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Case Report

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Chronic Myeloid Leukemia and Chronic Lymphocytic Leukemia: A Case Report on Rare Co-occurrence of both Conditions Simultaneously

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Abstract

Chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML) are two of the most common hematological malignancies among elderly individuals. While CLL is characterized by mature lymphocyte proliferation, CML is a myeloproliferative disease induced by the BCR-ABL gene. Coexistence of these two diseases is rare and can occur either sequentially or concurrently. In this case report, we describe a 74-year-old male patient with a medical history significant for multiple comorbidities, including prostate cancer, who presented with leukocytosis and found to have monoclonal B-cell lymphocytosis, a precursor to CLL on peripheral blood flowcytometry. Over time, the patient continued to have persistent lymphocytosis and developed basophilia, so repeat workup was done with flowcytometry and BCR/ABL1 on which he was diagnosed with both CLL and CML simultaneously. The patient was started on imatinib, which led to a major molecular response with significant improvement in leukocytosis and is being monitored for CLL. Our case report contributes to the limited literature on the simultaneous occurrence of CML and CLL and emphasizes the importance of considering the possibility of coexisting CML and CLL in patients presenting with features of both diseases.

Keywords: Chronic lymphocytic leukemia; Chronic myeloid leukemia; Hematological malignancies; Rare co-occurrence

Introduction

Chronic lymphocytic leukemia (CLL), a lymphoid malignancy characterized by mature lymphocyte proliferation and chronic myeloid leukemia (CML), a myeloproliferative disease induced by BCR-ABL gene are the most common hematological malignancies of the elderly population [1] [2]. Patients with CLL have a higher risk of developing second primary malignancy which is usually solid neoplasm, though occasional second primary hematological malignancy have also been reported related to impaired immune system or treatment of CLL [3]. However, coexistence CML and CLL has been rarely reported in the literature, which could be either sequential or concurrent manner as reported in our case. The mechanisms underlying the coexistence of CML and CLL are not yet fully understood, but it is believed that they may arise from a single stem cell capable of differentiating into two distinct cell lines. Treatment for these two neoplasms differs, with tyrosine kinase inhibitors being the primary treatment for CML and CLL treatment usually reserved for patients who develop disease-related complications.

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Case Presentation

We report a case of a 74-year-old male with medical history significant for hypertension, coronary atherosclerosis, type 2 diabetes mellitus, obesity, and prostate cancer (Gleason Grade 4+ 5 = 9 and T1cN0M0) treated with external beam radiation therapy and androgen deprivation therapy who was found to have a new onset leukocytosis with 11.4 x10E3 cells/microL with absolute lymphocytosis of 4560 cells/microL. He did not have fever, chills, night sweats, fatigue, decreased appetite, or weight changes and denied any previous history of easy bleeding or bruising. There was no family history of leukemia, lymphoma, or myeloproliferative disorders. Social history was positive for 24 pack year smoking with quit date more than 27 years ago, no alcohol or illicit drug use and used to work as building manager. On physical examination there was no palpable lymphadenopathy, and it was difficult to assess for hepatosplenomegaly due to his body habitus. Due to lymphocytosis peripheral blood flow cytometry was sent which confirmed monoclonal B-cell lymphocytosis a precursor to chronic lymphocytic leukemia. He was monitored with periodic bloodwork and over next few months he developed worsening of leukocytosis with increased neutrophils, lymphocytosis and absolute basophilia (table 1) (Figure 1).

Table 1: Showing complete blood count report on initial presentation and follow up visit.

