Thymic Hyperplasia With Lymphoepithelial Sialadenitis (LESA)-like Features

A Clinicopathologic and Immunohistochemical Study of 4 Cases

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Abstract

Four cases of an unusual type of thymic hyperplasia strongly resembling lymphoepithelial sialadenitis (LESA) of the salivary glands are described. The patients were 2 men and 2 women aged 37 to 53 years. On histologic examination, abundant lymphoid tissue with lymphoid follicles containing germinal centers and areas of plasma cell infiltration were seen. The epithelial component consisted of a proliferation of Hassall corpuscles and islands of thymic epithelial cells. Cystic changes and lymphoepithelial lesions were identified in all cases, but a monocytoid B-cell population was absent. On immunohistochemical examination, a mixed B- and T-cell population was identified, and polymerase chain reaction performed in 1 case showed polyclonality. Follow-up revealed that all patients were alive 5 months to 9 years after diagnosis. The cases in this series represent a distinct type of thymic hyperplasia that histologically strongly resembles LESA. The clinicopathologic and immunohistochemical features are presented, and a possible relationship with thymic mucosa-associated lymphoid tissue (MALT) lymphoma is discussed.

Lymphoepithelial sialadenitis (LESA) is a benign salivary gland lesion often found in patients with Sjögren disease. The histologic hallmark of LESA is a benign lymphocytic infiltrate of the salivary gland characterized by parenchymal atrophy, ductal hyperplasia, and lymphocytic epitheliolipstropism. The development of malignant lymphoma arising from LESA is also a well-known phenomenon, especially the development of mucosa-associated lymphoid tissue (MALT) lymphoma. In the thymus, primary MALT lymphomas are a rare occurrence. Although morphologically similar to MALT lymphomas of other organ systems, primary MALT lymphomas of the thymus are often cystic in nature and not always associated with autoimmune disease. Contrary to MALT lymphomas of the salivary or thyroid glands, a benign precursor lesion has not been described in the thymus, although early reports of thymic MALT lymphoma speculated about the existence of such a condition. Our cases appear to constitute a distinct form of thymic hyperplasia, which we believe may represent the thymic equivalent of LESA. In addition, the cases presented herein share certain consistent clinical and morphologic features with cases of thymic MALT lymphoma, thus raising the possibility of a close relationship between these entities.

Materials and Methods

Four cases of the lesions described herein were retrieved from the Department of Pathology, MD Anderson Cancer Center, Houston, TX. Histologic material derived from thymectomy specimens was evaluated in every case. Between 9 and 20 H&E-stained sections were available for review.
in each case. Representative paraffin blocks or unstained sections were available for immunohistochemical studies in all cases. Immunohistochemical studies for pancytokeratin (DAKO, Carpinteria, CA; 1:100), CD3 (DAKO; 1:100), CD20 (DAKO; 1:1400), κ antibody (DAKO; 1:20,000), and λ antibody (DAKO; 1:20,000) were performed with concurrent adequate controls. DNA extracted from the paraffin block of one of the cases was analyzed for immunoglobulin heavy chain (IgH) rearrangement using the polymerase chain reaction (PCR) method. Clinical follow-up information was obtained from the medical charts or by contacting the referring physicians.

**Results**

**Clinical Findings**

The clinical findings are summarized in **Table 1**. The patients were 2 men and 2 women aged 37 to 53 years (mean, 45 years). Three patients were asymptomatic, and the tumors were found incidentally on chest radiography performed for unrelated reasons. One patient who had a history of breast carcinoma experienced chest pain, prompting further investigations. None of the patients had a history of autoimmune disease. On radiography, the lesions presented as anterior mediastinal masses leading to surgical resection in all cases. No adjuvant treatment was administered in any of the cases.

**Gross Findings**

The surgical specimens consisted of enlarged and lobulated thymic glands with maximum dimensions ranging from 11.5 to 21 cm. The cut surfaces were of fleshy consistency and tan-yellow in color. They had a multinodular architecture with individual nodules measuring up to 4 cm in greatest dimension. Cystic areas containing smooth to granular cyst walls were appreciated macroscopically in 1 case. Areas of hemorrhage or necrosis were not identified in any of the cases. Areas of hemorrhage or necrosis were identified in any of the cases and neither were areas of hemorrhage or necrosis.

