ONKOLOGIE

Case Report · Kasuistik

Onkologie 2010;33:317–320
DOI: 10.1159/000313853

Published online: May 11, 2010

Bilateral Conjunctival MALT Lymphoma Mimicking Chronic Conjunctivitis

Mesut Seker[a] Burak Ozdemir[b] Ahmet Bilici[a] Bala Basak Ustaalioğlu[a] Berkant Sonmez[a] Burcak Erkol Yılmaz[a] Ekrem Kurnaz[b] Mahmut Gumus[a] Mustafa Yaylaci[a]

[a] Department of Medical Oncology,
[b] Department of Ophthalmology, Dr. Lutfi Kirdar Education and Research Hospital, Istanbul, Turkey

Key Word
Conjunctival MALT lymphoma · Chronic conjunctivitis

Schlüsselwörter
MALT-Lymphom der Bindehaut · Chronische Konjunktivitis

Summary

Background: The diagnosis of conjunctival lymphoid tumors is straightforward when they present with a characteristic salmon-pink, pebbly, multinodular appearance. However, rarely a diffuse clinical presentation is encountered, and this may mimic chronic conjunctivitis of other etiologies. **Case Report:** A 60-year-old man was referred to our clinic with bilateral conjunctival masses in May 2005. With the assumption of chlamydial conjunctivitis, without microbiological or histopathological evidence, tetracycline ointment and oral doxycycline 100 mg twice daily were prescribed. Although a partial response was achieved, 2 months after the treatment, the patient's complaints returned. On second referral to our clinic in March 2006, the patient was re-evaluated. He presented with bilateral conjunctival masses resembling conjunctival lymphoma, and a bilateral diagnostic biopsy was performed. Histopathological evaluation of the biopsy specimens revealed mucosa-associated lymphoid tissue (MALT) lymphoma. The patient received CVP chemotherapy (cyclophosphamide, vincristine, prednisolone). After 6 courses of chemotherapy, he achieved partial remission in both eyes. Currently, 28 months after CVP, sustained remission is obtained. **Conclusions:** In these cases, a high index of suspicion is required if one is to avoid a delay in diagnosis, and the importance of correct early diagnosis is obvious.

Zusammenfassung

Hintergrund: Lymphoide Tumore der Bindehaut sind leicht zu diagnostizieren, solange sie das typische lachsfarbene, kieselige, multinoduläre Erscheinungsbild aufweisen. In seltenen Fällen ist das klinische Bild jedoch verschwommen und könnte mit einer chronischen Konjunktivitis anderer Ursache verwechselt werden. **Fallbericht:** Im Mai 2005 wurde ein 60-jähriger Mann mit bilateralen konjunktivalen Läsionen an unsere Klinik überwiesen. Unter der Annahme, dass es sich um eine Chlamydien-Konjunktivitis handelt, wurden ohne vorherige mikrobiologische oder histopathologische Untersuchungen Tetracyclin-Augensalbe und orales Doxycyclin (100 mg, zweimal täglich) verschrieben. Obgleich ein partielles Ansprechen erreicht wurde, kehrten die Symptome des Patienten 2 Monate nach der Behandlung zurück. Bei seiner zweiten Überweisung an unsere Klinik im März 2006 wurde der Patient neu beurteilt. Er hatte bilaterale Bindehautgeschwülste, welche einem Bindehautlymphom ähnelten. Eine bilaterale diagnostische Biopsie wurde vorgenommen. Die histopathologische Untersuchung der Biopsieproben ergab ein MALT (mucosa-associated lymphoid tissue)-Lymphom. Der Patient erhielt CVP-Chemotherapie (Cyclophosphamid, Vincristin, Prednisolon). Nach 6 Zyklen war eine partielle Remission in beiden Augen zu verzeichnen. Derzeit, 28 Monate nach CVP, befindet sich der Patient in einer andauernden Remission. **Schlussfolgerungen:** In Fällen wie diesen ist ein hoher Grad an Vorsicht geboten, um eine verzögerte Diagnose zu vermeiden. Und die Wichtigkeit einer korrekten frühen Diagnose ist offensichtlich.

