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CASE REPORT

A case of conjunctival MALT lymphoma: successfully treated with solely extended rituximab therapy

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Abstract
Purpose Primary ocular adnexal lymphomas are cured by radiotherapy; however, complications are frequent and relapses may occur. In this case, we aimed to report the efficacy and safety of extended systemic rituximab (anti-CD 20 monoclonal antibody) therapy of conjunctival mucosa-associated lymphoid tissue (MALT) lymphoma.
Methods In the standard regimen, rituximab is used as four consecutive weekly infusions of 375 mg/m^2 in patients with low-grade lymphomas. We treated a patient who had bilateral conjunctival MALT lymphoma with rituximab 375 mg/m^2 intravenously once weekly for 10 weeks as a first-line therapy.
Results During the examination of the sixth week, we observed partial response of the lesions in both eyes. At the end of the tenth cure, complete remission was achieved. No local or systemic adverse effect was observed. The patient has no signs of recurrence during the 22-months follow-up period.
Conclusion Extended rituximab therapy may be an effective and well-tolerated first-line treatment option for bilateral conjunctival MALT lymphoma.

Keywords Anti-CD20 monoclonal antibody · Conjunctiva · Conjunctival MALT lymphoma · Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type · Non-Hodgkin lymphoma · Rituximab

Introduction

Ocular adnexal lymphomas (OALs) are the first cause of primary ocular malignancies, and among them, the most common are mucosa-associated lymphoid tissue (MALT) OALs [1]. MALT lymphoma (MALToma) is a low-grade variant of B-cell non-Hodgkins lymphoma (NHL) that originates from extranodal tissue of the gastrointestinal tract, thyroid, lung, salivary gland, lacrimal gland, orbit, and conjunctiva [2]. In recent years, systemic treatment approaches, including chemotherapy, monoclonal antibodies, immunomodulators, and targeted drugs, have been increasingly used in MALToma [3]. Rituximab is a chimeric human/mouse monoclonal antibody that has arisen in recent years as an effective therapy for NHL and other B-cell malignancies [4].

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Here, we report a patient with conjunctival MALToma successfully treated with single-agent rituximab therapy.

Case report

A 41-year-old lady was referred to our clinic in October 2015 with conjunctival tumor tissue in both eyes for a duration of 8 months. At the referral center, a diagnostic conjunctival biopsy had been performed and CD20(+), CD79a(+), Ki-67(MIB-1)(+), CD23(−), CD5(−), cyclin D1(−) conjunctival MALToma had been proven in histopathological evaluation (Fig. 1a–d). At the initial ophthalmologic examination, visual acuity (VA) was 20/20 in right eye (RE), 20/25 in left eye (LE), and the intraocular pressure (IOP) was 12 mmHg in both eyes. Slit-lamp examination revealed no cell reaction in the anterior chambers bilaterally. Subconjunctival, pink salmon-colored vascularized mass tumor lesions originated from the tarsal conjunctiva and extended to the forniceal and bulbar conjunctiva up to 4–6 mm posterior to the limbus in both eyes (Fig. 2a, b). No clinical abnormalities were appreciated upon examination of the retina and choroid with binocular fundoscopy of both eyes. The patient was referred to the hematology department for complete systemic evaluation. No signs of systemic involvement were detected by bone marrow biopsy and whole body positron emission tomography scan. The ophthalmic examination and immunohistopathological evaluation