**Histologic Findings**

All 4 cases had similar histologic findings. On low power, a lobulated solid and cystic cellular proliferation was observed surrounded by adipose tissue **Image 1A**. The cysts varied in size from 0.1 to more than 4 cm and were lined by squamous epithelium. These cysts were often filled with amorphous eosinophilic fluid with or without cholesterol clefts **Image 1B**. On higher magnification, the solid proliferation consisted of dense lymphoid tissue containing numerous lymphoid follicles with germinal centers **Image 1C**. Plasma cells were seen in the interfolllicular areas, some of which contained prominent Russell bodies **Image 1D**.

One of the most striking features, however, was an abundant proliferation of the thymic epithelium. This took the form of clusters, nests, and islands of bland thymic epithelial cells that were confluent in some areas with neighboring epithelial proliferations **Image 1E**. In some areas, the epithelium was crescent-shaped and stretched around lymphoid follicles. Hassall corpuscles were numerous, and some showed cystic dilatation or central calcification. Importantly, these epithelial changes appeared to be unrelated to the cyst walls and showed no cytologic atypia or mitotic activity. Lymphoepithelial lesions with lymphocytes penetrating the epithelial proliferation were also noted frequently, and another finding was the presence of cholesterol clefts leading to the formation of cholesterol cleft granulomas **Image 1F**, **Image 1G**, and **Image 1H**. Of note, an atypical lymphoid proliferation was not identified in any of the cases and neither were areas of hemorrhage or necrosis.

**Immunohistochemical and Molecular Findings**

All 4 lesions showed similar immunohistochemical features. Diffuse staining with CD20 highlighted the presence of B lymphocytes in the germinal centers and, to a minor degree, in the interfolllicular areas **Image 2A**. In turn, the interfolllicular areas were mainly populated by CD3-positive T lymphocytes **Image 2B**. CD20+ B cells were also seen infiltrating the epithelium in places, emphasizing the lymphoepithelial lesions. Pancytokeratin highlighted the outlines of the epithelial nests and Hassall corpuscles as well as the lining of the cystic structures **Image 2C** and **Image 2D**. κ and λ stains applied to one of the cases confirmed a polyclonal process. PCR performed on a single case demonstrated a polyclonal pattern of IgH amplification.

**Table 1**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age, y</th>
<th>Lesion Size, cm</th>
<th>Clinical Manifestations</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>53</td>
<td>21</td>
<td>Incidental</td>
<td>Surgery</td>
<td>A&amp;W at 5 mo</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>50</td>
<td>11.5</td>
<td>Chest pain; history of breast cancer</td>
<td>Surgery</td>
<td>A&amp;W at 8 y</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>41</td>
<td>NK</td>
<td>Incidental</td>
<td>Surgery</td>
<td>A&amp;W at 7 y</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>37</td>
<td>NK</td>
<td>Incidental</td>
<td>Surgery</td>
<td>A&amp;W at 9 y</td>
</tr>
</tbody>
</table>

A&W, alive and well; LESA, lymphoepithelial sialadenitis; NK: not known.
Follow-up

Follow-up data revealed that all 4 patients were alive and doing well 5 months to 9 years after the initial diagnosis without receiving any adjuvant therapy.

Discussion

Thymic hyperplasia includes 2 major types: true thymic hyperplasia (TTH) and follicular thymic hyperplasia (FTH). TTH is a rare condition characterized by a histologically unremarkable thymic gland that is enlarged in size and weight beyond normal limits. On the other hand, FTH is defined as a thymic gland with the presence of lymphoid follicles and germinal centers regardless of its size or weight. TTH predominantly affects younger patients at a mean age of 22 years and affects men and women equally, whereas FTH is more commonly seen in young female adults at a mean age of 24 years. The pathogenesis of the thymic enlargement in these conditions appears to be different depending on the type. TTH is thought to be an immunologic rebound phenomenon in response to stress or treatment of malignant tumors. It can also be seen in association with other processes such as endocrine anomalies or infectious diseases. FTH, on the other hand, is frequently associated with autoimmune disorders, most commonly myasthenia gravis. Regardless of the etiology,

