# Primary Thymic Mucosa-Associated Lymphoid Tissue Lymphoma

## *Diagnostic Tips*

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**Abstract:** Mucosa-associated lymphoid tissue (MALT) lymphoma arising in the thymus is extremely rare and little is known regarding its clinicopathological features. This study examined the clinicopathological features of nine cases of thymic MALT lymphoma. Most patients had autoimmune disease or hyperglobulinemia, and they also had cysts in the tumors. Both increased serum autoantibody levels and polyclonal serum immunoglobulin levels remained essentially unchanged after total thymectomy in all patients. Thymic MALT lymphoma needs to be included in the differential diagnosis in Asian patients with a cystic thymic mass accompanied by autoimmune disease or hyperglobulinemia.

**Key Words:** MALT lymphoma, Thymus, Autoimmune disease, Hyperglobulinemia.

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Extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) accounts for approximately 7 to 8% of all B-cell lymphomas, and the gastrointestinal tract is the most common site, accounting for 50% of all cases. Other common sites include the lung (14%), head and neck (14%), ocular adnexae (12%), skin (11%), thyroid (4%), and breast (4%).[1] Hodgkins disease, lymphoblastic lymphoma, and large cell lymphoma of B-cell origin arise in the thymus, whereas MALT lymphoma of the thymus is extremely rare.[2] We encountered nine cases of MALT lymphoma arising in the thymus and reviewed their clinicopathological features in this report.

## PATIENTS AND METHODS

### Tissue and Clinical Data

From the files of the Division of Thoracic and Visceral Organ Surgery, Gunma University Graduate School of Medicine and Division of Thoracic Surgery, National Cancer Center Hospital East, nine patients with thymic MALT lymphoma were identified. Four of these cases have been reported previously.[3–5] All specimens were obtained at initial presentation and were reviewed by a pathologist. All tissue samples were fixed in 10% buffered formalin and embedded in paraffin. Tissue sections cut at 3 $\mu$m were prepared and stained with hematoxylin and eosin (H&E). Medical records were reviewed to collect data on patient history, symptoms, laboratory data, and type of treatments. Follow-up information was obtained from clinical records and attending physicians. For the reported cases included in this series, the follow-up information was updated. Disease stage was assigned using an adaptation of the Ann Arbor staging system for extranodal lymphomas.

## RESULTS

### Clinical Findings

The clinical findings of the nine patients are summarized in the first nine lines of Table 1. All patients were Japanese. Three patients were men and six were women (male:female = 1:2). Their ages ranged from 30 to 75 years (mean, 58 years; median, 63 years). Eight patients were asymptomatic, and their tumors were detected incidentally on chest radiography at an annual health checkup or during follow-up studies for other diseases. One patient had back pain caused by the tumor. Cases 1, 7, and 8 had rheumatoid arthritis, and cases 5, 8, and 9 had Sjögren syndrome. Although the remaining three patients did not have autoimmune disease clinically, they showed serological findings suggestive of autoimmune disease. Patient 9 had concurrent MALT lymphomas in the lungs, which were discovered simultaneously. Physical examination did not reveal lymphadenop-

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**TABLE 1.** Summary of Clinicopathological Data of Primary Thymic MALT Lymphoma

