



Rare 2p Gain with Complex Karyotype in a Symptomatic Patient with Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia

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Abstract

Small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) is often an incidental finding in an elderly asymptomatic patient. We report a case of a 58 year old female, presenting with fever, night sweats and painless submandibular and supraclavicular lymphadenopathy. The left axillary lymph node excisional biopsy showed complete effacement of architecture by small mature lymphocytes. There were scattered pseudofollicles with pale nodular appearance containing large lymphocytes with open chromatin. The neoplastic cells were small with round nuclear contours, coarsely clumped chromatin and scant cytoplasm and they diffusely expressed CD20, CD5 and CD23 consistent with SLL/CLL. Ki-67 (20%) was increased outside of the proliferation centers. Flow cytometry revealed a clonal kappa population with coexpression of CD20, CD5 and CD23. Karyotyping revealed a complex abnormal karyotype with two neoplastic clones and several rearrangements, including a gain of 2p resulting from der (14) t (2;14), confirmed by concurrent FISH showing a MYCN (2p24) signal in the der (14). CLL with 2p gain is usually associated with unfavorable cytogenetic deletions (11q, 17p), unmutated status of immunoglobulin heavy chain (IGHV) and increased CD38. However, in our case, FISH showed loss of 13q and CD38 was low (5%), findings more often associated with a favorable prognosis.

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Introduction

Chronic lymphocytic leukemia/small lymphocytic lymphoma (SLL/CLL) is a mature B cell malignancy. It is the most common leukemia in the elderly (>50 years) in the United States accounting for 22-30% of all leukaemia cases [1,2]. It is often diagnosed as an incidental finding in asymptomatic individuals who show peripheral blood lymphocytosis with small mature lymphocytes and characteristic smudge cells. It is the most common cause of generalized lymphadenopathy in the same age bracket [1,2]. Histologically, the lymph node architecture is effaced by mature B lymphocytes with condensed chromatin. The flow cytometry establishes the malignancy by detecting monoclonal B cell population. The diagnosis of SLL/CLL is made by the expression of CD20, CD5 and CD23 cell surface antigens by the neoplastic cells. The clinical course is heterogeneous with most patients experiencing a stable clinical course and survival without treatment, while in a minority of cases, it has a progressive course [3-5]. The current clinical staging is not a reliable predictor of clinical behavior. Several biomarkers based on pregerminal versus postgerminal origin of SLL/CLL and recurrent cytogenetic abnormalities are used to predict the prognosis. The gain of short arm of chromosome 2 (2p) is a rare cytogenetic finding in SLL/CLL. In most studies, this finding is associated with adverse prognostic markers [6-8]. However, in our case, 2p gain was detected with conventional karyotyping, confirmed with subsequent fluorescent in situ hybridization (FISH) study and was associated with favorable prognostic markers.

Case Presentation

We report a case of a 58 year old female who presented with fever, night sweats and painless neck swelling. Complete blood count (CBC) showed white blood cell count of 10.5/microliters (3.2-10.6/microliters) with 24% lymphocytes on differential count, red blood cell count of 4.12 (3.77-5.28), hematocrit of 36.3 (34.0-46.6), hemoglobin of 11.9 g/dl (11.1-15.9 g/dl) and mean corpuscular volume (MCV) of 88 fl. CT scan showed bilateral submandibular and supraclavicular lymph node enlargement. Left axillary lymph node excision showed diffusely effaced architecture by a lymphoid

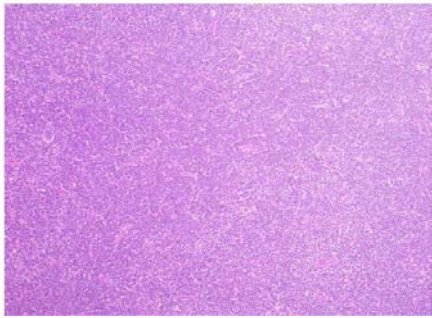


Figure 1: Diffuse effacement of lymph node architecture by small lymphocytes with pale areas (x100).

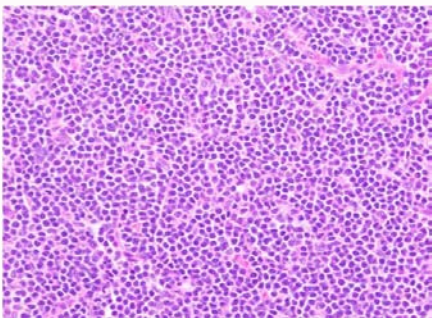


Figure 2: Sheets of small mature lymphocytes with condensed chromatin (x400).

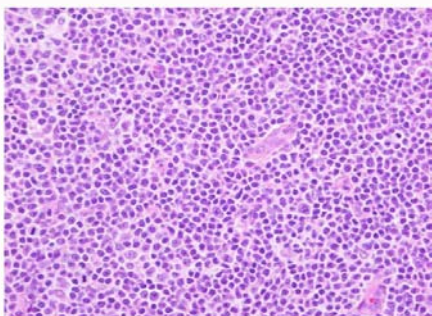


Figure 3: Prolymphocytes and paraimmunoblasts with pale cytoplasm and mitosis in proliferation centers (x400).

