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RARE CASE OF CD10$^+$CD23$^+$ HAIRY CELL LEUKEMIA WITH LEUKOCYTOSIS. CASE REPORT AND LITERATURE REVIEW

A rare case of hairy cell leukemia with CD10$^+$CD23$^+$ expression and leukocytosis is described. The key point marker for hairy cell leukemia is the presence of the BRAF V600E mutation regardless of the leukocyte count and atypical aberrant CD10$^+$ or CD23$^+$ expression. The presented clinical case report is important for understanding the biology of hairy cell leukemia and emphasizes the role of molecular genetic testing in atypical morpho-phenotyping disease presentation.

Keywords: hairy cell leukemia, leukocytosis, CD10$^+$CD23$^+$ aberrant expression, BRAF V600E mutation, case report.

Hairy cell leukemia (HCL) is a very rare lymphoproliferative disease currently classified by the World Health Organization (WHO) as a mature B-cell neoplasm [1, 2]. HCL represents 2% of all adult leukemias and is four times more common in men than in women. Approximately 1600 new HCL cases per year are diagnosed in Europe [3]. In Ukraine, the incidence of HCL is 1 case per 150,000 people per year [4, 5]. Leukocytosis due to absolute lymphocytosis is rarely observed in classic HCL [6—8]. Atypical phenotypes of CD10$^+$CD23$^+$ cells according to flow cytometry are also not often reported [9—11]. The presence of the *BRAF* V600E mutation is a key diagnostic marker for a classic HCL [2—4, 11—13]. This mutation of the *BRAF* gene plays an important role in the pathogenesis of this disease.

We describe one case from our clinical practice representing a classic HCL with an atypical presentation with aberrant CD10$^+$CD23$^+$ expression and leukocytosis.

Case presentation

A 65-year-old man presented to the Hematology department in February 2023 with pronounced fatigue, more than 7 kg weight loss during the previous 3 months, and night sweating. A physical examination revealed an enlarged palpable spleen, which protruded the costal arch by 6 cm, with no

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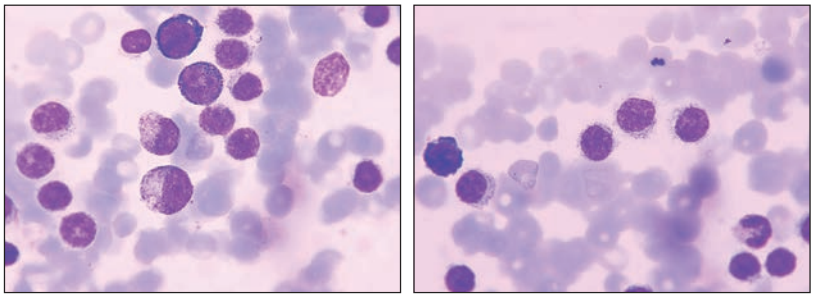

Fig. 1. Smear of the bone marrow. Staining: Romanovsky — Giemza. ×100

superficial lymphadenopathy. The results of the complete blood count revealed leukocytosis: white blood cell (WBC) count 24.34 × 10^9/L, absolute lymphocytosis 88%, mild anemia with a hemoglobin (HGB) level of 117 g/L, and thrombocytopenia: platelet (PLT) count 72 × 10^9/L. A lymphoproliferative neoplasm was supposed, and peripheral blood flow cytometry was performed in the CSD laboratory, Kyiv. This analysis revealed a population of atypical lymphoid elements that make up 71% of nucleated cells and carry the following immunophenotype: $CD45^+$ (100%), $CD3^-$, $CD4^-$, $CD5^-$, $CD8^-$, $CD10^+$ (60%), $CD11c^+$ (98%), $CD19^+$(100%), CD-20hi$^+$ (100%), CD22hi$^+$ (100%), $CD23^+$ (67%), $CD25^+$ (84%), $CD38^-$, $CD43^-$, $CD49d^+$ (100%), $CD79b^+$ (100%), CD103part$^+$ (58%), $CD123^+$ (68%), $CD200^+$ (51%), and lambda$^+$ (93%).

