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Case Report

IgG3 subclass-positive primary thymic MALT lymphoma without trisomy 3 and trisomy 18: report of a case and review of literature

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Abstract: The patient, a 42-year-old man, was diagnosed as having an anterior mediastinal tumor. Examination of the resected tumor showed findings consistent with a primary thymic mucosa-associated lymphoid tissue lymphoma, stage IA. Postoperative ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography demonstrated fluorodeoxyglucose accumulation at the site of tumor excision. This accumulation was interpreted as representing a residual lesion, and the patient was treated with rituximab. The patient has since been in a state of complete remission for about 3 years. Sporadic mucosa-associated lymphoid tissue lymphoma cells that appeared to have a propensity for differentiating into plasma cells in this case were analyzed for IgG and IgG subclass expression by immunohistochemical staining. The mucosa-associated lymphoid tissue lymphoma cells that showed a propensity for differentiating into IgG-positive plasma cells were IgG3-positive and IgG1-, IgG2- and IgG4-negative. An increase in IgG3 or IgG1 expression in immune cells has been previously demonstrated in immune responses to continuous exposure to the same proteins or peptide antigens and most mucosa-associated lymphoid tissue lymphomas show increased IgG3 and/or IgG1 expression. It is consistent with the fact that inflammation due to stimulation by a pathogenic antigen is considered to be etiologically responsible for the development of mucosa-associated lymphoid tissue lymphoma.

Keywords: Mucosa-associated lymphoid tissue (MALT) lymphoma, thymus, IgG1, IgG3, paraffin-embedded tissue section-fluorescence in situ hybridization (PS-FISH)

Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma may develop in various organs that have a background of chronic inflammation or of autoimmune diseases such as Helicobacter pylori infection-induced gastritis, Hashimoto's disease or Sjögren's syndrome. Malignant lymphomas account for approximately 10-20% of all primary mediastinal tumors and often occur in the anterior mediastinum in adult cases. Malignant lymphomas that are commonly encountered in clinical practice include Hodgkin's lymphoma, diffuse large cell lymphoma and T cell blastoid lymphoma. In contrast, primary thymic MALT lymphoma is extremely rare.

No more than about 50 cases of primary thymic MALT lymphoma have been reported since the first case was reported by Isaacson et al. in 1983 [1, 2]. The disease characteristically occurs in women aged about 50 years old who reside in East Asia, in whom the lesions are confined to the thymus, are usually not associated with symptoms and show slow progression [3]. Autoimmune disorders, cyst formation in the tumor, and IgA expression on the tumor cell surface are also frequently found, and the serum IgA may be elevated. The API2-MALT1 fusion gene is rarely demonstrated. Trisomy 3 is detected in about 50% of cases and trisomy 18 in about 7%, although neither trisomy was demonstrated in the case reported herein. In the