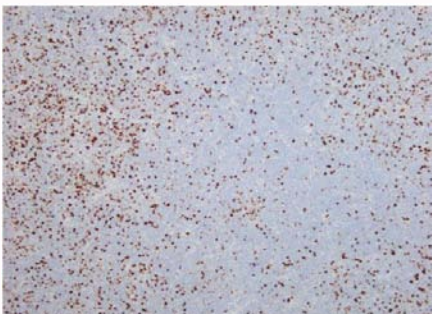


Figure 4: Ki67 is increased outside proliferation centers (x100).

population that extended through the capsule and involved perinodal adipose tissue. The infiltrate consisted of small round lymphocytes with condensed nuclear chromatin and scant cytoplasm (Figure 1,2). Admixed at regular intervals were proliferation centers which imparted a vague, pale nodular appearance. The proliferation

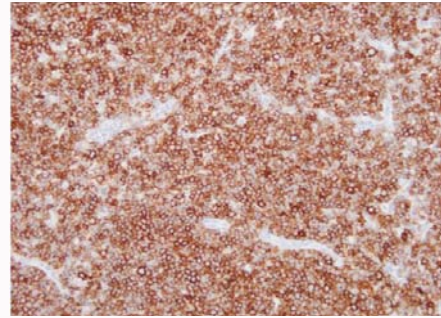


Figure 5: Tumor cells are diffusely positive for CD20 (X200).



Figure 6: Tumor cells are diffusely positive for CD5 (X200).

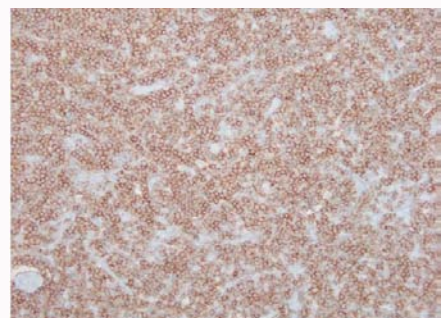


Figure 7: Diffuse expression of CD23 by tumor cells (x200).

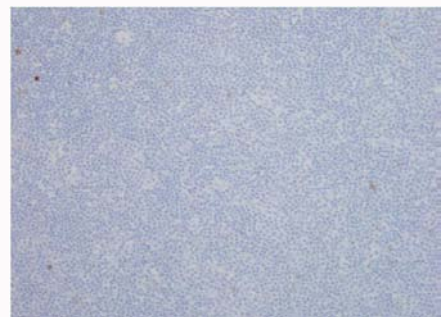


Figure 8: Tumor cells are negative for cyclin D1 (x200).

centers were composed of larger lymphoid cells with more abundant cytoplasm, open nuclear chromatin and more conspicuous nucleoli (Figure 3). Ki-67 showed increased proliferation (20%) outside the proliferation centers (Figure 4) that raised some concern of early transformation to large B cell lymphoma. However, confluent sheets of large cells were not observed. The small mature lymphocytes weakly expressed CD20, CD5 and CD23 (Figures 5-7) and more strongly

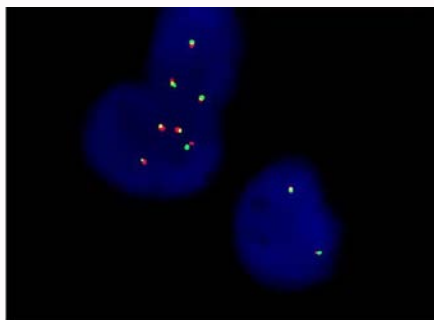


Figure 9: FISH showing MYCN (2p24) signal in der (14).

expressed BCL2. Cyclin D1, CD10 and BCL6 were not expressed by the neoplastic cells (Figure 8). Scattered reactive CD3 positive T lymphocytes were present. Flow cytometry revealed a clonal kappa positive, B cell population that co-expressed CD5, dim CD20 and CD23. CD38 was low (5%). These findings were consistent with SLL/CLL, stage II. Karyotyping revealed a complex abnormal karyotype with two neoplastic clones and several rearrangements, including a gain of 2p resulting from der (14) t (2;14), confirmed by concurrent FISH showing a MYCN (2p24) signal in the der (14) (Figure 9). The FISH panel for SLL/CLL showed loss of 13q14 (Rb gene) with no abnormality in other FISH probes.

Discussion

The terms SLL and CLL are used interchangeably, the former presenting with a leukemic picture and the latter being limited to disease in lymph nodes [9,10]. The most common clinical presentation is an asymptomatic patient with an incidental finding of SLL/CLL [11-15]. The peripheral blood smear shows lymphocytosis with small mature lymphocytes and smudge cells (fragile degenerating leukemic cells). SLL/CLL is the most common malignant cause of generalized lymphadenopathy in an elderly population (>50 years) with nonspecific symptoms of anorexia, fever, night sweats and weight loss. In some cases, SLL/CLL may be associated with warm or, less often, cold autoimmune hemolytic anemia [15-17].

