Composite Thymoma and Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Involving the Anterior Mediastinum

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• Simultaneous involvement of the anterior mediastinum by thymoma and B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), to our knowledge, has not been previously reported. We describe a composite tumor composed of thymoma and CLL/SLL incidentally discovered in a 62-year-old man who had no history of malignant diseases or immunologic disorders. The preoperative peripheral blood specimen showed a normal complete blood cell count and differential count. The diagnosis was established by histologic examination and immunophenotypic studies of the surgically excised anterior mediastinal mass. Postoperatively, bone marrow aspiration and biopsy specimens showed morphologic evidence of CLL/SLL, and the presence of neoplastic cells in peripheral blood and bone marrow was confirmed by flow cytometry immunophenotypic analysis.

(*Arch Pathol Lab Med.* 2003;127:e76–e79)

The incidence of synchronous and metachronous neoplasms in patients with thymoma has been reported to be higher than that observed in the general population or in patients with other types of neoplasms.[1] In fact, some patients with thymoma have been reported as having 4 or more other neoplasms. This propensity appears to be independent of thymoma-related immunologic disorders, such as myasthenia gravis, red cell aplasia, hypogammaglobulinemia, and lymphocytosis.[2] Among the neoplasms reported to be associated with thymoma are various types of carcinoma, Kaposi sarcoma, carcinoid tumor, and hematopoietic neoplasms, including Hodgkin disease, non-Hodgkin lymphoma, chronic myeloid leukemia, and multiple myeloma.[3–7] The most common types of lymphoma involving the thymus include T-cell lymphoblastic lymphoma, diffuse large B-cell lymphoma, and nodular sclerosis Hodgkin disease. Primary low-grade B-cell lymphoma involving the thymus is relatively uncommon. Most cases reported have been extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) type.[8] The simultaneous occurrence of thymoma and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) involving the mediastinum, a so-called composite tumor, to our knowledge, has not been reported previously. We describe a case of composite thymoma and CLL/SLL detected incidentally by radiologic studies during a stress myocardial perfusion study of a 62-year-old man.

REPORT OF A CASE

The patient was a 62-year-old man with a history of long-term smoking, hypertension, hypercholesterolemia, and inferior and inferoseptal myocardial scar, the latter shown by thallium stress test 3 years previously. He came to the outpatient clinic of The Methodist Hospital for follow-up technetium scan, which showed an enlarged myocardial scar and abnormal uptake in the mediastinum. The patient had no history of neuromuscular symptoms or neoplasms. Routine preoperative laboratory test results were normal, including a complete blood cell count, which revealed a normal total and differential white blood cell count. A computed tomography (CT) scan of the chest revealed a 4-cm, well-delineated anterior mediastinal mass, located inferior to the level of the transverse arch of the aorta and anterior to the main pulmonary artery. Several small nodules, each less than 1.0 cm and presumed to be lymph nodes, were observed within the anterior mediastinal adipose tissue adjacent to the mass. There was no other evidence of lymphadenopathy. The heart was normal in shape and size. The lungs were normal with no evidence of infiltrate, nodules, or pleural effusions. The spleen and liver were unremarkable. The patient underwent surgical excision of the anterior mediastinal mass. Pathologic examination led to the diagnosis of both thymoma and CLL/SLL. Postoperative assessment of the bone marrow showed morphologic evidence of CLL/SLL. Flow cytometry immunophenotypic analysis of bone marrow and peripheral blood confirmed involvement by CLL/SLL. The postoperative course was uneventful. Follow-up complete blood cell counts have shown continuous absence of absolute lymphocytosis with 21 months of clinical follow-up.

MATERIALS AND METHODS

The anterior mediastinal mass specimen was fixed and routinely processed. Histologic sections were prepared and stained with hematoxylin-eosin. Immunohistochemical studies were performed using fixed, paraffin-embedded tissue sections, standard antigen-retrieval techniques, and antibodies specific for CD1a (010, prediluted; Immunotech, Westbrook, Maine), CD3 (UCHT,

Accepted for publication May 14, 2002.

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1:250; Dako, Carpinteria, Calif), CD5 (1F6, 1:20; Novocastra, Newcastle upon Tyne, England), CD20 (L26, 1:1000; Dako), and a pan-keratin cocktail (AE1/AE3, 1:100). Peripheral blood and bone marrow aspirate smears were stained with Wright-Giemsa. Bone marrow biopsy and aspirate clot specimens were routinely processed and stained with hematoxylin-eosin.