A

B

C

D

Image A, Solid cystic growth pattern of thymic hyperplasia with lymphoepithelial sialadenitis (LESA)–like features (H&E, ×1.25). B, Characteristic cysts lined by squamous epithelium and filled with amorphous eosinophilic fluid (H&E, ×4). C, Florid lymphoid proliferation with lymphoid follicles containing germinal centers in thymic hyperplasia with LESA-like features (H&E, ×4). D, Plasma cell infiltrate with scattered Russell bodies (H&E, ×20).
the clinical presentation of both types is similar and often manifests as respiratory distress. The treatment often consists of steroid therapy in cases of TTH, whereas the treatment for FTH is generally thymectomy.⁸

Although the cases described herein appear to represent a form of thymic hyperplasia, the clinical and morphologic features of our cases are distinctly different from the conventional types of thymic hyperplasia. For one, the average age at presentation of 45 years in our cases is older than that described for the conventional types. In addition, the majority of our patients were asymptomatic and their lesions discovered incidentally. Autoimmune disease, in particular Sjögren syndrome or myasthenia gravis, was not diagnosed in any of our patients. Lastly, our cases displayed a distinct morphology characterized by a prominence of lymphoid tissue with scattered lymphoid follicles containing germinal centers, a plasmacytic infiltrate, a striking proliferation of Hassall corpuscles and thymic epithelium, lymphoepithelial lesions, and cystic changes that are different from the histologic features of conventional thymic hyperplasia and are highly reminiscent of the changes seen in LESA.

In the salivary glands, LESA is defined as a benign lymphocytic infiltrate leading to parenchymal atrophy, ductal hyperplasia, and lymphoepithelial lesions.¹ The lymphocytic...
proliferation is thought to be the salivary manifestation of MALT. LESA is considered an autoimmune lesion and is one of the defining components of Sjögren disease. It predominantly affects the parotid gland of female patients who are in the fourth to seventh decade of life. Importantly, patients who suffer from LESA are at high risk of developing lymphoma, especially MALT lymphoma. In fact, most if not all MALT lymphomas of the salivary glands are preceded by LESA, and distinction between the 2 conditions can pose diagnostic difficulties. Generally, MALT lymphoma is diagnosed if an expansion of clonal monocytoid B cells is identified either surrounding the lymphoepithelial islands in a halo-like fashion or as interconnecting strands. Ancillary studies such as immunohistochemistry, flow cytometry, or molecular genetics may be of additional help in the differential diagnosis of these lesions; LESA is normally a polyclonal lesion, whereas the contrary is true for MALT lymphoma. However, it has to be noted that in more than 50% of cases of LESA, clonal B-cell populations can be detected, thus limiting the value of molecular techniques in the evaluation of these lesions. Lastly, the period from the diagnosis of LESA to the development of malignant lymphoma is highly variable and has been documented to range from 6 months to up to 29 years.

**Image 2A.** CD20 antibody highlighting B lymphocytes in germinal centers and, to a lesser degree, in interfollicular areas in thymic hyperplasia with lymphoepithelial sialadenitis (LESA)-like features (×4). **B.** CD3 decorating T lymphocytes predominantly in the interfollicular areas and some germinal center lymphocytes (×4). **C.** Cytokeratin staining outlining the epithelial proliferation in thymic hyperplasia with LESA-like features (×4). **D.** Lymphocytes displacing the epithelial proliferation in lymphoepithelial lesions in thymic hyperplasia with LESA-like features (cytokeratin, ×10).
MALT lymphoma can on occasion also affect the thymic gland as a primary tumor. In this scenario, most of the reported cases are of middle-aged Asian women with Sjögren syndrome. However, in a recent report we were able to demonstrate that these tumors may also occur in whites and in a setting not related to autoimmune disease. In addition, this tumor can also affect male individuals in isolated cases. Histologically, thymic MALT lymphomas are cystic lesions separated by a lymphoid component with germinal centers, an atypical lymphoid population composed of monocytoid cells, remnants of thymic epithelium, and scanty Hassall corpuscles.

