



Case Report

Hairy cell leukemia - A case report with recent updates

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ABSTRACT

Hairy cell leukemia (HCL), a rare, chronic B-cell leukemia, first described as a distinct entity in 1958, was recognized as an entity by the World Health Organization in 2008. The disease accounts for 2% of all leukemias and is more frequent in middle-aged to older men. The diagnosis is based on the hairy lymphoid cells in the peripheral smear and the bone marrow aspiration cytology and the bone marrow biopsy showing a monotonous interstitial infiltrate with a fried egg appearance. The classic immunophenotypic profile in the flow cytometry and the *BRAF* V600E mutation confirm the diagnosis. Herein we report a 52-year-old male patient presented with pancytopenia, high-grade fever, and weight loss. The characteristic histomorphological and the flow cytometry features of this leukemia will be used to discuss further the recent updates on the distinct clinicopathologic features, differential diagnosis, treatment, and prognosis of the entity.

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1. Introduction

HCL and HCL-like disorders like the HCL variant (HCL-V), the splenic marginal zone lymphoma (SMZL), and the splenic diffuse red pulp small B cell lymphoma (SDRPL) are a heterogeneous group of mature lymphoid B-cell disorders which are characterized by the presence of hairy/villous cells. All these have a specific genetic profile, a different clinical course, and a different treatment strategy. So a correct diagnosis is inevitable. HCL usually presents with a triad of splenomegaly, pancytopenia, monocytopenia, and the characteristic hairy cells on peripheral smear. The *BRAF* V600E mutation is present in >85% of patients with classic HCL.

2. Case Report

A 52-year-old male patient was referred to our institution to evaluate pancytopenia, with a history of high-grade fever of 2 weeks duration, not associated with chills and rigor. He had a history of loss of appetite & loss of weight (4kg

over one month). He was a known case of Diabetes mellitus detected three years back.

On clinical examination, he was febrile, anemic, and had massive splenomegaly. No peripheral lymphadenopathy was detected, and all other organs were within normal limits.

His hemogram showed hemoglobin of 9gm/dl, Total WBC count of 4000/l, Platelet count of 70000 cells/mm³, Liver function test with S.Bilirubin of 1.2mg/dl, and SGOT/SGPT/ALP within normal limits. Cultures, viral serology, and malarial antigen were negative. CT abdomen showed massive splenomegaly (21.7x17.1x9.5 cm) with no hepatomegaly or abdominal lymphadenopathy.

Peripheral smear showed normocytic normochromic anemia, thrombocytopenia, and leucopenia, with 22% of large lymphoid cells having an oval nucleus, homogenous chromatin, inconspicuous nucleoli, moderate amount of pale blue cytoplasm with circumferential hairy projections (Figure 1)

Bone marrow cytology also revealed lymphoid cells ranging in size from 10 to 14 microns with moderate cytoplasm, exhibiting frayed cytoplasmic margins & feathery /hair-like projections along with oval and

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indented nuclei with inconspicuous nucleoli. These cells were seen interspersed in between normal erythroid and myeloid cells. (Figure 2).

Bone marrow biopsy showed hypercellular marrow spaces with monotonous interstitial infiltrate of lymphoid cells having rounded to focally indented nuclei, condensed chromatin, abundant cytoplasm, prominent cell borders producing a fried egg appearance of hairy cells (Figure 3). An increase in reticulin fibers was also noted (Figure 4)

Flow cytometric analysis of CD19 positive singlet cells revealed the expression of bright CD20, with co-expression of CD11c/ CD123/ CD103/ CD25/ FMC7 and negative for CD5.(Figure 5)

With the above clinical, cytomorphological, and immunophenotypic findings, the diagnosis of Hairy Cell Leukemia was made, which was confirmed by BRAFV600E mutation study.

The patient was treated with Cladribine. Minimal residual disease (MRD) analysis and peripheral smear after six months did not show neoplastic cells.

Unfortunately, one year later, the patient developed multi-drug resistant klebsiella and passed away.

