Composite Peripheral T-cell Lymphoma, Not Otherwise Specified and B-cell Small Lymphocytic Lymphoma Presenting with Hemophagocytic Lymphohistiocytosis

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ABSTRACT

We report a case of a 68 year old female patient who developed hemophagocytic lymphohistiocytosis (HLH) secondary to Peripheral T-cell Lymphoma (PTCL) Not Otherwise Specified (NOS) that developed in the setting of treatment resistant B-cell Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia (SLL/CLL). The patient's B-cell lymphoma had a good initial response to chemotherapy for 4 years, after which it became less responsive and was thought to have undergone transition to a higher grade lymphoma. Different regimens of chemo-radiotherapy were then tried with modest response until the patient presented 3 years later with signs and symptoms of HLH. One month later, the patient died and an autopsy was performed. Significant para-aortic lymphadenopathy and splenomegaly were found. Microscopic, immunohistochemical and molecular evaluations confirmed the presence of composite B-cell and T cell lymphoma in the para-aortic enlarged lymph nodes. Bone marrow examination showed hemophagocytosis. This report highlights the importance of searching for a possible underlying T-cell lymphoma in light of HLH. Different theories have been proposed to explain the rare occurrence of concurrent B- and T-cell lymphomas, but the development of HLH in this patient highlights the importance of immune dysregulation as a proposed mechanism to explain some cases of composite lymphomas.

BACKGROUND

The incidence of composite lymphoma varies between 1 and 4.7%. Immune dysregulation as a mechanism underlying the simultaneous occurrence of 2 lymphoid malignancies has been proposed, and the chronic stimulation of T-cells by the neoplastic B-SLL clone represent well-documented phenomena in the literature. HLH is a syndrome of pathologic immune activation characterized by severe inflammation and cytokinemia. The association between T-cell neoplasms and secondary HLH is a well-recognized in the literature. In this article, we report an unusual case of a patient with known low-grade B-cell lymphoma who succumbed to HLH and was found, postmortem, to have developed PTCL, NOS in a lymph node partially involved by the low-grade B-cell lymphoma.

CASE PRESENTATION

Our patient was a 68 year old woman who was diagnosed with Small lymphocytic lymphoma/Chronic lymphocytic leukemia (SLL/CLL) in a right axillary lymph node. The patient received 2 regimens of chemotherapy with excellent initial response until she was found to have residual right axillary mass. An excisional biopsy was performed and showed persistent lymphoma with slightly elevated prolymphocytes. The Ki-67 showed a proliferation index of 40-50%. In situ hybridization for EBV encoded RNA (EBER) was negative. Though the predominant population was still composed of small cells, note was made of the suspicion for SLL/CLL in progression. The patient subsequently received radiotherapy and a second course of chemotherapy. She had a suboptimal response and developed bulky para-aortic lymphadenopathy. Shortly thereafter, the patient presented with neutropenic fever, pancytopenia and mental status changes. She was found to have hypertriglyceridemia, high ferritin, elevated liver enzymes, bilirubin and IL-2 Receptor. A bone marrow aspirate and biopsy performed at an outside hospital

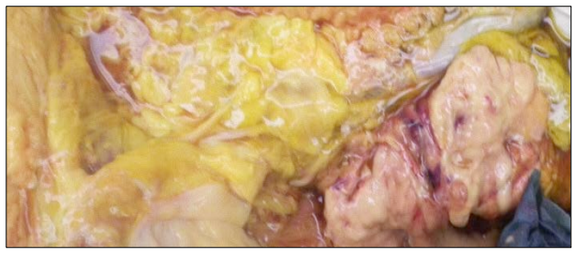

Figure 1. Enlarged and matted para-aortic lymph nodes.

