Nasal dissemination of a single-clone IgH-rearranged conjunctival MALT lymphoma through the nasolacrimal duct: A case report

CHUNG-YU HSIEH1, YI-PING LIAO1, CHIA-CHE WU1, SHENG-PO YUAN1, JENNIFER HUI-CHUN HO2,3,4, RACHEL ROAN5, PHUI-LY LIEW6,7, MING-TANG LAI1 and FEIPENG LEE1

Departments of 1Otolaryngology and 2Ophthalmology, Wan Fang Medical Center, Taipei Medical University, Taipei 11698; 3Graduate Institute of Clinical Medicine, Taipei Medical University, Taipei 11031, Taiwan R.O.C.; 4Institute of Engineering in Medicine, University of California, La Jolla, San Diego, CA 92093; 5Post-Baccalaureate Health Professions Program, UC Berkeley Extension, Berkeley, CA 94704, USA; 6Department of Pathology, Shuang Ho Hospital, Taipei Medical University, New Taipei City 23561; 7Department of Pathology, School of Medicine, College of Medicine, Taipei Medical University, Taipei 11031, Taiwan R.O.C.

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Abstract. The aim of the present study was to report a rare case of single-clone, immunoglobulin heavy chain (IgH)-rearranged mucosa-associated lymphoid tissue (MALT) lymphoma in the conjunctiva, with nasal cavity dissemination through the nasolacrimal duct. A 24-year-old female was diagnosed with MALT lymphoma of the nasal cavity at the Department of Otolaryngology, Wan Fang Medical Center, Taipei Medical University (Taipei, Taiwan) in October 2008. A biopsy of the relapsing conjunctival lesion revealed a MALT lymphoma by pathological staining, while a single-clone, IgH-rearranged tumor lesion in the nasal cavity and conjunctiva was confirmed using continuous sinus computed tomography scans and polymerase chain reaction. Tumor lesions were negative for Helicobacter pylori and Chlamydia infection, but exhibited bilateral neck lymph node dissemination. A combination of radiation therapy (a total dosage of 46.8 Gray, in two phases covering the left lacrimal sac, nasal cavity and bilateral neck region) and topical ciprofloxacin plus steroid (0.3% ciprofloxacin 4 times a day and betamethasone eye ointment before sleep for 1 month) was provided as an effective therapeutic strategy, and no recurrence was found in the next 3 years. The nasolacrimal duct serves as a channel for conjunctival tumor spreading and is easily neglected. IgH-involved translocation in MALT lymphoma is a factor in the progression of the disease, and aggressive combination therapy is essential for a high-risk, disseminated IgH-rearranged MALT lymphoma.

Introduction

Ophthalmic lymphomas account for 5-10% of extranodal lymphomas, and extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) are the leading subtype among ophthalmic lymphomas (1,2). However, only a few cases of sinonasal MALT lymphomas were reported in the past 20 years (3,4). The present study reports a rare case of a MALT lymphoma in the conjunctiva, lacrimal sac and nasal cavity, which occurred 4 years following the spontaneous regression of conjunctival atypical lymphoid hyperplasia. The pathological features, imaging study and a gene arrangement test were used to diagnose a single-clone MALT lymphoma in the conjunctiva and nasal cavity. The role of the immunoglobulin heavy chain (IgH) gene rearrangement and atypical infection in MALT lymphoma was also discussed. A successful combination treatment, with local radiotherapy and topical antibiotics plus steroid for a disseminated MALT lymphoma, was also demonstrated in the present study.