Flow cytometry immunophenotypic studies were performed using a cell suspension of the anterior mediastinal mass and a FACScan instrument (Becton Dickinson, San Jose, Calif). Peripheral blood and bone marrow aspirate specimens were also analyzed by flow cytometry. The panel of antibodies included those specific for CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11c, CD14, CD16+56, CD19, CD20, CD22, CD23, CD45, FMC-7, HLA-DR, and immunoglobulin κ and λ light chains. Excluding FMC-7, which was purchased from Immunotech, all other antibodies were obtained from Becton Dickinson. All antibodies were used at the dilutions recommended by the manufacturers.

Conventional cytogenetic studies were performed on a bone marrow aspirate specimen using standard techniques. Twenty cells were analyzed, 10 from a 24-hour unstimulated culture and 10 from a 72-hour lipopolysaccharide stimulated culture.

PATHOLOGIC FINDINGS

Gross Pathologic Findings

The anterior mediastinal excision specimen consisted of a rubbery, poorly circumscribed mass with attached adipose tissue, 5.0 cm in greatest dimension. The cut surface of the mass was lobulated, tan, and homogeneous and interspersed by fine fibrous septa. No lymph nodes were received.

Histologic and Immunohistochemical Findings

Histologic sections of the mass revealed the presence of 2 distinct cellular components, epithelial and lymphocytic (Figure 1). The epithelial component consisted of nests of spindle cells. Cytologically, the epithelial cells exhibited abundant, slightly eosinophilic cytoplasm and bland nuclear features. Foci of microinvasion into perithymic adipose tissue were present. The lymphocytic component was composed of uniform small lymphocytes with scant cytoplasm, round-to-oval nuclei, and condensed chromatin. Mitotic figures were not observed. Several proliferation centers (pseudofollicles), consisting of vague nodules with increased prolymphocytes and paraimmunoblasts, were identified. Numerous lymphocytes extended into the perithymic adipose tissue. A rim of normal cortical thymic tissue partially surrounding the mass was identified.

Immunohistochemical studies revealed that the epithelial cells were strongly positive for cytokeratin and negative for lymphoid markers. The neoplastic lymphocytes were positive for CD5 (dim) and CD20 and negative for CD3 (Figures 2 and 3). CD3 was prominent in the lymphocytes present in the surrounding thymic tissue and between the epithelial nests. CD1a was positive in a subset of lymphocytes in the surrounding thymic tissue.

Peripheral Blood and Bone Marrow

A preoperative complete blood cell count was within the normal limits. The total white cell count was 9.4×10^9/L (reference range, 4.5–11 $\times$ 10^9/L) with 42% lymphocytes (reference range, 25%–45%). The lymphocytes were predominantly small with scant, slightly basophilic cytoplasm and round–to–slightly oval nuclei. The chromatin was condensed. Immunophenotypic studies were not performed on this specimen.

A postoperative complete blood cell count showed a normal total white blood cell count of 9.8×10^9/L. The hemoglobin and hematocrit were 112 g/L (reference range, 140–180 g/L) and 33% (reference range, 41%–51%), respectively. The peripheral blood smear showed findings similar to the preoperative specimen.

The bone marrow aspirate smear showed hypocellular bone marrow particles. The bone marrow biopsy section was 10% to 20% cellular with several nonparatrabecular lymphoid aggregates of small, round lymphocytes consistent with CLL/SLL. The pattern of the neoplasm was entirely nodular. Proliferation centers were not identified.

Flow Cytometric Studies

Flow cytometric analysis of the anterior mediastinal mass revealed the presence of a monotypic B-cell population, representing 52% of the events analyzed, positive for monotypic immunoglobulin κ light chain, CD5, CD19, CD20, CD22 (dim), and CD23 and negative for CD10 and FMC-7. The remainder of the analyzed cells were predominantly T cells, which were positive for either CD4 or CD8, with a very small number of cells positive for both CD4 and CD8 (less than 1%). No CD1a-positive cells were identified.

Flow cytometric analysis of postoperative peripheral blood and bone marrow aspirate specimens showed immunophenotypic findings similar to the anterior mediastinal mass. A monotypic B-cell population was identified, representing 5% and 6% of the analyzed events in peripheral blood and bone marrow specimens, respectively.

Conventional Cytogenetic Studies

Cytogenetic studies of the bone marrow aspirate specimen showed deletion of chromosome Y in 5 of 20 cells analyzed. This abnormality can be detected in healthy, elderly men.[9] The clinical significance, if any, of this finding is uncertain.

COMMENT

In the present report, we describe a unique case of composite thymoma and CLL/SLL simultaneously involving the anterior mediastinum of a 62-year-old man. The anterior mediastinal mass was discovered incidentally by stress myocardial perfusion study and CT scan. The thymoma was circumscribed and localized to the anterior mediastinum, with no radiologic or gross evidence of invasion, although focal microinvasion of adipose tissue was present. The CLL/SLL was intermixed with the thymoma and postoperatively was shown to involve the bone marrow with low-level involvement (normal white blood cell count) of peripheral blood.

