results, complicating the treatment.

Prior to the availability of BRAF testing results, treatment with Cladribine was initiated due to the diagnosis of HCL and the patient's unstable condition. Given its favorable response in the patient, we opted to pursue the continued use of purine nucleoside analogs (Cladribine), which typically exhibit significant efficacy in classic HCL and limited effectiveness in BRAF-negative variants. This approach unexpectedly resulted in complete remission for the patient. Studies have indicated efficacy of Rituximab and Cladribine combination therapy in HCLvs, therefore prior usage of Rituximab in this patient may have helped unforeseen in this situation.

Covid-19 and HCL: Although the specific cause-and-effect link between SARS-CoV-2 infection and HCL is unknown, COVID-19 is known to produce transient hematologic abnormalities. Anemia, leukopenia, lymphopenia, thrombocytopenia, and anemia can worsen pre-existing cytopenia in patients with hematologic diseases. In this patient, virus-induced cytopenia may have caused severe and persistent pancytopenia before a formal diagnosis, complicating clinical assessment and perhaps delaying HCL diagnosis.⁷ EPICOVIDEHA registry data suggests that HCL patients with COVID-19 may have severe illness courses and blood count changes. So assessing hematologic data in this group of patients, recent infection must be considered.²⁵

Conclusion:

HCL should be considered a differential diagnosis in patients suspected of having CLL that is resistant to standard therapy. Certain BRAF-negative hairy cell leukemias have demonstrated favorable responses to therapy with purine nucleoside analogs (Cladribine), warranting consideration as a therapeutic strategy. Additional investigations and randomized controlled trials are necessary to establish suitable treatment protocols for HCL variations.

Ethics and Consent:

We confirm that the study complies with current ethical standards. No names or personal information is mentioned in the article. Informed consent was obtained from the patient for the use of his clinical data in this publication, and the study was conducted in accordance with the Declaration of Helsinki

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