KARGER

Fax +49 761 4 52 07 14
Information@Karger.de
www.karger.com

Accessible online at:
www.karger.com/onk

Mesut Seker, M.D.
Altaycesme Mah, Sarıgul sok.
Kuralkan Apt, A1 Blok 4/18, Maltepe
Istanbul, Turkey
Tel. +90-05055618756, Fax -2164422947
mnseker@hotmail.com

Introduction

Ocular adnexal lymphomas (OAL) represent 1% of all non-Hodgkin's lymphomas (NHL) and 5–15% of all extranodal lymphomas. These lymphomas develop as primary or secondary tumor manifestations in the conjunctiva, the lacrimal gland, the orbital fat, the eyelid, and the lachrymal sac [1]. Hence, primary bilateral conjunctival lymphoma is an extremely rare disease. The conjunctiva has a natural, submucosal reservoir of lymphoid tissue, the so-called conjunctiva-associated lymphoid tissue, which serves as a functionally active mucosal immune system [2]. Conjunctiva-associated lymphoid tissue may develop characteristics that are similar to acquired mucosa-associated lymphoid tissue (MALT) elsewhere in the body [3]. Neoplastic transformation of MALT leads to development of an extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue, a MALT lymphoma. Ocular adnexal MALT lymphoma (OAML) constitutes more than two thirds of OAL [4], and in one investigation, 83% of patients with a conjunctival lymphoma had a conjunctival MALT lymphoma [5]. Whereas follicular and diffuse large-cell lymphomas each account for approximately 10% [5, 6]. This is in marked contrast to the overall incidence of MALT lymphoma, which accounts for only 7–8% of all NHLs, being less common than the diffuse large-cell and follicular lymphomas [7–9]. The diagnosis of conjunctival lymphoid tumors is straightforward when they present with a characteristic salmon-pink, pebbly, multinodular appearance, particularly if they are located in the inferior fornices. However, rarely a diffuse clinical presentation is encountered, and this may mimic chronic conjunctivitis of other etiologies. In these cases, a high index of suspicion is required if one is to avoid a delay in diagnosis, and the importance of correct early diagnosis is obvious [10]. Here, we report on a patient with bilateral conjunctival MALT lymphoma originally misdiagnosed as chronic conjunctivitis, which was treated with CVP combination chemotherapy (cyclophosphamide, vincristine, prednisone).

Case Report

A 60-year-old man was referred with bilateral conjunctival masses in May 2005. He had a history of irritation and chronic discharge in both eyes for 12 months. Bilateral follicules with minimal subepithelial fibrosis and mild blepharitis were noted at the Department of Ophthalmology, and with the assumption of chlamydial conjunctivitis, without microbiological or histopathological evidence, tetracycline ointment and oral doxycycline 100 mg twice daily were prescribed. No conjunctival mass was detected. Although partial response (≥ 50% reduction of all measurable lesions) was achieved 2 months after treatment, the patient's complaints returned. He was lost to follow-up from our clinic. He was treated with steroids and artificial tear drops at different centers for the same chronic complaint, but he was unresponsive. On second referral to our clinic in March 2006, the patient was re-evaluated. On physical examination, the patient's visual acuity was 20/20 in both eyes. Slit-lamp biomicroscopy showed subconjunctival multinodular fleshy masses arising from the lower forniceal conjunctivas and extending to both lower tarsus including the caruncula, with areas of subepithelial fibrosis (fig. 1 a, b). Another mobile subconjunctival mass in the lateral half of the right upper forniceal and bulbar conjunctiva and thickening of the left upper forniceal conjunctiva were observed (fig. 1 c, d). There was no sign of intraocular pathology. In light of the bilateral conjunctival masses resembling conjunctival lymphoma, a bilateral diagnostic biopsy was performed. Histopathological evaluation of biopsy specimens revealed MALT lymphoma, and the patient was referred to oncology. No organ involvement was detected in an extensive systemic workup. The patient was accepted with stage 1-E MALT lymphoma. First surgery and then radiotherapy were planned, but neither were performed due to the patient's refusal. Instead, he received CVP chemotherapy. After 6 courses of chemotherapy, he achieved partial remission in both eyes. Currently, 28 months after CVP, sustained remission has been obtained (fig. 2 a, b).

