Massive Lymphadenopathy and Hypereosinophilia in CD5 Negative Small Lymphocytic Lymphoma

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Abstract:
Small lymphocytic lymphoma (SLL) is a relatively rare B-cell non-Hodgkin lymphoma that is considered to be the tissue equivalent of the much more common entity chronic lymphocytic leukemia (CLL). Most patients with SLL present with indolent generalized lymphadenopathy, which has frequently been present for several years. We hereby describe an unusual case of SLL in a patient who presented with a huge swelling at the right shoulder region and a single right enlarged axillary lymph node. The other uncommon findings were the presence of peripheral blood hypereosinophilia and CD5 immunonegativity.

Keywords:
CD5 negativity, hypereosinophilia, small lymphocytic leukemia

Introduction
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a mature B-cell lymphoid neoplasm characterized by the proliferation of monoclonal mature B-lymphocytes in the peripheral blood, bone marrow, and lymph nodes.[1-3] Most patients with SLL present with painless generalized lymphadenopathy, which has frequently been present for several years.[1] The basic immunohistochemical panel for the diagnosis of SLL/CLL includes CD5, CD23, and CD20.[4] In this case report, we describe a triad of three unusual features in SLL which include an isolated huge mass at the supraclavicular region, peripheral blood hypereosinophilia, and most importantly CD5 negativity and its relation to prognosis.

Case Report
A 67-year-old male laborer by profession, presented to the surgery outpatient department with the presence of a huge mass at the right supraclavicular region for the last 20 years which had increased in size gradually. The mass was initially painless, but the patient complained of local pain for 6 months. There was no history of fever, night sweats, weight loss, dysphagia, dyspnea, cough, or hoarseness of voice. A history of tobacco chewing and bidi smoking were present. On clinical examination, there was a right-sided huge, bulging, supraclavicular swelling measuring 15 cm × 15 cm in size extending to the right scapular area and was firm in consistency and had dilated veins all over the surface. Furthermore, a large, lobulated right axillary swelling measuring 15 cm × 15 cm in size was present [Figure 1a and b]. On further examination, small palpable lymph nodes of 1 cm × 1 cm size were present in the left cervical and left axillary region. There was no jaundice or hepatosplenomegaly.

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Complete blood count examination revealed hemoglobin – 9.6 g/dl and total leukocyte count (TLC: $12.3 \times 10^9$/L). Differential leukocyte count showed neutrophils (44%, absolute neutrophil count: $5.4 \times 10^9$/L), lymphocytes (22%, absolute lymphocyte count: $2.7 \times 10^9$/L), eosinophils (32%, absolute eosinophil count: $3.9 \times 10^9$/L), and monocytes (2%, absolute monocyte count: $0.24 \times 10^9$/L). Platelet count was adequate ($278 \times 10^9$/L). Peripheral smear showed only mature looking lymphocytes. No atypical cells or blasts were seen. Apart from it, many mature eosinophils were present. Reticulocyte count was 1%. Thus, the only hematological abnormalities were mild increase in TLC and marked eosinophilia. Biochemical tests revealed high serum potassium of 5.6 meq/l and high serum globulin of 6.76 g/l. X-ray chest revealed no abnormality. On clinical grounds, a differential diagnosis of a soft-tissue sarcoma was given.

Fine-needle aspiration cytology of both right supraclavicular and right axillary swellings was advised. Cytological smears were highly cellular comprising a diffuse, dispersed monotonous population of cells having small-to-medium round nuclei with fine granular chromatin, inconspicuous nucleoli, and scant cytoplasm. Occasional mitotic figures were seen. There was no necrosis. Few mature lymphocytes, eosinophils, histiocytes, and plasma cells were also seen. No lymphoglandular bodies were seen [Figure 1c]. A cytological diagnosis of a small round-cell tumor was given, including the possibility of small-cell carcinoma and lymphoma. A core biopsy from the right axillary swelling was done. Section examined showed a monomorphous population of uniform appearing lymphoid cells in sheets. An occasional pseudofollicle consisting of prolymphocytes and few paraimmunoblasts (proliferation center) was also present. Mitotic activity was low. However, no capsule was seen since it was a core biopsy [Figure 1d]. Based on all the above features, a diagnosis of non-Hodgkin lymphoma (NHL) was suggested with immunohistochemistry (IHC) confirmation. The patient was then referred to the department of medical oncology and hematology.

