Persistent Eosinophilia in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and TP53 Deletion is a Potential Predictor of Variant Richter’s Transformation

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ABSTRACT

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) progression to diffuse large B-cell lymphoma (Richter’s syndrome) is noted in approximately 3 - 16% of the patients. However, transformation to classical Hodgkin lymphoma occurs in only 0.5% of the patients and has no clinically well-defined predictors. We report three patients with CLL/SLL and TP53 deletion in whom persistent eosinophilia preceded the Hodgkin lymphoma transformation.

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**Introduction**

In July 1928, Dr. Maurice Richter \(^1\) published the first case of chronic lymphocytic leukemia transformation to a large cell tumor, later recognized as diffuse large B-cell lymphoma (DLBCL). Transformation to DLBCL (Richter’s syndrome) has an incidence of approx. 3-16\% in patients with CLL/SLL and represents the most commonly seen secondary malignancy in these patients. Classical Hodgkin lymphoma (CHL) transformation in patients with CLL/SLL, second in occurrence after DLBCL, sometimes designated variant Richter’s transformation, has a 10-year cumulative incidence of 0.5\%\(^,\)\(^2,\)\(^3\). Unlike more commonly seen transformation to diffuse large B-cell lymphoma, clinical and laboratory features predictive of transformation are not well defined in the variant transformation. Though peripheral blood eosinophilia is seen frequently in patients with CHL, the utility of eosinophilia as a marker for variant transformation is unknown. Here we report three patients with CLL/SLL all with associated TP53 deletion, who had or developed sustained peripheral blood eosinophilia at the time of their transformation to CHL. This unusual association suggests that peripheral blood eosinophilia could potentially be used as a marker for early identification of transformation of CLL/SLL to CHL.

**Case Reports**

The first patient is a 59-year old male with a 6-year history of CLL/SLL, with initially reported deletion 13q and trisomy 12, who subsequently developed TP53 deletion and was started on chlorambucil (switched from fludarabine, cytoxan and rituxan due to intolerance) but continued to show progression of his retroperitoneal lymphadenopathy and was diagnosed with progression to CHL on bone marrow and presacral biopsies. The Hodgkin/Reed-Sternberg (HRS) cells were CD30, PAX-5 and CD15 positive and were negative for CD45 and CD20 expression. His blood counts were remarkable for lymphocytosis and eosinophilia (fig.1A) at the time of variant Richter’s transformation. His CHL was treated with ABVD and his eosinophilia reverted in proportion to the response of CHL to chemotherapy. He died of sepsis 16 months after his diagnosis of variant Richter’s transformation.

The second patient is a 79-year old female, with a clinical history of thymoma (58 years ago), and invasive breast carcinoma (17 years ago) recently diagnosed with CLL/SLL with associated deletions of chromosome 13q and 17p (TP53). She underwent therapy with bendamustine and progressed to CHL 2 years after her CLL/SLL diagnosis. The HRS cells (fig. 1B) were positive for CD30 and Epstein-Barr virus latent membrane protein 1 (LMP1) and negative for CD15, CD20 and CD45 while the associated CLL/SLL lymphoid cells had a classic CLL/SLL immunophenotype. Two months before her CHL diagnosis the patient developed eosinophilia that disappeared after ABVD therapy. Interestingly, the biopsy sections showed an increased population of eosinophils in the residual CLL/SLL areas (fig. 1C). The patient died within a year after her diagnosis of CHL.

![Fig. 1: (left): Patient #1, A. Peripheral blood smear, lymphoid cells and an eosinophil (Wright-Giemsa stain, Ob. 50x, immersion oil); Patient #2, B. Hodgkin-Reed Sternberg cells (Hematoxylin and eosin stain, Ob. 50x, immersion oil); Patient #2, C. Area of CLL/SLL with increased population of eosinophils (Hematoxylin and eosin stain, Ob. 50x, immersion oil).](image)

![Fig. 2: (right): Patient #3, A. Area of CHL transformation, Ob. 50x, immersion oil, Hematoxylin and eosin stain; Patient #3, B. CD30 positive HRS-cells (Hematoxylin and eosin stain, Ob. 50x, immersion oil).](image)
The third patient is a 60-year old male with CLL/SLL diagnosed 7 years before, who was started on ibrutinib after being on conservative management for six years due to disease progression and identification of TP53 deletion. He was diagnosed with CHL transformation (fig.2A) while on ibrutinib. The HRS cells in this patient had a classic immunophenotype: CD30+ (fig.2B), CD15+, CD45- and CD79a- with a subset being positive with the anti-Epstein Barr virus latent membrane protein 1 (LMP1) antibody. The patient was also noted to have persistent eosinophilia for three months before his diagnosis of transformation, which reverted after initiation of treatment for Hodgkin lymphoma (R-ABVD and obinutuzumab). He is alive after he underwent bone marrow transplantation.