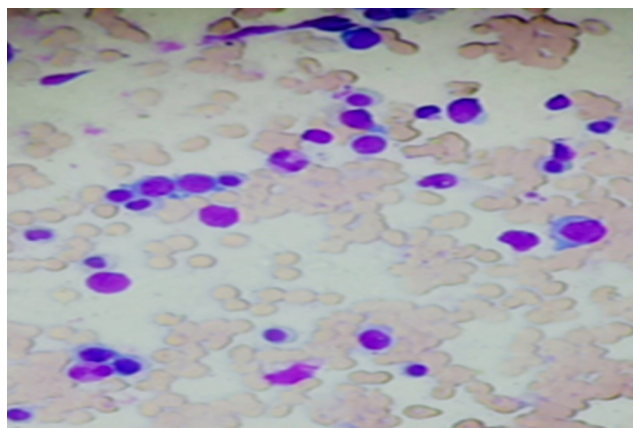


Fig. 2: Bone marrow aspiration cytology stained by May-Grunwald-Gemsa stain (MGG), 200x objective, showed hairy lymphoid cells.

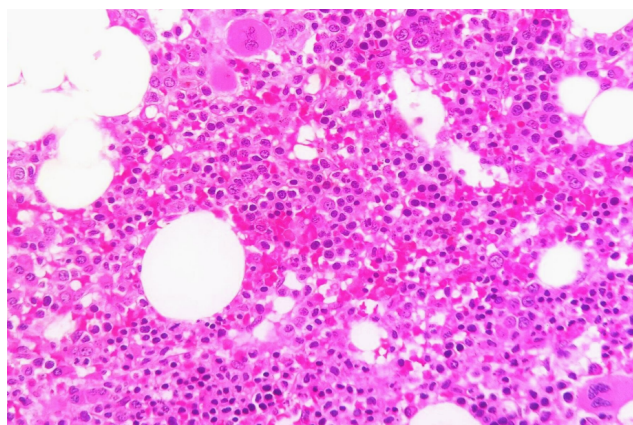


Fig. 3: Bone marrow biopsy, stained by Hematoxylin and eosin stain (H&E), 100x objective, revealed hypercellular marrow spaces with monotonous interstitial infiltrate of lymphoid cells having a fried egg appearance of hairy cells.

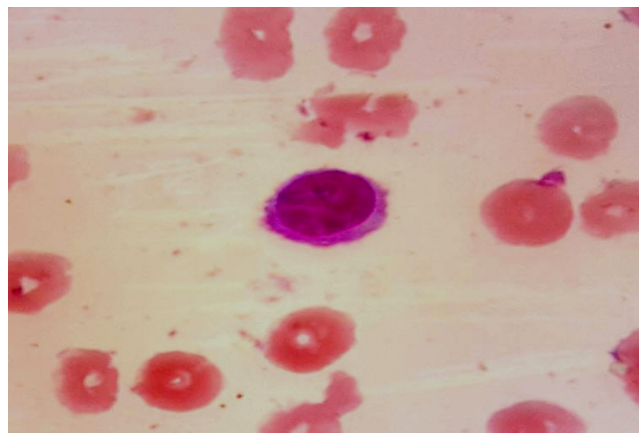


Fig. 1: Peripheral smear stained by May-Grunwald-Gemsa stain (MGG), 400x objective, showed large lymphoid cells with oval nucleus, homogenous chromatin, inconspicuous nucleoli, moderate amount of pale blue cytoplasm with circumferential hairy projections.

3. Discussion

Hairy cell leukemia is an indolent neoplasm of B cell lymphoid cells with circumferential hairy projections involving peripheral blood and diffusely infiltrating the bone marrow and splenic red pulp.^{1,2} The cell of origin of HCL is possibly the late-activated post-germinal center memory B-cells and the splenic marginal zone B-cells.³ Usually occur in an age group of 45-65 years with a mean age of 52 years, can range from 20-80 years, 80% of the patients being men. Patients usually present with

