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Sequential Occurrence of a Splenic Marginal Zone Lymphoma, Extranodal MALT Lymphoma, and Hodgkin Lymphoma

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Keywords

HL; SMZL; Clonality; MALT lymphoma

Introduction

Although Hodgkin lymphoma (HL) has been rarely reported to occur simultaneously with non-HLs (NHLs) in “composite lymphomas,” the sequential occurrence of HL after splenic marginal zone lymphoma (SMZL) is extremely rare. In this situation, the lymphomas could be clonally unrelated and represent an incidental simultaneous occurrence, or can be clonally related and represent transformation of 1 lymphoma to the other or the development of both lymphomas from a common precursor. The development of laser capture microdissection (LCM) techniques and polymerase chain reaction (PCR) amplification allow study of the immunoglobulin (Ig) gene rearrangements and somatic mutations, therefore facilitating the elucidation of the clonal relations between these lymphomas. We describe the sequential occurrence of SMZL, extranodal mucosa-associated lymphoid tissue (MALT) lymphoma, and HL in the same patient over a 12-year period and discuss the clonal relation between these lymphomas.

Case Report

A 58-year-old man presented in February 2009 with a growing painless left lower eyelid lesion that interfered with vision. The patient denied B-symptoms. The patient had a history of SMZL (Figure 1A) with villous lymphocytes and bone marrow involvement that was treated with splenectomy in 1998 that resulted in a durable remission. He had been since under surveillance with no evidence of recurrence. Past medical history included only

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hypertension and osteoarthritis. There was no family history of hematologic malignancies. On examination he had a small firm, nontender mass in the left lower eyelid. There were no other ophthalmological abnormalities, or cervical, axillary, or inguinal lymphadenopathy or hepatomegaly. Laboratory evaluation showed a white blood cell count (WBC) of $9.4 \times 10^6/\mu\text{L}$ (normal range [NR], $4\text{--}11 \times 10^6/\mu\text{L}$), hemoglobin 13.6 g/dL (NR, 12–16 g/dL), and platelet count $318 \times 10^6/\mu\text{L}$ (NR, $150\text{--}350 \times 10^6/\mu\text{L}$). The WBC differential was normal except for 3% atypical lymphocytes. Liver and kidney function tests were normal. The lactate dehydrogenase (LDH) was 210 IU/L (NR, 118–273 IU/L). Magnetic resonance imaging of the orbit confirmed a 2.5×1 cm solid mass in the left inferior periorbital soft tissue. Computed tomography (CT) scans of neck, chest, abdomen, and pelvis did not reveal other sites of disease.

The patient underwent an excisional biopsy of the lesion which showed a dense infiltrate of small lymphocytes with scant to moderate pale cytoplasm and a monocytoid appearance (Figure 1B). Immunohistochemical stains showed these atypical cells to be B-cells that were positive for CD20, CD43, B-cell leukemia (BCL-2) (weak), but negative for CD5 and CD10, consistent with a diagnosis of extranodal MALT lymphoma. Hepatitis B and C viral panels were negative. The patient was treated with 8 weekly doses of rituximab that were completed in June 2009. He was subsequently under surveillance until June 2010 when he started having increasing fatigue, night sweats, weight loss, and increasing left axillary lymph node enlargement. Blood counts remained unchanged, but LDH increased to 663 IU/L. A positron emission tomography/CT scan showed an intense uptake in enlarged left axillary lymph nodes, and moderate uptake in several mildly enlarged left external iliac and left inguinal lymph nodes, concerning for transformation. An excisional biopsy of the left axillary lymph nodes showed numerous large cells with abundant eosinophilic cytoplasm and prominent nucleoli, and occasional multinucleated cells consistent with Hodgkin and Reed-Sternberg (HRS) cells and variants (Figure 1C). The background was predominately composed of small lymphocytes with some plasma cells and histiocytes. There was no evidence of low grade B-cell lymphoma in this biopsy. The HRS cells stained positively for CD30, CD15, CD79a, BCL2, BCL6, and partially for dim CD20, consistent with a diagnosis of HL. An in situ hybridization for Epstein-Barr virus-encoded RNA was negative. Using consensus primers for the variable and joining segments of the Ig heavy chain (IgH) gene, a PCR analysis identified a peak migrating at 98 bases of the IgH gene with intensity consistent with clonal neoplasms, but little if any polyclonal component of IgH gene rearrangement products. This peak was similar to the peaks identified from samples of the SMZL from 1998 and the MALT lymphoma from 2009. It was not clear if this similar peak was related to a common clonal origin of these lymphomas or just reflected the presence of SMZL/MALT cells in the background of the HRS cells of HL. Unfortunately, there was not enough tissue to perform a LCM to isolate the HRS cells and confirm the clonality relation.

The patient was treated with 6 cycles of adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine chemotherapy that finished in December 2010, leading to complete remission. In September 2011, he was noted to have an elevated WBC count of $11.9 \times 10^6/\mu\text{L}$ with an absolute lymphocytosis that was kappa light chain-restricted, CD19⁺, and bright CD20⁺ using flow cytometry. These findings were consistent with recurrence of SMZL. Because he was asymptomatic, he was observed until April 2012 when he developed

worsening fatigue and diffuse myalgias, and therefore he was started on rituximab 375mg/m² weekly for 6 doses leading to lymphocytosis resolution and improvement of symptoms.