| Case No. | Nationality | Age | Sex | Symptoms | Autoimmunity | Hypergloblinemia (Increased Ig Type) | Treatments | Outcome | Macroscopic Cysts | Microscopic Cysts | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Japanese | 55 | F | Back pain | RA | NA | S | NED | No | Yes | 3 |
| 2 | Japanese | 63 | F | Asymptomatic | Yes[a] | P (IgG,A) | S | NED | Yes | Yes | 4 |
| 3 | Japanese | 75 | M | Asymptomatic | Yes[a] | P (IgG, IgA) | S | NED | Yes | Yes | 5 |
| 4 | Japanese | 30 | F | Asymptomatic | Yes[a] | P (IgG, IgM) | S | NED | Yes | Yes | 5 |
| 5 | Japanese | 67 | F | Asymptomatic | SjS | P (IgG, IgM) | S | NED | Yes | Yes | New case |
| 6 | Japanese | 65 | M | Asymptomatic | No | M (IgM) | S | NED | Yes | Yes | New case |
| 7 | Japanese | 65 | M | Asymptomatic | RA | M(IgA) | S | NED | Yes | Yes | New case |
| 8 | Japanese | 55 | F | Asymptomatic | RA,SjS | P(IgG,M) | S | NED | Yes | Yes | New case |
| 9 | Japanese | 49 | F | Asymptomatic | SjS | P(IgG, IgA, IgM) | S,RTx | NED | Yes | Yes | New case |
| 10 | Chinese | 55 | F | Asymptomatic | Yes[a] | M (IgA) | S,CTx | NED | Yes | Yes | 13 |
| 11 | Japanese | 59 | F | Chest pain | SjS | P (IgG,A,M) | S,RTx | NED | Yes | Yes | 14 |
| 12 | NA | 52 | M | Asymptomatic | No(but with skin lesion) | NA | S | AWD | Yes | Yes | 9 |
| 13 | Japanese | 64 | F | Back pain | No | No | S | NED | No | Yes | 15 |
| 14 | NA | 72 | F | Chest pain[b] | No | NA | S | NA | Yes | Yes | 8 |
| 15 | Japanese | 61 | M | Asymptomatic | SjS | M (IgA) | S,RTx | Lost | Yes | Yes | 16 |
| 16 | Japanese | 75 | F | Asymptomatic | SjS | M (IgA) | S,RTx | NED | No | Yes | 16 |
| 17 | NA | 63 | F | Asymptomatic[c] | Yes[a] | Polyclonal | S | NED | Yes | Yes | 10 |
| 18 | Japanese | 36 | F | Asymptomatic | SjS | P (IgG,A,M) | S,CTx | DOC | No | Yes | 17 |
| 19 | NA | 56 | F | NA | RA,SjS | NA | NA | NA | NA | Yes | 18 |
| 20 | NA | 45 | M | NA | Scleroderma | NA | NA | NA | NA | Yes | 18 |
| 21 | Japanese | 47 | F | Asymptomatic | SjS | M (IgA) | CTx,RTx | AWD | Yes | Yes | 19 |
| 22 | Japanese | 47 | F | Asymptomatic | SjS | P (IgG,A) | S,RTx | NED | Yes | Yes | 7 |
| 23 | Japanese | 46 | F | Asymptomatic | SjS | No | S,CTx | NED | Yes | Yes | 7 |
| 24 | Japanese | 67 | M | Asymptomatic | No | No | CTx,RTx | DOD | No | Yes | 7 |
| 25 | Chinese | 42 | F | Asymptomatic | No | NA | S | Lost | Yes | Yes | 7 |
| 26 | Chinese | 57 | M | Short breath | No | No | CTx | NED | NA | Yes | 7 |
| 27 | Chinese | 45 | F | Hemoptysis | SjS | M (IgA) | CTx,RTx | NED | NA | Yes | 7 |
| 28 | NA | 54 | F | Asymptomatic | SjS | NA | S | NED | NA | NA | 12 |
| 29 | NA | 36 | F | Asymptomatic | Childhood Lupus | M (IgG) | S, RTx | AWD | NA | NA | 12 |
| 30 | NA | 68 | M | Asymptomatic | No | NA | S | NA | NA | NA | 12 |
| 31 | Japanese | 46 | F | Asymptomatic | SjS | No | S | NED | Yes | Yes[d] | 20 |
| 32 | Korean | 43 | F | Asymptomatic | RA,SjS | No | S | NA | No | Yes | 11 |
| 33 | Caucasian | 40 | F | Asymptomatic | SjS | M(IgA) | S | AWD | NA | Yes | 21 |
| 34 | Japanese | 66 | F | Asymptomatic | SjS | NA | S | NED | Yes | Yes | 22 |
| 35 | Japanese | 55 | F | Asymptomatic | SjS | NA | S | NED | Yes | Yes | 22 |
| 36 | Japanese | 62 | F | Asymptomatic | SjS | NA | S | NED | Yes | Yes | 22 |
| 37 | Japanese | 34 | F | Asymptomatic | SjS | NA | S, CTx | NA | Yes | NA | 23 |

[a] Yes, probable autoimmune disease as suggested by serological findings.
[b] Chest pain proved to be due to acute myocardial infarction.
[c] Weight loss, cold hands, night sweats, dry eyes, and a dry mouth.
[d] Yes, recognized in Figure 3 of the literature.
SjS, Sjögren's syndrome; RA, rheumatoid arthritis; NA, not available; CTx, chemotherapy; RTx, radiotherapy; S, surgery; NED, no evidence of disease; AWD, alive with disease; DOD, death of disease; DOC, death of other causes; MALT, mucosa-associated lymphoid tissue.

