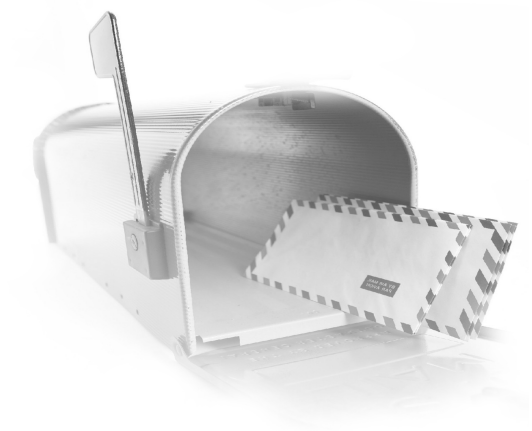

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Letters to the Editor

Synchronous hairy cell leukemia and chronic lymphocytic leukemia: a case report with a brief review of literature

TO THE EDITOR: Hairy cell leukemia (HCL) is a rare indolent mature B-cell neoplasm comprising 2% of all lymphoid leukemias [1]. Typically, a patient presents with splenomegaly, pancytopenia and characteristic monocytopenia, and usually a few circulating lymphoid cells with circumferential hair-like cytoplasmic projections. The diagnosis is based on typical morphological and immunophenotypic features of the neoplastic cells in peripheral blood and bone marrow aspirate.

With the advent of various new chemotherapeutic agents, the survival of patients with HCL has greatly improved; however, population-based studies have highlighted an increased risk of second malignancies on long term follow-up in such patients. Among these, Hodgkin lymphoma, non-Hodgkin lymphoma, and thyroid cancer are common second malignancies [2]. Occasionally, synchronous occurrences of HCL with other hematolymphoid neoplasms at the time of diagnosis have been reported [3-12]. Among these, B-cell lymphomas, followed by T-cell lymphomas and myeloid malignancies are common types. These second malignancies most frequently coexist with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), although only a few case studies have been reported.

Here, we report a case of HCL with a synchronous clone of CLL/SLL cells in peripheral blood and bone marrow in a patient with splenomegaly and pancytopenia.

