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Case Report

Pathology Section

Hairy Cell Leukaemia with Leucocytosis: A Rare Case Report with Review of Literature

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ABSTRACT

Hairy Cell Leukaemia (HCL) is an uncommon disease that accounts for 2% of all lymphoid leukaemias. It is characterised by the proliferation of lymphoid cells with abundant cytoplasm with circumferential fine hairy projections involving the peripheral blood, Bone Marrow (BM), and expanding splenic red pulp. A 50-year-old male presented to the medicine outpatient department with a history of weakness and breathlessness for three days hampering his daily chores. There was no history of any other chronic illness. The review of the peripheral blood smear demonstrated marked leucocytosis showing lymphocytosis. Some of these lymphocytes displayed hairy cytoplasmic projections. Red blood cells showed a dimorphic blood picture. BM aspiration was performed which was insufficient for opinion. BM cell block revealed mononuclear cells with perinuclear clearing giving a fried egg appearance. BM biopsy revealed a predominance of mononuclear cells with round nuclei suggestive of lymphoid cells. These cells showed an interstitial pattern of infiltration. Clear zones are seen around the nucleus (fried egg appearance). A diagnosis of lymphoproliferative disorder with the closest resemblance to HCL was made which was confirmed on Flow Cytometry (FCM) with these lymphoid cells showing positivity for CD45, CD20, CD25, and CD123. HCL with leukocytosis is relatively a rare presentation. Immunophenotyping plays a crucial role in making its diagnosis.

Keywords: Bone marrow, Fried egg appearance, Lymphoid cell

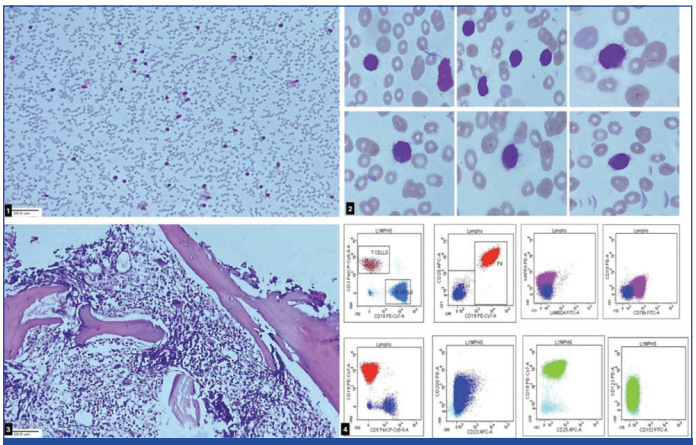
CASE REPORT

A 50-year-old man presented to the outpatient department of medicine with a history of weakness for one month and breathlessness for three days. There was no associated history of numbness, fever, cough, nausea, vomiting, and headache. Also, there was no history of any other chronic illness. On systemic examination, hepatosplenomegaly was present. Haematological examination revealed the following findings [Table/Fig-1].

Hb (12-15 gm/dL)	5.8
RBC (4.5-5.5 million/mm^3)	1.92
MCV (80-100 fL)	90
MCH (27-32 pg)	29.9
MCHC (31.5-34.5 gm/dL)	33.4
RDW (11.6-14%)	16.3
TLC (4000-11000 cells/mm^3)	23600
Platelets (1.5-4.5 lacs/mm^3)	50,000

[Table/Fig-1]: Haematological findings of patient.

