Case Report

A case of chronic lymphocytic leukemia with beta thalassemia trait: A case report

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is a monoclonal lymphoproliferative disorder. It is one of the common hematolymphoid neoplasms in elderly adults. Co-existence with hemoglobinopathies is a less-known presentation. Here, we present the case of an 82-year-old male patient who was under evaluation for elective surgery for a hernia. He also has a previous history of ischemic heart disease and is a known case of beta-thalassemia trait. On routine evaluation for surgery, he was found to have leukocytosis of 26,200 cells/cu.mm and absolute lymphocyte count of 17,816 cells/cu.mm, hemoglobin of 10.1 mg/dL, red blood cells of 5.15×10^6, and mean corpuscular volume of 63.2 fL. Further evaluation of lymphocytosis by flow cytometry showed immunophenotypic results consistent with CLL. Beta thalassemia trait is a common hemoglobinopathy, and CLL is also a common hematological neoplasm. However, co-existence of both is rare and under-reported.

Key words: Beta-thalassemia trait, Chronic lymphocytic leukemia, Flow cytometry, Microcytic blood picture

Thalassemias are one of the most common causes of microcytic anemia, and they are due to impaired synthesis of the globin component of hemoglobin. Beta-thalassemia refers to an inherited mutation of the beta-globin gene, causing a reduced beta-globin chain of hemoglobin. The highest prevalence of beta-thalassemia mutations is in people of Mediterranean, Middle Eastern, and Asian descent [1]. The three classifications of beta-thalassemia are defined by their clinical and laboratory findings. Beta-thalassemia minor, also called carrier or trait, is the heterozygous state that is usually asymptomatic with mild anemia [2]. Chronic lymphocytic leukemia (CLL) is a monoclonal lymphoproliferative disorder. Globally, CLL accounts for 25–30% of leukemia cases [3]. Epidemiological data from 2021 reported more than 100,000 new cases and over 40,000 deaths worldwide. It predominantly affects older adults and occurs more frequently in males [4]. Its incidence also varies significantly across geographic regions and ethnic groups, with higher rates observed in white populations in North America and Europe, and notably lower rates in Asian populations [5]. The occurrence of hematological malignancies such as leukemia and lymphoma in thalassemia patients could be a pure coincidence or a combination of genetic and environmental factors. CLL causes the accumulation of abnormal lymphocytes that are less competent in intrinsic immune regulation and can result in immunodeficiency and autoimmune disorders. There is accurate data about the incidence of autoimmune hemolytic anemia among CLL patients, although most series suggest a rate of 5–10% [6]. Previously, Quattrin *et al*. rejected the possibility of a definite genetic link between thalassemia syndromes and lymphoma, who reported the incidence of leukemia in patients with β-thalassemia and the general population [7].

Co-existence of beta thalassemia and CLL can impact the assessment of anemia, response monitoring, evaluation of CLL-related complications, and prognostication. Assessment of anemia becomes difficult as anemia due to beta-thalassemia can be confounded with anemia secondary to autoimmune hemolysis, progression of CLL, and therapeutic toxicity on blood and bone marrow [8]. Co-existence of chronic lymphocytic anemia with beta-thalassemia is rare and is not well documented in the literature. In our case, both these conditions are co-existent, and it was an incidental lymphocytosis that, on evaluation, was found to be CLL.

CASE PRESENTATION

An 82-year-old male was posted for elective surgery for a hernia. He is a known case of ischemic heart

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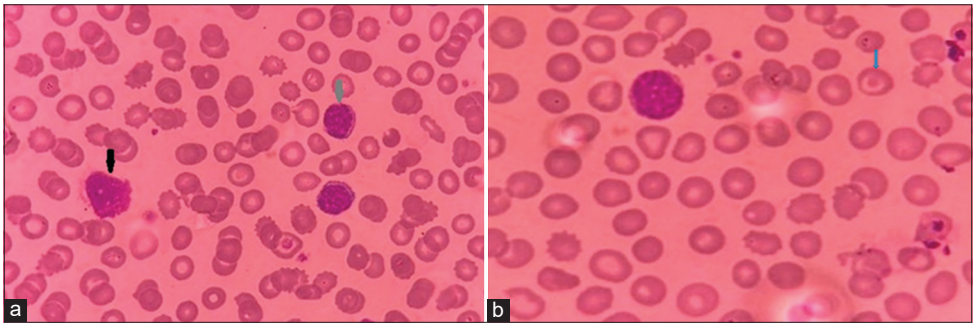


Figure 1: (a) Gray arrow showing atypical lymphoid cell and black arrow showing smudge cell, microcytes in background; (b) Microcytic red blood cell, blue arrow showing target cell

disease, status post percutaneous transluminal coronary angioplasty.