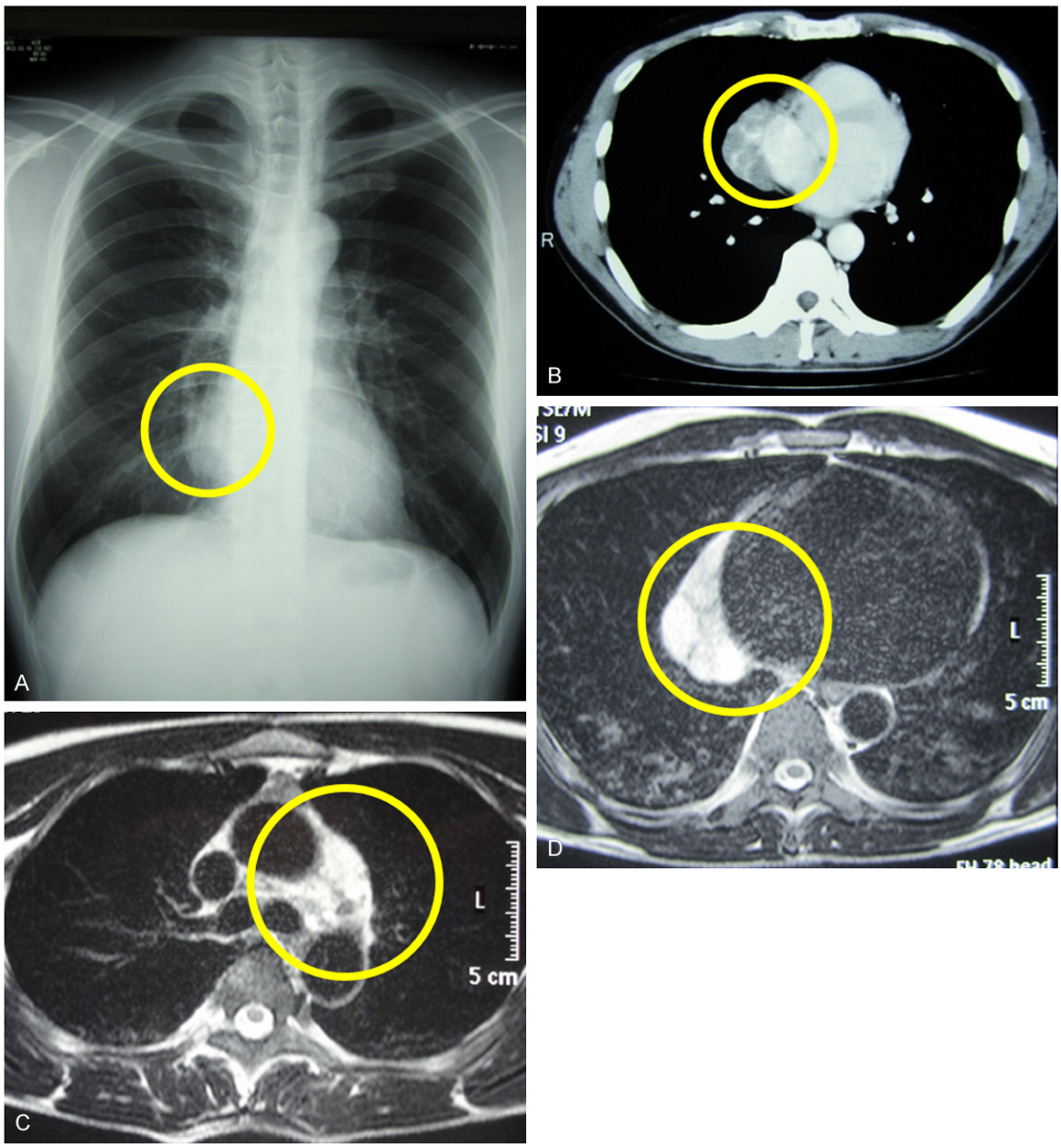

Figure 1. Chest X-ray, Computed tomography (CT) and magnetic resonance imaging (MRI). A: Chest X-ray. A mass shadow overlapping the right atrial segment of the cardiac silhouette is indicated (yellow encircled). B: Chest CT image showing a tumor consisting of an admixture of calcification and cyst formation in the area encompassing the anterior to middle mediastinum, immediately adjacent to the heart. C, D: T2-weighted images of chest MRI. An irregular mass measuring 1.5 cm in diameter is noted in the mediastinum, with a continuous irregular bifurcating mass extending downwards to around the heart. In particular, the mass abutting the right cardiac margin is a multilocular cystic mass lesion measuring 6 cm in anteroposterior diameter and 3 cm in width, and was strongly suspected to extend into the thymus and pleura. A slightly increased intensity was noted in the furcal region.

