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Case Report

Delayed Diagnosis of T-Cell Prolymphocytic Leukemia: Approach to Chronic Lymphocytosis

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Lymphocytosis · T-prolymphocytic leukemia · Flow cytometry

Abstract
We present a case of lymphocytosis assumed and managed initially as a chronic lymphocytic leukemia. Shortly after initial visit, the patient's condition deteriorated rapidly with hepatosplenomegaly, pleural effusion, ascites, and skin lesions. Flow cytometry (FC) showed the presence of clonal T-cell population, reported as T-cell lymphoma. Due to rapid clinical deterioration, urgent therapy with cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone was initiated, but with minimal response. This prompted further diagnostic testing and demonstrated tumor cells positivity for CD3, CD30, and TCL1 markers. The diagnosis was changed to T-cell prolymphocytic leukemia. The patient responded well to alemtuzumab (anti-CD52 monoclonal antibody) and reached complete remission. FC is an essential modality for assessing and screening circulating lymphocytes when a lymphoproliferative disorder (LPD) is suspected. There are several LPDs that present with different degrees of clonal lymphocytosis. Reactive lymphocytosis should be appropriately investigated. Indolent LPDs can be surveyed by the internist or family physician, while more aggressive LPDs typically require management by hematologists.

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Introduction

Lymphocytosis is a common, but ambiguous, finding. Chronic lymphocytosis is defined as an increased number of circulating lymphocytes in the peripheral blood (PB), usually >4,000/mL [1, 2] persisting for more than 3 months, and can arise secondary to an increase in B, T, or natural killer lymphocytes. Reactive lymphocytosis is a physiological response to various stimuli, most commonly infection and inflammation [3], whereas neoplastic lymphoproliferative disorders (LPDs) arise from the pathological proliferation of different cell types and present with a variety of signs and symptoms. Understanding the common causes, appropriate initial investigations, and the indicators of a potentially aggressive disease requiring urgent referral is a vital skill for a well-rounded internist physician. History and examination should direct physicians toward likely primary or reactive etiologies. In many cases, flow cytometry (FC) can discriminate a clonal or abnormal lymphocyte population from a reactive process, help establish correct diagnosis, and determine further management. Recognizing the presence of alarming clinical symptoms or red flags should trigger an urgent referral to hematology, regardless of FC results.

Case Report

A 61-year-old female was referred to our cancer center for further management of chronic lymphocytic leukemia (CLL). She initially presented with asymptomatic, low-grade lymphocytosis (WBC 19,900/mL, total lymphocyte count 12,500/mL) and had been on active surveillance for 4 years. By the time of referral, the patient's condition had worsened with increasing fatigue, diffuse lymphadenopathy, and new skin lesions. The patient had erythematous papillomatous, a nodular and maculopapular rash with erythroderma, affecting approximately 10% of her body's surface area. Repeat complete blood count (CBC) revealed mild normocytic anemia (hemoglobin 11 g/dL) and hyperleukocytosis (WBC 333,000/mL). WBC differential showed absolute neutrophil count of 6,230/mL, absolute lymphocyte count of 296,000/mL, and mild monocytosis (monocyte count of 2,080/mL) with no left shift or leukoerythroblastosis. A PB smear revealed multiple smudge cells (shown in Fig. 1 a) and atypical, small-to-intermediate-sized mature lymphocytes (shown in Fig. 1 b). Biochemistry was largely unremarkable, except for a lactate dehydrogenase of 564 IU/L (upper limit of normal 320). Baseline pathology report was requested. Shortly after her initial visit, her condition deteriorated rapidly. She developed profound fatigue, dyspnea, and progression of a skin rash, pleural effusions (shown in Fig. 2), and ascites, dysphagia, and new abdominal pain. Computerized tomography (CT) scan showed hepatosplenomegaly (spleen size 15 × 10 cm) (shown in Fig. 3) and multiple enlarged lymph nodes above and below the diaphragm. There were several enlarged lymph nodes in the retroperitoneum, surrounding the splenic vein and portal vein. Some of the individual lymph nodes measured at least 3.5 × 2 cm in diameter; however, the confluence measured several centimeters (shown in Fig. 4). No peritoneal or pleural lymph nodes, however, were found on the CT scan. Imaging was not escalated to a positron emission tomography scan as the referring institution did not have access to one. Upon review, we found that no baseline FC was done. FC was ordered and showed the presence of cell population homogeneously expressing T-cell surface markers CD 2/3/4/5/7, without expression of CD 34, CD1a, CD10, CD8, CD11c, CD56, CD57, CD38, CD25, CD30, or B-cell surface markers (CD 19/20/79). Thus, the FC was reported as T-cell lymphoma with no evidence of B-cell monoclonality. A bone marrow aspiration and biopsy showed diffuse interstitial and intrasinusoidal infiltration by small lymphocytes with minimal cytoplasm, condensed nuclear chromatin, and indistinct nucleoli (shown in Fig. 1 c). The lymphocytosis was composed of CD2+/CD3+/CD5+/CD7+/CD4+ T-cells. Immunohistochemistry for TCL1