In addition to its association with a variety of autoimmune diseases, thymoma appears to be a predisposing factor for the development of secondary neoplasms. The pathogenic basis of this association is not clear. Proposed hypotheses include aberrant stimulation of T lymphocytes by neoplastic thymic epithelial cells and abnormal natural killer cell function.[7,10] Primary involvement of the thymus by non-Hodgkin lymphoma is common. The most common types of non-Hodgkin lymphoma involving the anterior mediastinum are T-cell lymphoblastic lymphoma and diffuse large B-cell lymphoma. Primary low-grade B-cell lymphoma of the thymus is uncommon, and most of the cases reported were classified as extranodal marginal zone B-cell lymphoma of MALT type.[8] To our knowledge, simultaneous involvement of the anterior mediastinum by

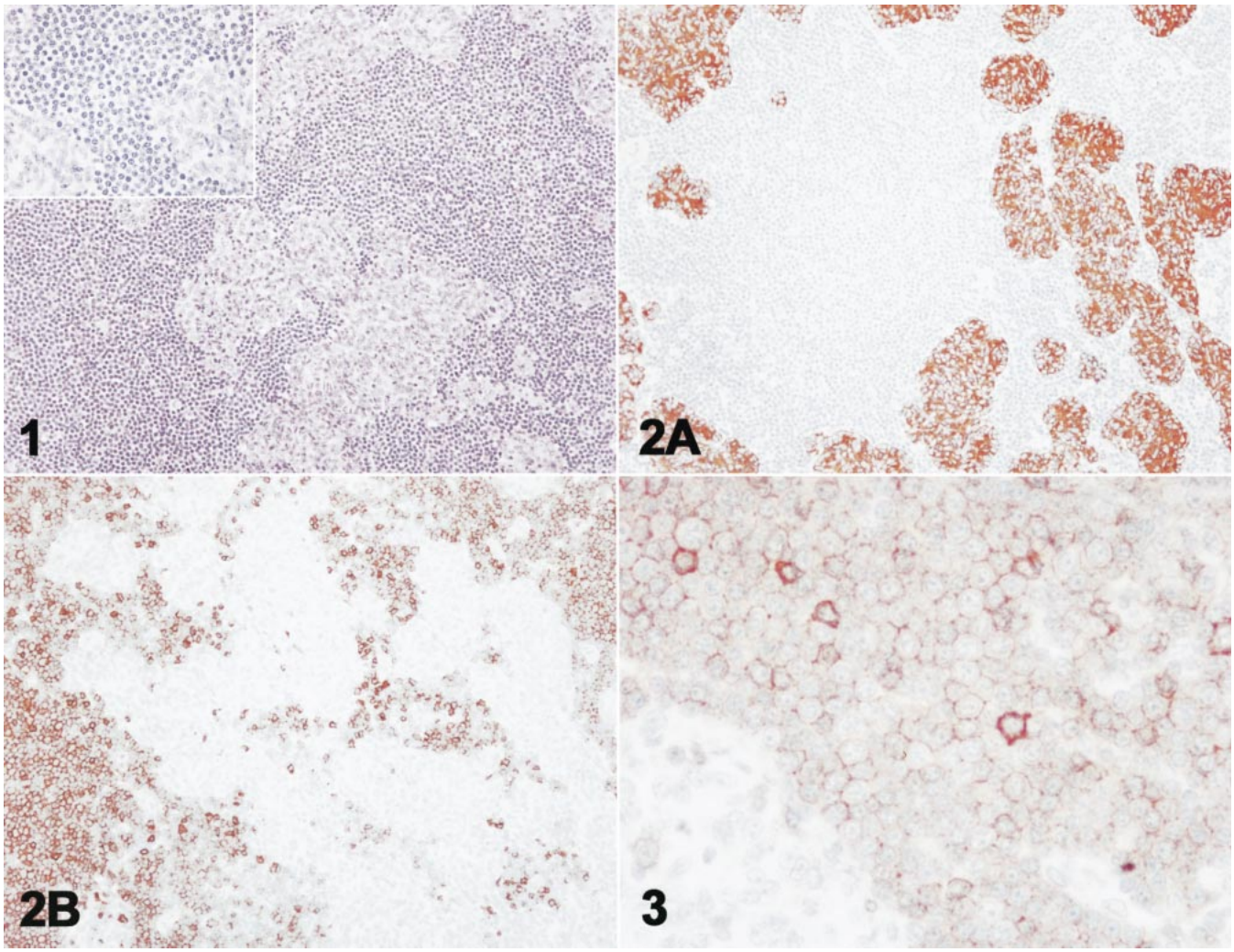

Figure 1. *Composite thymoma and chronic lymphocytic leukemia/small lymphocytic lymphoma. The anterior mediastinal mass is composed of 2 distinct cellular populations, epithelial and lymphocytic. The epithelial cells are polygonal with abundant, pale eosinophilic cytoplasm and slightly oval nuclei. The lymphocytes are uniform, with scant cytoplasm, round nuclei, and inconspicuous nucleoli (hematoxylin-eosin, original magnifications ×100 and ×200 [inset]).*