Case report

A 24-year-old female initially presented to the Department of Ophthalmology, Wan Fang Medical Center, Taipei Medical University (Taipei, Taiwan) in November 2004 with a painful salmon pink-like lesion in the left inferior conjunctiva that had lasted for several months (Fig. 1A). A tissue biopsy was performed by an ophthalmologist and sent to the Department of Pathology, Wan Fang Medical Center, Taipei Medical University, where it was formalin-fixed and paraffin-embedded. Immunohistochemical staining was performed using an automated stainer (BenchMark XT, Ventana Medical Systems, Inc., Tucson, AZ, USA) with 4-µm thick sections from formalin-fixed and paraffin-embedded
Figure 1. (A) In November 2004, the initial presentation was a salmon pink-like patch lesion at the left lower conjunctiva. Immunohistochemical staining revealed that the lesion was (B) positive for CD20 and (C) negative for CD3 staining. (D) In October 2008, a soft-tissue mass in the left nasal cavity with bone destruction was detected by a sinus computed tomography scan. Histopathological staining revealed the diffuse proliferation of (E) CD20-expressing atypical lymphoid cells and (F) surrounding lymphoid follicles. (G) Recurrent salmon pink-like lesion of the left inferior conjunctiva with bulging of the lacrimal punctum was also found in 2008. A conjunctival biopsy demonstrated the (H) atypical B-cell infiltration and (I) lymphoma involvement with epitheliotropism. CD, cluster of differentiation.

Figure 2. (A) Continuous imaging sections from the inferior orbit to the nasal cavity on sinus CT scan showed the soft-tissue mass extension in lacrimal duct and sac. (B) Gene rearrangement of immunoglobulin heavy chain by polymerase chain reaction illustrated a single-clone disease of mucosa-associated lymphoid tissue lymphoma in the nasal cavity and conjunctiva. (C) Lymph node enlargements in the bilateral submandibular spaces and neck region were noted on the CT scan. (D) Conjunctival mass was regressed after administering topical ciprofloxacin eye drops and betamethasone eye ointment for 1 month. (E) Tumor mass in nasal cavity and lacrimal sac were invisible (upper) and one stationary neck lymph node was noted following radiotherapy (bottom). CT, computed tomography.
tissues. Tissue sections were deparaffinised and rehydrated in graded alcohols and xylene. After retrieval by the autoclave retrieval technique (10 mM citric acid buffer; 10-20 min) and inhibition by endogenous peroxidase activity (0.3% H₂O₂; 5 min), sections were incubated with primary antibodies. The primary antibodies used were CD20 monoclonal mouse (dilution, 1:200; catalog no., CM004; Biocare Medical, Concord, CA, USA) and CD3 monoclonal mouse (dilution, 1:200; catalog no., NCL-L-CD3-565; Leica Microsystems GmbH, Wetzlar, Germany). Negative controls were performed by omitting primary antibodies. After washing with Tris buffer, sections were incubated for 30 min with a polyclonal secondary antibody against mouse and rabbit from the ultraView Universal DAB Detection Kit (dilution, 1:100; catalog no., 760-500; Ventana Medical Systems, Inc.), re-incubated with 100 μg/ml peroxidase-conjugated streptavidin, and colored with 0.02% 3,3′-diaminobenzidine tetrahydrochloride (0.05M Tris-HCL buffer with 0.03% H₂O₂). The sections were counterstained with hematoxylin, dehydrated and mounted. The surgical specimens revealed atypical B-lymphoid hyperplasia (Fig. 1B and C). Spontaneous tumor regression was observed in the following 6 months.

The patient visited the Department of Otolaryngology, Wan Fang Medical Center, Taipei Medical University in October 2008 complaining of left nasal pain that had lasted for 2 months. A lobulated left nasal tumor (18.8x24.6x37.4 mm in size) with a bony destruction was noted on a sinus computed tomography (CT) scan (Fig. 1D). Two incisional biopsies performed by an otolaryngologist and sent to the Department of Pathology, Wan Fang Medical Center, Taipei Medical University confirmed a stage II mucosa-associated lymphoid tissue (MALT) lymphoma with B-cell origin (Fig. 1E and F). Tissues were formalin-fixed and paraffin-embedded to be used for immunohistochemistry and routine hematoxylin-eosin staining. A histological diagnosis was performed according to the WHO classification (5). In addition, a relapse of the salmon pink-like lesion of the left inferior conjunctiva was also found (Fig. 1G), and MALT lymphoma was diagnosed by histopathological findings (Fig. 1H and I). Continuous imaging sections on the sinus CT scan revealed a soft-tissue mass filled lacrimal duct and sac (Fig. 2A; red arrows). The homology of the MALT lymphoma in the nasal cavity and conjunctiva was confirmed using polymerase chain reaction (PCR) and evidenced by the sharing of the same IgH gene rearrangement. IgH-rearrangement was not present in the conjunctival lesion in 2004 (Fig. 2B).