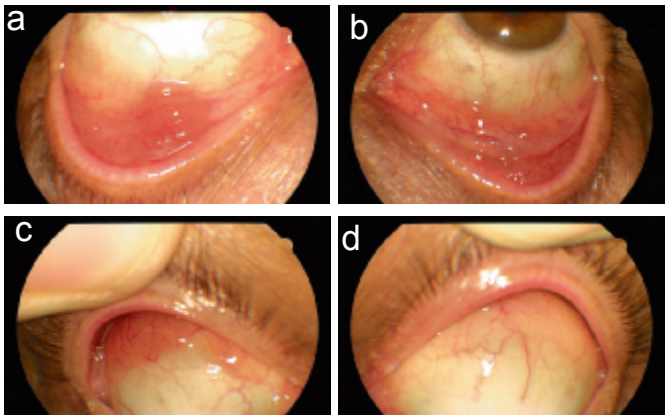

Fig. 1. a, b Slit-lamp biomicroscopy showed subconjunctival, multinodular, fleshy masses arising from lower forniceal conjunctivas and extending to both lower tarsus including the caruncula, with areas of subepithelial fibrosis; **c, d** Another mobile subconjunctival mass in the lateral half of the right upper forniceal and bulbar conjunctiva and thickening of the left upper forniceal conjunctiva.

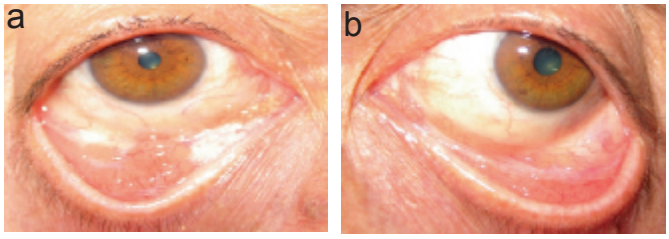

Fig. 2. a, b Sustained remission was obtained.

Discussion

Ferreri et al. [11] showed that doxycycline was effective in both *Chlamydia psittaci*-positive and -negative patients. For this reason, we used oral doxycycline and tetracycline ointment in the first instance. OAML is an indolent and rarely lethal malignancy that can often be managed with observation alone. A 'watchful waiting' strategy in 36 asymptomatic OAML patients has been analyzed, showing that, at a median

follow-up of 7.1 years, 69% of patients did not require any further treatment after biopsy or surgical resection. The median time until the initiation of treatment for patients who required therapy (11 patients, 31%) was 4.8 years. Among these 11 patients, only 1 required treatment for distant disease, and the others experienced local recurrence or progression [12]. Spontaneous regression after surgical biopsy was prospectively documented in 7 out of 8 patients with conjunctival MALT lymphoma and without subconjunctival extension or systemic dissemination. The real impact of this phenomenon cannot be fully interpreted as many patients in this series [13] received topical corticosteroids and/or antibiotics, which could modify the natural history of the disease due to the potential correlation between OAML and some bacterial agents [14, 15]. All of these observations suggest that a 'wait and watch' strategy after biopsy or resection could be a valid approach in selected patients with indolent and asymptomatic lesions. Elderly patients with severe comorbidity, whose conditions could seriously be impaired due to the adverse effect of chemo- or radiotherapy, are the best candidates for this strategy.

The OAML incidence is growing remarkably, with an annual increase of more than 6% [16]. Causes for these epidemiologic features are unknown. Chronic antigenic stimulation due to infections or autoimmune disorders and chromosomal abnormalities are thought to play a relevant role in lymphomagenesis and long-term lymphoma cell growth maintenance. Occasionally, presenting symptoms could be relevant, thus requiring an immediate treatment. Surgical resection, radiotherapy and oral chlorambucil are the most frequently applied therapeutic strategies for OAML. With these strategies, clinical behavior of OAML is usually favorable. New experimental therapeutic strategies were rituximab [17], bacteria-eradicating antibiotic therapy, anti-hepatitis C virus (HCV) therapy, and intralesional injections of interferon. These approaches could be associated with a lower incidence of severe sequelae. The therapeutic decision should result from a well-balanced analysis of patient- and lymphoma-related variables, as well as the risk of treatment-related toxicity [18]. Combined anthracycline-containing chemotherapy regimens, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-like combinations, have been sporadically used in patients with OAML with a more aggressive and disseminated disease. In a retrospective study, no significant difference in cause-specific or overall survival rates for OAML patients treated with radiotherapy alone or exclusive single-agent or anthracycline-containing chemotherapy has been detected [1]. However, anthracycline-based chemotherapy is not recommended as an upfront therapy in OAML patients. CVP regimen may be an alternative option with OAML patients with disseminated disease [19]. In our case, surgery could not be performed and radiation therapy was not administered because of the patients' refusal. Therefore, the patient was treated with the CVP regimen, although his disease was not disseminated.

