Primary Marginal Zone Lymphoma of the Thymus

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Abstract

Primary low-grade B-cell lymphomas of the thymus are rare, with only 7 reported cases in the literature. We describe 3 cases of primary low-grade thymic lymphoma. All had histologic features of extranodal marginal zone lymphoma and were composed predominantly of small lymphocytes with variable components of monocytoid cells and plasma cells. Overt transformation to large cell lymphoma occurred in 1 case. The neoplastic cells were immunoreactive for the B-cell marker CD20 and were positive for bcl-2 in 2 cases. Two of 3 patients had a long-standing history of autoimmune disease. Based on these findings and those of previously reported cases, marginal zone lymphoma is the predominant type of low-grade thymic B-cell lymphoma. These tumors seem to be more common in patients with autoimmune disorders, and as observed with marginal zone lymphoma arising at other anatomic sites, they may undergo transformation to a higher grade lymphoma.

The thymus is the primary anatomic site of T-cell development. Not surprisingly, many lymphoid malignant neoplasms arising within the thymus are T-cell neoplasms, mostly T-cell lymphoblastic lymphoma. However, malignant neoplasms of B-cell lineage, such as primary mediastinal large B-cell lymphoma, are not infrequently encountered mediastinal lymphoid malignant neoplasms and are presumed to arise within the thymus in some cases.1-3

In contrast with these higher grade lymphoid malignant neoplasms, primary low-grade B-cell lymphomas of the thymus are exceedingly rare. In 1990, Isaacson et al4 first described 2 cases of primary low-grade thymic lymphoma, both of which had histologic and immunophenotypic features of extranodal B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), or marginal zone lymphoma (MZL) of MALT as proposed in the World Health Organization classification. However, since this original description, few additional cases have been reported.5-10 We sought to further define the morphologic and immunophenotypic features of these neoplasms. We describe 3 additional cases of low-grade thymic B-cell lymphoma, the largest series to date, and review the pathologic and clinical features of the reported cases in the literature.

Materials and Methods

The 1987-1999 surgical pathology files of the Brigham and Women’s Hospital, Boston, MA, were searched for all cases of low-grade lymphoma of the thymus or mediastinum. Three cases were retrieved, and the corresponding clinical data were obtained by review of the patient’s medical record. Cases were included in the present study as primary thymic lymphoma if there were histologic features compatible with a thymic origin and there was no clinical or radiologic evidence...
of lymphomatous involvement at anatomic sites other than the anterior mediastinum at the time of diagnosis.

All tissues were fixed in either 10% buffered formalin or B-5 fixative. Five-micrometer-thick paraffin sections were prepared and stained with H&E. Immunoperoxidase staining was performed on paraffin sections of formalin-fixed tissue as previously described.11 Sections were used for immunoperoxidase analysis after baking for 1 hour at 60°C, deparaffinization, and rehydration. The tissue sections were then treated with 3% hydrogen peroxide in absolute methanol for 5 minutes and microwave treated at 800 W (General Electric, Louisville, KY) at 93°C for 30 minutes in a preheated 10-mmol/L concentration of citrate buffer, pH 6.0; microwave antigen retrieval was omitted for CD20 staining. Slides were cooled for 15 minutes at room temperature, washed in phosphate-buffered saline, incubated with biotinylated horse antimouse IgG antibody (Vector Laboratories, Burlingame, CA) for 30 minutes at room temperature, and washed with phosphate-buffered saline. Next, the sections were incubated with avidin–biotinylated-peroxidase complex (Vector) for 40 minutes at room temperature, followed by reaction with diaminobenzidine–hydrogen peroxide. The sections subsequently were stained with 2% Gill hematoxylin. The following antibodies were used: CD20 (L26, DAKO, Carpinteria, CA), CD3 (rabbit polyclonal, DAKO), CD5 (NCL-CD5-4C7, Novocastra Laboratories, Newcastle upon Tyne, England), CD43, bcl-2 (clone 124, DAKO), p53 (clone 1801, BioGenex, San Ramon, CA), and cytokeratin proteins (AE1/AE3, DAKO). Immunoperoxidase staining for immunoglobulin heavy and light chains was performed as previously described,12 using rabbit polyclonal antibodies for immunoglobulin kappa and lambda light chains and IgG, IgA, and IgM heavy chains (DAKO).

Routine cytogenetic karyotyping was performed on metaphase cells prepared from an overnight direct harvest.

