Low-grade B-cell Lymphoma of Mucosa-associated Lymphoid Tissue in the Thymus of a Patient with Pulmonary Amyloid Nodules

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Low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-type lymphoma) is a rare thymic tumor, with only seven previous cases described worldwide to date. We describe the only case to have presented with pulmonary amyloid nodules. A 63-year-old Japanese female was found to have an anterior mediastinal tumor and multiple bilateral pulmonary nodules during a medical check-up in 1990 followed by chest radiography and computerized tomography. Because the mediastinal tumor grew larger, she was referred to the National Cancer Center Hospital East and hyperglobulinemia was pointed out. The thymus was resected through median sternotomy and pulmonary nodules were also resected through left thoracotomy. The solid and nodular tumor with several small satellite extensions and cyst formation was completely confined to within the thymus and the resected pulmonary nodules consisted of solid masses with a rough surface. Histologically, monotonous medium-sized centrocyte-like cells occupied the medulla of the thymus and infiltrated Hassall’s corpuscles (lymphoepithelial lesions) and the resected pulmonary nodules consisted of eosinophilic amorphous deposits which showed birefringence on Congo Red staining. Immunohistochemically, the tumor cells were positive for CD20 and CD79a. IgG and kappa light chain restrictions were also found in plasmacytoid cells in the tumor. Clonal rearrangement of the immunoglobulin heavy chain gene was demonstrated by polymerase chain reaction. We diagnosed this case as low-grade B-cell MALT-type lymphoma in the thymus and nodular pulmonary amyloidosis. Since the patient had only localized amyloid deposits in the lung far from the thymic malignant lymphoma and had high serum immunoglobulins, the pulmonary amyloid deposits might be derived from a circulating precursor associated with hyperglobulinemia.

Key words: thymus – malignant lymphoma – MALT – amyloidosis – lung

INTRODUCTION

Malignant lymphoma of mucosa-associated lymphoid tissue (MALT) is a neoplasm originating from MALT, which was normally present in parts of the gastrointestinal tract such as the small intestine (1). The great majority of malignant lymphomas of MALT (MALT-type lymphoma) were found to be B-cell type, involving not only the gastrointestinal tract but also salivary gland, lung and thyroid and they tended to remain localized for prolonged periods and responded well to local therapy (2). Histologically, these lymphomas were characterized by centrocyte-like (CCL) cells, infiltration of plasma cells with monotypic immunoglobulins and formation of lymphoepithelial lesions (LELs) (3).

The thymus is derived from the third and part of the fourth pair of pharyngeal pouches and is a complex organ with both lymphoid and epithelial components. It is well known that Hodgkin’s disease, lymphoblastic lymphoma and large cell lymphoma of B-cell origin arise in the thymus (4), but low-grade B-cell MALT-type lymphoma of the thymus is very rare (5). In 1990, Isaacson et al. (6) reported two cases of MALT-type lymphoma arising in the thymus and they were followed
MALT lymphoma in thymus associated with nodular pulmonary amyloidosis

by reports of five similar cases (4,6–9). No cases of MALT-type lymphoma of the thymus accompanied by amyloid nodules of the lung, however, have ever been reported. We describe here a case of MALT-type lymphoma of the thymus in a patient with nodular pulmonary amyloidosis.

CASE REPORT

A 63-year-old Japanese female was found to have an anterior mediastinal tumor and multiple bilateral pulmonary nodules during a medical check-up in 1990. She was subsequently followed-up by chest radiography and computerized tomography (CT) twice a year. Because the mediastinal tumor grew larger, she was referred to the National Cancer Center Hospital East in 1995. A chest radiograph showed multiple bilateral pulmonary nodules (Fig. 1) and a chest CT showed a post-sternal multinodular tumor (Fig. 2). Serum rheumatoid factor was positive (845 IU/ml) and immunoglobulins G (IgG) and A (IgA) were elevated (2735 and 819 mg/dl, respectively). Anti-nuclear antibody was negative. Anti-SS-A antibody was positive, but anti-SS-B antibody was negative. Percutaneous needle biopsies of the anterior mediastinal tumor and the multiple right pulmonary nodules were performed under CT guidance. The biopsy specimens showed atypical lymphoid infiltration, suggesting MALT lymphoma of the mediastinum and amyloid deposition in the lung. A solid and nodular mediastinal tumor was completely resected through median sternotomy and two solid nodules were resected from the left lung through a left thoracotomy on March 18, 1996. The mediastinal tumor was confined within the thymus and was found to occupy both lobes on the transverse cut surface. The tumor showed lobules and multiple macroscopic cysts (Fig. 3a). The non-tumorous region of the thymus was fatty without any apparent tumor. The interface between the tumor and thymic fatty tissue was well demarcated, but focally ill-defined and several small satellite extensions were present. The resected pulmonary nodules were 2.0 × 1.3 and 0.9 × 0.6 cm in size and consisted of solid masses having a rough surface.

