---Case Reports---

A Definitive Diagnosis of Mucosa-associated Lymphoid Tissue Lymphoma Made at a Second Biopsy

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Abstract

Introduction: A case of mucosa-associated lymphoid tissue (MALT) lymphoma, the most frequent of the various conjunctival lymphoproliferative disorders, in which the initial biopsy was inconclusive but the second biopsy provided a definitive diagnosis, is reported.

Case Report: A 26-year-old woman with a 3-month history of bilateral conjunctival swelling was referred by a local physician for suspected MALT lymphoma. A salmon-pink elastic swelling was found to involve both eyes and to extend from the lower palpebral conjunctiva to the bulbar conjunctiva. Tonsillar swelling was also found, and ophthalmologic (left eye) and otolaryngologic biopsies were therefore performed simultaneously under general anesthesia. The otolaryngologic diagnosis was chronic tonsillitis. Light microscope examination of the conjunctival tissue showed proliferation of lymphocytes and small aggregates of small to medium-sized atypical lymphocytes. On immunohistochemical studies, atypical lymphocytes were positive for CD20 and CD79a, but differentiation to plasmacytes was not prominent, and neither Dutcher bodies nor evidence of immunoglobulin light chain restriction was found. The results were not incompatible with MALT lymphoma but were not definitive. A second biopsy of the right eye was therefore performed 3 months later. Staining with hematoxylin and eosin showed proliferation of small lymphocytes and monocyteid B cells and differentiation to plasmacytes. The hyperplastic cells were positive for CD19, CD79a, and CD20, and their cytoplasm were positive for Bcl-2 and slightly positive for Bcl-6. Cells positive for CD38 were noted where differentiation to plasmacytes and immunoglobulin light chain κ restriction was evident on immunohistochemical studies and in situ hybridization. The Ki-67-positivity rate was approximately 5%. The results of paraffin-embedded tissue section fluorescence in situ hybridization were negative for MALT-1 (18q21). A diagnosis of MALT lymphoma was made, and treatment with rituximab was started.

Discussion: Few findings lead directly to a definitive diagnosis of MALT lymphoma, and its differential diagnosis from benign lymphoproliferative disorders is difficult. In the present case definitive diagnosis was possible only after a second biopsy. This case suggests repeated biopsy may be necessary when a single biopsy is not definitive.

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Key words: conjunctiva, definitive diagnosis, mucosa-associated lymphoid tissue, mucosa-associated lymphoid tissue lymphoma, second biopsy

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Introduction

Mucosa-associated lymphoid tissue (MALT) occurs in mucosal tissue invaded by antigens and is a lymphatic apparatus peculiar to mucous membranes which governs local immunity. Immune cells that induce and control the activity of mucosal immunity systems aggregate in MALT, and antigen-specific lymphocytes thereby induce home via the common mucosal immune system on the effective tissues of the lamina propria mucosa and glandular tissues and produce secretions consisting chiefly of immunoglobulin A. The conjunctiva contains conjunctiva-associated lymphoid tissue, a type of MALT. The term “MALT lymphoma” was first applied in 1983 by Isaacson et al. to a malignant lymphoma developing from MALT, and similar lesions have since been found at various locations in the gastrointestinal tract, lung, bronchi, thyroid gland, and other systems. In the field of ophthalmology, although MALT lymphoma originating in the orbit or conjunctiva has lower malignant potential and metastasizes less frequently than usual malignant lymphomas, MALT lymphoma must be clearly differentiated from systemic malignant lymphoma. For diagnosis and treatment in the present case, conjunctival tumors were excised from both eyes and were subjected to pathological and immunohistochemical analysis. We describe the details of this case, which was diagnosed as MALT conjunctival malignant lymphoma originating in the palpebral conjunctiva of both eyes.

Case Report

A 26-year-old woman with a 3-month history of bilateral conjunctival swelling and suspected MALT lymphoma was referred to the Nippon Medical School Musashikosugi Hospital, where she underwent hematologic, otolaryngologic, and ophthalmologic examinations. Salmon-pink elastic conjunctival swelling, extending from the lower palpebral conjunctiva to the bulbar conjunctiva (Fig. 1a and b), was found in both eyes. No other ophthalmologic abnormality was found.

18F-fluorodeoxyglucose (FDG) positron emission tomography (PET/CT) was performed with a PET-CT scanner and a 16-slice multislice CT scanner (Gemini TF 16, Philips-Healthcare, Amsterdam, Netherlands). Early (Fig. 2a and b) and delayed (Fig. 2c and d) images were acquired 60 and 120 minutes after administration of FDG. The PET/CT images showed intense FDG uptake in the bilateral tumors located in the lower palpebral conjunctiva and bulbar conjunctiva (Fig. 2e and f) (maximum standardized uptake value [SUVmax] right side early: 2.12; right side delayed: 2.55; left side early: 1.81; right side delayed: 2.18). Right-sided palatine tonsillar swelling with high FDG uptake was seen (SUVmax early: 4.50; delayed: 5.18).