Blood serum examination revealed a slight increase in β_2-microglobulin to 2962.0 μg/L and the lactate dehydrogenase level within the normal range of 238.6 U/L. The multislice computed tomography (MSCT) screening detected splenomegaly (spleen of normal structure, size 186 × 75 × × 136 mm), and the chest and abdominal and pelvic lymph nodes were not swollen. These results corresponded to those of HCL, but the aberrant expression of $CD10^+$ and $CD23^+$ and leukocytosis confused the diagnosis.

We continued the patient's examination. The bone marrow aspiration showed hypercellularity, an undetected blast count of 0%, 1% lymphoblasts, 89% lymphocytes, 6% mature neutrophils, 0% basophils, 0% eosinophils, 2% polychromatophilic megaloblasts, 2% plasma cells, and 0% monocytes. The bone marrow smears (Fig. 1) revealed total infiltration by lymphoid cells with hairy cytoplasm.

According to the results of the trephine biopsy morphological examination, the bone marrow was hypercellular with reticulin fibrosis (MF-1) and diffuse lymphoid infiltrates in all clusters. Immunohistochemical analysis revealed that the tumor cells were positive for CD20, cyclin D1, CD11c, CD103, CD123, annexin A1, and T-bet and negative for CD3 and SOX-11 (Fig. 2, *a*—*f*). These results indicated that HCL injures the bone marrow.

The final HCL diagnosis was confirmed by the presence of a *BRAF* gene mutation in the V600 codon, which was assessed by the real-time polymerase chain reaction.

The patient underwent one course of CT with cladribine 10 mg/day for 5 days in March 2023. After completion of treatment, complications of therapy were observed, namely grade 4 neutropenia (0.2 × 10^9/L), grade 3 anemia (HGB 78 g/L), and grade 3 thrombocytopenia (46 × 10^9/L). These conditions involved treatment with colony-stimulating factors and erythropoietin, and no blood transfusions were performed. The patient's condition was evaluated after 3 months in July 2023, with no complaints, and the spleen was not palpable. There were no changes in the complete blood count: WBC 5.14 × 10^9/L; RBC 4.40 × 10^{12}/L; HGB 145 g/L; PLT 174 × 10^9/L; basophils 1%; eosinophils 1%; banded neutrophils 6%; segmented neutrophils 72%; lymphocytes 14%; and monocytes 6%. In the myelogram, the bone marrow was normocellular with reactive changes after CT, slightly dysplastic and megaloblastic erythropoiesis, and the cell distribution was normal, with 7.5% lymphocytes and no lymphocytes with hairy cytoplasm. MSCT revealed a normal spleen size. The patient achieved a complete response (CR). After 15 months in July 2024, the patient was still in CR with no complaints, normal blood and bone marrow parameters, and normal spleen size. Given the patient's response to the standard treatment, the prognosis is favorable.

Discussion and Literature Review

HCL is a rare disorder typically affecting middle-aged to older adults, with a median age at diagnosis