Interestingly, in the first description of thymic MALT lymphoma, Isaacson et al. alluded to the morphologic resemblance of this tumor to LESA and hypothesized that “there may be a still undescribed benign condition of the thymus similar to myoepithelial sialadenitis or Hashimoto’s disease that is the precursor to the development of MALT lymphoma.” Based on the morphologic similarities, we believe that the cases described herein are likely to represent the thymic equivalent of LESA. Furthermore, when one compares the characteristics of LESA-like hyperplasia and MALT lymphoma of the thymus, certain consistencies can be observed. The average age at onset of thymic hyperplasia with LESA-like features is about a decade younger than that of thymic MALT, providing sufficient time for the development of a malignant lymphoma. In either case, both lesions are rather unusual and to some extent treated in the same way, that is, they will most likely require complete surgical resection. More important for the time being is to separate these lesions because they may share overlapping histologic features.

From a diagnostic point of view it is also important to separate thymic hyperplasia with LESA-like features from other cystic lesions of the anterior mediastinum. Further cystic lesions of the thymus primarily include multilocular thymic cysts and cystic thymoma. Multilocular thymic cysts are acquired cysts of the thymic gland composed of multiple cysts lined by squamous or low cuboidal epithelium, lymphoid hyperplasia, cholesterol cleft granulomas, fibrosis, and remnants of thymic epithelium. In a similar fashion to thymic

Table 2
Characteristics of Conventional Thymic Hyperplasia, Thymic Hyperplasia With LESA-like Features, and Thymic MALT Lymphoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>True Thymic Hyperplasia</th>
<th>Follicular Thymic Hyperplasia</th>
<th>Thymic LESA-like Hyperplasia</th>
<th>Thymic MALT Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age</td>
<td>3rd decade F</td>
<td>3rd decade F</td>
<td>5th decade M = F</td>
<td>6th decade F</td>
</tr>
<tr>
<td>Sex</td>
<td>M = F</td>
<td>F</td>
<td>Chest pain, often incidental</td>
<td>F</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>respiratory distress No</td>
<td>Respiratory distress Myasthenia gravis</td>
<td>No</td>
<td>Shortness of breath, chest pain, or incidental</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>Retained normal thymic morphology; solid</td>
<td>Presence of lymphoid follicles with germinal centers; solid</td>
<td>Prominent lymphoid tissue with scattered lymphoid follicles containing germinal centers, plasmacytic infiltrate, proliferation of Hassall corpuscles and thymic epithelium, lymphoepithelial lesions; cystic</td>
<td>Cystic lesions separated by a lymphoid component with germinal centers, an atypical lymphoid population composed of monocytoid cells, remnants of thymic epithelium, and scanty Hassall corpuscles</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial component</td>
<td>Inconspicuous T cell predominance</td>
<td>Inconspicuous Mix of B and T cells</td>
<td>Prominent Mix of B and T cells</td>
<td>Inconspicuous Mix of B and T cells</td>
</tr>
<tr>
<td>Lymphoid component</td>
<td>Polyclonal</td>
<td>Polyclonal</td>
<td>Polyclonal</td>
<td>Polyclonal</td>
</tr>
<tr>
<td>Clonality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LESMA, lymphoepithelial sialadenitis; MALT, mucosa-associated lymphoid tissue.
LESA-like hyperplasia, some of these lesions can also show an exuberant epithelial proliferation termed “pseudoepitheliomatous hyperplasia.” However, in these cases, the epithelial changes are confined to the cyst lining, which is composed of atypical squamous cells with large hyperchromatic nuclei, prominent nucleoli, and occasional mitotic figures. This contrasts with the bland epithelial changes that are unrelated to the cyst wall in cases of thymic hyperplasia with LESA-like features. Cystic thymomas, on the other hand, have cystic changes confined to the cyst lining, which is composed of atypical squamous cells with large hyperchromatic nuclei, and numerous Hassall corpuscles are not components of conventional thymomas.

In summary, we have presented 4 cases of an unusual type of thymic hyperplasia that we believe may represent the thymic equivalent of LESA. Contrary to most cases of the salivary gland, thymic hyperplasia with LESA-like features may not be associated with autoimmune disease. Furthermore, certain similarities in the clinical, morphologic, and prognostic features between LESA-like hyperplasia and MALT lymphoma of the thymus mirror the close relationship of these lesions in the head and neck region, suggesting that the same intimate association may exist in the thymic gland. However, evaluation of a larger series of cases is required to confirm this impression.

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References