Theodore described the masquerade syndrome in 1967 as chronic blepharoconjunctivitis due to an underlying conjunctival carcinoma [20]. Although the originally described neoplasms were squamous cell carcinomas, many of the tumors producing such clinical pictures are believed to be sebaceous in origin [21]. Clinical manifestations of conjunctival lymphomas may vary from mild irritation and redness to masses in the forniceal, bulbar, and palpebral conjunctiva, with a predilection for the fornices. Typical presentation is with mobile, flesh-colored, or salmon pink subepithelial tumors with a pebbly appearance corresponding to follicle formation, in the inferior fornices or bulbar conjunctiva. However, conjunctival lymphoma is a rare disease, and with nonspecific clinical presentations, diagnosis may be extremely difficult depending on suspicion. A diffuse lesion may masquerade as chronic conjunctivitis [10]. We describe a patient who was misdiagnosed as chronic conjunctivitis. He initially presented with bilateral follicules with minimal subepithelial fibrosis and without an elevated mass or typical infiltrates. Akpek et al. [10] presented 2 cases without classical masses, one with bilateral chronic inflammation and subconjunctival cicatrisation, and the other with unilateral papillary conjunctivitis and a few follicles. As in our case, these patients were unresponsive to treatment, and diagnoses were made with examination of biopsies. In one series of 7 patients with conjunctival lymphoma, 5 of which were bilateral, only 1 presented with chronic conjunctivitis without a noticeable mass [22]. And another previously reported case actually described a patient with conjunctival lymphoma masquerading as scleritis unresponsive to immunosuppressive treatment [23].

This case and previous reports emphasize that conjunctival lymphomas may rarely present as a diffuse lesion and can be misdiagnosed and treated as chronic conjunctivitis. Like with other malignancies, the importance of early diagnosis of lymphoma is obvious. Therefore, in patients unresponsive to treatment, it should be kept in mind that chronic conjunctivitis may be a masquerading syndrome; other possible underlying rare causes should be investigated, and a diagnostic biopsy should not be delayed.

Acknowledgement

This manuscript was not supported by any financial or other relationships.