athy or splenomegaly. The laboratory findings within 2 weeks before and after total thymectomy are shown in Table 2. Nine patients were seropositive for rheumatoid factor both before and after surgery, except for case 3, who became seropositive only after surgery. Eight patients were seropositive for antinuclear antibody both before and after surgery. All patients showed hypergammaglobulinemia: serum Immunoglobulon G (IgG), IgA, and IgM levels were increased in six, five, and five patients, respectively. Anti-SS-A antibody was detected in seven patients and anti-SS-B antibody in four patients. Eight patients had stage I disease and one had stage IV disease. All patients underwent total thymectomy and only patient 9 received radiotherapy. Both the increased serum autoantibody levels and polyclonal increases in the serum Igs

**TABLE 2.** Laboratory Findings Before and After Thymectomy

| | Case 1 Pre/Post | Case 2 Pre/Post | Case 3 Pre/Post | Case 4 Pre/Post | Case 5 Pre/Post | Case 6 Pre/Post | Case 7 Pre/Post | Case 8 Pre/Post | Case 9 Pre/Post |
|---|---|---|---|---|---|---|---|---|---|
| Autoantibodies in serum | | | | | | | | | |
| Rheumatoid factor[a] | +/+ | +/+ | −/+ | +/+ | +/+ | +/+ | +/+ | +/+ | +/+ |
| Antinuclear antibody[b] | +/+ | +/+ | +/+ | +/+ | +/+ | −/− | +/+ | +/+ | +/+ |
| Anti-SS-A antibody | +/+ | +/+ | −/− | +/+ | +/+ | −/− | +/+ | +/+ | +/+ |
| Anti-SS-B antibody | −/− | −/− | −/− | +/+ | +/+ | −/− | −/− | +/+ | +/+ |
| Serum protein | | | | | | | | | |
| IgG (mg/dl)[c] | −/− | +/+ | +/− | +/+ | +/+ | −/− | −/− | +/+ | +/+ |
| IgA (mg/dl)[d] | −/− | +/− | +/+ | −/− | −/− | −/− | +/+ | −/+ | +/− |
| IgM (mg/dl)[e] | −/− | +/+ | −/− | +/+ | +/− | +/+ | −/− | +/+ | −/− |
| ESR[f] | +/NA | +/NA | +/NA | +/NA | +/NA | +/NA | +/NA | +/NA | +/NA |
| CRP[g] | 0.5/NA | 0.1/NA | 0.7/NA | <0.1/NA | <0.1/NA | <0.1/NA | <0.1/NA | 0.4/NA | 0.4/NA |
| sIL-2R[h] | 318/NA | 433/NA | 477/NA | 252/205 | NA | NA | 509 | 376/357 | NA |

Normal range: [a] <15 IU/ml.
[b] <40.
[c] 777–1762 mg/dl.
[d] 109–434 mg/dl.
[e] 30–188 mg/dl.
[f] Male <10 mm, female <15 mm.
[g] <0.5.
[h] <519 U/ml.
Pre, before total thymectomy; post, after total thymonectomy; ESR, erythrocyte sedimentation rate in the first hour; CRP, C-reactive protein; sIL-2R, soluble interleukin-2 receptor; +, above normal range; −, within normal range; NA, not available.

remained essentially unchanged after the total thymectomy (Table 2). In cases 5 and 6, the serum Ig and autoantibody levels remain increased 5 years after the thymectomy. To date, all patients are well, without signs of recurrence.

## Radiologic Findings and Gross Appearance

Computed tomography and magnetic resonance imaging (MRI) of the chest showed a cystic thymic mass in all eight of our cases with macroscopic cysts. On MRI, these cysts were of increased signal intensity compared with cerebrospinal fluid on T1-weighted images and of markedly increased signal intensity (similar to that of cerebrospinal fluid) on T2-weighted images (Figure 1A). All tumors were confined to the thymus. Cross-sections revealed a solid tumor with gray-white to light tan cut surfaces. Eight tumors contained single or multiple macroscopic cysts (Figure 1B).

## Histologic Findings

Histologically, all the tumors were separated from the thymic fatty tissue by a thin fibrous capsule. Multiple cysts and reactive lymph follicles with active germinal centers were scattered within the tumors in all cases (Figure 2*A*). The cyst walls were lined by flat epithelial cells. Morphologically, these cysts were clearly distinguishable from the perivascular spaces characteristic of thymoma. Epithelium-lined macro/microscopic cysts were recognized in eight patients, whereas microscopic cysts alone were observed in case 1.