Lymphoid antigen receptor gene rearrangements were assessed by Southern blot analysis, as previously described.13,14 Blots were hybridized with probes to the joining region of the heavy chain immunoglobulin gene, the constant region of the kappa or lambda immunoglobulin light chain gene, or the T-cell receptor beta-chain gene. Restriction-digested placental DNA served as a germline control.

## Results

### Clinical Features

**Case 1**

A 54-year-old woman with a history of Sjögren syndrome was found to have a mediastinal mass. The patient underwent median sternotomy, and a large thymic mass was resected. She received no additional treatment for her lymphoma. The patient remained free of disease after 10 years of follow-up.

**Case 2**

A 36-year-old woman with a history of autoimmune disorders, including childhood lupus, first sought care at an outside hospital with symptoms of gastritis. Histologic examination of gastric biopsy specimens revealed a mild lymphoplasmacytic infiltrate in the lamina propria with an associated crystal-storing histiocytosis. However, diagnostic features of lymphomatous involvement were not present. She was referred to this institution owing to a worsening hyperviscosity syndrome; laboratory studies revealed hypogammaglobulinemia with an IgG kappa M protein. She had no peripheral lymphadenopathy or splenomegaly. A positron emission tomography scan revealed a 1.5 × 1.5 × 0.8 cm thymic mass, which was resected. The patient received mediastinal radiation therapy, resulting in transient clinical improvement. However, she experienced recurrent hypogammaglobulinemia and hyperviscosity symptoms, necessitating continued plasmapheresis. A bone marrow biopsy obtained 5 months after resection of the thymic mass revealed a focal (<5% of marrow cellularity) lymphomatous infiltrate.

**Case 3**

A 68-year-old man was admitted to an outside hospital for coronary artery bypass grafting. He had a history of bladder cancer and coronary artery disease. At surgery, an anterior mediastinal mass, which was infiltrating adjacent pericardium, was identified and resected. Further follow-up was not available.

### Histopathologic Findings

The histopathologic findings in each case were similar and revealed typical morphologic features of extranodal MZL. There was effacement of thymic architecture by an infiltrate of small to intermediate-sized lymphoid cells with irregular nuclei, inconspicuous nucleoli, and variable amounts of cytoplasm.21 Scattered, admixed immunoblasts were noted within the neoplastic infiltrate. Invasion and expansion of Hassall corpuscles by the neoplastic cells was present, a feature more readily apparent in immunostains for cytokeratin proteins.22 Scattered, admixed immunoblasts were noted in all cases. However, there was overt transformation to a higher grade lymphoma in case 3, as manifested by sheets of large cells with vesicular nuclei, prominent nucleoli, and a high mitotic rate, in addition to the low-grade component.
In case 2, there was a history of gastritis. Histologic examination of gastric biopsy specimens obtained before resection of the patient’s thymic mass revealed a mild lymphoplasmacytic infiltrate in the lamina propria with an associated crystal-storing histiocytosis (not shown). Immunohistochemical staining performed on this biopsy specimen showed polyclonal staining of the plasma cells for immunoglobulin heavy and light chains; the crystalline material within histiocytes showed weak polyclonal reactivity for immunoglobulin gamma and alpha heavy chains and kappa and lambda light chains, and no reactivity for immunoglobulin mu heavy chain. Thus, there was no immunophenotypic evidence of gastric involvement by MZL.

**Immunophenotyping**

The immunohistochemical findings are detailed in Table 1. In each case, the neoplastic cells were reactive for the B-cell marker CD20 [Image 4] and failed to coexpress CD5. Immunostains performed on paraffin sections revealed immunoglobulin light chain restriction of the associated plasma cells (Image 4). Reactivity for bcl-2 protein was observed in 2 of 3 cases. Interestingly, in case 3 in which
there was transformation to diffuse large cell lymphoma, immunoreactivity for bcl-2 was present only in the low-grade component, whereas the large neoplastic cells were uniformly negative.

**Cytogenetic and Molecular Diagnostic Analyses**

Cytogenetic studies were performed in 1 case (case 2) and revealed a 46XX karyotype, with no consistent chromosomal aberrations detected in 9 metaphases analyzed (data not shown).

Southern blot analysis to assess for lymphoid antigen receptor gene rearrangements was performed on 1 of the tumors (case 1). A single nongermline band was demonstrated in analyses using probes for the immunoglobulin heavy chain gene or the immunoglobulin kappa light chain gene, indicating a clonal B-cell population. No bands were apparent when probes to either the immunoglobulin lambda light chain gene or the T-cell receptor beta chain gene were used (data not shown).