**Discussion**

CLL/SLL, though generally thought to have an indolent course, can progress to a higher-grade lymphoma in 1-11% patients at rate of 0.5 to 1% per year.\(^5\) Most of these patients fall into category of well-characterized classic Richter’s transformation with development of diffuse large B-cell lymphoma (DLBCL).\(^5\) The “variant” transformation, the transformation of CLL/SLL to CHL has a lower incidence, but has been recognized in various case reports and case series in the literature\(^2,5,19\) with approximately 100 cases reported in the medical literature to date. CHL can occur in CLL/SLL patients with active disease as well as in patients in remission,\(^6\) with a median time of diagnosis from CLL/SLL diagnosis of 4.3 to 6.2 years (range 0-26 years).\(^3,20-21\)

Similar to Richter’s transformation, variant transformation is associated with an overall significant reduction of median survival (0.8 to 1.7 years after diagnosis of CHL) in comparison to de novo classical Hodgkin lymphoma cases, survival being worse in patients who had prior treatment for CLL.\(^9,19-20\) The variant transformation consists most often of the mixed cellularity subtype and may be associated by Epstein-Barr virus.\(^19\)

The cell of origin is not well established, but is hypothesized to be transformed B lymphoid cells arising in V(H) mutated CLL, though clonal similarity studies have shown conflicting results, unlike in cases of transformation to DLBCL, where up to 80% of the cases arise from the same clone.\(^9,20,22-24\) Patients with clonally unrelated DLBCL, have prognosis comparable to DLBCL arising de novo, in contrast to the cases with related clones.\(^22\)

Whether a similar difference is present in cases of variant transformation is unclear, but it may be important in management decisions.\(^20\) Furthermore, the cellular milieu of RS cells in CHL can consist of CLL/SLL cells or a background of inflammatory cells. It is still unclear whether clonal similarity between CHL and CLL/SLL cells has any impact on the cellular milieu.\(^19,23,25-27\) It might appear from the current literature that at least few of the instances of CHL arising in CLL/SLL could represent a CLL/SLL independent neoplasia. In the single case published of systemic eosinophilia accompanying CHL transformation in CLL, the results of fragment length comparison analysis of IGHV PCR suggested no clonal relationship between the two components.\(^28\) Irrespective of whether all the cases represent transformation of CLL/SLL clone, early identification of CLL/SLL patients who are developing CHL is important.

While different molecular risk factors like homology of immunoglobulin heavy chain, absence of del13q14, aberrant high CD38 and ZAP70 expression as well as presentation with high CLL/SLL tumor burden (defined by lymph nodes, Binet stage and serum LDH) are significant predictors of future transformation to DLBCL, no similar well-defined predictors are known for progression to CHL.\(^4,29\) Similarly, TP53 loss/mutations and MYC amplification/ translocations are thought to be high risk factors for future DLBCL transformation, while the role of these factors in context of variant transformation is unclear.\(^25\) The patients with variant transformation presented in this study had TP53 deletion, but this observation needs to be validated.

Primary systemic eosinophilia is known to be associated with clonal lymphoid and myeloid disorders, with systemic eosinophilia being seen in up to 15% of patients with Hodgkin lymphoma. Eosinophilia has been reported in 2% of the patients with non-Hodgkin lymphomas and is considered reactive in nature.\(^30-34\) Based on the current literature, eosinophilia is not a common accompaniment to treatment of naïve CLL/SLL. Andersen et al. evaluating the association of peripheral blood eosinophilia with future diagnosis of lymphoreticular malignancies demonstrated an odds ratio of 2.57 for mild and 5.0 for severe eosinophilia with CLL.\(^35\) In the same study, the incidence of eosinophilia was low (0.11%) and was noted in a small group of patients who either had (89%) or developed CLL later. The clinical course of CLL/SLL in these patients, especially whether any of them underwent transformation to CHL, is not known. Eosinophilia is reported as a response to fludarabine treatment, and it is not clear if any of the patients in the above series were undergoing such treatment.\(^36-38\) Patients with prior fludarabine treatment for CLL/SLL are known to have poor survival after transformation to CHL, fludarabine treatment by itself does not appear to increase the incidence of CHL transformation.\(^20,39-42\) One of our patients received one course of fludarabine - based chemotherapy. However, in his case, the eosinophilia appeared prior to the treatment and persisted even after discontinuation of the drug.
Conclusion
Association of systemic eosinophilia and risk of CHL transformation in CLL/SLL patients with eosinophilia has been previously reported to our knowledge in only one case of variant Richter transformation diagnosed postmortem. This association, though it needs to be validated in a larger series, appears to be of significance as it was found in all three patients with CLL/SLL with TP53 deletion and variant Richter’s transformation.

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Reference