An IHC panel [Figure 1e-h] was advised consisting of leukocyte common antigen (CD45), CD20, CD5, CD23, CD10, CD30, CD3, and Cyclin D1 [Table 1]. Further, IHC with SOX-11 and lymphoid-enhancer-binding factor-1 (LEF-1) was performed, and the neoplastic lymphocytes stained positively with LEF-1 confirming the diagnosis of small-cell lymphoma (SLL) [Figure 2a and b].
A bone marrow examination was further done to rule out bone marrow involvement. Bone marrow aspiration and biopsy were done. Smears were normocellular for age, M:E ratio was 3:1, and there was an increase in eosinophils (29%). There was no infiltration by atypical cells. Bone marrow biopsy section was adequate for comment and normocellular for age. One of the marrow spaces showed a focal presence of an aggregate of monomorphic lymphoid cells surrounded by the normal hematopoietic cell islands [Figure 1i]. Apart from this, there was an increase in eosinophilic precursors. To confirm the nature of the focal lymphoid aggregate, IHC employing CD21 was done, which was negative hence excluding the possibility of a reactive lymphoid follicle. Further, CD20 and CD3 were done to determine the clonality of the aggregate [Table 1]. CD20 was positive, hence indicating the B-cell lineage and confirming the metastatic deposit of SLL [Figure 1j]. CD3 was negative. A final diagnosis of SLL was given. The patient was subsequently treated with six cycles of rituximab and bendamustine and has achieved a complete response.

### Discussion

CLL/SLL is the most common leukemia in Western countries accounting for approximately 30% of all leukemias in the United States. It is an indolent lymphoma mainly diagnosed in elderly patients above the age of 60 years. The most common finding is lymphadenopathy which may be generalized or localized, and individual lymph nodes can vary greatly in size. The most commonly affected sites include cervical, supravclavicular, and axillary. Lymph nodes in CLL/SLL are firm, rounded, discrete, nontender, and freely mobile on palpation. Exceptions to these generalizations are encountered, particularly when the nodes have grown rapidly. Occasionally, several enlarged nodes in the same anatomical site (e.g., cervical triangle, axilla, or femoral-inguinal areas) may become confluent, forming large spherical lymphoid masses.

In this case report, we present the unusual case of a 67-year-old male who presented with a very large, bulky, right supraclavicular mass with a duration of 20 years. This uncommon presentation may be due to the fact that several cervical lymph nodes in that localized area might have increased in size during the course of several years and merged together to form a huge mass. Low socioeconomic status of the patient, ignorance, and lack of awareness also may have significantly contributed to the huge size of the swelling.

The second rare finding, in this case, is marked peripheral blood hypereosinophilia (32%). It has been reported in 2% of patients with NHLs and is considered to be reactive in nature. Andersen et al. evaluated the association of eosinophilia with lymphoreticular malignancies and found a positive association with eosinophilia. It was concluded that eosinophilia should be regarded as an indicator of the disease. However, the prognostic impact was not established. Eosinophilia is also reported as a potential predictor of the transformation of CLL/SLL into classical Hodgkin’s lymphoma (CHL), a phenomenon known as variant Richter’s transformation. Ouseph et al., in their study, had evaluated the presence of eosinophilia in three cases of CLL/SLL with TP53 deletions which had converted to CHL. In this case, the presence of eosinophilia was correlated with possible transformation into CHL. However, on histopathology, no Reed–Sternberg cells were seen. Furthermore, on IHC, CD30 was negative, hence excluding the diagnosis of Hodgkin’s Lymphoma. Fludarabine therapy in CLL/SLL has also been reported to cause eosinophilia. However, in the present case, this possibility was ruled out as eosinophilia was present even before starting therapy.