All the tumors consisted mainly of dense centrocyte-like cells and had a lobular structure. Centrocyte-like cells invaded Hassall's corpuscles (Figure 2B) and the cyst wall epithelium (Figure 2C), forming lymphoepithelial lesions (Figures 2*B, C*). In all cases, lymphoepithelial lesions and plasma cell differentiation were observed. Plasma cells were often found to aggregate around the vessels (Figure 2*D*). Immunostaining for cytokeratin highlighted the lymphoepithelial lesions that were formed predominantly by the expanded Hassall's corpuscles and epithelium lining the cysts. The tumor cells were immunoreactive for CD20 but not for CD3 or CD5.

## *API2-MALT1* Fusion Transcripts

Four samples (case1–4) were analyzed for expression of the *API2-MALT1* fusion transcripts by multiple reverse-transcriptase polymerase chain reaction method described previously.[6] Case 2 sample showed no $\beta$-actin reverse-transcriptase polymerase chain reaction product, so we could not analyze the transcripts. The *API2-MALT1* fusion transcripts were not detected in the other three cases.

# DISCUSSION

MALT lymphoma arising in the thymus is extremely rare. Including the current series, 37 cases have been reported (Table 1).[3–5,7–23] It is noteworthy that at least 28 (76%) of these patients are Asians, and at least 30 (81%) of them had autoimmune disease or hyperglobulinemia.[4–23] All nine of our patients were Japanese and were seropositive for rheumatoid factor or antinuclear antibody. Eight of them had increased serum Ig levels, which remained almost unchanged after total thymectomy. In two of the cases, the immunoglobin and antibody abnormalities remain unchanged 5 years after thymectomy. These data suggest that immunologic disorders are strongly associated with thymic MALT lymphoma tumorigenesis and that thymic MALT lymphoma did not cause these disorders.

Expression analysis of *API2-MALT1* fusion transcripts in four of our patients detected no *API2-MALT1* fusion transcripts. Inagaki et al.[7] investigated *API2-MALT1* gene

 

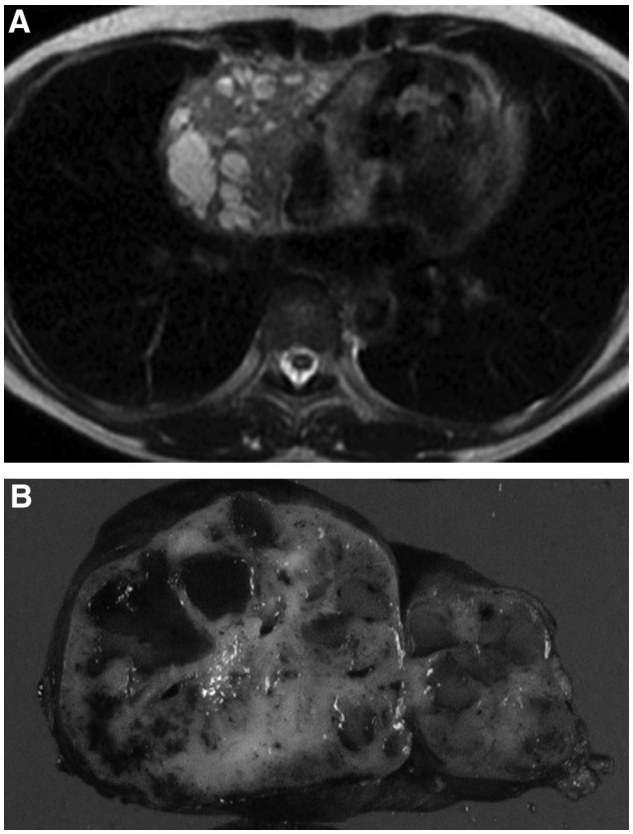


**FIGURE 1.** Magnetic resonance imaging (MRI) and gross appearance of mucosa-associated lymphoid tissue (MALT) thymic lymphoma. Case 4:, upper image, transverse T2-weighted MRI showed a multilocular cyst in the right anterior mediastinum. Lower image: the cut surface of the tumor shows multiple follicular cysts.

fusion in 15 thymic MALT lymphoma cases, and found no *API2-MALT1* gene fusion in any of them, which was consistent with our results. These findings suggest that oncogenic events other than *API2-MALT1* gene fusion are responsible for thymic MALT lymphoma development.