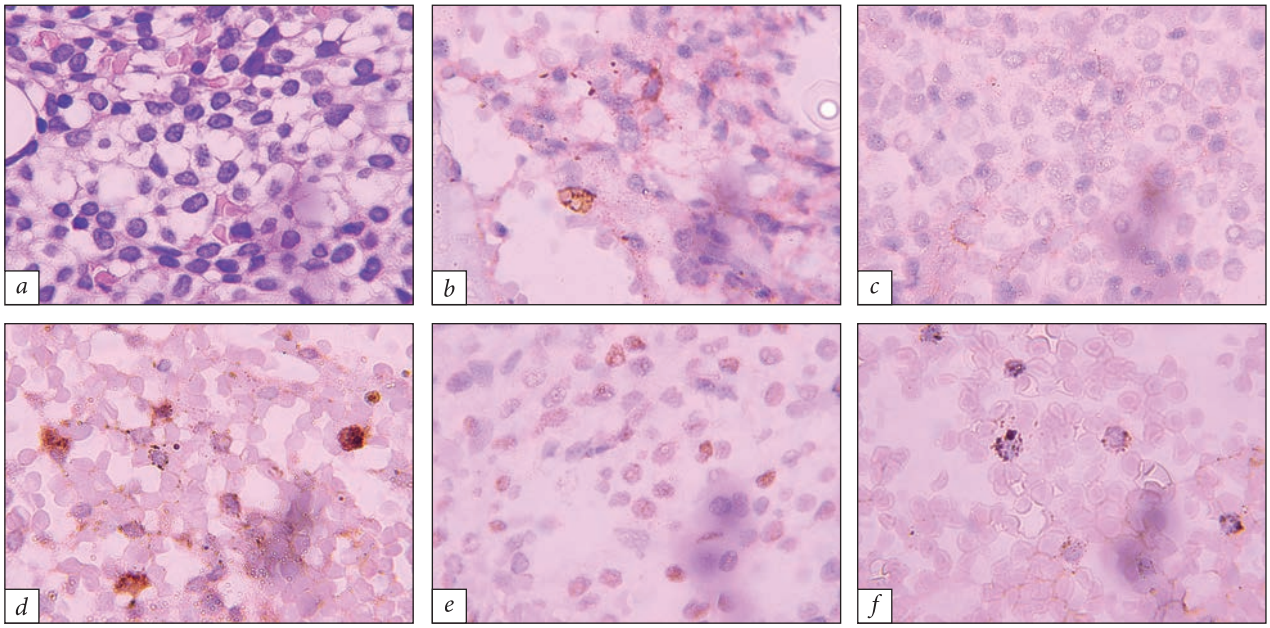

Fig. 2. Biopsies of the bone marrow. Staining: hematoxylin and eosin (*a*); CD103 (*b*); CD123 (*c*); annexin A1 (*d*); cyclin D1 (*e*); T-bet (*f*). ×100

of approximately 52—60 years [2, 13]. HCL was first recognized by Ewald in 1923 and was described as *Leukaemische reticuloendotheliose* [8]. Later, in 1958, Bouroncle described it as a distinct clinicopathologic entity, and in 1966, Schrek and Donnelly coined the term "hairy cell leukemia" when describing the irregular cytoplasmic projections of the abnormal malignant cells circulating in the blood or originating in the bone marrow [8, 14].

The frequency of clinical and laboratory manifestations of HCL is as follows: splenomegaly is noted in 80% of patients, leukopenia in 70%, neutropenia in 75%, monocytopenia in 90%, "hairy" lymphocytes in peripheral blood smears in 95% of patients, thrombocytopenia in 80%, anemia in 70% of patients, abdominal lymphadenopathy in 15—25%, and monoclonal gammopathy in 10% of patients [4, 5]. HCL with leukocytosis is a rare condition, reported mainly in cases of variant HCL without *BRAF* V600E [6—8]. According to current concepts, HCL-variant (HCL-V) is an indolent lymphoid neoplasm that may sometimes mimic "hairy cells" morphologically but has another specific biology, treatment options, and prognosis, and according to the WHO classification, HCL-V is no longer related to classic HCL [1—3, 15].

The classic HCL morphologically presents neoplastic cells in the peripheral blood smears, which are twice the size of a lymphocyte and have a round or kidney-shaped nucleus with loose chromatin and abundant pale cytoplasm with projections. Monocytopenia and macrocytosis are very common; other cytopenias may be present. Bone marrow biopsy reveals a diffuse or interstitial infiltration of hairy cells. The cells typically have a "fried-egg" appearance. Bone marrow aspiration may yield a "dry tap" due to significant reticulin fibrosis [3]. The typical HCL immunophenotypic picture shows the clonal proliferation of mature B-cells arrested at a late stage of differentiation with a strong light chain restricted surface immunoglobulin with the following immunophenotype: bright expression of CD19, CD20, CD22, and CD200. Clonal hairy cells are usually negative for CD5, CD23, CD10, and CD27 and positive for CD11c, CD103, CD123, and CD25 [2, 11, 13, 15, 16]. The aberrant expression of CD5, CD10, and CD23 and the loss of expression of CD103 and CD123 have been reported infrequently [9—11]. Wang et al. [10] notice that only approximately 14% of HCL cases may be seen with $CD10^+$ leukemic cells. Chen et al [11] found $CD23^+$ in 17% of classic HCL patients, while the co-expression of $CD10^+/CD23^+$ only in 3% of patients. The combination of $CD10^+$and $CD23^+$ markers and leukocytosis is more typical for small mature B-cell lymphoma, follicular lymphoma, and Burkitt lymphoma, which is why the peripheral blood flow cytometry results were not enough in our case. We continued examination, which included trephine biopsy of the bone marrow and molecular genetic test-

ing to make a differential diagnosis between these mature B-cell neoplasms.