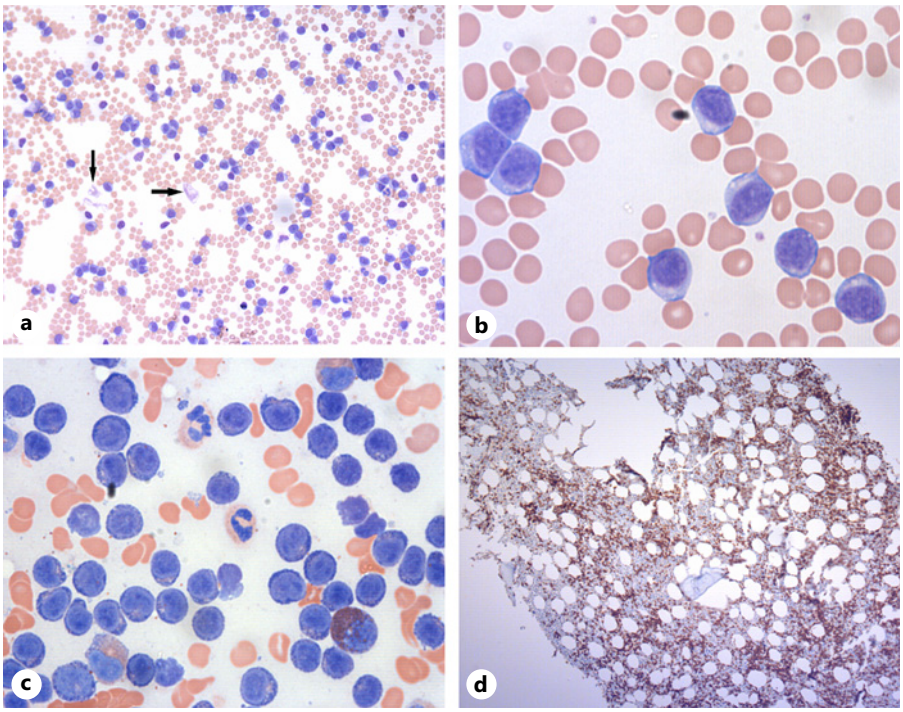

Fig. 1. **a** Lymphocytes and smudge cells in PB, objective ×20. **b** Atypical small-to-intermediate-sized mature lymphocytes in PB, objective ×60. **c** Bone marrow infiltration by small lymphocytes with minimal cytoplasm, condensed nuclear chromatin, and indistinct nucleoli, objective ×20. **d** Bone marrow: small lymphocytes express CD3 positivity, objective ×20.

and TCRab demonstrated positive staining matching the pattern noted with CD3 and CD5 cells. Cytogenetic analysis showed normal female karyotype 46,XX. Due to rapid clinical deterioration, urgent therapy with cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone (CHOEP) was initiated, but with minimal response. This prompted further diagnostic testing and demonstrated tumor cells positivity for CD3 (shown in Fig. 1 d), CD30, and TCL1 markers. The diagnosis was thus changed from T-cell lymphoma to T-cell prolymphocytic leukemia (T-PLL). Given the new findings and the lack of therapeutic response, CHOEP was discontinued and induction therapy with alemtuzumab (anti-CD52 monoclonal antibody) was initiated. The patient rapidly reached a complete remission with complete resolution of clinical symptoms, including her skin lesions. She had ongoing asymptomatic anemia (hemoglobin 10.7 g/dL), neutropenia (ANC 1,500/mL), lymphopenia (absolute lymphocyte count 100/mL), and a normal platelet count of 152,000/mL. She was referred for allogeneic bone marrow transplant (allo-SCT). The patient remained in complete remission for 2 months but relapsed and progressed rapidly. She received one course of bendamustine, with no response, and subsequently died.