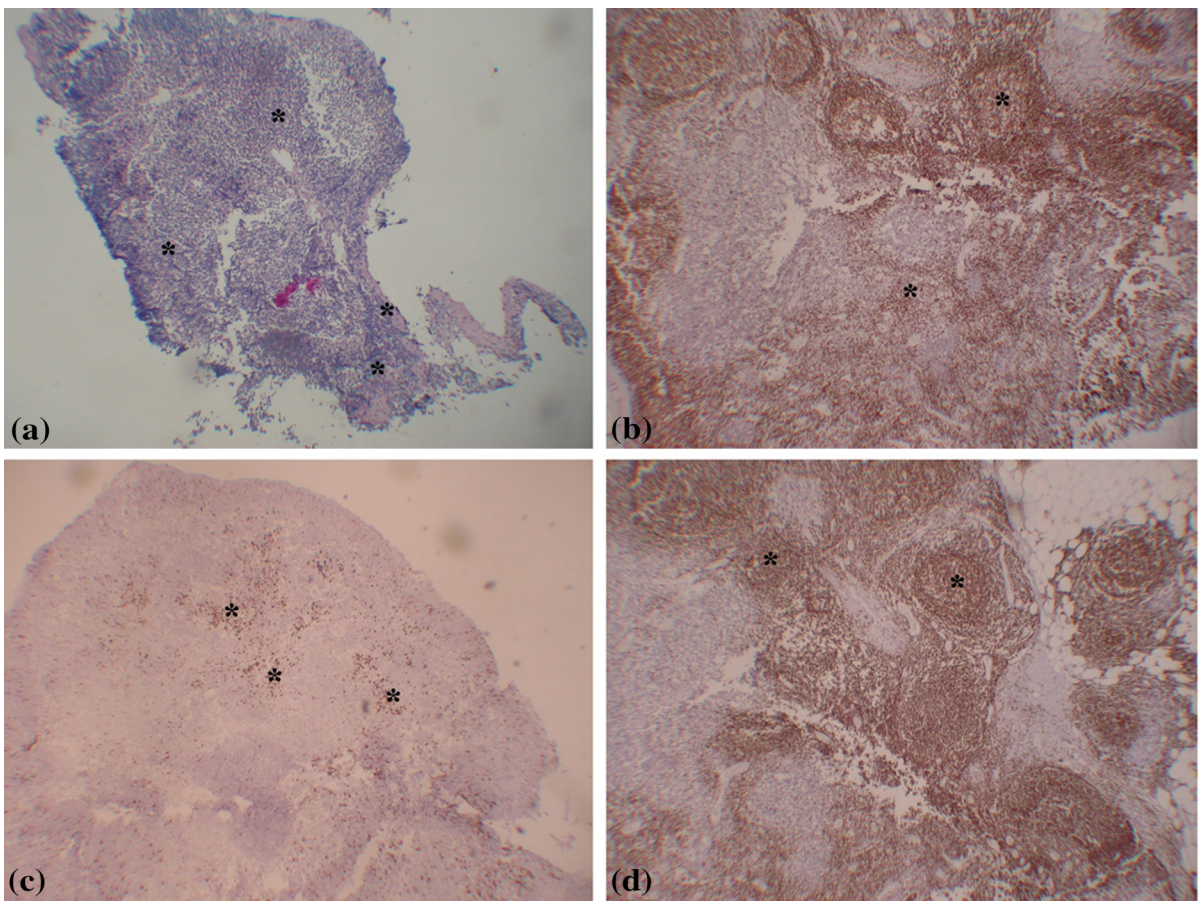

Fig. 1 Histological lesion stainings in conjunctival biopsy, extranodal marginal zone B-cell lymphoma of the Mucosa-Associated Lymphoid Tissue/MALT lymphoma (4× magnification). a Hematoxylin and eosin staining demonstrating diffuse lymphocytic infiltrates which invaded multi-stratified epithelium of conjunctiva (asterisks). **b** Immunohistochemical staining positive for CD79a (asterisks). **c** Immunohistochemical staining positive for Ki-67 (MIB1) (asterisks). **d** Immunohistochemical staining positive for CD20 (asterisks)

