



Systemic Rituximab for Conjunctival Marginal Zone (Malt) Lymphoma is not Protective for Subsequent Disease Development in the Contralateral Eye

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Abstract

Purpose: We report a case of a 35-year old male who presented with unilateral conjunctival extranodal marginal zone (MALT) lymphoma and underwent systemic Rituximab immunotherapy as primary treatment. After an excellent initial response and four years of complete remission he presents with MALT lymphoma to the contralateral conjunctiva.

Methods: MALT lymphoma is the most common lymphoid neoplasm of the conjunctiva, and has an indolent clinical course. Rare cases of spontaneous remission, bilateral involvement, systemic dissemination, and common local and contralateral relapses have been reported. Rituximab is a chimeric anti-CD20 antibody, currently used as first-line treatment of CD20 positive non-Hodgkin's lymphoma. Several mechanisms can be responsible for rituximab resistance. Transformation of CD20 positive indolent to aggressive CD20 negative form is one of them.

Results: In this case, the patient did not demonstrate any systemic or orbital involvement. Both histological reports of the incisional biopsies revealed CD20 positive immunohistochemistry.

Conclusion: This is a highly unusual case of new primary conjunctival MALT lymphoma to the contralateral eye after systemic Rituximab treatment. This further supports the assumption that rituximab does not suppress MALT lymphoma formation in the long term in the other eye, suggesting that the predisposing immune factors are not annihilated by the course of rituximab. Long term review of these patients is therefore warranted.

Keywords

Conjunctiva, Orbit, MALT, Marginal zone, Lymphoma, Rituximab, CD20, B cell, Antibody

Introduction

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is the most common lymphoid neoplasm of the conjunctiva. Orbital involvement and rarely a choroidal component [1] can occur, and this type of lymphoma is different to primary intraocular lymphoma of the vitreoretinal type [2,3]. It is characterized by painless, salmon-pink patches in the fornix or bulbar conjunctiva, and has an indolent clinical course (Figure 1). MALT lymphomas are diagnosed by their strong staining for CD20 and negative staining for CD10, CD23, and bcl6 (Figure 2). Both orbits are involved in 15% of the cases - some synchronous and some metachronous [4].

It has been reported that all orbital lymphomas have a 5-year relapse-free survival of 65%, although this increases to 85-90% for purely conjunctival lymphomas treated by conventional radiotherapy. Such cases usually involve the contralateral orbit and distant extranodal organs. Systemic dissemination occurs in 5-10% of cases, being rare in patients with conjunctival lymphoma [5]. In 10% of orbital lymphomas there is bilateral disease, despite the absence of direct lymphatic connections between the orbits- a fact that supports the theory of systemic predisposition rendering both orbits at risk of the disease. Only immunosuppression, for example related to organ transplantation [6], thyroid eye disease [7], or chronic chlamydial infection [5] are known predisposing factors.

Case Report

A 35-year-old white male presented with a salmon pink conjunctival mass in the right eye. Visual acuity was 6/6 in both eyes. There was no prior history of Chlamydial infection or thyroid eye disease. A diagnostic biopsy confirmed CD20 positive MALT