Discussion

In the case we present, the initial diagnosis of "CLL," not otherwise specified, made by the referring institution, was presumptive and made solely on the basis of lymphocytosis on CBC and smudge cells on PB smear. The lack of a well-defined baseline immunophenotyping of the involved disorder misclassified the clinical status and resulted in a delay in appropriate

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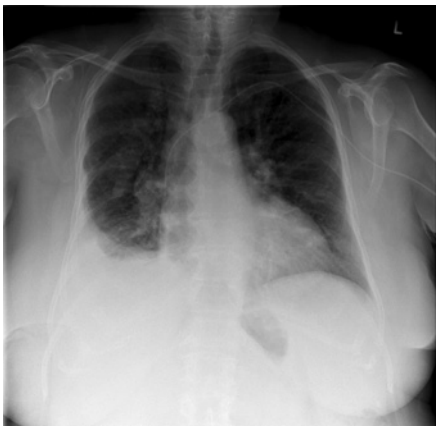

Fig. 2. Chest X-ray showing right-sided pleural effusion, extensive lung consolidation, and patchy ground glass on the right side with air bronchograms throughout the right lower lobe.

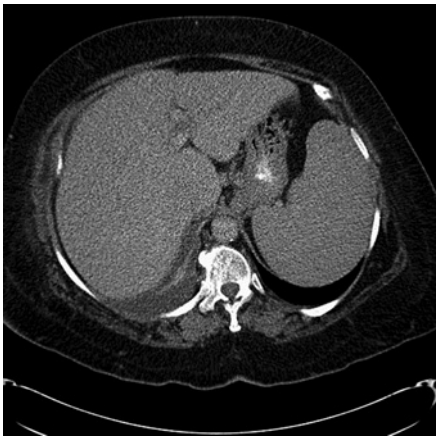

Fig. 3. CT abdomen: hepatosplenomegaly and enlarged upper abdominal adenopathy.

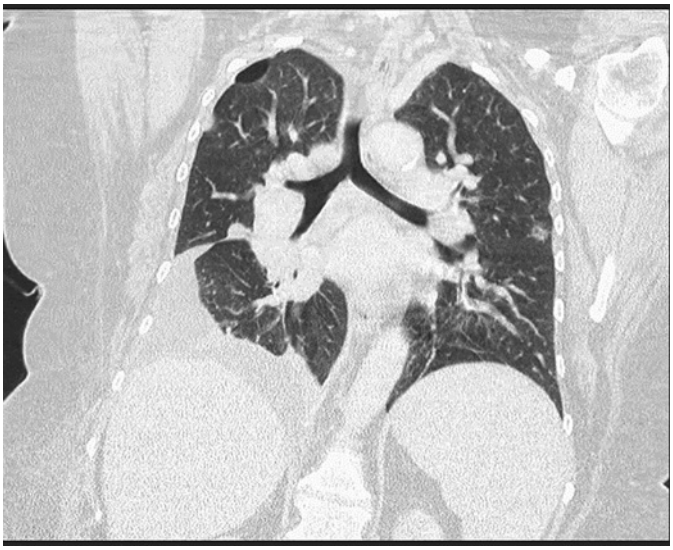

Fig. 4. CT chest: bulky bilateral hilar and mediastinal adenopathy and loculated pleural fluid located posterolaterally on the right.

investigations, diagnosis, and treatment. To avoid this, persistent and slowly increasing peripheral lymphocytosis should be phenotypically classified at presentation. A proper diagnosis determines a patient's clinical course, including frequency of testing and required appointments.

Moreover, once the T cell prevalence has been assessed with a first-level screening, the flow laboratory should come to a satisfactory conclusion by applying a second-level phenotyping panel including, but not limited to, cytoplasmic TCL1, CD30, CD25, HLA-DR, CD1a. If the laboratory is unable to perform this analysis in-house, then the immediate referral of the sample to a better equipped laboratory is mandatory. It is easier and safer to perform such analysis earlier in the course of the disease. In this case, the lack of such second-level phenotyping at the time of referral caused further delay with diagnosis, start of an ineffective initial therapy, and ultimately leads to a poor outcome.