present case, the tumor was negative for the immunoglobulin M protein. However, since immunostaining demonstrated that the tumor cells with a predilection for differentiating into plasma cells were IgG-positive, we explored the IgG subclass expression profile of these cells. The results showed that the plasma cells that were sporadically seen among the tumor cells of the MALT lymphoma were positive for IgG3, and negative for IgG1, IgG2 and IgG4. This is the first report to document IgG3 expression on tumor cells that are sporadically seen in MALT

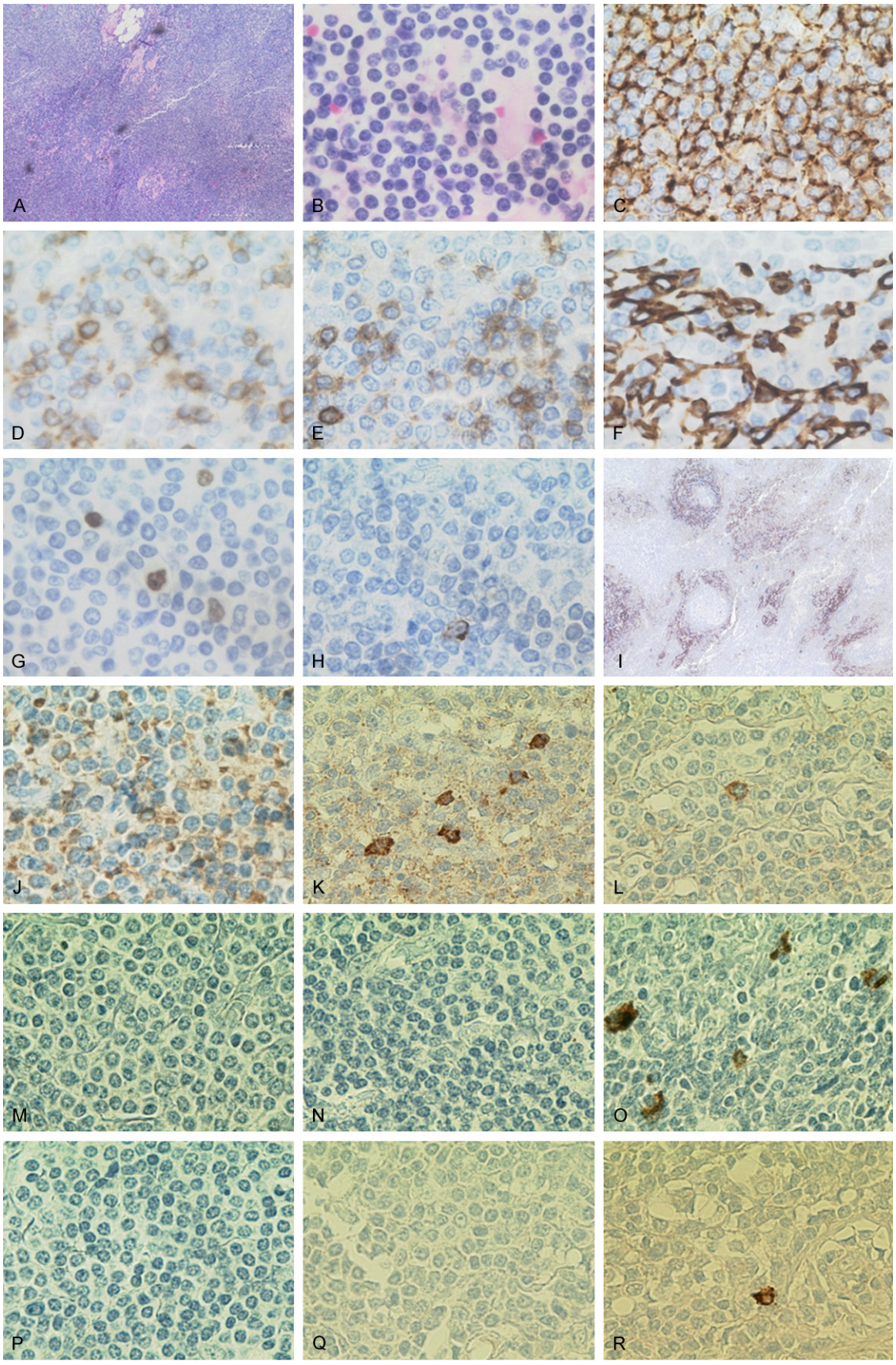
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Figure 2. Pathology of the thymic MALT lymphoma. A-B: Hematoxylin and eosin-stained (H & E) sections of thymic MALT lymphoma (A, B). (A) (×40), (B) (×600). The normal follicular architecture of the thymus is almost completely destroyed, with intense infiltration by ellipsoid, relatively small to medium-sized monocytoid cells which occasionally have Dutcher bodies; some of the cells have pale cytoplasm. Plasma cells with amyloid deposits surrounded by lymphocytes are sporadically seen. (C-I) mmunostaining of monocytoid cells. (C) CD20 (×600), positive; (D) CD3 (×600), negative; (E): CD5 (×600), negative, and (F) keratin (×600), showing partial infiltration of epithelial cells. These data indicate the presence of CD20-positive, CD5-negative B cells. A lymphoepithelial lesion (LEL) consisting of small to medium-sized lymphocytes was noted in the keratin-positive glandular tissue of some Hassall's corpuscles. G-I: Immunohistochemical staining of follicular colonization of the MALT lymphoma. (G) Ki-67 (×600), almost completely negative; (H) CD10 (×600), negative and (I) CD21 (×600). CD10-negative lymphocytes and was devoid of CD21-positive follicular dendritic cells (FDCs). (J-R) Immunostaining of IgG-subclass expression in sporadic plasma cells. (J) IgG (×600); positive, (K) (×600), positive; and (L) (×600), negative. (M-R) Immunostaining of the IgG subclass profile of some of the IgG-positive plasma cells. (M) IgG1 (×600), negative; (N) IgG2 (×600), negative; (O) IgG3 (×600), positive; (P) IgG4 (×600), negative; (Q) IgA (×600), negative and (R) IgM (×600), negative.