References

1 Sasai K, Yamabe H, Dodo Y, Kashii S, Nagata Y, Hiraoka M: Non-Hodgkin's lymphoma of the ocular adnexa. Acta Oncol 2001;40:485–90.
2 Knop N, Knop E: Conjunctiva-associated lymphoid tissue in the human eye. Invest Ophthalmol Vis Sci 2000;41:1270–9.
3 Wotherspoon AC, Diss TC, Pan LX, Schmid C, Kerr-Muir MG, Lea SH, Isaacson PG: Primary low-grade B-cell lymphoma of the conjunctiva: a mucosa-associated lymphoid tissue type lymphoma. Histopathology 1993;23:417–24.
4 Auw-Haedrich C, Coupland SE, Kapp A, Schmitt-Gräff A, Buchen R, Witschel H: Long term outcome of ocular adnexal lymphoma subtyped according to the REAL classification. Br J Ophthalmol 2001;85:63–9.
5 Coupland SE, Krause L, Delecluse HJ, Anagnostopoulos I, Foss HD, Hummel M, Bornfeld N, Lee WR, Stein H: Lymphoproliferative lesions of the ocular adnexa: analysis of 112 cases. Ophthalmology 1998;105:1430–41.
6 Nakata M, Matsuno Y, Katsumata N, Takenaka T, Kobayashi Y, Narabayashi M, Kagami Y, Ikeda H, Kaneko A, Tobinai K: Histology according to the Revised European-American Lymphoma Classification significantly predicts the prognosis of ocular adnexal lymphoma. Leuk Lymphoma 1999;32:533–43.
7 Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Delsol G, De Wolf-Peeters C, Falini B, Gatter KC: A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84:1361–92.
8 Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, Lister TA, Bloomfield CD: World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting – Airlie House, Virginia, November 1997. J Clin Oncol 1999;17:3835–49.
9 Jaffe ES, Harris NL, Diebold J, Muller-Hermelink HK: World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: a progress report. Am J Clin Pathol 1999;111:S8–S12.
10 Akpek EK, Polcharoen W, Ferry JA, Foster CS: Conjunctival lymphoma masquerading as chronic conjunctivitis. Ophthalmology 1999;106:757–60
11 Ferreri AJ, Ponzoni M, Guidoboni M, Resti AG, Politi LS, Cortelazzo S, Demeter J, Zallio F, Palmas A, Muti G, Dognini GP, Pasini E, Lettini AA, Sacchetti F, De Conciliis C, Doglioni C, Dolcetti R: Bacteria-eradicating therapy with doxycycline in ocular adnexal MALT lymphoma: a multicenter prospective trial. J Natl Cancer Inst 2006;98:1375–81.
12 Tanimoto K, Kaneko A, Suzuki S, Sekiguchi N, Maruyama D, Kim SW, Watanabe T, Kobayashi Y, Kagami Y, Maeshima A, Matsuno Y, Tobinai K: Long-term follow-up results of no initial therapy for ocular adnexal MALT lymphoma. Ann Oncol 2006;17:135–40.
13 Matsuo T, Yoshino T: Long-term follow-up results of observation or radiation for conjunctival malignant lymphoma. Opthalmology 2004;111:1233–7.
14 Ferreri AJ, Guidoboni M, Ponzoni M, De Conciliis C, Dell'Oro S, Fleischhauer K, Caggiari L, Lettini AA, Dal Cin E, Ieri R, Freschi M, Villa E, Boiocchi M, Dolcetti R: Evidence for an association between Chlamydia psittaci and ocular adnexal lymphomas. J Natl Cancer Inst 2004;96:586–94.
15 Hara Y, Nakamura N, Kuze T, Hashimoto Y, Sasaki Y, Shirakawa A, Furuta M, Yago K, Kato K, Abe M: Immunoglobulin heavy chain gene analysis of ocular adnexal extranodal marginal zone B-cell lymphoma. Invest Ophthalmol Vis Sci 2001;42:2450–7.
16 Moslehi R, Devesa SS, Schairer C, Fraumeni JF Jr: Rapidly increasing incidence of ocular non-Hodgkin lymphoma. J Natl Cancer Inst 2006;98:936–9.
17 Salepci T, Seker M, Kurnaz E, Guler DO, Bilici A, Dane F, Aliustaoglu M, Atesoglu EB, Gumus M, Yaylaci M: Conjunctival malt lymphoma successfully treated with single agent rituximab therapy. Leuk Res 2009;33:e10–3.
18 Ferreri AJ, Assanelli A, Crocchiolo R, Dognini GP, Resti AG, Politi LS, Doglioni C, Cappio FC, Dolcetti R, Ponzoni M: Therapeutic management of ocular adnexal MALT lymphoma. Expert Opin Pharmacother 2007;8:1073–83.
19 Zinzani PL, Stefoni V, Musuraca G, Tani M, Alinari L, Gabriele A, Marchi E, Pileri S, Baccarani M: Fludarabine-containing chemotherapy as frontline treatment of nongastrointestinal mucosa-associated lymphoid tissue lymphoma. Cancer 2004;100:2190–4.
20 Theodore FH: Conjunctival carcinoma masquerading as chronic conjunctivitis. Eye Ear Nose Throat Mon 1967;46:1419–20.
21 Boniuk M, Zimmerman LE: Sebaceous carcinoma of the eyelid, eyebrow, caruncle and orbit. Int Ophthalmol Clin 1972;12:225–57.
22 Wotherspoon AC, Diss TC, Pan LX, Schmid C, Kerr-Muir MG, Lea SH, Isaacson PG: Primary low-grade B-cell lymphoma of the conjunctiva: a mucosa-associated lymphoid tissue type lymphoma. Histopathology 1993;23:417–24.
23 Hoang-Xuan T, Bodaghi B, Toublanc M, Delmer A, Schwartz L, D'Hermies F: Scleritis and mucosal-associated lymphoid tissue lymphoma: a new masquerade syndrome. Ophthalmology 1996;103:631–5.