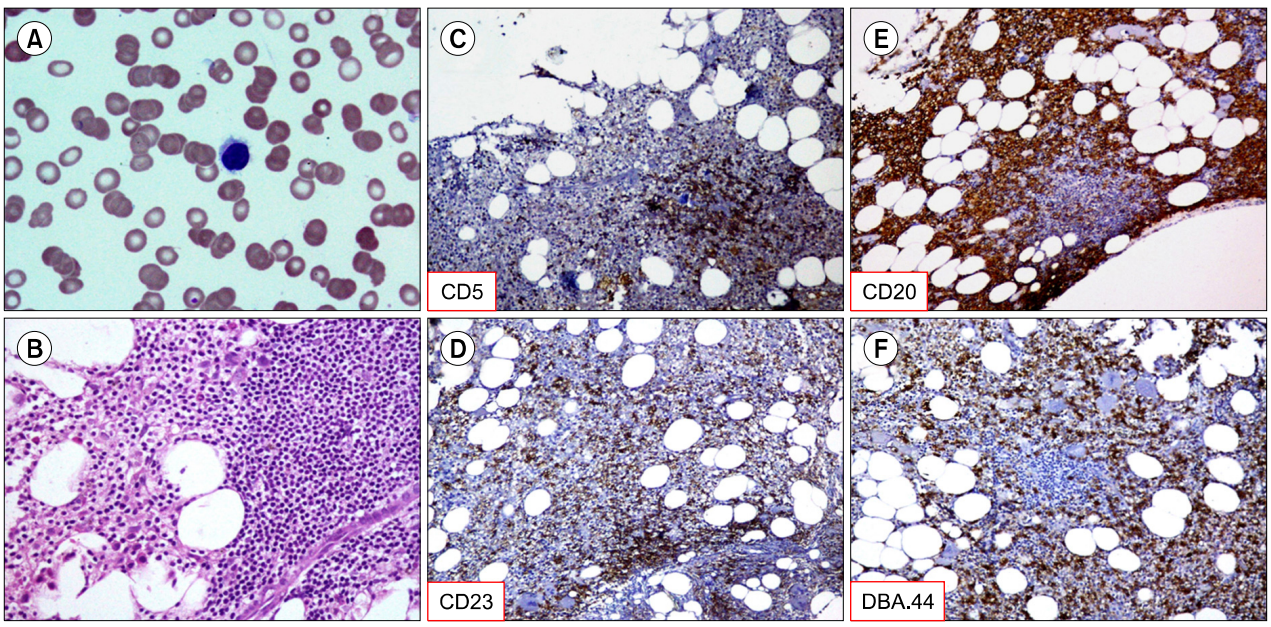

Fig. 1. Morphological and immunophenotypic findings of the neoplastic cells. **(A)** Peripheral blood smear showing a typical "hairy" cell (May-Grunwald Giemsa stain, ×1,000). **(B)** Trephine biopsy showing predominantly "hairy" cells with fried egg appearance and an interstitial nodule of mature appearing lymphoid cells (H & E stain, x600). **(C, D)** Immunohistochemistry for CD5 and CD23 respectively showing positivity in interstitial nodules of lymphoid cells (Hematoxylin counterstain, ×400). **(E, F)** Immunohistochemistry for CD20 and DBA.44 highlighting the "hairy" cells and negative in lymphoid nodule (Hematoxylin counterstain, ×400).

The patient was 75-year-old male with history of generalized weakness, loss of weight and appetite along with early satiety, and abdominal distension over a 3-month period. On examination, there was sub-centimetric axillary and inguinal lymphadenopathy along with hepatosplenomegaly. Complete blood count (CBC) analysis revealed pancytopenia (hemoglobin, 6.4 g/dL; total leukocyte count, 4.1×10^9/L; absolute neutrophil count, 0.94×10^9/L; and platelet count, 60×10^9/L). The peripheral blood smear had predominantly mature-appearing lymphocytes (77%). However, some of these cells (approximately 5%) had a moderate amount of cytoplasm with fine hairy circumferential projections (Fig. 1A). The aparticulate and hemodiluted bone marrow aspirate predominantly showed lymphocytes and a few (13%) "hairy" cells. Flow cytometric immunophenotyping of the bone marrow aspirate revealed two populations of CD19 bright positive cells. The larger population (approximately 36%) was positive for CD5, CD23, CD20, CD43, and CD200 along with weak lambda light chain restriction, and was negative for CD79b, CD10, and FMC-7, consistent with a phenotype of CLL/SLL. A smaller proportion (approximately 6%) of CD19 bright positive cells displayed positivity for CD20, CD11c, CD103, CD25 and lambda light chain restriction, indicative of a phenotype of HCL (Fig. 2). The trephine biopsy section had lymphoid infiltrates. The marrow spaces were hypercellular with extensive interstitial infiltration by characteristic "hairy" cells having abundant cytoplasm and distinct cell borders, giving them a "fried egg" appearance (Fig. 1B). In addition, there were multiple well-defined interstitial nodules of mature-appearing lymphoid cells. The characteristic pericellular distribution of fibrosis seen in HCL was identified in the interstitial infiltrates on reticulin stain. On immunohistochemistry, the two distinct populations were well characterized with the lymphoid nodules showing positivity for CD5 and CD23 (Fig. 1C, D) and the hairy cells showing positivity for CD20 and DBA.44 (Fig. 1E, F).

The diagnosis of a composite lymphoma-predominant HCL with a minor clone of CLL/SLL was made. The patient declined therapy.