The patient described above had T-PLL, a rare T-cell neoplasm that typically involves the PB, bone marrow, lymph nodes, spleen, and skin. T-PLL has a more aggressive and rapidly progressive course compared to CLL, with a median survival of 1 to 2 years [4, 5]. Even for experts, the diagnosis is frequently delayed, as was evident in this case. In this case, reinvestigation of the diagnosis was indicated by the lack of response to CHOEP therapy. Due to T-PLL's aggressive course, most patients require a consolidative allo-SCT. Given the difficulty of incurring an unrelated bone marrow donor, an earlier T-PLL diagnosis can be lifesaving. In the above case, the patient was referred for allo-SCT too late in her disease course, and the patient died while awaiting a donor match.

Lymphoproliferative Disorders

A clonal proliferation of lymphocytes in the PB, lymphatic system, and/or bone marrow is defined as a LPD [6]. These proliferations occur due to acquired mutations that result in a clonal neoplastic process [1, 2]. All neoplastic LPDs are clonal, although rarely, transient B- or T-cell clones can occur in reactive conditions.

Acute lymphoblastic leukemia and Burkitt leukemia/lymphoma, although rare, are the most aggressive LPDs [7]. Both occur most frequently in children. Patients frequently present with rapidly developing generalized symptoms, including fever, fatigue, weight loss, bone pain, bruising, bleeding, and/or rapidly enlarging lymph nodes. Initial blood work can provide warning signs such as significant cytopenias and the presence of abnormal, immature cells, called blasts, in the PB. These findings are usually verbally communicated by the laboratory or pathologist to the referring physician to ensure immediate action. Patients with suspected acute leukemia or Burkitt leukemia/lymphoma should be urgently referred to hematology or the emergency department.

The majority of LPDs are chronic and indolent, occurring almost exclusively in adults. CLL is the most common adult chronic leukemia in Western countries. The incidence of CLL increases with age, reaching >20 cases per 100,000 individuals over 70 years of age [8]. The American Cancer Society predicts about 18,740 new cases of CLL in 2023 [9]. Almost one-half of patients with CLL are diagnosed incidentally when lymphocytosis is found on a CBC obtained for an unrelated reason [10]. Monoclonal B lymphocytosis is characterized by small clonal B-cell presence in the PB (less than 5,000/μL), in the absence of other signs of an LPD. Monoclonal B lymphocytosis can be a precursor to CLL and rarely other LPDs [11].

Non-Hodgkin lymphoma (NHL) may in some cases present with lymphocytosis. NHLs compromise 90% of all lymphomas diagnosed in the USA, making them the 7th most common cancer. NHL represent 4.2% of all new cancer cases in 2022 [12]. T-cell LPDs are less common and more difficult to diagnose because FC is not always definitive for T-cell disorders. The key clinical and laboratory features and management plans for LPDs are outlined in Table 1.

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Table 1. Most common LPDs presented with PB lymphocytosis

	Clinical features	Lymphocytosis	Management
Monoclonal B-cell lymphocytosis	Asymptomatic. No lymphadenopathy or splenomegaly	Clonal B-cells are less than 5×10^9/L	Does not require therapy. Surveillance for progression
CLL/small lymphocytic lymphoma	Variable lymphadenopathy. Splenomegaly is common in the later stages. May be associated with autoimmune cytopenias	Most often significant in CLL but may be absent in SLL. Often increases with disease progression	Often indolent. Surveillance is adequate until complications (significant B-symptoms, end-organ damage, cytopenias) arise
Follicular lymphoma	Almost always present with lymphadenopathy. Widespread at diagnosis, extranodal site involvement is common. Splenomegaly is rare	Absent or mild	Usually indolent. Active surveillance is adequate in early stages
Hairy cell leukemia	Splenomegaly is common and sizable. Lymphadenopathy is rare. Presents with prominent fatigue and pancytopenia	Variable, usually mild	Usually indolent. Surveillance is adequate in early stages unless significant cytopenias or massive splenomegaly develop
Lympho-plasmacytic lymphoma	Splenomegaly is common. Associated with anemia, hyperviscosity, bleeding	Mild (lower than in CLL)	Usually indolent. Surveillance is adequate until complications arise
Mantle cell lymphoma	Lymph nodes are most commonly involved. Splenomegaly, extranodal involvement are common	Variable, can mimic CLL.	More usually aggressive but can be indolent. Management varies
LGL leukemia	Mainly asymptomatic. Severe neutropenia is frequent. Can be associated with autoimmune disorders	Mild	Surveillance if asymptomatic. Therapy initiated for neutropenia causing recurrent infections

CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; LGL, large granular lymphocyte.