Peripheral blood lymphocytosis in an elderly patient should raise suspicion for SLL/CLL. The diagnosis of malignancy is established with flow cytometry revealing a monoclonal B cell population. In cases with lymphadenopathy, the lymph node architecture is completely effaced by small mature lymphocytes having condensed nuclear chromatin. Pseudofollicles have pale nodular appearance due to the proliferation of large lymphocytes having open nuclear chromatin and more abundant cytoplasm. SLL/CLL is a low grade B-cell malignancy having a low proliferation index except the pseudofollicles which may show increased Ki67. The expression of CD20, CD5 and CD23 by the neoplastic cells either by flow cytometry or by immunohistochemistry is consistent with SLL/CLL.

SLL/CLL is clinically heterogeneous with an indolent course in most patients with good prognosis who may survive without treatment for a considerable period of time [3-5]. In some patients, SLL/CLL behaves as a progressive malignancy with decreased survival. The current staging systems, Rai and Binet, identify patients with advanced stage disease, who require treatment; but these staging systems are not able to predict the clinical course [18]. The prognosis of SLL/CLL depends upon pregerminal versus postgerminal origin of malignancy [19]. Several molecular and cytogenetic markers are used to classify SLL/CLL into distinct groups with prognostic significance.

The clinical course of SLL/CLL depends upon the somatic hypermutation status of the immunoglobulin heavy chain variable (IGHV) region. The somatic hypermutation of IGHV increases affinity of the B cell receptor with antigen during an immune response. The unmutated IGHV status (>95% homology to germline sequences) is consistent with pregerminal center origin and poor prognosis. The mutated IGHV status is consistent with postgerminal center origin and predicts good outcome [20,21]. CD38, a cell surface antigen and 70-kd zeta-chain T-cell receptor-associated protein kinase (ZAP-70) are used as surrogate markers for IGHV mutation status [22,23]. These biomarkers can be evaluated with flow cytometry or immunohistochemistry. Increased CD38/ZAP-70 expression > 30% is consistent with unmutated IGHV status, pregerminal center origin and poor prognosis in SLL/CLL patients.

Recurrent cytogenetic abnormalities represent independent markers for disease progression in SLL/CLL. Fluorescence in situ hybridization (FISH) is the standard for detection of cytogenetic abnormalities [24-26]. Loss of 13q14 (Rb gene) is established as a favorable prognostic marker. Trisomy 12 is associated with intermediate prognosis. Loss of 11q22 (p53 gene) and 17p13 (ATM gene) carry poor prognosis [27,28]. SLL/CLL has low proliferative index; therefore, limiting the role of conventional karyotyping in evaluation of cytogenetic abnormalities.

Whole genome sequencing, comparative genomic hybridization and single nucleotide polymorphism (SNP) arrays have been used in the evaluation of novel cytogenetic abnormalities in SLL/CLL from a prognostic standpoint [29,30]. There are a few studies that have identified gain of short arm of chromosome 2 (2p) as a rare novel cytogenetic abnormality in SLL/CLL. These studies have linked the 2p gain with poor prognostic markers such as CD38/ZAP-70 high expression and loss of 11q22 and 17p13 [6-8,31,32]. The rare 2p gain is considered to be a marker of adverse prognosis in limited studies. The gene transcription profiling has identified a few proto-oncogenes, mapped to 2p, such as MYCN and REL. The dysregulation of these oncogenes is suggested as a potential pathogenetic mechanism for progression of SLL/CLL [33].

MicroRNAs are short, noncoding single-stranded RNA molecules with length of approximately 22 nucleotides. MicroRNAs may be useful as prognostic markers for B-cell malignancy because their expression allows specific cell differentiation stages to be identified [34,35]. The pathogenesis of CLL is better understood after studying the expression of miRNAs. Loss of miR-15a/16-1 cluster was identified from 13q14 locus in 2002. This cluster regulates BCL2 and apoptosis, which explains BCL2 overexpression in CLL [36]. Some studies showed that expression of miRNA-29 decreased as the disease progressed, suggesting its role as a favorable prognostic marker [37,38].

The 2p gain has been reported in at least 86 cases of CLL. Overall, unfavorable cytogenetic deletions (11q22, 17p13) were more frequent in 2p gain cases as well as unmutated IGHV status and increased CD38/ZAP-70 expression [6-8,31,32]. However, in our case the 2p gain was associated with favorable biomarkers, including low CD38 and 13q14 loss. This case study warrants additional studies to establish the prognostic significance of 2p gain in SLL/CLL. Furthermore, even though mitotic activity is very low in CLL, karyotyping should be attempted because novel cytogenetic abnormalities can be identified, which can be further evaluated by FISH [24-26].

Conclusion

The prognosis of SLL/CLL depends upon recurrent cytogenetic abnormalities and somatic hypermutation status of immunoglobulin heavy chain region. The rare 2p gain in SLL/CLL has been reported to occur with poor prognostic markers. In our case, 2p gain is associated with low CD38 and loss of 13q14, often considered favorable prognostic markers. This paradoxical association of 2p gain in our case warrants further studies on its role as a prognostic marker in SLL/CLL.

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