Physical examination revealed no evidence of lymphadenopathy and hepatosplenomegaly.

Ultrasonography of the abdomen showed no evidence of hepatosplenomegaly. On routine surgical evaluation, complete blood picture revealed leukocytosis with absolute lymphocytosis (total leukocyte count of 26,200 cells/cu.mm, ALC of 18,780 cells/cu.mm). Red blood cell (RBC) picture showed RBC count of 5.15 million per mm3, hemoglobin of 10.1 mg/dL, hematocrit of 32.6%, mean corpuscular volume of 63.2 fL, mean corpuscular hemoglobin (MCH) of 19.6 pg, and MCH concentration of 30.9 g/dL. Peripheral examination revealed leukocytosis with absolute lymphocytosis. There is a prominence of atypical small to medium lymphoid cells with scant to moderate pale cytoplasm, round to ovoid nuclei, and clumped chromatin (Fig. 1a). RBCs are microcytic, and occasional target cells are seen (Fig. 1b).

High-performance liquid chromatography revealed a chromatogram pattern with hemoglobin A2 of 5.4% and HbF of 0.8%, suggestive of beta-thalassemia trait (Fig. 2). Flow cytometry analysis was performed by BD FacsCanto II using the stain-wash-lyse method in BD Facs Diva 9.2.1.CD45/SSC and CD19/SSC gating strategy was used to evaluate the immunophenotyping of the atypical lymphocytes. The atypical cells showed bright CD45, low side scatter, bright CD19, CD20, dim CD5 (partial), moderate CD200, CD38, CD43 (subset), positive lambda, negative Kappa, negative CD23 (atypical immunophenotype), negative ZAP-70 (Fig. 3). These cells are negative for CD10, CD2, CD3, CD4, CD7, CD8, CD26, CD30 (Fig. 4) and also negative for FMC-7, CD11C, CD103, CD25, CD123. Due to the positive expression of CD200 and partial expression of CD43, the possibility of peripheral blood involvement by mantle cell lymphoma was excluded.