Discussion

Hodgkin lymphoma is a unique type of lymphoma because of the rarity of the lymphoma cells, the HRS cells, and because the HRS cells show a very unusual immunophenotype very different from the typical mature B-lymphocytes, from which HRS cells have been suggested to originate.^{1,2} Specifically, HRS cells have been shown to derive from a germinal center (GC) preapoptotic or post-GC mature B-lymphocyte counterparts by demonstrating that the clonally rearranged variable gene regions in the IgH and Ig light chain (IgL) have undergone somatic hypermutations.^{2,3} In contrast, though most cases of SMZL and MALT lymphomas have also been shown to derive from mature post GC B-cells that displayed somatic hypermutations in the Ig genes but without evidence of ongoing mutation, about one-third of cases had unmutated Ig genes, consistent with a pre-GC B-cell origin.⁴

Hodgkin lymphoma has been rarely reported to occur simultaneously with NHLs in what is usually referred to as a “composite lymphoma.”⁵⁻⁹ The occurrence of HL in composite lymphomas has previously suggested the B-cell origin of the HRS cells before this fact was confirmed using molecular studies.¹⁰ Similarly, HL has been reported synchronously with SMZL including extranodal MALT lymphomas.^{10,11} In these situations, the 2 lymphomas can be clonally unrelated and represent an incidental simultaneous occurrence, or can be clonally related and represent transformation of 1 lymphoma to the other or development of both lymphomas from a common precursor. The development of LCM techniques and PCR amplification of the Ig genes to assess for rearrangements and somatic mutations have facilitated the elucidation of the clonal relations in composite lymphomas involving HL and in cases of sequential development of lymphomas in the same patient.^{9,11,12} In 1 case with concurrent HL and MALT lymphoma of the larynx, it was concluded that there was a Hodgkin-like transformation of the MALT lymphoma rather than a mere coexistence of the 2 lymphomas.¹³ This was based on the absence of typical HL background of heterogenous inflammatory cells surrounding the HRS cells and the presence of the HRS cells within the MALT lymphoma rather than having 2 distinct cell populations.¹³

We found only 2 other case reports in which HL developed sequentially after SMZL.^{12,14} In these cases, the patients developed HL 11 years and 6 years, respectively, after achieving a remission from SMZL.^{12,14} In 1 case, the authors used the micromanipulation technique to isolate a single HRS cell, and then amplified the rearranged Ig genes in a seminested PCR analysis using region-specific primers for the variable Ig genes to study the clonal relation of the 2 lymphomas.¹² In contrast to previously reported NHL-HL combinations in which the HRS cells showed mutated V gene rearrangement in all cases, this SMZL-HL combination carried germ line sequences except for 1 similar nucleotide difference in both lymphomas from the germ line sequences.^{6-8,12,15-18} The authors concluded that both lymphomas likely arose from a common precursor carrying unmutated V gene rearrangements.¹² In contrast to our patient, this patient died with a severe pneumonia after 4 cycles of adriamycin (doxorubicin), bleomycin, inblastine, and dacarbazine. To our knowledge, our case

represents the first report of the sequential occurrence of SMZL, MALT lymphoma, and HL over a 12-year period. The similar clonal peak in absence of polyclonal IgH gene rearrangement products between HL, SMZL, and MALT lymphomas could be because of a clonal relation between these lymphomas. Nonetheless, whether the HL in our patient originated directly from a transformed the SMZL, developed from a common B-cell precursor with the SMZL, or is a completely unrelated occurrence could not be determined.

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Clinical Practice Points

- The malignant cells of classic Hodgkin lymphoma (HL), Hodgkin and Reed-Sternberg cells, have been shown to derive from B-lymphocyte counterparts.
- Although HL has been rarely reported to occur simultaneously with non-Hodgkin lymphomas, the sequential occurrence of HL after splenic marginal zone lymphoma (SMZL) is extremely rare.
- Development of cellular microisolation and molecular techniques has allowed evaluation of the clonal relation between lymphomas occurring in concurrent or sequential settings.
- We describe the sequential occurrence of SMZL, extra-nodal mucosa-associated lymphoid tissue lymphoma, and HL in the same patient over a 12-year period and discuss the clonal relation between these lymphomas.

Figure 1. Pathologic Specimens From the Sequential Lymphomas. (A) A Low-Power View of the Splenic Marginal Zone Lymphoma (SMZL), Composed of Monotonous Small Lymphocytes Expanding the White Pulp of the Spleen (H & E, Magnification $\times 100$). (B) A Low-Power View of the Extranodal Marginal Zone B-Cell Lymphoma of Mucosa-Associated Tissue (MALT Lymphoma), With Monotonous Small Lymphocytes Dissecting Through Stroma (H & E, Magnification $\times 100$). (C) A Medium-Power View of the Classic Hodgkin Lymphoma (HL), With Scattered Reed-Sternberg Cells Admixed With a Background of Smaller Lymphocytes and Plasma Cells (H & E, Magnification $\times 200$)