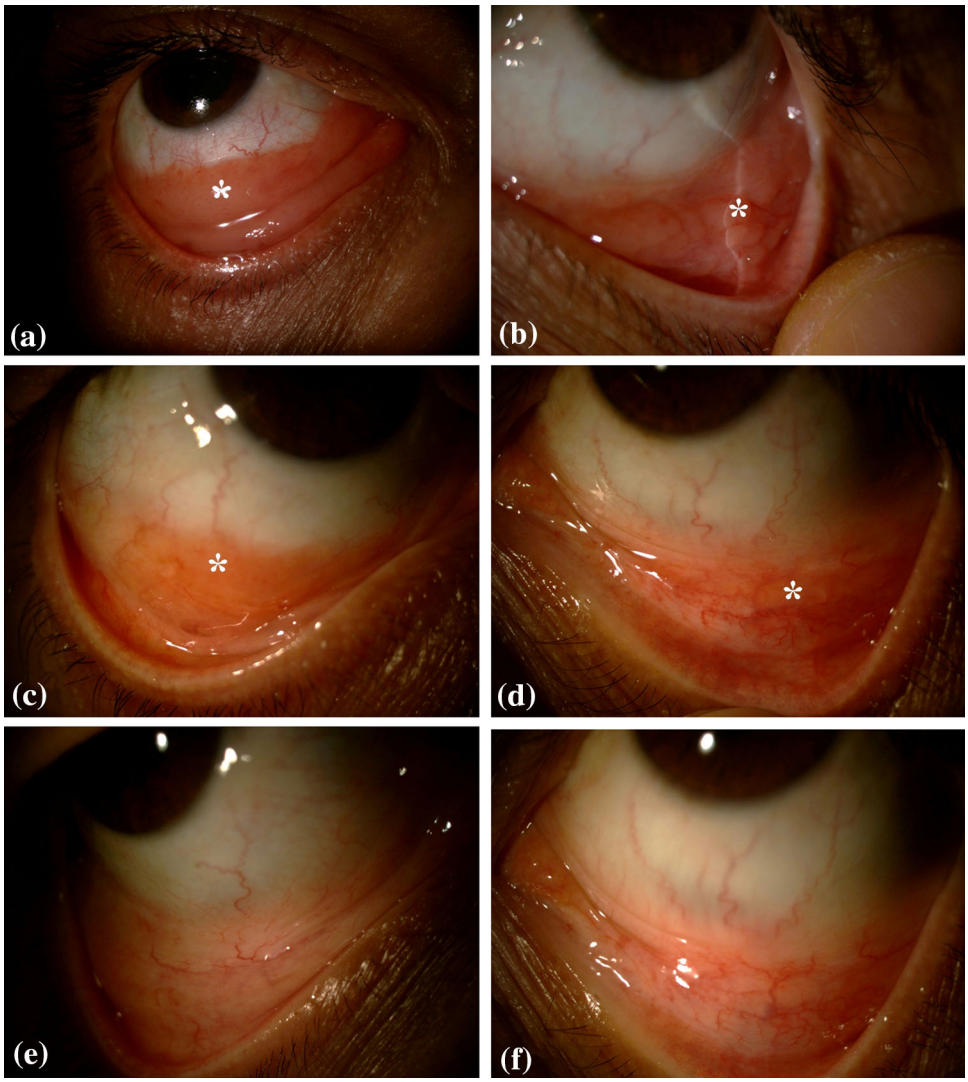

Fig. 2 MALT lymphoma of the conjunctiva of both eyes. **a** Initial examination, pink salmon-colored mass tumor lesion in the lower forniceal and bulbar conjunctiva in the right eye (RE) (asterisk). **b** Initial examination, pink salmon-colored mass tumor lesion in the lower forniceal conjunctiva in the left eye (LE) (asterisk). **c** At the end of the sixth week, biomicroscopic examination showed regression of the lesions in RE, approximately 2 × 8 mm remained (asterisk). **d** At the end of the sixth week, biomicroscopic examination showed regression of the lesions in LE, little conjunctival follicular lesions remained) (asterisk). **e** After ten cycles of rituximab, complete regression was achieved in RE. **f** After ten cycles of rituximab, complete regression was achieved in LE