Component	**Initial Presentation**	**Follow Up Visit 3 months**	**Follow Up Visit 6 months**
Latest Ref Rng			
White Blood Cell Count	**11.4 (H)**	**29.2 (H)**	**32.1 (H)**
3.7 - 10.6 x10E3 cells/uL			
Red Blood Cells	5.13	5.04	4.64
3.70 - 5.90 x10E6 cells/uL			
HEMOGLOBIN	14.8	15.2	14
11.5 - 18.0 g/dL			
Hematocrit	45.8	48	44.7
35.0 - 50.0 %			
Mean Corpscular Volume	89.3	95.2	96.3
81.0 - 99.0 fL			
Mean Corpuscular Hematocrit	28.8	30.2	30.2
27.0 - 33.5 pg			
Mean Corpuscular Hemoglobin Concentration	32.3	31.7	31.3
31.5 - 35.5 g/dL			
Red Cell Distribution Width	48.7	55.4	58
37.3 - 49.0 fL			
PLATELET COUNT	153	269	192
140 - 425 x10E3 cells/uL			
Mean Platelet Volume	10.7	10.9	10.4
8.0 - 12.0 fL			
Neutrophils Relative	53	43	31
40.0 - 70.0 %			
Neutrophils Absolute	6,042	13,320	10,272
1,500 - 7,400 cells/uL			
Lymphocytes Relative	38	33	41
12.0 - 50.0 %			
Lymphocytes Absolute	**4,560 (H)**	**11544 (H)**	**13482 (H)**
950 - 3,500 cells/uL			

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Monocytes 2.0 - 14.0 %	6	3	5
Monocytes Absolute 150 - 940 cells/uL	684	888	**1605 (H)**
Eosinophils Relative 0.0 - 6.0 %		4	3
Eosinophils Absolute 0 - 550 cells/uL		**1184 (H)**	**963**
Basophils Relative 0.0 - 3.0 %		1	2
Basophils Absolute 0 - 175 cells/uL		**296 (H)**	**642 (H)**
Differential Type	Manual	Manual	Manual

Legend: (H) High

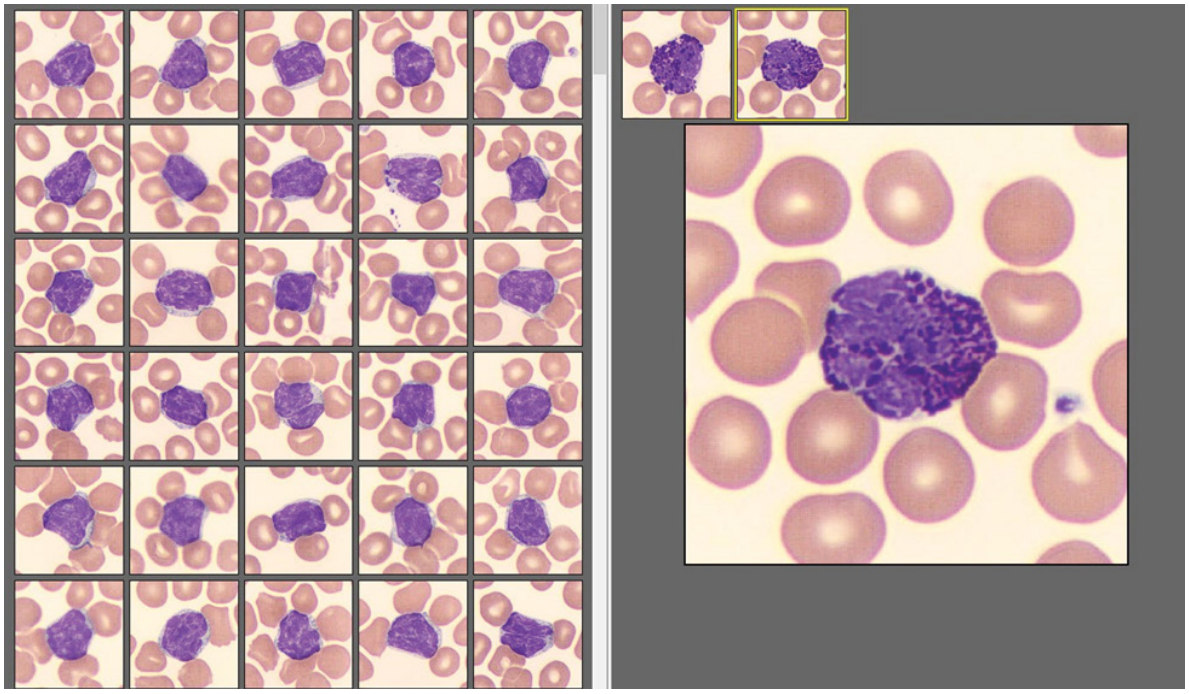

Figure 1: Peripheral Blood showing Basophils: Courtesy of Chaudhary, Jitendra, Clinical Laboratory Technical Specialist