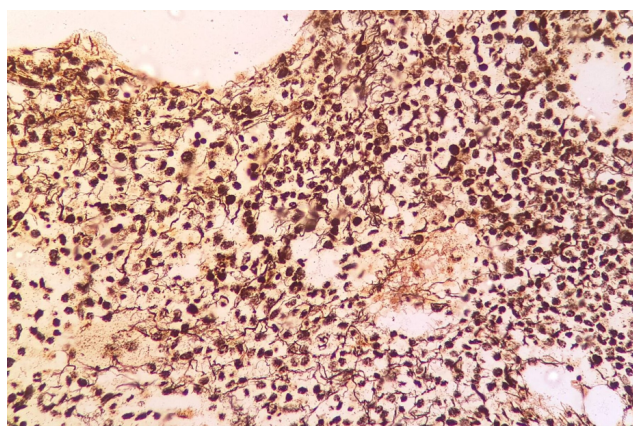


Fig. 4: An increase in fibrosis highlighted by reticulin stain, 100x Objective

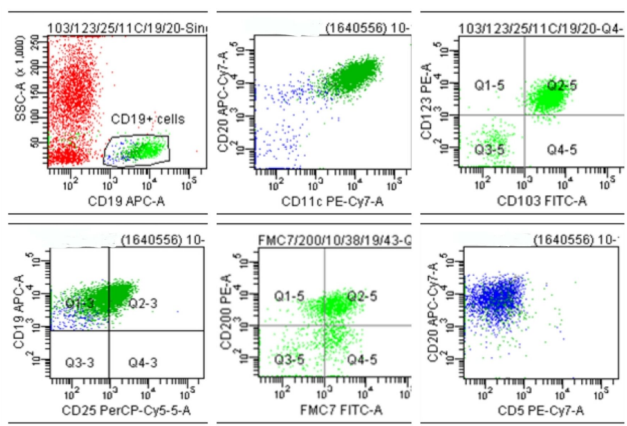


Fig. 5: Flow cytometric analysis of CD19 positive singlet cells revealed the expression of bright CD20, with co-expression of CD11c/ CD123/ CD103/ CD25/ FMC7 and negative for CD5.

fever, weight loss, and frequent infections - commonly atypical mycobacterial infections. Lab investigations show pancytopenia (50%)/ monocytopenia. Patients typically have massive splenomegaly, and 55% may have hepatomegaly. The lymph node involvement is usually rare.²

Ewald, in 1923 first noticed hairy cells and described them as “Leukamische Reticuloendothelie.” Later Bouroncle et al.⁴ in 1958 represented 26 case series with distinct clinical and pathologic features, and in 1966 Schrek & Donnelly used the term “Hairy cell Leukemia” to describe the entity.⁵

Peripheral smear shows pancytopenia and the presence of small to medium-sized hairy lymphoid cells with an oval or indented nucleus, homogenous, spongy, ground glass chromatin, absent/inconspicuous nucleoli, and abundant cytoplasm with circumferential hairy projections.^{1,2} Bone marrow shows diffuse or focal involvement of irregular/poorly demarcated infiltrates with widely spaced cells.^{1,2} The cells can have a perinuclear halo in formalin-fixed tissue due to abundant cytoplasm. The prominent cell borders give a ‘fried-egg appearance’ with formalin fixation. Mitotic figures are usually rare or absent. A reticulin stain highlights the marked increase in fibrosis, and an increase in mast cells is also commonly seen.^{1,2}

Cytometry with strong granular cytoplasmic positivity for tartrate resistant acid phosphatase (TRAP) is seen. Immunohistochemistry shows positivity for CD20, CD22, CD11c, CD103, CD123, CD25, T bet, Annexin A1, DBA44 (CD72), FMC7 and Cyclin D1 and lack CD10 and CD5 expression.^{1,2}

The salient histomorphological and immunophenotypic features of HCL and its differentials are summarized in Table 1.

Hairy cell morphology is due to the overexpression and activation of members of the RHO family of small GTPases

and up-regulation of growth arrest-specific molecule GAS7. Basic fibroblast growth factor (bFGF) and transforming growth factor-beta 1 is the cause for reticulin fibrosis. The minimal lymph node involvement is due to the downregulation of chemokine receptors such as CCR7 and CXCR5.^{1,2}

3.1. The various genomic alterations:³

MAPK Pathway - BRAF V600E somatic mutation was found in a patient with HCL by using whole-exome sequencing (WES) in 2011 and constitute 70- 100% of the cases. The other rare alterations include MAP2K1: **Cell cycle**- COKN1B (p27): **NFKB pathway** - KLF2 : **Spliceosome**- TP53: **NOTCH Pathway** - NOTCH 1:

Epigenetic regulators- KMT2C (histone methyltransferase), ARID1A (SWI/SNF family), KDM6A (histone demethylase), CBEBBP : **TF repressor** - BCOR.