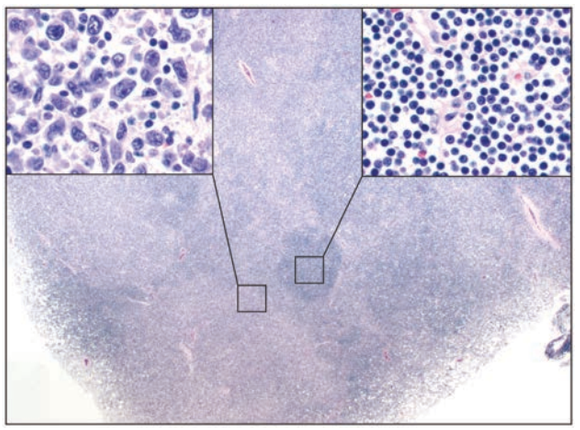

Figure 2. Low power image of the node showing intimate association between B and T cell lymphoma. Right upper inset SLL/CLL. Left upper inset showing PTCL-NOS.

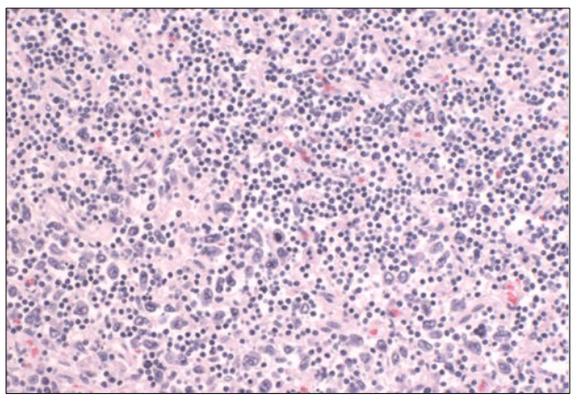

Figure 3. Association of the neoplastic B and T cells.

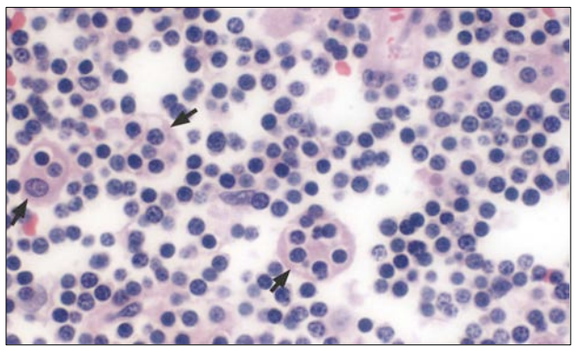

Figure 4. Hemophagocytic lymphohistiocytosis in the lymph node (arrows).

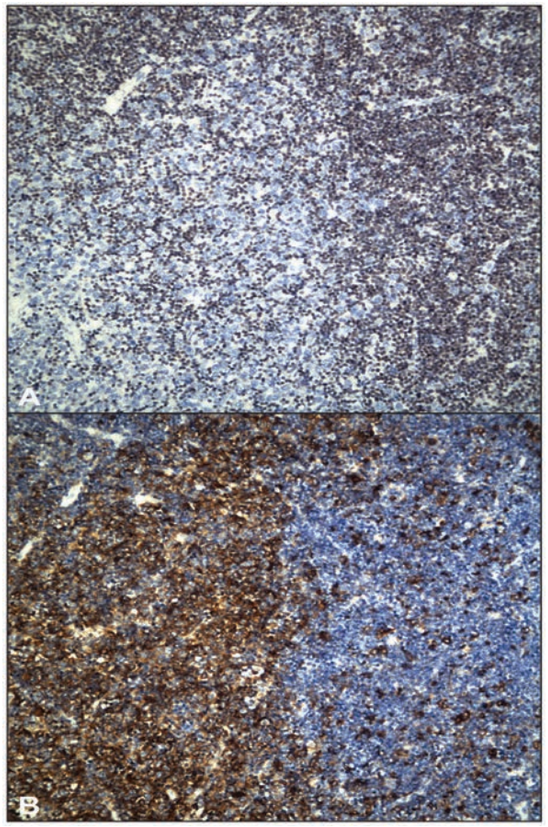

Figure 5. (A) PAX-5 staining highlights the monomorphic B- lymphocytes. **(B)** CD3 staining highlights the T- lymphocytes.