Peripheral blood smear examination revealed leukocytosis with 93% atypical lymphoid cells, 4% monocytes, and 3% polymorphs. These neoplastic cells were small to medium sized, characterised by a round to indented nucleus, homogenous ground glass chromatin, and inconspicuous nucleoli. These cells had abundant pale blue cytoplasm with circumferential hairy projections [Table/Fig-2]. Additionally, the red blood cell morphology exhibited a dimorphic pattern, characterised predominantly by microcytic hypochromic anaemia and markedly reduced platelets with normal morphology. BM aspiration was markedly haemodiluted. BM biopsy revealed hypercellular marrow with a predominance of neoplastic mononuclear cells infiltrating marrow in the interstitial pattern. These atypical lymphoid cells had single oval to round nuclei, abundant clear cytoplasm, and prominent cell borders producing fried egg appearance [Table/Fig-2]. There was a reduction in normal haematopoietic elements with an occasional group of erythroid cells showing micronormoblastic maturation. The myeloid series was reduced in number with occasional eosinophils along with few interspersed megakaryocytes. Based on clinical, peripheral blood and BM findings, a provisional diagnosis of HCL was given.



[Table/Fig-2]: 1) Peripheral blood film showing lymphocytosis with neoplastic cells with hairy projections. (Leishman stain. 400X); 2) Peripheral blood film showing neoplastic cells with round to indented nucleus, homogenous ground glass chromatin and inconspicuous nucleoli. These cells had abundant pale blue cytoplasm with circumferential hairy projections (Leishman stain 1000X); 3) Bone Marrow (BM) biopsy showing hypercellularity with a predominance of neoplastic mononuclear cells with an interstitial pattern of infiltration. These atypical lymphoid cells have round nuclei and abundant cytoplasm producing fried egg appearance (Leishman stain. 400 X; Inset - 1000X); 4) Flow Cytometry (FCM) on side scatter/CD19 plot revealing lymphoid cell positive for CD19, CD20, kappa, CD79b, CD200, CD25, CD123, and negative for lambda, CD10, CD5, CD23, and CD103.

Further, FCM was performed with 89% of the gated events on side scatter/CD19 plots revealed CD19, CD20, CD25, CD123, and CD45 positivity [Table/Fig-2]. Final diagnosis of HCL was given. The patient remained almost asymptomatic for next one year and received only supportive treatment in the form of haematinics and two blood transfusions. However, six months ago, he began experiencing weakness which was progressively increasing. He was referred to a higher center where he underwent three cycles of chemotherapy and symptomatic improvement was observed as per information received telephonically from patient.

DISCUSSION

The HCL is a mature lymphoid B cell disorder with an incidence of 2% of lymphoid leukaemias. Classical triad of HCL presents with splenomegaly, pancytopenia, and hairy cells in BM but leucocytosis may be rarely observed in only 10-20% of HCL cases. In 1923, Ewald introduced the term leukaemic reticuloendotheliosis to describe a haematologic disorder marked by splenomegaly, pancytopenia, and circulating monocytic cells. Further, this entity was recognised by Bouroncle, Wiseman, and Doan as a distinct clinicopathologic entity in 1958 and since then it has undergone enormous advances [1,2]. HCL was recognised as an entity by the World Health Organisation (WHO) since in 2008. It was included under the category of mature B cell neoplasms and the HCL variant was classified under the subcategory of splenic lymphoma/leukaemia unclassifiable [3]. However, in the latest 2022 revision of the WHO classification of lymphoid neoplasms, HCL is included under the category of splenic B cell leukaemia/lymphoma along with splenic marginal zone lymphoma, splenic diffuse red pulp small B cell lymphoma and splenic B cell lymphoma/leukaemia with prominent nucleoli encompassing HCL variant [4].

It is a mature lymphoid B cell disorder that is characterised by the identification of hairy cells in peripheral blood smear and BM, a specific immunophenotype profile, a different clinical course, and the need for appropriate treatment. Late activated post germinal center memory B cells and splenic marginal zone B cells are possibly considered as the cell for its origin. Unlike most mature B cell malignancies, it usually lacks lymph node involvement but often presents with splenomegaly with involvement of red pulp, atrophy of white pulp, and pancytopenia [5]. It shows a higher incidence in males with an M:F ratio- 4:1 and a median onset age of 52 years [6]. Typical symptoms include fatigue, weight loss, fever, bleeding, moderate to massive splenomegaly, and hepatomegaly in approximately 50% of cases. Recurrent infections are a significant manifestation and leading cause of mortality [7].