Reactive Lymphocytosis

Reactive lymphocytosis indicates that the increase in lymphocytes is secondary to another process, most commonly inflammatory or infectious disease. Reactive lymphocytosis can be seen in response to viral infections, including but not limited to, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, measles, mumps, varicella, influenza, hepatitis A/B/C, and rubella. Certain bacterial infections may also be causative agents (e.g., *Bordetella pertussis*, *Bartonella henselae*, *Mycobacterium tuberculosis*, *Brucella*, *Treponema pallidum*). Parasitic, protozoal, and rickettsial infections are also possible causes. Noninfectious causes of reactive lymphocytosis include autoimmune disease, medications (carbamazepine, vancomycin, allopurinol), and stress reactions (trauma, acute cardiac ischemia, vigorous exercise, smoking) (Table 2) [2, 13]. Generalized leukocytosis, including lymphocytosis, can be seen chronically postsplenectomy. Reactive lymphocytosis is usually transient and most commonly resolves in tandem with recovery from infection/inflammation; however, some patients may have long-term mild reactive lymphocytosis secondary to chronic conditions. To ensure high-quality patient-centered care, excluding a malignant cause is encouraged to alleviate patient anxiety.

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Table 2. Common causes of secondary lymphocytosis; Hamad [2], Chabot-Richards [13]

Infections	Viral	Infectious mononucleosis, cytomegalovirus, HIV, HTLV-1, adenoviruses, mumps, varicella, influenza, hepatitis A/B/C, rubella, roseola
	Bacterial	*Bordetella pertussis, Bar*tonella *henselae, Mycobacterium tuberculosis, Brucella, Treponema pallidum*
	Parasitic	*Babesia*
	Protozoal	*Toxoplasma gondii*
	Rickettsial	*Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*
Autoimmune	Rheumatoid arthritis, thymoma	
Drugs	Carbamazepine, vancomycin, allopurinol	
Stress	Trauma/injury, cardiac, postoperative, vigorous exercise, smoking	

HIV, human immunodeficiency virus; HTLV-1, human T-lymphotropic virus type 1.

Diagnostic Approach to Lymphocytosis

As with all presentations, patient age, history, and physical examination are at the root of the diagnostic process for patients with possible LPDs. Warning signs in the history can include significant unexplained fatigue or constitutional symptoms (fever, drenching night sweats, or unexplained weight loss). Physical examination should assess for head, cervical, axillary, inguinal or femoral lymphadenopathy, and hepatosplenomegaly. In addition to lymphocytosis, the CBC may show significant anemia, neutropenia, or thrombocytopenia. The presence of any of these findings should be considered red flags requiring referral to hematology as a matter of urgency [14].

FC is a diagnostic pillar in the investigation of patients with persistent lymphocytosis. It provides qualitative analysis of circulating lymphocytes, can identify whether the proliferation of circulating lymphocytes is due to a specific subset of lymphocytes, and can in many cases determine whether lymphocytosis is due to a clonal (primary) or non-clonal (secondary) process [15–17]. FC is a quick and affordable test available to all physicians that allows for the formulation of an informed management plan. Patients with either a monoclonal B-cell lymphocytosis or an abnormal T-/natural killer cell population identified by FC should be referred to hematology for further investigation of possible malignancy. If FC results reveal no clonal or abnormal populations, investigations should then be adjusted based on history and examination findings. Referral to hematology is not warranted unless any red flag signs/symptoms arise. Identifying and treating a secondary etiology should result in the resolution of the lymphocytosis.

Conclusion

Lymphocytosis is a common finding in general internal medicine. History and examination should direct physicians toward the most likely etiology. FC is an essential modality in assessing circulating lymphocytes when an LPD is suspected. In many cases, FC can discriminate a clonal or abnormal lymphocyte population from a reactive process. Patients with abnormal FC results should be referred to hematology. It is also important to recognize the presence of alarming clinical symptoms or red flags. These should trigger referral regardless of FC results, since not all hematologic malignancies can be identified by PB FC. Indolent LPDs can be surveyed by the internist or family physician, while more aggressive LPDs typically require management by hematologists. Reactive lymphocytosis should be

appropriately investigated and managed by the internist physician. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531592).

Statement of Ethics

Ethical approval is not required for this study in accordance with our local guidelines. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent for publication was obtained from the patient's daughter (next-of-kin) for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.G., N.K., and R.K. wrote and reviewed the manuscript. All authors approved the final version to be published and agreed to act as guarantors of the work.

Data Availability Statement

All data that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author.

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