Table 1: Composite B-cell SLL/CLL and PTCL: Review of Literature

Reference	Number of cases	Synchronous vs. Metachronous	Outcome
Strickler et al	2	1. 5yr hx of CLL 2. Synchronous	1. DOD within 1 wk 2. DOD within 4 mths
Lee et al	1	2yr hx of CLL	DOD at diagnosis
Ansell et al	1	Hx of CLL	Alive with persistent disease 10 mths after diagnosis
Novogrudsky et al	1	10 yr hx of CLL	DOD
Martin-Subero et al	1	6 yr hx of CLL	DOD
Martinez et al	6	4 case are Metachronous CLL predating composite lymphoma 10 mths to 14 yrs. 2 Unknown. Only 2 had both in the same LN	2 DOD; 1 Alive with persistent disease 7 mths after diagnosis
Campidelli et al	2	Synchronous.	Both DOD within 1 year

CASE PRESENTATION

Showed findings consistent with HLH. Despite aggressive treatment, she did not improve and died of treatment resistant metabolaic acidosis and hepatic encephalopathy one month after her initial diagnosis with HLH.

RESULTS

At autopsy, there were enlarged and matted para-aortic lymphadenopathy (Figure 1) and mild splenomegaly. Microscopic examination of the para-aortic lymph nodes showed two distinct cell populations (Figure 2, 3 and 5). A portion of the nodal architecture was effaced by a low-grade Non-Hodgkin B-cell lymphoma with morphologic features consistent with SLL/CLL. Ki-67 showed a low (approximately 10-20%) proliferation index in this portion of the specimen. The second population was composed of large pleomorphic lymphocytes with a staining profile characteristic of PTCL-NOS. Ki-67 staining in this portion of the specimen was approximately 80-90%. Scattered within the lymph node were numerous hemophagocytic histiocytes (Figure 4). Bone marrow sections showed interstitial infiltration by the neoplastic CD3 positive T-cells. Scattered CD163 positive hemophagocytic macrophages were seen.

B-cell gene rearrangement was positive in the monomorphic small B-cell population as well as in the T-cell rich area. T cell gene rearrangement was also positive in both areas. The B-cell clone identified in the prior 2008 biopsy was reviewed for comparison and found to demonstrate identical clonality.

CONCLUSIONS

Upon review of the existing literature, we found very rare cases of composite mature T- and small B-cell lymphocytic lymphoma/chronic lymphocytic leukemia (See Table 1). A few of these show precedence by the SLL/CLL and make note of the possibility of an atypical evolution of the preexisting low-grade B-cell lymphoma. The first studies to suggest the composite of CLL/SLL with a subsequent T-cell lymphoma makes use of the term Richter's transformation, typically applied to the transformation into a higher grade non-Hodgkin lymphoma. Less commonly, such patients may demonstrate subsequent Hodgkin lymphoma, described as Hodgkin variant of Richter's transformation. It has been postulated that the occurrence of the subsequent T-cell lymphoma may be supported by the finding that T-cells in CLL patients demonstrate greater resistance to apoptosis than T-cell populations in healthy donors [1].

In the largest series to date, Jaffe et al [2] report six cases of PTCL arising subsequent to an initial diagnosis of CLL. While all of these cases showed concomitant involvement by both lymphomas in peripheral blood and bone marrow, only 2 demonstrated lymph node involvement typical for composite tumors. These, like ours, also reveal sharp segregation of the two tumors within the same specimen.

To the best of our knowledge this is the first report of HLH developing in the setting of composite lymphoma.

REFERENCES

1. Momose H, Jaffe ES, Shin SS, Chen YY, Weiss LM. Chronic lymphocytic leukemia/small lymphocytic lymphoma with Reed Sternberg-like cells and possible transformation to Hodgkin's disease. Am J Surg Pathol 1992:16:859-867.
2. Martinez A, Pittaluga S, Villamor N, et al. Clonal T-cell population and increased risk for cytotoxic T-cell lymphomas in B-CLL patients: clinicopathologic observations and molecular analysis. Am J Surg Pathol 2004;28:849 – 58.