**Discussion**

Lymphoblastic lymphoma, diffuse large cell lymphoma, and nodular sclerosis Hodgkin disease represent the most frequent lymphoid neoplasms to arise in the thymus, and all are higher grade malignant neoplasms. By contrast, primary low-grade B-cell lymphoma of the thymus is extremely rare, and to date, only 7 cases have been described. In 2 additional reports, there was...
antecedent or concurrent lymphomatous involvement at other anatomic sites,\textsuperscript{6,7} precluding their definitive classification as primary thymic lymphomas.

We have presented 3 cases of primary low-grade B-cell lymphoma of the thymus. Similar to previous reports, all of our cases had the typical morphologic and immunophenotypic features of extranodal MZL. In each instance, the tumor was composed predominantly of centrocyte-like cells with variable components of plasma cells and monocytoid B cells. Reactive lymphoid follicles were present in all cases. In addition, there was infiltration of Hassall corpuscles by neoplastic cells, the thymic equivalent of lymphoepithelial lesions. In some instances, this was a relatively subtle feature in routine histologic sections, and immunostaining for cytokeratin proteins was useful for confirming the extent of lymphomatous invasion of epithelial structures.

In contrast with previously reported thymic MZLs, which have been uniformly low-grade, overt transformation to large cell lymphoma was present in 1 of our cases (case 3). This latter observation suggests that thymic MZL may represent, at least in some cases, a low-grade precursor to primary mediastinal large cell lymphoma, a possibility that has been speculated by others.\textsuperscript{15} An antecedent or concurrent low-grade component has not been described in any of the major reported series of primary mediastinal large cell lymphoma.\textsuperscript{1-3,15-18} However, this simply may be due to “overgrowth” of a preexisting low-grade component by large cell lymphoma, a distinct possibility in the mediastinum where a thymic lymphoma could remain clinically occult before the development of a bulky mediastinal mass.

We were unable to demonstrate p53 overexpression in any of our cases. Others have reported similar findings in MZL.\textsuperscript{19,20} Du and colleagues\textsuperscript{19} have shown that the
frequency of point mutations and loss of heterozygosity at the p53 locus is greater in high-grade MZL than in low-grade tumors. In addition, overexpression of p53 was present in 60% of high-grade neoplasms, as determined by immunohistochemistry, whereas no p53 protein was detectable in 11 cases of low-grade MZL. Thus, aberrant p53 expression due to genetic mutations at the p53 locus is associated with the progression of MZL to high-grade neoplasms. Other pathogenetic factors, such as overexpression of bcl-6, have been implicated as well in the high-grade transformation of MZL.

Bcl-2 is a constituent of the inner mitochondrial membrane and has an important role in blocking programmed cell death. This protein is expressed in the bulk of follicular lymphomas, in which overexpression usually is linked to a t(14;18) involving the bcl-2 locus. There are

**Image 5** Thymic marginal zone lymphoma. Reactivity for bcl-2 is present only in low-grade marginal zone lymphoma (A) and not in the high-grade component (B). (Original magnification, ×400.)

**Table 2**

Reported Low-Grade Thymic Lymphomas

<table>
<thead>
<tr>
<th>Report</th>
<th>Age (y)/Sex</th>
<th>Associated Disorders</th>
<th>Other Sites of Concurrent Disease</th>
<th>Clinical Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isaacson et al⁴</td>
<td>50/M</td>
<td>No</td>
<td>No</td>
<td>NED, 4 y</td>
</tr>
<tr>
<td></td>
<td>55/F</td>
<td>No; globulins, 6.1 g/dL</td>
<td>No</td>
<td>Involved left axillary lymph node 2 mo after thymic mass</td>
</tr>
<tr>
<td>Takagi et al⁵</td>
<td>59/F</td>
<td>Sjögren syndrome; polyclonal hypergammaglobulinemia</td>
<td>Regional lymph node involved</td>
<td>NED, 1 y</td>
</tr>
<tr>
<td>DiLoreto et al⁶*</td>
<td>51/M</td>
<td>No</td>
<td>Antecedent mucosa-associated lymphoid tissue lymphoma of submandibular gland</td>
<td>Cutaneous involvement 1 y later</td>
</tr>
<tr>
<td>Royer et al⁷</td>
<td>38/F</td>
<td>Sjögren syndrome</td>
<td>Parotid gland, stomach</td>
<td>Partial remission</td>
</tr>
<tr>
<td>Yamasaki et al⁸</td>
<td>61/M</td>
<td>Sjögren syndrome; hypergammaglobulinemia (IgG and IgA) with IgA kappa M protein</td>
<td>No</td>
<td>NED, 3 y</td>
</tr>
<tr>
<td>Yokose et al⁹</td>
<td>55/F</td>
<td>Rheumatoid arthritis</td>
<td>NA</td>
<td>NED, 2 y</td>
</tr>
<tr>
<td></td>
<td>75/F</td>
<td>Sjögren syndrome; polyclonal hypergammaglobulinemia with IgA kappa M protein</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Kim et al¹⁰</td>
<td>72/F</td>
<td>No</td>
<td>No</td>
<td>NED, 5 mo</td>
</tr>
<tr>
<td>Present report</td>
<td>54/F</td>
<td>Sjögren syndrome</td>
<td>No</td>
<td>NED, 10 y</td>
</tr>
<tr>
<td></td>
<td>36/F</td>
<td>Lupus; IgG kappa M protein</td>
<td>No</td>
<td>Bone marrow involvement; persistent hyperviscosity syndrome</td>
</tr>
<tr>
<td></td>
<td>68/M</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not available; NED, no evidence of disease.