lymphomas and that show a propensity for differentiation into plasma cells.

Case report

A 42-year-old man presented with the chief complaints of cough and fever. He had undergone an appendectomy when he was 16 years old and suffered from a gastric ulcer when he was 21. The patient was examined for the chief complaints of cough and fever of the present illness at the Department of Respiratory Medicine of this hospital in February 2011. Computed tomography (CT) and magnetic resonance imaging (MRI) of the chest revealed a tumor of the anterior mediastinum. The patient was referred to the Department of General Thoracic Surgery, where thoracoscopic excision of the mediastinal tumor was performed. In May 2011, a final diagnosis of primary thymic extranodal marginal zone lymphoma of MALT lymphoma was made. The patient was referred to the Department of Hematology of this hospital in June 2011.

Status at initial examination: height, 179 cm; weight, 71 kg; temperature, 36.9°C; blood pressure, 118/86 mmHg; and pulse, 78/min, regular. He was mentally alert and general physical examination revealed no pallor or icterus. No pulmonary flow murmurs or heart murmurs were heard. The liver and spleen were not palpable. There was no superficial lymphadenopathy, nor any edema.

Laboratory findings at the time of the first visit: The white blood cell (WBC) count was slightly decreased to 3.8×10^9/L; the serum IgG level was slightly increased to 1804 mg/dL; serum M protein was not detected; the rest of the laboratory tests were non-contributory. Images of the chest X-ray and chest CT obtained before surgical excision of the mass lesion are shown in **Figure 1A**, **1B**. The images showed a tumor with an admixture of calcification and cyst formation, encompassing the anterior to middle mediastinum, immediately contiguous with the heart. No other lesions were noted on whole-body CT-scanning. T2-weighted MRI scans of the chest obtained prior to tumor excision are presented in **Figure 1C**, **1D**. An irregular mass measuring 1.5 cm in diameter was noted in the mediastinum with a continuous irregular bifurcating mass extending downwards to around the heart. In particular, the mass abutting the right cardiac margin was a multilocular cystic mass lesion measuring 6 cm in anteroposterior diameter and 3 cm in width, and this mass was strongly suspected to extend into the thymus and pleura. A slightly increased intensity was noted in the furcal region.