Although macroscopic findings were not described in eight previously reported cases, eight of our nine patients and 15 (75%) of the previous 20 cases had macroscopic cysts in the tumor. Even in cases without macroscopic cysts, microscopic cysts were identified in all cases, except for four reported cases in which no microscopic findings were described. Epithelium-lined cysts appear to be a distinct, constant feature of thymic MALT lymphoma. As Chan[24] speculated, cyst formation may be related to the tendency toward cystic transformation of medullary duct epithelium-derived structures, including Hassall's corpuscles, when the tumor grows in the thymic gland. Yi et al.[8] concluded that thymic MALT lymphoma should be considered in the differential diagnosis whenever a solid mass with cystic changes is found. In our eight cases with macroscopic cysts, cysts were observed as a solid thymic mass with cystic changes on computed tomography and MRI. Cystic changes have been observed in neoplastic thymic lesions, including thymoma, non-Hodgkin lymphoma, Hodgkin disease, mediastinal seminomas, and certain types of thymic carcinoma, and in non-neoplastic thymic lesions.[25] Cystic changes do not show specific histologic features, and it is difficult to diagnose these lesions definitively based on radiologic findings or small biopsy specimens. In thymic MALT lymphomas, prevalence in Asians and a strong association with autoimmune disease or hyperglobulinemia are distinctive clinically and may be helpful in diagnosing the disease. On the basis of our experience, we recommend the diagnostic flow chart for a cystic thymic mass shown in Figure 3.

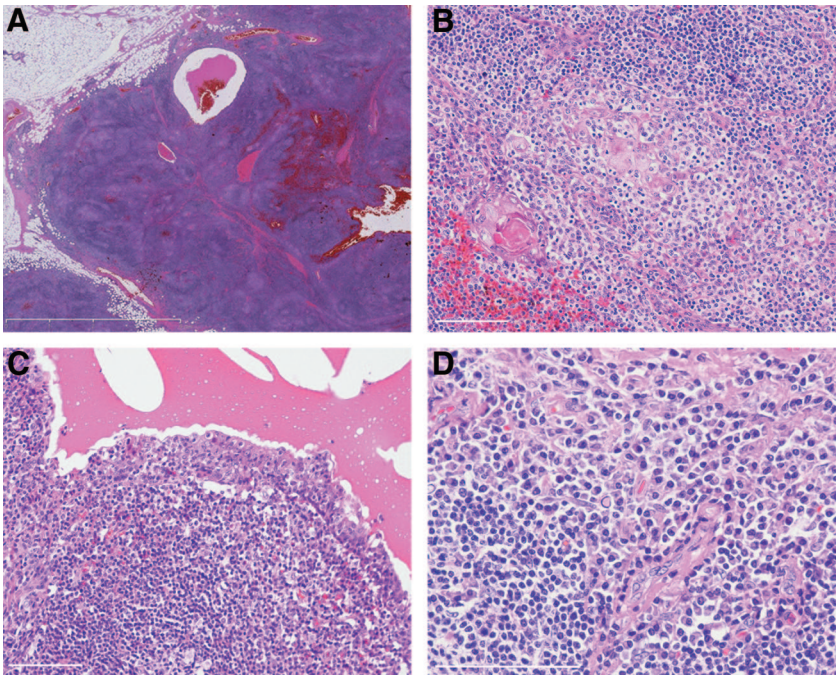


**FIGURE 2.** Histologic appearance of thymic mucosa-associated lymphoid tissue (MALT) lymphoma. *A*, Reactive lymph follicles with germinal center and cystic formations in the tumor. *B*, Lymphoepithelial lesion formed by a Hassall's corpuscle infiltrated by centrocyte-like (CCL) cells. *C*, The epithelium lining the cyst is invaded by CCL cells forming the lymphoepithelial lesion. The cyst contains eosinophilic material. *D*, Mature plasma cells are found around the vessels. HE, hematoxylin and eosin.

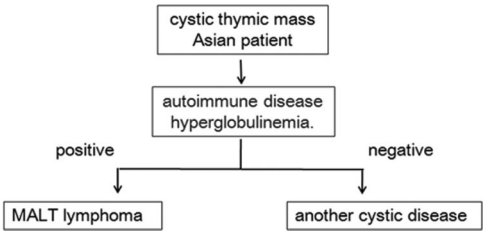


**FIGURE 3.** Diagnostic flow chart for thymic mucosa-associated lymphoid tissue (MALT) lymphoma.

In conclusion, thymic MALT lymphoma needs to be included in the differential diagnosis in Asian patients with thymic masses accompanied by cystic changes and autoimmune disease/hyperglobulinemia.

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