The third unusual feature is CD5 negativity. CLL/SLL usually express CD5 and CD43 and is strongly positive for CD23 and CD200. CD10 is negative, and FMC7 is usually negative or only weakly expressed. However, some cases have an atypical immunophenotype (CD5−, CD23−, and FMC7+). The possibility of other differential diagnoses of small-cell B-cell NHL was also considered which included predominantly cyclin

**Table 1: IHC PANEL**

| Immunohistochemical marker | Result     |
|----------------------------|------------|
| CD45                       | Positive   |
| CD23                       | Positive   |
| CD20                       | Positive   |
| CD5                        | Negative   |
| CD10                       | Negative   |
| CD3                        | Negative   |
| CD30                       | Negative   |
| Cyclin D1                  | Negative   |
| LEF-1                      | Positive   |
| SOX-11                     | Negative   |
| CD20 (bone marrow deposit) | Positive   |
| CD3 (bone marrow deposit)  | Negative   |
| CD21 (bone marrow deposit) | Negative   |

LEF-1=Lymphoid enhancer-binding factor-1; SOX-11 (SRY-related HMG-box)

**Figure 2:** (a) ×400 shows focal and moderate staining of atypical lymphocytes with lymphoid-enhancer-binding factor-1, (b) ×400 shows no staining of atypical lymphocytes with SOX-11
D1-negative mantle cell lymphoma (MCL), follicular lymphoma (FL), and nodal nodal marginal zone lymphoma (NMZL). Although CD23 is negative in MCL, SOX-11 was employed to further rule out cyclin D1 negative MCL. SOX-11 was immunonegative, thereby ruling out the possibility of MCL. FL was also excluded as CD10 was negative, and moreover, the follicular pattern on histopathology was absent. Nodal MZL, especially of diffuse type, was excluded by the lack of monocytoid or centrocytic appearance of neoplastic lymphocytes and CD23 immunopositivity. After excluding the other small B-cell NHL, we narrowed our diagnosis to CLL/SLL due to the histological appearance, low mitotic activity, and strong CD23 positivity. To further confirm the diagnosis, LEF 1, a novel specific marker for CLL/SLL was employed, which showed diffuse nuclear positivity in tumor cells. Tandon et al. in their study of 290 cases of B-cell NHLs had first studied the expression of LEF-1 and found strong nuclear positivity in all (92/92) cases of CLL/SLL including 2 CD5-negative patients. It was concluded that LEF-1 is a useful marker to differentiate CLL/SLL from other low-grade B-cell NHLs irrespective of CD5 expression. Hence, a diagnosis of SLL was made. Staging bone marrow biopsy with IHC revealed CD20-positive focal small lymphoid cell aggregate, suggestive of marrow involvement by SLL. Fluorescent in situ hybridization for CLL-associated genetic abnormalities and whole-body positron emission tomography scan could not be done due to financial constraints. The patient was hereby treated with a combination of six cycles of rituximab and bendamustine (28 days cycle: bendamustine 90 mg/m²/day on days 1 and 2 and rituximab 375 mg/m² on day 1 of each cycle). The patient has achieved complete response and is doing well on follow-up.

Shapiro et al. had reported 15 cases of CD5–ve CLL in their study and had classified a CD5–ve variant of CLL. CD23 was positive in all the cases which further strengthened the diagnosis of CLL in these patients. It was also evaluated that these cases differ from the CD5+ve CLL cases in terms of having a lower WBC count, lower absolute lymphocyte count, presence of splenomegaly, and an advanced stage. While few studies have documented that CD5–ve CLL cases have a poor prognosis and short 5-year survival rate than CD5+ve CLL cases, a few others, Demir et al., Cartron et al., and De Rossi et al. found no difference in survival as compared to CD5+ve groups. In contrast to these studies, Efstathiou et al. had reported a survival rate of 13 months longer in CD5–ve CLL patients than CD5+ve CLL patients. In the present case also, the prognosis is favorable as the patient has responded well to the combination chemotherapy.

## Conclusion
We present a case of SLL/CLL with three unusual features: the presence of a huge supraclavicular mass, marked peripheral blood eosinophilia, and CD5 negativity. The clinical presentation of an isolated huge mass is a rare finding in patients of SLL/CLL who generally have multiple, discrete, generalized lymphadenopathy. Reactive peripheral blood eosinophilia can be associated with CLL. It has also been emphasized that CD5–ve variant of CLL/SLL has no significant effect on the prognosis.

## Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest
There are no conflicts of interest.

## References
1. Müller-Hermelink HK, Montserrat E, Catovsky D, Martínez A. Chronic lymphocytic leukaemia/small lymphocytic lymphoma. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008. p. 180-2.
2. Tanda P, Krishnamurthy J, Bhattacharjee VN, Newman K, Armitage JO, Akhtari M. Autoimmune cytopenias in chronic lymphocytic leukemia, facts and myths. Mediterr J Hematol Infect Dis 2013;5:e2013068.
3. Hallek M. Chronic lymphocytic leukemia: 2013 update on diagnosis, risk stratification and treatment. Am J Hematol 2013;88:803-16.
4. Rizzo K, Nassiri M. Diagnostic workup of small b cell lymphomas: A laboratory perspective. Lymphoma 2012;2012:15.
5. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212-36.
6. Keating MJ, O’Brien S, Lenz G, Koller C, Beran M, Robertson LE, et al. Long-term follow-up of patients with chronic lymphocytic leukemia (CLL) receiving fludarabine regimens as initial therapy. Blood 1998;92:1165-71.
7. Andersen CL, Siersma VD, Hasselbalch HC, Lindegaard H, Vestergaard H, Felding P, et al. Eosinophilia in routine blood samples and the subsequent risk of hematological malignancies and death. Am J Hematol 2013;88:843-7.
8. Ouseph MM, Butera JN, Griffith RC, Stachurski D, Treaba DO. Persistent eosinophilia in patients of chronic lymphocytic leukaemia/small lymphocytic lymphoma and TP53 deletion is a potential predictor of variant Richter’s transformation. Ann Pathol Lab Med 2016;4:123-6.
9. Sezer O, Schmid P, Hallek M, Schweigert M, Beinert T, Langelotz C, et al. Eosinophilia during fludarabine treatment of
chronic lymphocytic leukemia. Ann Hematol 1999;78:475-7.
10. Tandon B, Peterson L, Gao J, Nelson B, Ma S, Rosen S, et al. Nuclear overexpression of lymphoid-enhancer-binding factor 1 identifies chronic lymphocytic leukemia/small lymphocytic lymphoma in small B-cell lymphomas. Mod Pathol 2011;24:1433-43.
11. Shapiro JL, Miller ML, Pohlman B, Mascha E, Fishleder AJ. CD5- B-cell lymphoproliferative disorders presenting in blood and bone marrow. A clinicopathologic study of 40 patients. Am J Clin Pathol 1999;111:477-87.
12. Kurec AS, Threatte GA, Gottlieb AJ, Smith JR, Anderson J, Davey FR. Immunophenotypic subclassification of chronic lymphocytic leukaemia (CLL). Br J Haematol 1992;81:45-51.
13. Huang JC, Finn WG, Goolsby CL, Variakojis D, Peterson LC. CD5- small B-cell leukemias are rarely classifiable as chronic lymphocytic leukemia. Am J Clin Pathol 1999;111:123-30.
14. Demir C, Kara E, Ekinci Ö, Ebinç S. Clinical and laboratory features of CD5-negative chronic lymphocytic leukemia. Med Sci Monit 2017;23:2137-42.
15. Cartron G, Linassier C, Bremond JL, Desablens B, Georget MT, Fimbel B, et al. CD5 negative B-cell chronic lymphocytic leukemia: Clinical and biological features of 42 cases. Leuk Lymphoma 1998;31:209-16.
16. De Rossi G, Mauro FR, Lo Coco F, Caruso R, Niscola P, Pasqualetti D, et al. CD5 negative lymphocytosis mimicking typical B-chronic lymphocytic leukaemia. Description of 26 cases. Nouv Rev Fr Hematol 1993;35:451-5.
17. Efthathiou S, Tsioulos D, Zacharos I, Tsiakou A, Mastorantonakis S, Salgami E, et al. The prognostic role of CD5 negativity in B-cell chronic lymphocytic leukaemia: A case-control study. Haematologia (Budap) 2002;32:209-18.