fulfilled the classification of the disease as an extranodal marginal MALToma in 1E stage. After evaluating different treatment alternatives (such as radiotherapy or chemotherapy), she was treated with the anti-CD20 antibody rituximab (MabThera®, Roche, Grenzach-Wyhlen, Germany), six cycles weekly i.v. infusions at a dose of 375 mg/m^2. The mass tumoral conjunctival lesions started to regress after the initial infusion. At the end of the sixth week, biomicroscopic examination showed regression of the lesions in both eyes (approximately 2 × 8 mm in the RE; little conjunctival follicular lesions remained in the LE) (Fig. 2c, d). The treatment was extended to the tenth week; then, at the end of the tenth cure, complete remission was obtained (Fig. 2e–f). There was no local or systemic adverse effect. The patient has no signs of recurrence during the 22-month follow-up period.

Discussion

Ocular MALToma represents 8% of all extranodal NHL and just 1% of all NHLs [5, 6]. According to our knowledge, this is the first bilateral conjunctival MALToma case who responded to an extended course of rituximab (ten cycles) without any systemic adverse effects. Radiotherapy (RT) is the standard treatment for the conjunctival lymphomas [7]. RT results in a high rate of local control ranging, from 85 to 100%, even in the presence of systemic disease [8, 9]. When RT treatment is decided, frequent local ophthalmic toxicity should be considered [10]. In the present case, when we were choosing the appropriate treatment, these handicaps led us to select the rituximab treatment as the first-line therapy. Rituximab has become a part of standard therapy for patients with CD20-expressing B-cell lymphoma [4]. The drug binds to the CD20 antigen, which is an attractive target for monoclonal antibody therapy, as in almost all malignant B cells [4]. Rituximab demolishes B cells by complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and induction of apoptosis [11].

Annibali et al. [1] reported the outcome of seven consecutive patients with primary MALT OALs, of whom six were treated with single-agent rituximab. All patients received six cycles of rituximab 375 mg/m^2 every 3 weeks. Four patients (67%) achieved a complete remission, and two (33%) achieved a partial response. After a median follow-up of 29 months (range 8–34), no recurrences were observed. None of the cases needed additional RT or other therapies. Nückel et al. [12] reported two conjunctival MALToma cases who had been initially treated with RT and showed recurrence after 2 years. Rituximab was initiated once weekly for 4 weeks. With a follow-up of 32 months, one partial remission and one complete remission were obtained. Tuncer et al. [13] reported 11 eyes of ten patients with ocular MALToma treated with rituximab monotherapy [an average of seven cycles (range 6–8)]. After a follow-up of 31 months, complete response was achieved in four eyes (36%). Additional RT was required in six patients (seven eyes; 64%) with partial response or recurrence [13]. Ferreri et al. [14] reported eight patients with ocular MALToma treated with rituximab for 4 weeks, at diagnosis (five cases) or in relapse (three cases). Two of these patients having unilateral conjunctival involvement received rituximab as the first-line therapy. Complete remission was achieved in one patient while the other had partial response. Salepçi et al. [15] reported complete remission after six cycles of rituximab therapy in a patient with bilateral conjunctival MALToma unresponsive to initial RT. In the literature, most of the patients received four cycles or an extended treatment of eight cycles at maximum. As partial response was observed after the sixth cycle, we decided to prolong rituximab treatment until complete remission; thus, present case received an even longer treatment duration of ten cycles. There are some reports about adverse effects of rituximab therapy. Infusion-related syndrome occurs within a few hours of starting the first infusion with symptoms of transient fever, nausea, and headache. Severe adverse effects including anaphylaxis, infections, myocardial infarction, ventricular fibrillation, cardiogenic shock, and delayed-onset neutropenia have also been reported [4]. We did not observe any adverse effect in the present case.

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Compliance with ethical standards

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

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