HCL is an indolent B-cell neoplasm with a good prognosis due to the availability of effective therapeutic agents [2]. Although metachronous lymphomas and malignancies have been well characterized in HCL patients undergoing chemotherapy, synchronous hematolymphoid malignancies have rarely been reported as case reports. Among the synchronous hematolymphoid malignancies, CLL [3, 4, 11, 12], multiple myeloma [5], chronic myelogenous leukemia [6], peripheral T-cell lymphoma [7], large granular lymphocytic leukemia [8], Hodgkin lymphoma [9] and hepatosplenic T-cell lymphoma [10] have been reported. CLL has an unusual propensity for being one of the components for reasons that remain unclear.

To the best of our knowledge, only five cases of synchronous HCL with CLL/SLL have been reported. Giné *et al.* [3] reported two cases of synchronous and one case of metachronous CLL with HCL. This combination may in fact be rare, or is being missed, and therefore under-reported. The salient clinico-pathologic features of the reported cases are compared with the current case in Table 1.

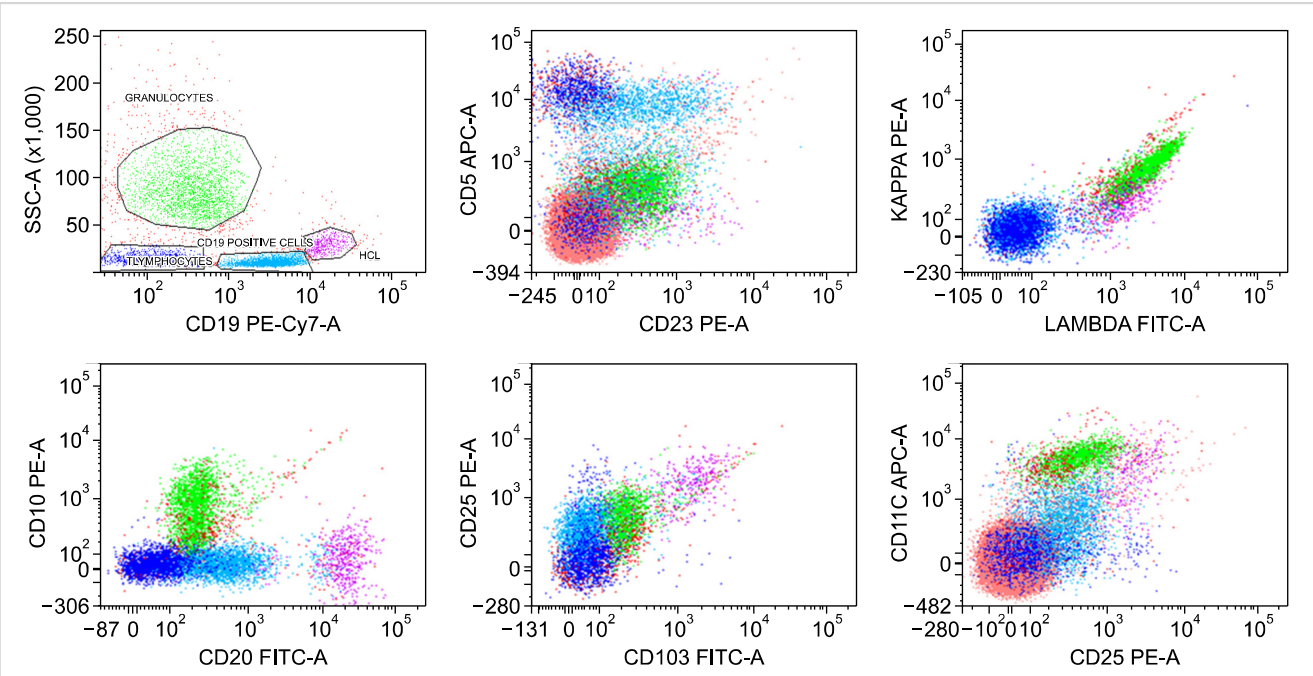

Fig. 2. Immunophenotyping of the neoplastic cells in bone marrow aspirate at the time of diagnosis by four-color flow cytometry (dot-plot analysis). CLL/SLL cells (sky-blue) showing characteristic phenotype: $CD5^+$, $CD23^+$, sIg^{weak+}, $CD20^{weak+}$ and $CD10^-$ whereas HCL cells (purple) showing $CD20^{bright+}$, $CD25^+$, $CD103^+$, $CD11c^{bright+}$, $sIg\lambda^+$, $CD23^-$, $CD5^-$, and $CD10^-$.