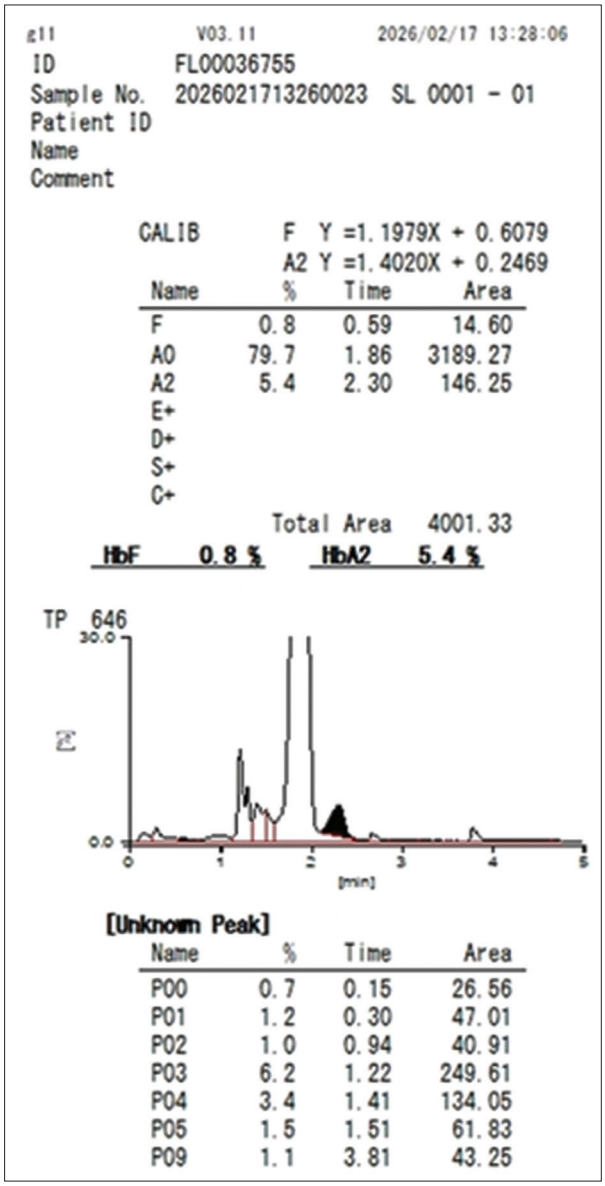


Figure 2: High-performance liquid chromatography revealed a chromatogram pattern with hemoglobin A2 OF 5.4% and HbF of 0.8%, suggestive of beta-thalassemia trait

DISCUSSION

CLL is a B-cell neoplasm, common in the elderly. Absolute lymphocytosis of more than 5000 cells/cu.mm is a prerequisite for the diagnosis of CLL. It is not well-documented about the association of CLL with beta-thalassemia. In our case, the patient presented with a history of beta-thalassemia (trait) and incidental lymphocytosis, which on further evaluation was found to be CLL. According to Taher *et al*., there is an increased incidence of hematological malignancies in patients with thalassemia (including non-transfusion-dependent and transfusion-dependent) by 1.47 fold [9]. Shirinova *et al*. did a retrospective study of 848 chronic myeloid leukemia cases, in which 15% of the cases showed co-existent beta-thalassemia trait. They found that beta-thalassemia

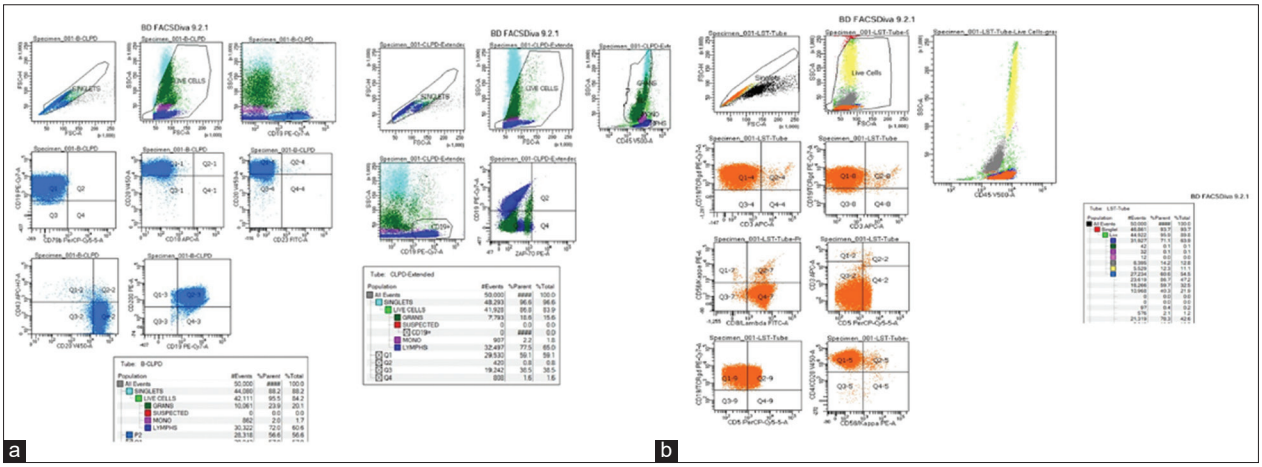


Figure 3: (a) CD45/SSC, CD19/79b, CD10/CD20, CD20/CD23, CD20/CD43, CD19/CD200, CD19/ZAP70 dot plots showing bright CD45 population (blue events) with positive expression of (bright) CD19, CD200, CD20 and negative expression for CD79b, CD23; (b) D45/SSC, CD19/CD3, CD56/CD8, CD3/CD5, CD19/CD5, CD20/Kappa dot plots showing bright CD45 population in lymphocyte gate (orange events) that showed positive expression of CD19, Lambda, CD20, and partial expression of CD5