Various differential diagnosis for HCL include reactive lymphocytosis, chronic lymphocytic leukaemia, prolymphocytic leukaemia, splenic diffuse red pulp small B cell lymphoma, splenic marginal zone lymphoma, and mantle cell lymphoma. Chronic lymphocytic leukaemia is characterised by small, mature-looking lymphocytes on peripheral film which express CD5 and lacking expression of CD103. Prolymphocytic leukaemia is defined by the presence of >55% prolymphocytes in peripheral smear which are medium to large size lymphoid cells with round to indented nuclei and prominent nucleolus. These cells express positivity for CD20, CD79a, and CD79b and lack expression of CD23 [8].

Splenic diffuse red pulp small B cell lymphoma features massive splenomegaly and atypical lymphoid cells with broad base cytoplasmic extensions in the polar distribution in circulation. These atypical lymphoid cells lack expression of CD25. Splenic marginal zone lymphoma presents with massive splenomegaly and small lymphocytes with fine villous cytoplasmic projections in circulation which are characterised by the lack of expression of CD103, CD11c and CD25. Mantle cell lymphoma may show small to medium monomorphic lymphoid cells with inconspicuous nucleoli. These cells strongly express cyclin D1 but do not express CD25 or CD103 [8].

The Complete Blood Count (CBC) and careful review of the peripheral blood smear is the first step in its identification. The neoplastic cells are typically sparse in circulation and display round to oval nuclei with indentation, abundant cytoplasm, and discernible circumferential hairy projections in both peripheral blood and BM [9]. As per WHO 5th edition, 2022 (WHO-HAEM5), an immunological scoring system was proposed based on expression of CD11c, CD103, CD123, and CD25, assigning one point to each marker when expressed. A score of 3 or 4 is observed in 98% of cases of HCL whereas in HCL-like disorders the score is usually 0 or 1. These hairy cells are negative for CD5, CD23, CD10 and, CD27. Also, the neoplastic cells can infiltrate BM, thus BM study is crucial for determining the extent of BM involvement and to aid in the diagnosis of challenging cases in which immunohistochemical markers like CD 20, CD 72, and annexin A1 are used to reach the final diagnosis. Annexin A1 is considered as most specific marker since it is not expressed in any B cell lymphoma other than HCL [10,11].

Factors such as splenomegaly exceeding 3 cm above normal, leukocytosis over 1000/µL, the presence of more than 5000/µL hairy cells in the blood, elevated beta2 microglobulin levels more than twice the normal value, increased lactic dehydrogenase, and unmutated Immunoglobulin Heavy-Chain Variable (IGVH) are indicative of a poor prognosis [12]. Treatment is administered only in symptomatic cases or when haematological parameters are deteriorating. The specific haematological criteria indicating the need for treatment include any of the following: haemoglobin levels below 11 gm/dL, platelet count less than 100,000/µL, or an absolute neutrophil count below 1,000/µL. Additionally, symptomatic splenomegaly may also warrant treatment [10,13].

In a study by Galani KS et al., conducted in Mumbai in 2012, 28 cases of HCL were included which were diagnosed over a period of nine years and only two cases (7.14%) were documented with leukocytosis. Patients' ages ranged from 26-69 years with a median age of 47 years, with M:F-6:1. Physical examination revealed splenomegaly in 92% and hepatomegaly in 28% of patients [14]. In another study by Patel K et al., from Gujarat in 2018, done over a period of four years and diagnosed 18 cases of HCL among 300 chronic lymphoproliferative disorders with only four cases (22.2%) of HCL presented with leukocytosis. Patients' ages ranged from 35 to 69 years with male predominance (M:F-6:1) and clinical findings of splenomegaly (78%) and hepatomegaly (22%). Immunophenotype indicated CD19 gated on lymphocytes with co-expression of CD103, CD11c, and CD25 [15]. They concluded that HCL can occur at a younger age, potentially due to geographical factors with unusual presentations like lymphadenopathy and leukocytosis. In another study by Chatterjee T et al., 15 cases of HCL were studied over a period of two years of which only one case (6.6%) had leukocytosis [16]. [Table/Fig-3] discuss the review of literature of HCL case reported with leukocytosis [7,8,15-17].