As seen in **Figure 2**, hematoxylin and eosin (H&E)-stained sections of the lesion showed almost complete disappearance of the thymic follicular architecture that was associated with intense infiltration by ellipsoid, relatively small- to medium-sized lymphocytes and sporadic intercalated plasma cells. Immunohistochemical examination demonstrated monocytoid B-cells with pale cytoplasm that were positively stained for CD20 and negatively stained for CD5. Amyloid deposits that were surrounded by lymphocytes were present, as well as a lymphoepithelial lesion (LEL) composed of small to medium-sized lymphocytes in the glandular tissue of Hassall's corpuscles. Thus, follicular colonization of a MALT lymphoma was found that consisted almost entirely of Ki-67-negative, CD10-negative lymphocytes and was devoid of CD21-positive follicular dendritic cells (FDCs); sporadic MALT lymphoma cells showing a predilection for differentiating into IgGκ-positive plasma cells were also noted.

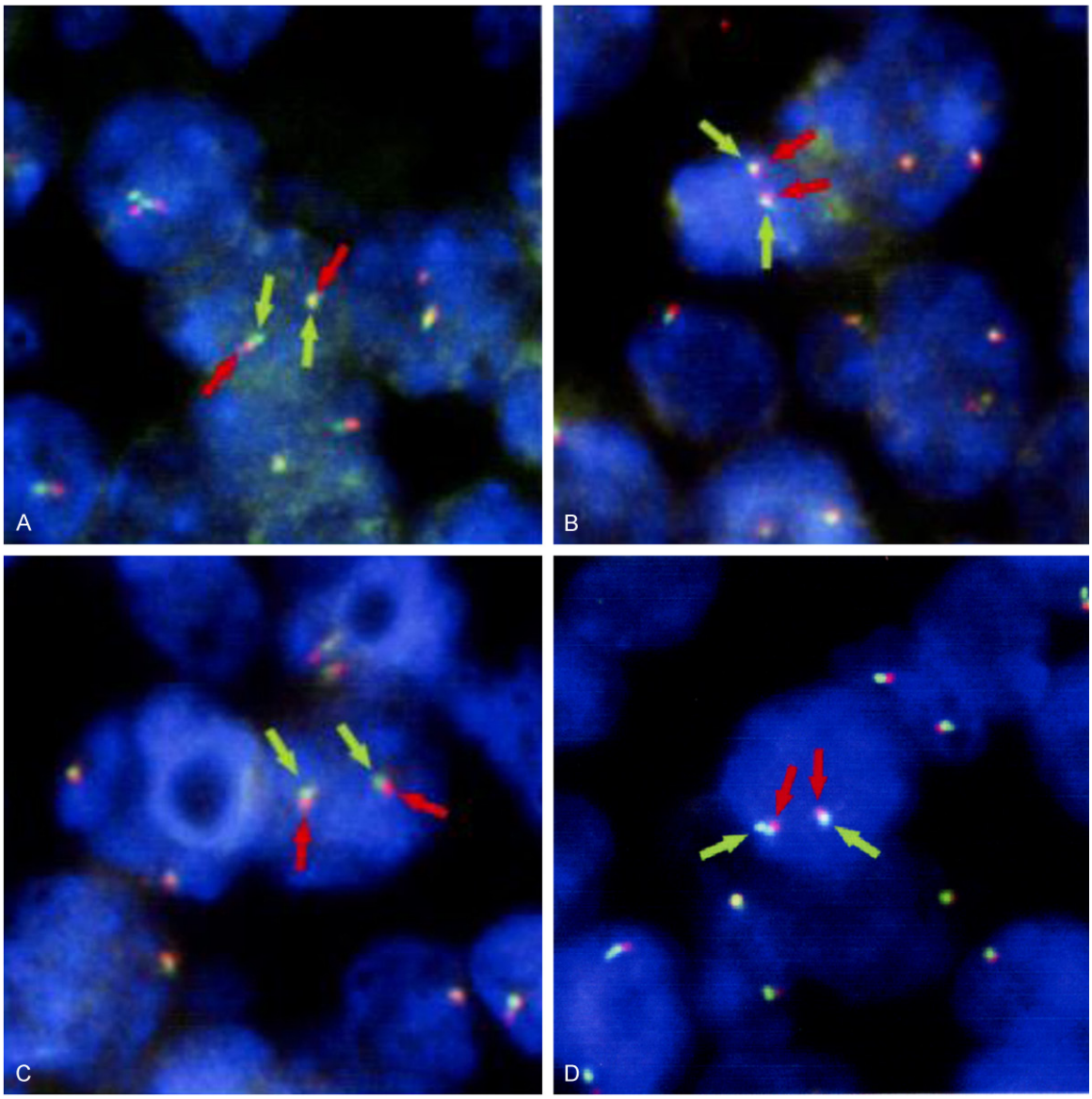

Figure 3. Paraffin-embedded tissue section-fluorescence in situ hybridization (PS-FISH) analysis of the thymic MALT lymphoma. The percentage of cells that presented features (split signals) suggestive of splitting of the gene regions of (A) IgH (14q23); 3.0%, (B) MALT1 (18q21.1); 0.0%, (C) BCL2 (18q21.3); 0.0% and (D) BCL6 (3q27); 0.0% was determined using PS-FISH analysis. No trisomy 18 (B, C) or trisomy 3 (D) was detected. For (A) and (B); Red signals (centromeric side) and green signals (telomeric side). For (C) and (D); Green signals (centromeric side): red signals (telomeric side).