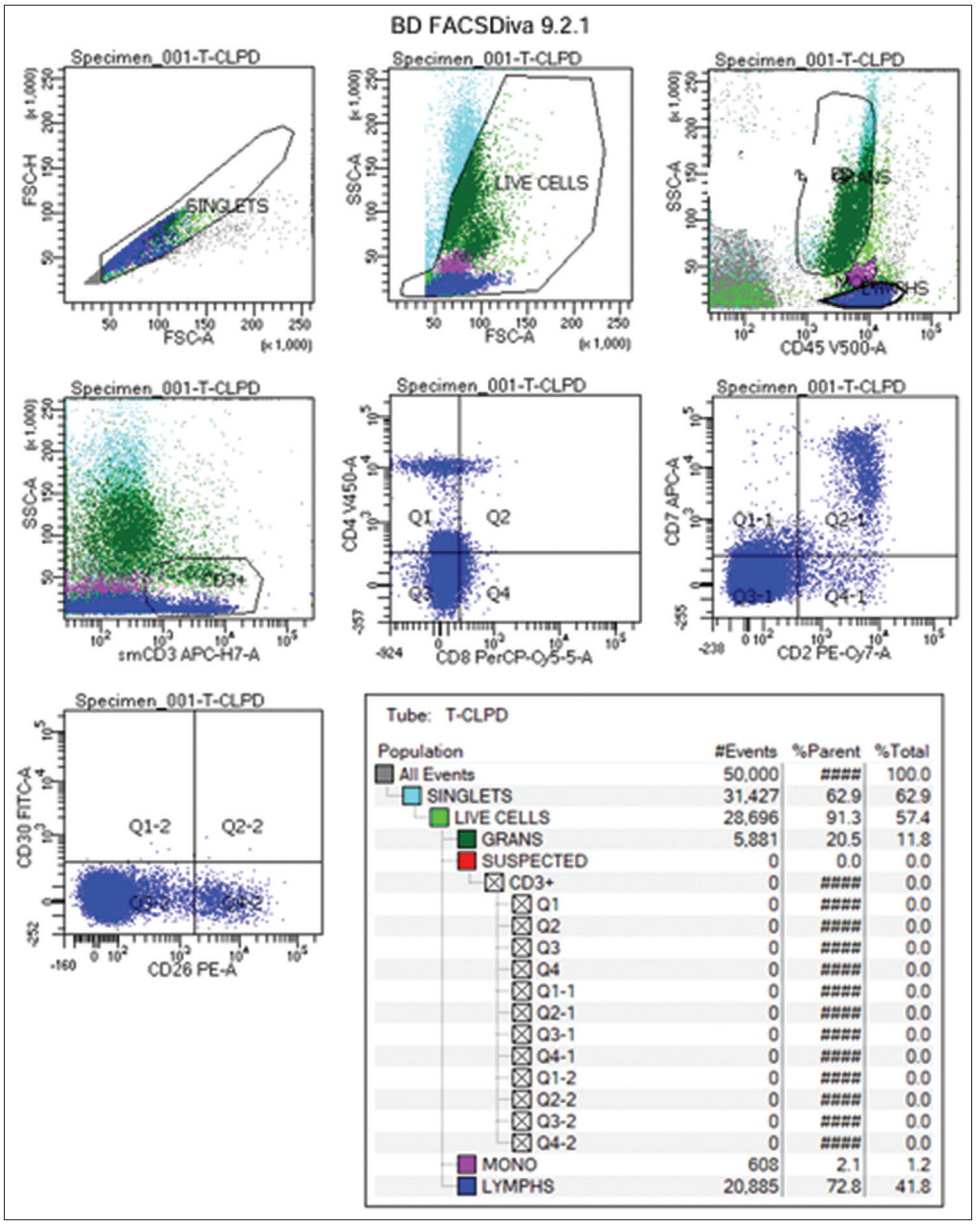


Figure 4: CD45/SSC, SSC/SmCD3, CD30/CD26, CD4/CD8, CD2/CD7 dot plots showing dual population (blue events) of B cells and T cells with absence of the markers in B-cell population and expression of CD3, CD4, CD8, CD2, CD7, CD26 by T-cell component. Both populations were negative for CD30