PATHOLOGICAL FINDINGS

GROSS APPEARANCE

The resected thymus was 17 × 9 cm in size and weighed 120 g. A well-demarcated, homogeneous and tan-to-white tumor was confined within the thymus and was found to occupy both lobes on the transverse cut surface. The tumor showed lobules and multiple macroscopic cysts (Fig. 3a). The non-tumorous region of the thymus was fatty without any apparent tumor. The interface between the tumor and thymic fatty tissue was well demarcated, but focally ill-defined and several small satellite extensions were present. The resected pulmonary nodules were 2.0 × 1.3 and 0.9 × 0.6 cm in size and consisted of solid masses having a rough surface.

HISTOLOGY

The tumor was widely separated from the thymic fatty tissue by a thin fibrous septum but had focally infiltrated the fatty tissue and small tumor nodules were occasionally observed away from the tumor. The tumor consisted of dense lymphoid infiltrates and formed lobular structures within which Hassall’s corpuscles and epithelium-lined cysts were recognized. Reactive lymph follicles with active germinal centers were scattered within the tumor, but they were small in number and abortive. The corticomedullary junction of the thymus was obscure owing to almost complete replacement by monotonous infiltration with medium-sized CCL cells characterized by moderately abundant, clear or very finely granular cytoplasm and round or indented nuclei with a clear cell border (Fig. 3b). The CCL cells had invaded the Hassall’s corpuscles and infiltrated the epithelial components, forming LELs (Fig. 3c). Some plasma cells or plasmacytoid cells infiltrated in the CCL cells. Cysts were present and their walls were covered by flat epithelial cells and had been invaded by CCL cells. The tumor cells did not show any extracapsular invasion around the thymus.
The tumor was considered to be stage I by the Ann Arbor classification.

The resected pulmonary nodules consisted of amorphous eosinophilic deposits (Fig. 4a) and the deposits were demonstrated to be amyloid because they were positive for Congo Red staining and showed an apple-green color with birefringence (Fig. 4b). After oxidation with permanganate solution, the Congo Red-associated birefringence of the deposits was retained, indicating that the amyloid was non-amyloid A protein-derived type.

PHENOTYPIC AND GENOTYPICAL FINDINGS

The CCL cells showed a B-cell phenotype expressing CD20 and CD79a and infiltrating the Hassall’s corpuscles which were positive for keratin. These cells were negative for cyclinD1 and CD45RO. A positive immunoreaction to IgG and kappa light chain was found in the plasma cells or plasma-cytoid cells in the CCL cell infiltrates, but the typical CCL cells did not show any positive immunoreaction to these markers. Using primers FR3A and LJH for PCR yielded a single faint band, indicating the presence of a clonal B cell population in the lesion. This was further confirmed by a subsequent semi-nested PCR method (using primers FR3A and VLJH), which yielded a more definite single band on the gel (data not shown).

DISCUSSION

Only seven cases of MALT-type lymphoma of the thymus have ever been reported (Table 1) (4,6–9). Six of the eight
Table 1. Clinicopathological review of seven previously reported cases and the present case with MALT-type lymphoma in the thymus