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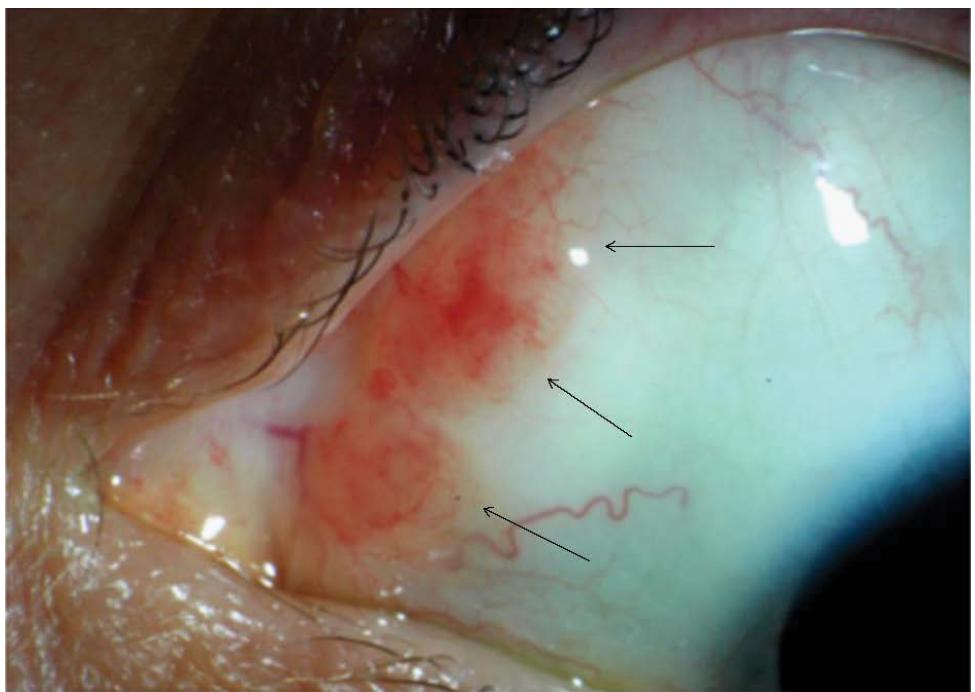


Figure 1: The slit-lamp examination of the left eye revealed a salmon-pink gelatinous lesion in the superonasal bulbar conjunctiva, confirmed immunohistochemically as mucosa-associated lymphoid tissue (MALT) lymphoma (arrows), 4 years after systemic rituximab for the treatment of conjunctival MALT lymphoma to the right eye.