* Owing to antecedent or concurrent disease, case may not represent a primary thymic neoplasm.
conflicting reports as to the frequency of bcl-2 expression in MZL. Ngan et al21 found no immunoreactive bcl-2 protein in 7 cases of MZL. By contrast, Ashton-Key et al22 demonstrated bcl-2 expression in their analysis of 21 cases of low-grade MZL. In agreement with the latter report, we found detectable bcl-2 expression in 2 of our cases. Interestingly, in the case with large cell transformation (case 3), immunoreactive bcl-2 expression was observed only in the small neoplastic cells, a pattern of reactivity observed by others.22-24

Although the thymus is primarily a T-cell lymphoid organ, several recent reports have documented the existence of a minor population of B cells in the thymus of both humans and mice.25-29 These cells are located in the medulla, primarily around Hassall corpuscles, constituting approximately one third of all medullary cells, and they have an activated phenotype. Their physiologic role is unknown, but it has been speculated that they may have a role in thymic negative selection.

Whether low-grade thymic MZL arises from these thymic B cells or from a B cell derived from an extrathymic source is uncertain. In several cases, the development of thymic MZL has been associated with autoimmune disorders, particularly Sjögren syndrome. Interestingly, no case of thymic MZL has been reported in association with myasthenia gravis, a condition in which there is often marked thymic follicular hyperplasia and in which, morphologically, there would seem to be the most “fertile” substrate for development of a MZL. Therefore, it is uncertain whether thymic MZL arises in a setting of acquired MALT, as has been postulated for extranodal MZL arising at other anatomic sites that are normally devoid of MALT. The analysis of additional cases of low-grade thymic MZL is needed to further clarify these issues.

There seems to be a strong association clinically between low-grade thymic B-cell lymphoma and autoimmune disease. Seven of 12 reported cases of thymic MZL, including 2 of the present cases, have developed in a setting of autoimmune disease. Of these 7 patients, 5 had Sjögren syndrome, 1 had lupus, and 1 had rheumatoid arthritis. Given the association with autoimmunity, thymic MZL not surprisingly occurs more frequently in females. Although the low number of reported cases precludes a definitive analysis, it is interesting to note that the frequency of autoimmunity in females with thymic MZL seems greater than that for males with this type of lymphoma (75% vs 25%). Whether this represents a sex-dependent difference in the biology of thymic MZL will require the clinical analysis of additional cases. Interestingly, in 1 of our patients (case 2) who had a history of lupus, an antecedent gastric biopsy revealed a minor lymphoplasmacytic infiltrate and a prominent associated crystal-storing histiocytosis. Immunophenotypic studies demonstrated the polytypic nature of the plasmacytic infiltrate and the crystalline immunoglobulin within the histiocytes. It is therefore likely that the crystal-storing histiocytosis was reflective of the patient’s underlying immune dysfunction secondary to her autoimmunity, rather than being related to her lymphoproliferative disorder.

Overall, thymic MZL exhibits relatively indolent clinical behavior. Of the 10 patients for whom clinical follow-up has been reported, 6 were free of disease (mean clinical follow-up, 3.4 years), and 4 had extrathymic disease. No tumor-related deaths have been reported. However, as is evident in our cases, these neoplasms may undergo transformation to a higher grade lymphoma, or they may be associated with clinically significant morbidity, such as a hyperviscosity syndrome. Therefore, recognition of these low-grade thymic neoplasms is important for appropriate clinical management.

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References