Figure 2. *Composite thymoma and chronic lymphocytic leukemia/small lymphocytic lymphoma. A, Epithelial cells in the anterior mediastinal mass are positive for keratin. The surrounding lymphocytes are negative for cytokeratin. B, CD20 is positive in the lymphoid infiltrate and negative in the epithelial component (A and B, immunoperoxidase with hematoxylin counterstain, original magnification ×100).*

Figure 3. *Composite thymoma and chronic lymphocytic leukemia/small lymphocytic lymphoma. CD5 is dimly positive in the neoplastic B lymphocytes of the anterior mediastinal mass. Scattered T lymphocytes present within the lymphoid infiltrate are strongly positive for CD5 (immunoperoxidase with hematoxylin counterstain, original magnification ×400).*

CLL/SLL and thymoma, a so-called composite tumor, has not been reported previously.

The distinction between MALT lymphoma and CLL/SLL is usually possible by morphologic analysis. The neoplastic infiltrate in MALT lymphoma consists of a heterogeneous mixture of small lymphocytes with irregular nuclei and variable amounts of cytoplasm. Similar to other extranodal anatomic locations, monocytoid B cells and plasmacytoid differentiation are 2 morphologic features commonly encountered in MALT lymphoma of the mediastinum.[8] Moreover, thymic MALT lymphoma may have distinct lymphoepithelial lesions involving Hassall corpuscles. One striking clinical feature observed in patients with thymic MALT lymphoma is the high frequency of Sjogren syndrome, which may implicate underling immunologic abnormalities.[8] MALT lymphomas are B-cell neoplasms that express monotypic immunoglobulin light chain and B-cell antigens but are typically negative for CD5 and CD23.

In contrast, the CLL/SLL component of this composite tumor was composed of uniform, mature small lymphocytes with proliferation centers and lacked evidence of monocytoid B lymphocytes, plasmacytoid differentiation, or lymphoepithelial lesions, and the patient had no clinical evidence of Sjogren syndrome. Furthermore, immunophenotypic analysis demonstrated that the neoplastic cells were positive for monotypic immunoglobulin κ light chain, B-cell antigens, CD5, and CD23, supporting the diagnosis of CLL/SLL.

Although this patient did not have absolute lymphocytosis, the total white blood cell count and differential lymphocyte count were high normal. Possibly, one would have

suspected the presence of CLL/SLL on the basis of these laboratory findings. However, patients with thymoma can develop reactive T-cell lymphocytosis that often can be marked, simulating CLL/SLL. The explanation of peripheral nonneoplastic T-cell lymphocytosis in patients with isolated thymoma is not understood. Spillover from the thymoma into peripheral blood and/or thymic hormone dysregulation are explanations that have been proposed.[10]

The differential diagnosis of an abnormal population of small lymphocytes infiltrating thymoma of epithelial type also includes lymphocyte-predominant thymoma. Lymphocyte-predominant thymoma often effaces normal thymic architecture, and the identification of the thymic epithelial cells may be difficult morphologically, particularly in cases with markedly dense lymphocytic infiltration. Lymphocyte-predominant thymoma sometimes exhibits medullary differentiation, a morphologic feature not expected in a thymoma infiltrated by malignant lymphoma. Immunophenotypic studies show that the lymphocytes of lymphocyte-predominant thymoma are of immature T-cell lineage. In contrast, the lymphocytic infiltrate in the present case was relatively less abundant, proliferation centers were present, and flow cytometric immunophenotypic studies confirmed that the lymphocytic infiltrate was of B-cell lineage and positive for CD5 and CD23, typical of CLL/SLL. Unlike lymphocyte-predominant thymoma, the thymic epithelial component in this case was easily identified and medullary differentiation was absent.

In conclusion, we describe a rare case of composite thymoma and CLL/SLL involving the anterior mediastinum. Both neoplastic components were intermixed throughout the mass. This case highlights the importance of diligent histologic examination of thymomas to exclude the rare possibility of simultaneous involvement by malignant lymphoma. Ancillary studies, such as immunohistochemical staining and immunophenotypic analysis, to confirm or exclude the coexistence of a lymphoproliferative disorder need to be performed when indicated.

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