The IgG subclass expression of the MALT lymphoma cells that showed a propensity for differentiating into IgGk-positive plasma cells was analyzed by immunohistochemical staining. This analysis showed that the cells stained positive for IgG and negative for IgA and IgM. Regarding IgG subclass expression, the cells stained positive for IgG3 and negative for IgG1, IgG2 and IgG4.

As seen in **Figure 3**, fluorescence in situ hybridization of paraffin-embedded tissue sections (PS-FISH) showed immunoglobulin heavy chain (IGH) split signals in 3% of the cells, while none of the cells exhibited MALT1 or B-cell lymphoma 2 (BCL2) split signals; there was no evidence of trisomy 18. None of the cells exhibited BCL6 split signals and there was no evidence of trisomy 3. Based on these data, a final diagnosis of primary thymic MALT lymphoma was made. Since no fresh specimens were available, neither IgH-JH locus assay by Southern blotting nor chromosomal analysis was feasible.

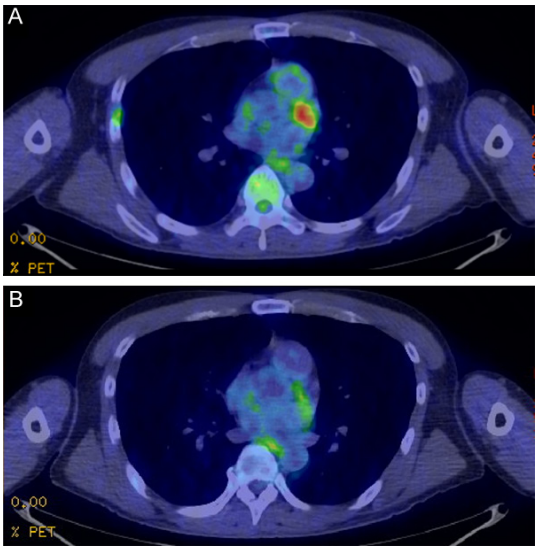

Figure 4. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography. A: A post-tumor excision residual lesion (maximum standardized uptake value: 3.2) was noted in the mediastinal lymph node. B: The abnormal accumulation of ^{18}F-fluorodeoxyglucose was not observed after rituximab therapy.