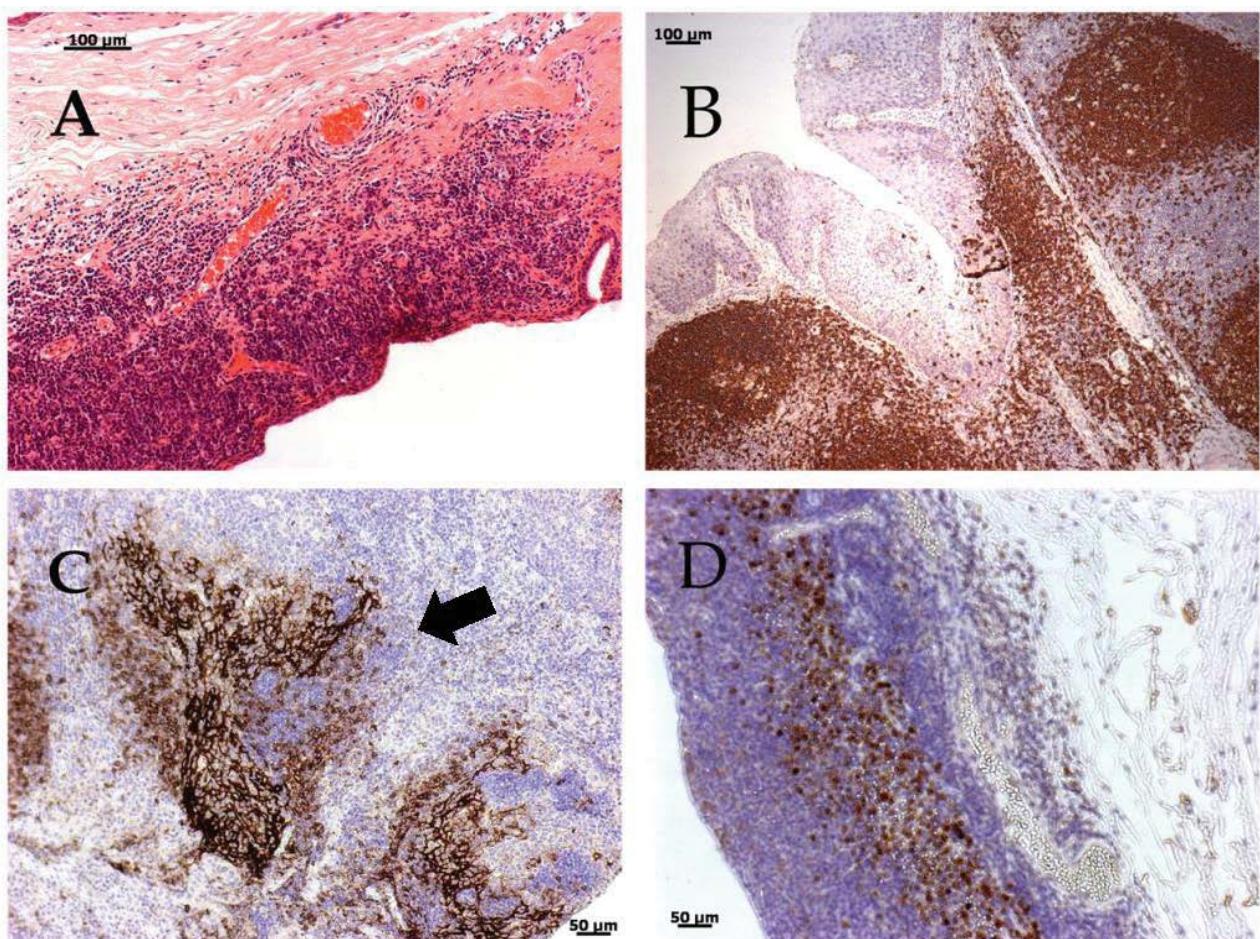


Figure 2: Immunohistochemistry of the lymphomatous tissue of the left eye. (A) H&E staining showing diffuse infiltrate of monomorphic small round blue cells. (B) CD20 positive staining of the majority of lymphoma cells (brown). (C) CD23 staining reveals expanded and disrupted germinal centers. The remnants of germinal centers are intensely stained, while the neoplastic cells are negative (Arrow), classically seen in MALT lymphoma.(D) BCL-6 negative staining for the majority of lymphomatous population, excluding follicular lymphoma.

lymphoma. The patient had no systemic symptoms. MRI scans of the head and orbits excluded intracranial or retrobulbar involvement.

Due to the young age of the patient, rituximab immunotherapy was commenced as primary treatment in order to avoid the side-effects of radiotherapy. A total of 6 courses of weekly rituximab at a dose of 375mg/m² were delivered intravenously with excellent response. There was complete remission clinically without any evidence of lesion recurrence in a 4-year follow-up period.

After 4 years a similar conjunctival lesion appeared in the superior bulbar conjunctival surface of the contralateral eye ([Figure 1](#)). Diagnostic biopsy showed the same type of CD20 positive MALT lymphoma ([Figure 2](#)), and treatment with further intravenous rituximab has been successful.

Discussion

Rituximab is a chimeric antiCD20 monoclonal antibody that induces a rapid depletion of benign and malignant CD20 positive cells. Its cytotoxicity is based on the lysis of B cells by a complement and antibody dependent mechanism that induces apoptosis of malignant cells. Complete B cell depletion occurs in a matter of days, with B cells reaching normal levels usually after a period of 9–12 months [[8,10](#)].

Rituximab has shown efficacy in the treatment of conjunctival MALT lymphoma, with response rates between 50-87%. However, response duration is usually less than a year with a high relapse rate [[4](#)]. The response rate at relapse after use in prior responders is lower than 50% and probably less durable. This secondary resistance can be attributed to loss of CD20 expression after rituximab therapy or to conformation of the CD20 receptor that can be produced by the effect of medication such as statins [[9,2](#)].

This case is highly unusual in that there was contralateral involvement 4 years after successful treatment with systemic

rituximab. This supports the notion that rituximab does not suppress MALT lymphoma formation in the long term in the other eye – perhaps demonstrating that the predisposing immune factors are not eradicated by the course of rituximab, and advocating for the long term follow-up of these patients.

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