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Race</th>
<th>Autoimmune disease/other complications</th>
<th>Maximum size of tumor (cm)</th>
<th>Macroscopic cyst</th>
<th>Treatment</th>
<th>Time course</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>M</td>
<td>White</td>
<td>-/petit mal epilepsy</td>
<td>9</td>
<td>+</td>
<td>SUR</td>
<td>No recurrence (4 years)</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>F</td>
<td>Chinese</td>
<td>Hyperglobulinemia/cellulitis of the foot, colloid nodule of the thyroid</td>
<td>12</td>
<td>–</td>
<td>SUR</td>
<td>Axillary LN recurrence (2 months)</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>F</td>
<td>Japanese</td>
<td>Sjögren’s syndrome/–</td>
<td>13</td>
<td>+</td>
<td>SUR + RT</td>
<td>Complete remission</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>M</td>
<td>Japanese</td>
<td>Sjögren’s syndrome/–</td>
<td>9.5</td>
<td>+</td>
<td>SUR + RT</td>
<td>No recurrence (2 years)</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>F</td>
<td>Japanese</td>
<td>Sjögren’s syndrome/–</td>
<td>13.1</td>
<td>–</td>
<td>SUR</td>
<td>No recurrence</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>F</td>
<td>Japanese</td>
<td>Rheumatoid arthritis/–</td>
<td>7.5</td>
<td>–</td>
<td>SUR</td>
<td>No recurrence (5 years)</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>72</td>
<td>F</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>+</td>
<td>NR</td>
<td>NR</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>F</td>
<td>Japanese</td>
<td>-/pulmonary amyloidosis</td>
<td>17</td>
<td>+</td>
<td>SUR</td>
<td>No recurrence (3.5 years)</td>
<td>Present case</td>
</tr>
</tbody>
</table>

M, male; F, female; SUR, surgical resection; LN, lymph node; RT, radiation therapy; NR, not reported.

patients (including the present case) were Asian and the male to female ratio was 2:6. Three of the patients had Sjögren’s syndrome (4,6) and one had rheumatoid arthritis (8). The present patient had no symptoms of autoimmune disease, but she did have high serum immunoglobulin levels and rheumatoid factor and anti-SS-A antibody were positive. We speculate that immunological abnormalities were strongly related to the genesis of the MALT-type lymphoma.

Microscopically, we thought that MALT-type lymphoma of the thymus in the present case should be differentiated from lymphofollicular hyperplasia and thymoma of lymphocyte predominant type. Lymphofollicular hyperplasia of the thymus is characterized by prominent lymph follicle formation which is also observed in MALT-type lymphoma of the thymus (10). However, close inspection indicated that the lymph follicles of the current case were so poorly formed and generally small in size that they were clearly different from well-developed follicles observed in lymphofollicular hyperplasia. Hassall’s corpuscles may be occasionally involved in thymoma and these lesions may be mistaken for LELs (10). However, even if lymphocytes are rich in thymoma, epithelial cells can be found in the lymphoid component. The presence of perivascular spaces with lymphocytes is highly specific for thymoma and is absent in thymic MALT-type lymphoma. Finally, definitive diagnosis of MALT-type lymphoma of the thymus rests on the demonstration of the monoclonal nature using immunohistochemical or IgH gene rearrangement study (7).

The present case showed macroscopic cysts and six of the previous seven cases also showed macroscopic or microscopic cysts (Table 1). Yi et al. reported that MALT-type lymphoma should be considered in the differential diagnosis whenever a solid, cystic thymic mass is found (9). We also consider cyst formation to be one of the characteristic findings in MALT-type lymphoma.

Non-Hodgkin’s lymphoma has rarely been associated with the development of amyloidosis, but some previously reported cases have described widespread deposition of amyloid in a typical pattern of primary systemic amyloidosis (11). Our case was unique because the patient had pulmonary amyloid nodules and this is the first report of MALT-type lymphoma in the thymus with pulmonary nodular amyloidosis. Most patients with B-cell lymphoma have detectable monoclonal immunoglobulin in the serum that is identical in isotype with that borne by the malignant cells (12). Whether the light chain fragments from light chain-derived amyloid (AL) represent synthetic or catabolic products has never been established, but amyloidosis develops in only a small percentage of patients with overproduction of light chains. This may be because only some light chains are inherently amyloidogenic or because other pathological factors in the host induce amyloid development. In vitro, 15–20% of light chains precipitate as fibrillar material resembling amyloid after proteolytic digestion (13). This amyloidogenic property is associated with the variable regions of the light chain and is found more commonly with lambda (λ) than kappa (κ) monoclonal light chains (14), in keeping with the clinical observation that the light chain class in AL is more frequently λ than κ (15). The present case, however, had monoclonal κ light chains. Little is known about the factors that determine the characteristic tissue distribution of different types of amyloid. There are two possibilities: first, in systemic AL amyloidosis the amyloid deposits may be derived from a circulating precursor whose deposition is determined by its affinity for certain tissues; second, monoclonal light chains may be processed immediately adjacent to sites of synthesis to form amyloid fibrils (16). The findings that the patient had only localized amyloid deposits in the lung far from the thymic malignant lymphoma and had high serum immunoglobulins seem to support the former possibility.
References