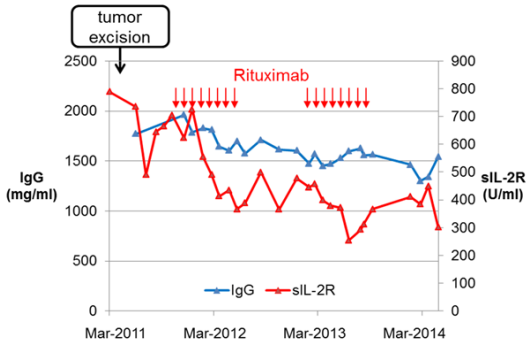

Figure 5. Clinical course. Changes in the level of parameters such as leukocyte count, serum soluble interleukin-2 receptor (sIL-2R) and serum IgG levels over the clinical course are shown. Times of tumor excision, and of administration of eight cycles of rituximab monotherapy, which was initiated when post-tumor excision ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) raised the suspicion of a residual lesion, are indicated. Complete remission was determined based on normal sIL-2R and serum IgG levels and a repeat FDG-PET/CT, which could not detect any residual lesion. The state of complete remission has been maintained since for about 3 years.

Regarding clinical progression, the blood leukocyte count returned to normal and the serum soluble interleukin-2 receptor (sIL-2R) level decreased slightly following tumor excision. Since post-tumor excision ^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography (FDG-PET/CT) raised the suspicion of a probable postoperative residual lesion (**Figure 4**), the patient was administered eight cycles of rituximab starting from November 2011 (**Figure 5**). A subsequent FDG-PET/CT showed disappearance of the residual lesion, with normalization of the serum sIL-2R and IgG levels. Complete remission has since been maintained for about 3 years.

Discussion

The features of the present case are collated along with the documented characteristics of primary thymic MALT lymphomas in **Table 1** [3-17]. The shared features are: patients of Japanese ethnicity, similar tumor size, tumor surface negative for immunoglobulin κ-light chain and the API2-MALT1 fusion gene, and no disease progression. Sjögren's syndrome may be associated with chronic inflammation of the thymic glandular tissue but Sjögren's syndrome was not present in our case. Surgical excision is usually indicated for the treatment, disease progression is uncommon and the prognosis is favorable.

We reviewed the literature regarding the association of chromosomal aberrations with MALT lymphomas. Of the 13 cases assessed for t(11;18)(q21;q21), t(14;18)(q32;q21) and t(1;14)(p22;q32), no case showed any of these chromosomal aberrations, although trisomy 3 was reported in 50% (7/14) of the cases and trisomy 18 in 7% (1/14) [15]. The chromosomal aberration profile of the above 14 cases was similar to that seen in MALT lymphomas of the thyroid and salivary glands. MALT lymphomas can probably be grossly classified into two subtypes; cases with trisomy 3, and cases with t(11;18)(q21;q21), since concurrence of these two chromosomal aberrations in these tumors is extremely rare. Although there has been a report suggesting that trisomy 3 is associated with MALT lymphoma cells that show a predilection for differentiating into plasma cells [18], there is also the view that such an association is unlikely, because conspicuous differentiation into plasma cells is often observed even in cases without trisomy 3 [15]. Furthermore, for CD10-negative low-grade B cell lymphomas, the likelihood of a tumor being a MALT lymphoma is greater if FISH analysis of BCL6 (3q27)

Table 1. Comparison of clinical characteristics between primary thymic MALT lymphoma cases and the present case