	Adley BP et al., [9] (2003)	Kataria SP et al., [17] (2012)	Sapre JP et al., [7] (2013)	Fugere T et al., [18] (2021)	Kumari L et al., [19] (2021)
Age/sex	42/M	50/M	29/F	44/M	75/M
Clinical features	-	Fever and weight loss	Fever, fatigue and weakness	Dizziness, bleeding gums and epistaxis	Severe fatigue and weight loss
Organomegaly	Splenomegaly	-	Splenomegaly, hepatomagelay and inguinal lymphadenopathy	Splenomegaly and lymphadenopathy	Massive splenomegaly
Hb (g/dL)	9.9	10	3.1	3.0	10.9
TLC (cells/mm^3)	15400	16000	38000	25000	40200
Platelet (/mm^3)	1.5 lac	1.5 lac	<10000	31000	10800
IPT	CD19, CD20, CD25, CD11c, CD103	CD20, CD103, CD11c, CD25	CD19, CD20, DBA44, TRAP, CD11c, and CD103	CD19, CD22, CD25, CD23, CD103, CD200	CD19, CD22, CD79b, CD11c, CD103, CD200, CD123

Treatment	2-chlorodeoxyadenosine (2- CdA)	No treatment	-	Cladribine+rituximab	Cladribine, acyclovir and cotrimoxazole
Follow-up	Complete remission	No cytopenia, organomegaly	-	Complete remission	Complete remission

[Table/Fig-3]: Review of literature of HCL case reports with leukocytosis [7,9,17-19].

In a study by Adley BP et al., it was concluded that patients with HCL usually present with pancytopenia and only rarely with leukocytosis. This rare presentation of HCL should be kept in mind in order to provide accurate diagnosis and proper treatment of this disease [9].

In a case reported by Fugere T et al., a 44-year-old male presented with dizziness and history of falling on the ground. Initial laboratory results revealed leukocytosis (25,000/mm^3), anaemia (3 gm/dL), and thrombocytopenia (31000/mm^3) [18]. Imaging study revealed a subdural haematoma, massive splenomegaly and diffuse lymphadenopathy. FCM revealed CD45 bright neoplastic B cells with bright co-expression of CD19 and CD22, dimmer CD20, CD25, CD103, CD23, CD200, and FMC7 and were negative for CD5 and CD10. The patient was given cladribine and rituximab which was continued on weekly basis for four weeks after completion of the cladribine. After the fourth cycle of rituximab, his haemoglobin improved to >11 g/dL, platelets to >100,000/µL, and absolute neutrophil count to >1500/µL, indicating a complete response [18].

Single case reports of HCL presenting with leukocytosis were also observed by Sapre JP et al., Kataria SP et al., and Kumari L et al., [7,17,19]. In all these cases, the detection of hairy cells in peripheral blood associated with leukocytosis clinched the diagnosis however final diagnosis was confirmed by immunophenotyping.

Our case also represents another uncommon instance of HCL, with diagnosis confirmed through morphology and immunophenotyping. Furthermore, this case along with potentially preceding cases highlights that while HCL typically presents with pancytopenia, rare occurrences may manifest with significant leukocytosis. This potentiality should be considered to ensure early diagnosis and appropriate treatment. This disease is curable and notably responsive to nucleosides (purine analogs). Delayed diagnosis due to atypical disease presentation may result in preventable mortality.

CONCLUSION(S)

This case highlights that the possibility of HCL should be suspected in all patients presenting with atypical lymphocytosis and splenomegaly. Although immunophenotyping is essential for confirming the diagnosis, most cases are picked by insightful observation of hairy cells in peripheral smear examination by pathologists.

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