The *BRAF* V600E mutation is found in 95% of HCL cases, which distinguishes HCL from other B-cell lymphoproliferative diseases, as well as from variant form of HCL. The classic HCL responds well to purine analogs, whereas HCL-V often requires alternative treatments [2, 3, 13]. Understanding these differences is essential for accurate diagnosis and choosing the appropriate treatment strategy for each patient. In our case, molecular genetic testing for *BRAF* mutation helped us recognize the classic type of HCL, which resulted in proper treatment assignment.

Generally, various treatment options have been explored for HCL, including chemotherapy (cladribine and pentostatin) [3, 7, 17], immunotherapy (rituximab, moxetumomab) [2, 16, 18], and targeted therapy (vemurafenib for BRAF V600E mutation-positive HCL, ibrutinib) [2, 4, 13]. Notably, the purine analogs cladribine and pentostatin induce long-term remission in the majority of HCL patients, and they have remained the standard treatment for this type of leukemia for more than 30 years. Standard supportive therapy including treatment for tumor lysis syndrome, cardiotoxicity, and hepatotoxicity prevention is recommended for patients receiving chemotherapy [3, 19]. Ongoing studies have investigated novel therapeutic approaches for relapsed or resistant HCL including new drug targets, combination therapies, and participation in clinical trials to evaluate their efficacy and safety [16—18, 20]. Clinicians should always remember that the diagnosis "leukemia" has a tremendous impact on the patient's social life and may significantly influence the quality of life, which is an extremely important point when making treatment choices [21, 22].

To sum up, HCL is a rare lymphoproliferative disorder that, along with a typical clinical picture and morphological changes, can debut unusually with leukocytosis and aberrant expression of various CD markers as reported in our case. A proper diagnosis results in a good response. The key point marker for HCL is the presence of the BRAF V600E mutation, regardless of the leukocyte count and atypical aberrant $CD10^+$ or $CD23^+$ expression.

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РІДКІСНИЙ ВИПАДОК CD10$^+$CD23$^+$ ВОЛОСАТОКЛІТИННОЇ ЛЕЙКЕМІЇ З ЛЕЙКОЦИТОЗОМ. КЛІНІЧНИЙ ВИПАДОК ТА ОГЛЯД ЛІТЕРАТУРИ

Представлено клінічний випадок з метою змінити парадигму розуміння біології волосатоклітинної лейкемії та підкреслити важливість молекулярно-генетичного тестування при атипових морфології та фенотипі захворювання. Нами було діагностовано класичний варіант волосатоклітинної лейкемії на підставі результатів комплексного обстеження пацієнта, що включали об'єктивні зміни у вигляді вираженої спленомегалії, лейкоцитоз, морфологічну інфільтрацію кісткового мозку лімфоїдними клітинами з волосатою цитоплазмою та імунофенотипом CD45$^+$CD5$^-$CD10$^+$CD11c$^+$CD19$^+$ CD20$^+$CD22$^+$CD23$^+$CD25$^+$CD103$^+$ з наявністю мутації *BRAF* V600E. Лікування першої лінії стандартними дозами кладрибіну дозволило досягти повної ремісії після одного циклу. Слід підкреслити, що ключовим маркером волосатоклітинної лейкемії є наявність мутації *BRAF* V600E, незалежно від кількості лейкоцитів і атипової аберантної експресії CD10$^+$ або CD23$^+$.

Ключові слова: волосатоклітинна лейкемія, лейкоцитоз, аберантна експресія CD10$^+$CD23$^+$, BRAF V600E мутація, клінічний випадок.