Factors	Reported cases (*n*=72)	Present case
Age (years)	14-75 (mean 52)	45
Gender	Female (55)*, Male (18)	Male
Ethnicity	Japanese (36)*, Chinese (4), Korean (7), Caucasian (2), Canada (1)	Japanese**
Symptoms	Absent (26)*, Discomfort (2), Pain (4), Hemoptysis (2), Cough (1), Other (5)	cough
Other site	None (18)*, Salivary (5), LN (8), Lung (3), Stomach (2), Other (3)	LN
Autoimmune	SiS (33)*, RA (6), Other (6), Absent (13)	Absent
Size (cm)	1.5-17.5 (mean 8.1)	6**
Cyst formation	Present (36)*, Absent (6)	Present**
Serum Ig	IgA (37)*, IgG (10), IgM (6), Monoclonal (12)*, Polyclonal (11)	IgG
Surface Ig	κ (29)*, λ (18), IgA (12)*, IgG (3)	κ**, IgG
API2-MALT1	Present (1), Absent (38)*, IgH (0/20)	Absent**
Chromosome	NA (40)*, Normal (1), Trisomy 18 (3), 46Xdup(X)(p11q22) (1) Trisomy 3* (8/20), Other (1)	NA**
Treatment	TE (29)*, CT (1), TE&CT (5), TE&RT (5), CT&RT (4), Ope&R (1)	TE&R
Prognosis	Alive (26)*, Dead (1), Transformation (1), LN metastasis (1)	Alive**

Abbreviations: CT chemotherapy, LN lymph node, NA not available, Prog prognosis, RA rheumatoid arthritis, Rit rituximab, RT Radiation therapy, SjS sjögren's syndrome, TE tumor excision, *frequent matters; **consistent with this present case.

reveals trisomy 3, whereas the likelihood of the tumor being a follicular lymphoma (FL) is greater if such FISH analysis reveals a BCL6 translocation. These findings may be of value for diagnostic differentiation between FL and MALT lymphomas.

It is of great interest that, in our case, the sporadic cells in the MALT lymphoma that showed a propensity for transformation into plasma cells were positive for IgG3 expression, but were negative for IgG1, IgG2 and IgG4. Although the relevant data are not presented here, many of the sporadic plasma cells in the MALT lymphoma were negative for both IgG2 and IgG4, and positive for IgG3 and/or IgG1. According to a previous report, the frequency of lymphocyte surface IgG subclass expression in patients with non-Hodgkin's lymphoma is as follows: IgG1 > IgG3 > IgG2 > IgG4 [19]. In particular, plasma cells are liable to emerge in MALT lymphomas, which arise on a background of inflammation due to chronic infection. The fact that the sporadic cells that we observed showed marked expression of IgG3 or IgG1 was of profound interest in terms of tumor development since these IgG subclasses have been demonstrated to be increased in immune responses to continuous exposure to the same protein or peptide (e.g., viruses). The increased expression of these IgG subclasses in the tumor cells may therefore represent a reaction to pathogens that leads to the development of MALT lymphoma. This finding may be of use in diagnosing MALT lymphoma, as well as in determining the etiology of the disorder.

In summary, we encountered a case of primary thymic MALT lymphoma. The patient was a man with relatively typical clinical features of the disease, except that he did not have Sjögren's syndrome. Since such lymphomas do not show t(11;18)(q21;q21) and are frequently associated with trisomy 3 according to the literature, the present data suggest the potential usefulness of PS-FISH (BCL6) analysis for cases where diagnostic discrimination between FL and MALT lymphoma is difficult. With regards to IgG subclass expression, the plasma cells that were differentiated from MALT lymphoma cells and the plasma cells admixed with the tumor cells in the MALT lymphoma were found to be solely IgG1- and/or IgG3-positive. This feature is considered useful for the diagnosis of MALT lymphoma and for the determination of its etiology. In the future, we plan to study the relationship between IgG subclass expression and disease state of this disorder.

Disclosure of conflict of interest

None.

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