Table 1. Clinicopathologic characteristics of patients with synchronous HCL and CLL/SLL.

Case No.	Age	Gender	Splenomegaly	Lymphadenopathy	TLC ($\times 10^9$/L)	Hairy cells (%) in aspirate/trephine biopsy	Reference
1	59	M	Moderate	Retroperitoneal	9.53	54% on aspirate	Giné *et al.* [3]
2	49	M	Moderate	None	1.7	41% on aspirate; Diffuse infiltration in trephine biopsy	Giné *et al.* [3]
3	83	M	Mild	Asymptomatic peripheral	21.8	90% in trephine biopsy	Sokol *et al.* [4]
4	63	M	Mild	None	4.03	Biopsy findings not mentioned (12% on aspirate smears)	Garrido *et al.* [11]
5	77	M	Mild	None	2.5	40% in trephine biopsy	Zhang *et al.* [12]
6	75	M	Moderate	Sub-centimetric peripheral and approximately 1 cm periportal	4.1	13% on aspirate; 80% in trephine biopsy	Present case

All six cases occurred in elderly males, with mild to moderate splenomegaly and asymptomatic lymphadenopathy, bi-/pancytopenia, and a predominant HCL population in trephine biopsy. Four of the cases had relative lymphocytosis. Immunoglobulin heavy chain gene rearrangement studies at the time of diagnosis were performed in cases 2 and 5 and revealed two clonal bands, whereas for cases 1 and 4, this was performed post-chemotherapy and showed one and two bands, respectively. The presence of *BRAF V600E* and *RB1* (L343fs*6) mutations in distinct clonal populations of HCL and CLL, respectively, was demonstrated in case 5. Because of cytopenia/symptomatic organomegaly, cases 1 to 5 were initially treated with 2'-Deoxycoformycin (dCF)/2-Chlorodeoxyadenosine (2-CdA) chemotherapy regimen for the HCL component and showed a good clinical and hematological response, but the CLL/SLL clone was still detectable on flow cytometry/molecular studies. After completion of chemotherapy, case 3 showed progression in the form of severe anemia due to CLL infiltration in the bone marrow, and was then treated with rituximab, and became stable. Our patient did not opt for therapy.

In these cases, there was a predominant component of HCL, persistence of CLL/SLL component post-chemotherapy, and presence of either a single clone or two different clones giving rise to two distinct neoplastic populations. The clonal origin of these cells was established only in two cases and was not available in other cases at the point of diagnosis; hence, making it unclear as to whether the same or a different clone gave rise to two different neoplastic cell populations.

The favored cell of origin in HCL is the post-germinal center memory B-cell [13] whereas for CLL, this remains unclear. Germinal-center experienced cells or memory-like B cells generated in a T cell–independent reaction have been shown to be the initiating cells for CLL pathogenesis [14]. It can only be conjectured as to which came first, either HCL or CLL, and whether the CLL clone gave rise to HCL or vice-versa, as both can also arise from post-germinal center cells. Either one could have contributed to the occurrence of the other because of associated impaired immune surveillance in patients with lymphoid neoplasms [15]. Patients with two clones initially may show differential response to chemotherapy with the susceptible clone rendered undetectable and the less susceptible clone proliferating and dominating over time. This is unlikely in the pathogenesis of the index case since the patient was naïve to lymphoreductive therapy. Further studies would be helpful to elucidate the pathogenetic mechanisms of the evolution of these clonal neoplasms. CLL can be detected early, even without organomegaly and before the anemia and thrombocytopenia supervene due to lymphocytosis. Concurrent HCL with marrow fibrosis in this case may have contributed to the lack of absolute lymphocytosis.