A series of systemic surveys revealed several visible lymph nodes in the bilateral submandibular spaces and neck region (Fig. 2C; white arrows). The blood examination revealed elevated IgG for cytomegalovirus and Epstein-Barr virus. In addition, specimens from the conjunctival and nasal MALT lymphoma were negative for Helicobacter pylori and Chlamydia by staining (data not shown). In contrast, genetic rearrangement and chronic infectious stimulation (8,9) result in the activation of nuclear factor κ-light-chain-enhancer of activated B-cells, and subsequently contributes to the malignant transformation of MALT lymphomas (10). Chromosomal abnormalities involving IgH gene translocation, including t(1;14)(p22;q32), t(14;18) (q32;q21), and t(3;14)(p14;q32), are frequently associated with gastric or pulmonary MALT lymphomas but seldom found in conjunctival MALT lymphomas (1,8). In contrast with IgH rearrangement, infectious agents associated with MALT lymphomas are more common including H. pylori, Chlamydia and hepatitis C virus. Infection with these pathogens and infectious antigen stimulation of conjunctival tissue is not uncommon during life (9). Different from gastric MALT lymphomas, the prevalence of H. pylori infection is relatively low in the conjunctiva (11); however, Chlamydia and hepatitis C virus infections are frequently associated with conjunctival MALT lymphomas (9,12). In the present study, the patient suffered a rare conjunctival MALT lymphoma with IgH rearrangement (Fig. 2B), but tested negative for H. pylori and Chlamydia infection. Notably, although H. pylori and Chlamydia were undetectable in the conjunctival and nasal MALT lymphomas, the conjunctival tumor lesion showed a good response to topical antibiotics therapy (Fig. 2D), indicating that an atypical infection played a role in the present case.

Ophthalmic MALT lymphoma is a malignancy with an indolent course, and neither the clinical stage, ocular region
localization, nor therapeutic strategy affects the 5-year survival or progression-free survival rate, with the exception of IgH translocation involvement. For an IgH-translocated ophthamalid MALT lymphoma, aggressive treatment is necessary due to the high-risk of tumor progression. MALT lymphomas are sensitive to external beam radiation, chemotherapy, chemoimmunotherapy, and oral doxycycline for Chlamydia infection. The systemic anti-CD20 antibody, rituximab, is reserved for refractory MALT lymphomas. In the present case, to avoid radiation-related ocular complications, a topical ciprofloxacin and steroid were chosen to treat the conjunctival MALT lymphoma, and radiotherapy was given covering bilateral neck, left nasal cavity, and left lacrimal sac. Ciprofloxacin is a broad-spectrum antibiotic covering atypical infections with a low resistance rate, chosen for the present patient, who was negative for H. pylori and Chlamydia infection. The current study demonstrated that a combination of radiation therapy, topical ciprofloxacin and a topical steroid was an effective therapeutic strategy for an IgH-rearranged conjunctival MALT lymphoma with nasal cavity dissemination (Fig. 2D and E).

In summary, a single-clone MALT lymphoma in the conjunctiva with nasal cavity dissemination is rare, but possible. In patients diagnosed with conjunctival MALT lymphoma, thorough clinical examination should be performed to exclude the possibility of conjunctival tumor spreading via the nasolacrimal duct. Otolaryngologist may play a role in nasal examination. The nasolacrimal duct may serve as a channel for conjunctival tumor spreading. IgH-involved translocation is a disease progression factor, and combination therapeutic approach, including topical antibiotics for conjunctival tumor and radiotherapy for extra conjunctival lesions, may successfully control high-risk, disseminated MALT lymphomas.

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References