Repeat peripheral blood cytometry was sent along with BCR/ABL on which he has positive BCR/ABL1 p210 mRNA transcripts were detected and estimated to represent 25.0% total ABL1 (%BCR/ABL1 (p210):ABL1) and repeat flow cytometry showed B-cell neoplasm most consistent with chronic lymphocytic leukemia with lymphocyte gate containing 30% of total events of which 75% are Lambda (dim) restricted monoclonal B cells which expressed CD 19, CD20, CD5 and CD200 while negative for CD10. 10% of CD3 positive T cells with CD4/CD8 ratio of 1. No aberrant T cell population was identified. Later abdominal ultrasound was done which showed mild splenomegaly measuring approximately 14.2 x 8.0 x 6.9 centimeter. Bone marrow biopsy was offered but patient refused it.

Patient was diagnosed with chronic myeloid leukemia and chronic lymphocytic leukemia He was started on imatinib for his CML, and his leukocytosis improved with excellent response measuring BCR-ABL to 0.1% total. He continues to have major molecular response to imatinib and his CLL is being monitored closely.

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Discussion

Chronic myeloid leukemia (CML) is a type of myeloproliferative neoplasm, largely comprised of proliferative granulocytes, which affects peripheral blood and bone marrow and is characterized by the presence of the Philadelphia chromosome, a shortened chromosome 22 due to reciprocal translocation t(9;22)(q34;q11) which creates a BCR-ABL1 fusion gene. This gene encodes a constitutively active tyrosine kinase that is implicated in the pathogenesis of CML and is the primary target for treatment of the disease [4].

Chronic lymphocytic leukemia (CLL) is a mature B-cell neoplasm characterized by the proliferation of monoclonal B lymphocytes in various organs, including the peripheral blood, bone marrow, liver, and lymphoid tissues [5].

CML and CLL are most common hematological malignancies of elderly population and incidence for both increases with age with a slight male predominance. The median age at presentation is 45-55 years for CML while CLL presents slightly later in life and has median age at diagnosis around 70 years [6].

Predisposing risk factors for CML are not known however, exposure to ionizing radiation is the only known risk factor [7]. It is presumed that genetic factors are implicated in CLL but there are few environmental factors like exposure to certain chemicals including benzene and heavy solvent, radiation exposure, and tobacco use which have shown to increase risk for of CLL [8, 9].

Around half of CML patients are asymptomatic and disease is first suspected on routine blood tests. While symptomatic patients may present with fatigue, generalized weakness, excessive sweating, abdominal fullness from splenomegaly and weight loss and bleeding. On examination splenomegaly is most common finding. Most of the patients are in chronic phase at the time of diagnosis of CML which is characterized by blast cells less than 2% of white blood cells and granulocytes are morphologically normal with no evidence of dysplasia. In accelerated phase which has progressively impaired neutrophil differentiation and may show 10-19% blast cells on peripheral smear and bone marrow aspirate. In blast crisis blast with myeloid or lymphoid differentiation proliferate uncontrollably and peripheral blood and bone marrow aspirate will show more than 20% blast [10].

CLL patients are mostly asymptomatic and often routine blood test showing lymphocytosis leads to further workup and CLL diagnosis. A small population of patients with CLL may present with constitutional symptoms like unexplained fever, fatigue, night sweats, decreased appetite, and weight loss. Localized or generalized lymphadenopathy is most common physical finding with splenomegaly being second most common finding. Minority of patient have hepatomegaly, and some may show skin involvement with macules, papules, plaques, ulcers, or blisters commonly involving face [11].