To conclude, this case highlights a rare association of the two B cell lymphoid neoplasms detected from marrow infiltrates. This case adds to the existing pool of cases with synchronous HCL and CLL, highlights the power of flow cytometry in identifying them with certainty, and underlines the need for detection of as yet unknown pathways in the pathobiology of lymphoid neoplasms.

Pulkit Rastogi[1], Preethi Jeyaraman[2], Man Updesh Sachdeva[1], Pankaj Malhotra[2], Jasmina Ahluwalia[1]

[1]Department of Hematology, [2]Department of Internal Medicine, Postgraduate Institute of Medical Education & Research, Chandigarh, India

Correspondence to: Jasmina Ahluwalia
Department of Hematology, Postgraduate Institute of Medical Education and Research, 5th Floor, Research Block A, Chandigarh, 160012 India
E-mail: japgi@live.com, jasminapgi@gmail.com

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Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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The first concurrent diagnosis of acute symptomatic Babesiosis and chronic myeloid leukemia in a healthy young adult

TO THE EDITOR: Babesiosis is an infectious disease caused by hemoparasite *Babesia* and transmitted by certain ticks or transfusions. Few *Babesia* species (*B. microti*, *B. venatorum*, *B. duncani*, *B. divergens*) are associated with human infection. Although many patients are asymptomatic and recover spontaneously, the infection can be persistent, refractory, and life-threatening in immunosuppressed hosts, especially those receiving chemotherapy or immunosuppression, transplant, or splenectomy [1-4].

We report the case of a healthy young patient who was concurrently diagnosed with acute symptomatic Babesia infection and chronic myeloid leukemia (CML). A 23-year-old man, living in New Hampshire, presented with fever, fatigue, myalgia, and arthralgia for 2 weeks. The patient had no history of any malignancy, transfusion, chemotherapy, or immunosuppression. He had no recent travels or did not recall any tick exposure.

At admission, the patient complained of sweating, body aches, and headache. Physical examination was unremarkable except fever (40°C). Blood tests showed left-shifted neutrophilic leukocytosis (white blood cell: 89.6×10^3/μL; myelocyte 17%, metamyelocyte 8%, band/segmented neutrophil 69%, lymphocyte 3%, monocyte 3%) and normocytic anemia (hemoglobin 9.3 g/dL; mean corpuscular volume 84.5 fL). Serum liver function tests were normal except increased lactate dehydrogenase (654 U/L). Abdominal computed tomography scan showed splenomegaly. After specimen collection for blood culture and serologic tests to rule out the infectious etiology, the patient was started on general antimicrobial therapy. The blood culture for aerobic and anaerobic microorganisms was negative. Serologic tests showed positive *B. microti* immunoglobulin M (IgM; >1:320; reference range, <1:20) and cytomegalovirus (CMV) IgM (2.57; reference range, <0.89). Human immunodeficiency virus screening, Lyme IgM/IgG, Epstein-Barr virus anti-viral capsid antigen IgM, *B. microti* IgG, and *Anaplasma phagocytophilum* IgM/IgG antibodies were negative. Monospot test result was negative.

Given the presence of marked left-shifted neutrophilic leukocytosis in peripheral blood (PB), bone marrow (BM) biopsy was performed to rule out leukemoid reaction or underlying myeloid neoplasm. BM biopsy showed hypercellularity (100%) and left-shifted granulocytic hyperplasia. Megakaryocytes were slightly increased with many having small hypolobated (dwarf) forms (Fig. 1A, B). Sea-blue histiocytes were increased. However, there were no increased blasts or significant dysplasia. Flow cytometric analysis showed no evidence of a lymphoma or leukemia. Results