trait alters the basic hematological profile and risk stratification but does not alter the effectiveness of tyrosine kinase inhibitors and overall survival [7]. Co-existence of beta thalassemia and CLL can impact the assessment of anemia, response monitoring, evaluation of CLL-related complications, and prognostication. Assessment of anemia becomes difficult as anemia due to beta-thalassemia can be confounded with anemia secondary to autoimmune hemolysis, progression of CLL, and therapeutic toxicity on blood and bone marrow.

Persistent microcytic blood picture after completion of treatment of CLL should be delineated from ongoing disease activity that can induce hematological changes. Autoimmune hemolytic anemia, as a complication of CLL, can be misdiagnosed due to baseline shift of hematological parameters in patients with beta-thalassemia trait. For instance, in patients with beta-thalassemia trait, reticulocyte count and RBC count are mildly elevated.

In autoimmune hemolysis, reticulocyte count is increased as a compensatory mechanism, and RBC usually is decreased due to erythrocyte destruction. In patients with beta-thalassemia due to pre-existing erythrocytosis and mildly elevated reticulocyte count, features of autoimmune hemolytic anemia may not be clearly evident. Chronic mild anemia in beta-thalassemia may cause challenges in using hemoglobin as one of the parameters of prognosis assessment. Thus, autoimmune hemolytic anemia in CLL is a differential diagnosis of beta-thalassemia with CLL.

Alavi *et al*. reported two cases of beta-thalassemia with Hodgkin's lymphoma and beta-thalassemia with chronic myeloid leukemia. They emphasized long-term screening of thalassemic patients for hematological malignancies [10]. Hepatocellular carcinoma is a frequent solid tumor associated with thalassemia (transfusion-dependent) [11-13]. De Sanctis *et al*. have reported a case of thalassemia with micropapillary carcinoma of the thyroid [14]. They also described endocrine dysfunction, namely hypothyroidism in patients with thalassemia [15]. Pellegrino *et al*. reported a case of acute promyelocytic leukemia in a 24-year-old female patient with beta-thalassemia intermedia [16]. Rare cases of acute lymphoblastic leukemia in pediatric patients with beta-thalassemia major were described by Borgna-Pignatti *et al*. [11] Zent and Kay described the possibility of autoimmune hemolytic anemia in patients with CLL, which, when co-existent with beta-thalassemia, can lead to therapeutic challenges and difficult prognostication. In our case, the patient was asymptomatic and asked to follow up. Thus, according to the literature, the association of beta-thalassemia with malignancies was found more frequently in transfusion-dependent patients and is commonly associated with solid tumors like hepatocellular carcinoma. No cases with association of CLL with beta-thalassemia were found across the literature (Table 1).

Table 1: Illustrates the association of beta-thalassemia with malignancies in various sites

Author (Reference)	Malignancy/Site reported
Shirinova *et al*.[7]	Chronic myeloid leukemia in a patient with β-thalassemia trait
Taher *et al*.[9]	Review of malignancies associated with thalassemia, including hematological and solid tumors
Alavi *et al*.[10]	Hodgkin lymphoma; Chronic myeloid leukemia in patients with β-thalassemia
Borgna-Pignatti *et al*.[11]	Hepatocellular carcinoma (most common solid tumor); rare cases of acute lymphoblastic leukemia in pediatric β-thalassemia major
De Sanctis *et al*. [12]	Hepatocellular carcinoma in β-thalassemia – review of frequency, risk factors, and surveillance
De Sanctis *et al*. [14]	Endocrine complications (including hypothyroidism) in β-thalassemia
De Sanctis *et al*. [15]	Papillary thyroid microcarcinoma in a patient with thalassemia

CONCLUSION

We report this case to highlight the diversity of the genetic mutations and epigenetic propensity toward the development of secondary malignancies in patients with beta-thalassemia. Association of beta-thalassemia with CLL, as in our case, is rare/under-reported.

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