The usual lab abnormalities of CML include leukocytosis ranging from 12000 to 1000000/microL with white blood differential showing cells of neutrophilic series. Absolute basophilia is present in virtually all cases and absolute basophilia is present in more than 90% of cases. Finding of Philadelphia chromosome using cytogenetics, fluorescent in situ hybridization (FISH), and reverse transcriptase-polymerase chain reaction (PCR) or BCR/ABL1 on peripheral blood is diagnostic of CML [12].

As per 2018 iwCLL update of the National Cancer Institute guidelines, diagnosis of CLL can be made when there is both (i) absolute B lymphocyte count in the peripheral blood ≥5000/microL [5 x 109/L], sustained for at least three months and (ii) flow cytometry of the peripheral blood demonstrating immunoglobulin light chain restriction (kappa or lambda) and the following pattern of markers: extremely low levels of surface membrane immunoglobulin (SmIg); expression of B cell associated antigens (CD19, CD20, and CD23); and expression of CD5 [13].

CML can evolve in a blast crisis over time, but development of secondary malignancy is very rare. On the other had CLL patients have higher risk of secondary malignancy which is usually non hematological but occasionally hematological malignancies have been reported in literature [3]. Coexistence of myeloproliferative and lymphoproliferative disorders, while very rare, has been reported in some cases which could be sequential of concurrent. While it is more common for CLL to occur before CML, there are also reported cases where CML occurs first or at the same time as CLL [14,15,16]. Our case report presents a rare occurrence of simultaneous CML and CLL in same patient. The co-occurrence of these two conditions may suggest a possible link and one hypothesis is that they originated from a single stem cell which could differentiate in two cell lines, but mechanism of underlying coexistence has not been fully understood and more research is needed for understanding the etiology. [17].

Tyrosine kinase inhibitors (TKI) which inhibit tyrosine kinase encoded from BCR-ABL oncogene is the primary target for treatment of CML. Among tyrosine kinase inhibitors imatinib has been shown to be highly effective and is the primary treatment for CML [10]. Other drugs like hydroxyurea, Interferon and Omacetaxine mepesuccinate can be used for treatment of CML when tyrosine Kinase inhibitors cannot be used safely like pregnancy, while awaiting mutation analysis to relieve symptoms or prevent complication, and in cases of TKI resistance however, their efficacy is limited when compared with TKI. In advanced

cases of CML or when patients develop resistance to tyrosine kinase inhibitors Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) can be considered [18].

In CLL not all patients require treatment, and it is usually indicated for those who develop active disease with disease related complications like high tumor burden, severe constitutional symptoms, anemia, thrombocytopenia, and advanced stage. Initial treatment option include targeted agents like Bruton's tyrosine kinase inhibitors, (ibrutinib, acalabrutinib), BCL-2 inhibitor (venetoclax), Monoclonal antibodies (rituximab, ofatumumab, obinutuzumab) and PI3K inhibitor (idelalisib) or chemoimmunotherapy agents like Purine analogs (fludarabine, pentostatin) and Alkylating agents (cyclophosphamide, chlorambucil, bendamustine). In rare refractory cases Allogeneic Hematopoietic Stem Cell Transplantation has been used [13].

The treatment of patients with both CLL and CML requires a personalized approach, taking into account the specific characteristics of each disease and the individual patient's needs. Our patient in this case report was started on imatinib on which he had excellent treatment response and is being monitored for CLL at the time of this publication.

Conclusion

In summary, simultaneous presence of CLL and CML is a rare and challenging diagnosis that requires careful evaluation and management. Our case report contributes to the limited literature on the simultaneous occurrence of CML and CLL. While the coexistence of these two neoplasms is uncommon, it is important to consider their possibility in patients presenting with features of both CML and CLL. The co-occurrence of these two diseases may suggest a possible link between them, but further research is needed to understand the underlying mechanisms and to optimize treatment strategies for patients with coexisting CML and CLL.

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Author Contributions: Amrat Kumar and Anush Patel conceived the idea. Amrat Kumar, FNU Meena and Muhamad Idrees designed the case report, searched literature, and wrote manuscript. Anush Patel reviewed case report, provided final corrections, and approved the manuscript.

Data Availability: The authors declare that data supporting the findings of this study are available within the article.

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