90% of HCL patients have a mutated immunoglobulin gene heavy chain variable rearrangement (IGHV) profile.³

3.2. Treatment strategies

Treatment is needed if the patients are symptomatic or if the hematologic parameters are declining. The hematologic parameters indicating a need for treatment include at least one of the following: hemoglobin <11 g/dL; platelet count <100 G/L; absolute neutrophil count <1 G/L. Symptomatic splenomegaly may serve as an indication for treatment.⁵

Chemotherapy with Purine nucleoside analogs (PNA) like Cladribine (2-CdA) or Pentostatin (DCF) is the standard first-line treatment for HCL, conferring in most cases a more prolonged overall survival. The second-line therapy is by Cladribine/ Pentostatin with Rituximab and Bendamustine.^{4,5}

The uncontrolled infections require Alpha-Interferon (IFN- α), which is also used as an alternative in pregnant women.

Relapsed/ Refractory cases with BRAF V600E mutations are treated with BRAF inhibitors like Vemurafenib, Dabrafenib, or Moxetumomab/ Pasudotox or BRAF inhibitors plus MEK inhibitors like Trametinib/ Cometinib. In BRAF wild-type relapsed/ refractory cases, Moxetumomab/ Pasudotox is used.^{4,5}

Splenectomy may be considered in patients with resistant massive symptomatic splenomegaly with a low-level bone marrow infiltration and pregnant patients with progressive HCL and those refractory to nucleoside analogs and IFN- α .^{6,7}

Allogeneic stem cell transplantation is recommended in younger patients with multiple relapses and refractory to purine analogs and Rituximab.⁸

The response criteria are summarized in Table 2.

The minimal residual disease (MRD) can be done after 4-6 months of therapy.

Table 1: The salient histomorphological and immunophenotypic features of HCL and its differentials.

Leukemia / Lymphoma	Morphology	IHC
Hairy Cell Leukemia (HCL)	Hairy cells- Circumferential hairy projections with a homogenous ground glass chromatin, nucleoli are absent/ inconspicuous. Bone marrow infiltrate- patchy / interstitial	Bright co expression of CD20, CD22 and CD11C with expression of CD103, CD25,CD123, FMC7, Tbet, AnnexinA1, DBA.44 Negative for CD10, CD5
Hairy cell Leukemia Variant (HCL-V)	Hairy cells- Circumferential hairy projections with a condensed chromatin and prominent nucleoli. Bone marrow infiltrate- diffuse / interstitial	Positive for CD20,CD72,CD117,CD103,FMC7 Negative for CD25,CD123, AnnexinA1
Splenic Marginal Zone Lymphoma (SLVL)	Villous Lymphocytes- Plasmacytoid with short polar villi. Bone marrow infiltrate – Nodular / interstitial	Positive for CD20, CD79a Negative for CD23, CD103, CD43,Cyclin D1, CD5, CD10, AnnexinA1
Splenic Diffuse Red Pulp Small B Cell Lymphoma (SDRPL)	Villous lymphocytes- plasmacytoid with short polar villi, vesicular chromatin, and occasional distinct nucleoli. Bone marrow infiltrate- intrasinusoidal / nodular / interstitial	Positive for CD20, CD72 Negative forCD25, CD123,CD23,CD11c

WHO 2017²**Table 2:** Response criteria for HCL

Response Categories	Criteria
Complete Response	Absence of hairy cells on peripheral blood, bone marrow aspiration or biopsy specimens, and the normalization of organomegaly and peripheral blood count.
Partial Response	The normalization of peripheral blood counts, at least 50% reduction in organomegaly and bone marrow hairy cells, and <5% circulating hairy cells.
Relapse	Any deterioration in blood counts related to the detection of hairy cells in peripheral blood and/or bone marrow and/or increasing splenomegaly

Adapted from Robak T et al.⁶

Flow cytometry, using an 8 color panel (CD103/CD305/CD19/CD123/CD25/CD3/CD45/CD20), can be a useful and sensitive tool for detecting blood MRD.¹

3.3. Prognosis

Massive splenomegaly, leukocytosis with an increased number of hairy cells in the peripheral blood, and an immunoglobulin heavy chain variable region gene mutation are considered the worst prognosis. The VH4-34 positive cases are often associated with a poor prognosis.⁹

As the patients are at increased risk of developing second cancers like Hodgkin Lymphoma, Non-Hodgkin lymphomas, and thyroid cancer, a close follow-up is highly recommended. The increased risk may be related to the disease and/or the treatment. The role of Pentostatin or Cladribine in the development of secondary malignancies remains debatable.⁹

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5. Conflict of Interest

The authors declare they have no conflict of interest.

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