Fig. 1 Slit-lamp examination at presentation.
Slit-lamp examination reveals a salmon-pink conjunctival tumor (a, right eye; b, left eye).
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Fig. 2: 18F-FDG-PET/CT and magnetic resonance images of the present case.
Early images of PET/CT show intense FDG uptake in the tumors in lower palpebral conjunctiva and bulbar conjunctiva of both eyes (SUVmax right side: 2.12; left side: 1.81) (a, b, e). Delayed images of PET/CT show retention of uptake in the lesions (SUVmax right side: 2.55; left side: 2.18) (c, d, f). Right-sided palatine tonsillar swelling with high 18F-FDG uptake is seen (SUVmax early: 4.50; delayed: 5.18). Determining whether this lesion was chronic tonsillitis or MALT was difficult with only PET/CT images (g, h). With magnetic resonance, T1-weighted images show low intensity (i), T2-weighted images show high intensity (j), and T1-weighted images show contrast enhancement in the lesions.

Determining whether this lesion was chronic tonsillitis or MALT was difficult with only PET/CT images (Fig. 2a and b). Magnetic resonance imaging was also performed. The T1-weighted images showed low intensity (Fig. 2g), and T2-weighted images showed high intensity (Fig. 2h), with contrast enhancement in the tumors. These findings did not contradict the diagnosis of MALT.

Because tonsillar swelling was also found, ophthalmologic (left eye) and otolaryngologic biopsies were performed simultaneously under general anesthesia. The tonsillar swelling was diagnosed pathologically as chronic tonsillitis.

Pathological examination of the conjunctival tissue from the left eye (Fig. 3) showed proliferation of small to medium-sized atypical lymphocytes. Atypical lymphocytes were positive for CD20 and CD79a, but differentiation to plasmacytes was not prominent, and neither Dutcher bodies nor evidence of immunoglobulin light chain restriction was found.

The results were not incompatible with MALT lymphoma but were not definitive, and a second biopsy of the right eye was therefore performed 3 months later. Pathological examination of conjunctival tissue from the right eye (Fig. 4) showed proliferation of small lymphocytes and monocytoid B cells with large irregular lymph follicles. In addition, a few scattered transformed centroblast-like cells were present. In this case, however, centrocyte-like cells were not prominent in
Fig. 3 Pathological findings of conjunctival tissue of the left eye (first biopsy).
(a) Low magnification (>40) of conjunctival tissue shows monotonous proliferation of lymphocytes without the formation of lymph follicles (hematoxylin and eosin [HE] stain). (b) Aggregated lymphocytes are small to medium-sized lymphocytes with relatively abundant pale cytoplasm, indicating a monocyted appearance (HE stain, >600). Plasma cell differentiation and follicular colonization are not prominent, and Dutcher bodies were not detected. Atypical lymphocytes are positive for CD20 (c, >400) and negative for CD3 (d, >600). On in situ hybridization for κ (e, >600) and λ (f, >600), immunoglobulin light chain restriction is not evident, because plasmacytic differentiation is not prominent in the specimen.

Discussion

Lymphoid neoplasms originating in the orbit and subconjunctiva are broadly classified as malignant lymphoma or benign reactive lymphoid hyperplasia, which includes inflammation and pseudolymphoma. Chronic inflammation is clearly associated with an increased risk of malignancy. The most frequent malignant lymphoma is MALT lymphoma. Despite their low malignant potential, MALT lymphomas differ little from reactive lymphoid hyperplasia in age at onset, clinical presentation, and morphological findings, and differential diagnosis is difficult. Both disorders, as in the present case, characteristically present with well-defined, smooth-suraced, salmon-pink lesions and are slowly progressive. Histopathological and immunohistochemical

the conjunctival tissue. Cells positive for CD38 were prominent in regions with differentiation to plasmacytes; in parts of these regions immunohistochemical studies and in situ hybridization showed that κ was greater than λ by a factor of 10 or more, indicating immunoglobulin light chain λ restriction (Fig. 5).

Atypical lymphocytes were positive for CD19, CD79a, and CD20, and their cytoplasm was positive for Bcl-2 and slightly positive for Bcl-6. The Ki67 positivity rate was approximately 5%. A small number of CD3s was also observed, and CD5 and CD43 were found in a similar distribution. Other findings were CyclinD- and CD10+. The results of paraffin-embedded tissue section fluorescence in situ hybridization were negative for MALT-1 (18q21). A diagnosis of MALT lymphoma was made, and treatment with rituximab was started.
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Fig. 4 Pathological findings of conjunctival tissue of the right eye (second biopsy).
(a) Low magnification (<×40) of conjunctival tissue shows monotonous proliferation of lymphocytes with irregular large lymph follicles (HE stain, ×600). (b) Aggregated lymphocytes are small to medium-size lymphocytes with relatively abundant pale cytoplasm, indicating a monocytoid appearance (HE stain, ×600). (c) Dutcher bodies (arrows in c and d) are prominent in monocytoid B cells (c: HE stain, ×1,000) and plasmacytic cells (d: HE stain, ×1,000). Atypical lymphocytes are positive for CD20 (e, ×400) and negative for CD3 (f, ×400).

Fig. 5 Plasmacytic differentiation and immunoglobulin light chain restriction (second biopsy).
Immunohistochemical studies for CD38 (a, ×600) show prominent plasmacytic differentiation. Immunohistochemical studies for κ (b, ×600) and λ (c, ×600) show immunoglobulin light chain κ restriction. In addition, immunoglobulin light chain κ is detected in Dutcher bodies (arrows in d, ×1,000). In situ hybridization for κ (e, ×600) and λ (f, ×600) also shows immunoglobulin light chain κ restriction.
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In conclusion, a rigorous approach to the initial diagnosis and staging of MALT lymphoma is needed. The recognition of MALT lymphoma requires appropriate immunohistochemical staining or genetic confirmation or both.

Conflict of Interest: The authors declare that they have no conflict of interest.

References


