

Primary conjunctival follicular lymphoma treated with the anti-CD20 antibody rituximab and low-dose involved-field radiotherapy

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Letter

Primary Conjunctival Follicular Lymphoma Treated with the Anti-CD20 Antibody Rituximab and Low-Dose Involved Field Radiotherapy

Follicular lymphoma (FL) *originating in the* ocular adnexa is rarely reported, and curative radiotherapy for it is still questionable. Herein, we report a case of primary FL treated with rituximab, a monoclonal antibody therapy, followed by low-dose involved field radiotherapy (LD-IF-RT).

Case Report

A 67-year-old Japanese male patient was referred with a 2-month history of a progressive tumor in the conjunctiva of his right eye (Fig. 1a, b). A tumor sample was obtained by incisional biopsy. By histopathological analysis, it was found to consist of proliferated medium-sized atypical centrocytic lymphoid cells, forming a follicular nodule (Fig. 2a, c). Large centroblastic cells were very few in the nodule (Fig. 2c). The lymphoid cells showed positive immunoreactivity for CD20, CD79 α , CD10, *bcl-6* (Fig. 2d), and *bcl-2* (Fig. 2e). Polymerase chain reaction (PCR) using the tumor DNA detected a fusion product of the major breakpoint region of the *bcl-2* gene and IgH J region¹ (Fig. 2f). Based on these findings, the lesion was diagnosed as a follicular lymphoma (FL) grade 1, according to the World Health Organization classification (2001). Consecutive general examinations (including whole-body computed tomography, and Ga-scintigraphy) did not detect any other primary or metastatic lesions. One month after the initial visit, a similar lesion appeared in the conjunctiva of the left eye of the

patient (Fig. 1c), and also proved to be an FL grade 1 by an additional biopsy (Fig. 2b) and immunohistochemical studies.

The patient underwent anti-CD20 antibody therapy (rituximab, 375 mg/m² intravenously once weekly for 4 weeks), and the lesions decreased in size gradually. Subsequently, LD-IF-RT with a regimen of 2 days of 2 Gy X-ray (4 Gy total) for both orbital regions was performed. The conjunctival lesions in both eyes diminished approximately one month after the LD-IF-RT (Fig. 1d), and no local recurrence or metastasis was observed during the following 22 months.

Comments

Primary conjunctival FL is very rare. RT-PCR was useful to detect a t(14;18) (q32;q21) translocation¹ from a very small sample of the conjunctival lesion. Until several years ago, the management of FL was basically palliative. Recently, the efficacy of rituximab therapy for follicular lymphoma was evaluated. In a few clinical trials using rituximab alone for untreated follicular lymphomas, response rates ranged between 61% and 80%.² So far, only one case of conjunctival follicular lymphoma treated with rituximab alone was reported.³ However, the evidence for diagnosis was not shown and the follow-up period was only 5 months.³ Generally, the common side effects of rituximab are not severe, and include fever, chill and nausea. No side effect of rituximab was observed in this case.

Radiotherapy with curative intent for early stage follicular lymphoma is still questionable because of the recurrence rate of approximately 50% and the treatment side effects. LD-IF-RT (2 x 2 Gy regimen) was initially applied to treat recurrences of advanced follicular lymphoma. Recent studies showed high response rates (>80%) in indolent lymphoma patients.⁴ We combined rituximab therapy and LD-IF-RT, since it is too early to evaluate the efficacy of each of them on survival. Minimizing radiation-induced disorders of eyes, i.e., cataract, was also another reason to select LD-IF-RT. As it happens, this therapeutic idea is supported by a recent

study showing that pretreatment with rituximab enhances the radiosensitivity of non-Hodgkin's lymphoma cells.⁵

In conclusion, for early stage conjunctival follicular lymphoma, the combination of anti-CD20 antibody therapy and LD-IF-RT may be an alternative therapy.

Key Words : conjunctiva, follicular lymphoma,, gene translocation, low-dose involved field radiotherapy, rituximab

Masayuki Takahira¹, Hirokazu Okumura², Hiroshi Minato³, Norimasa Urushisaki¹,
Mayumi Sakurai¹, and Kazuhisa Sugiyama¹

¹Department of Ophthalmology, Kanazawa University School of Medicine, Kanazawa, Japan;

²Department of Hematology, Kanazawa University School of Medicine, Kanazawa, Japan;

³Pathology Section, Kanazawa University Hospital, Kanazawa, Japan

e-mail: takahira@kenroku.kanazawa-u.ac.jp

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Correspondence to: Masayuki Takahira, Department of Ophthalmology, Kanazawa University School of Medicine, 13-1 Takara-machi, Kanazawa, Ishikawa 9208640, Japan

For Publisher only Phone: 076-265-2404

Fax: 076-222-9660

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Figure Legends

Figure 1. Conjunctival tumor before and after the treatment with rituximab and low-dose involved field radiotherapy (**a, b**). Anterior segment photos show follicular tumor in the conjunctiva of the right eye at the initial visit. (**c**) Follicular lesion (arrowheads) appeared in the conjunctiva of the left eye one month after the initial visit. (**d**) The tumor in the right eye diminished two months after treatment.

Figure 2a - f. (**a**) A light microscopic image of the tumor in the conjunctiva of the right eye. A follicular or nodular lymphoid aggregation is seen in the conjunctival submucosa. The follicles lack tangible (*tangible means “can be touched – or seen” How about “visible”?*) ANSW: “*tangible-body macrophage*” (TBM) is a specific word in histopathological field. Please do not change. body macrophages and cellular polarization. Mantle zone is very thin (arrows) or inconspicuous *because of* the expansion of the follicular center cells. H-E staining, scale bar = 500 μm . (**b**) One month later, a tumor appeared in the conjunctiva of the left eye, also showing follicular proliferation of lymphocytes. H-E staining, scale bar = 500 μm . (**c**) Higher magnification of the follicular center of the conjunctival tumor in the right eye. The cells consist mostly of small cleaved centrocyte-like cells. Large centroblastic cells are very few. H-E staining, scale bar = 20 μm . (**d**) Immunostaining of *bcl-6* in the conjunctival tumor in the right eye. The follicle center shows diffuse nuclear staining for *bcl-6*. Scale bar = 500 μm . (**e**) Immunostaining of *bcl-2* in the conjunctival tumor in the right eye. The follicle center shows diffuse cytoplasmic staining for *bcl-2*. Scale bar = 500 μm . (**f**) The tumor DNA was amplified between the V-region of IgH (immunoglobulin heavy chain) (lane 1), a major breakpoint region (mbr) (lane 2), or a minor cluster region (mcr) (lane 3) of the *bcl-2* gene and the consensus J region of IgH¹. A band

indicated by an asterisk (lane 2) was confirmed to contain the *bcl-2* sequence by direct sequencing:

TCTGTTGTCCCTTTGACCTTGTTTCTTGAAGGTTTCCTCGTCCCTGGGCAA
TTCCGCATTTAATTCATGGTATTCAGGATTACATGCATGTTTGGTTAAACC
CATGAGATTCATTCAGTTAAAAATCCAGATGGCAAATGACCAGCAGATTC
AAATCTATGGTGGTTTGACCTTTAGAGAGTTGCTTTACGTGGCCTGTTTC
AACACAGACCCACCCAGAGCCCTCCTGCCCTCCTTCCGCGGGGGCTTTC
TCATGGCTGTCCTTCAGGGTCTTCCTGAAATGCAGTGGTGC. Other bands
were not specific. M: size marker lane.



