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Ocular B-cell marginal zone lymphoma: case report and literature review

Linfoma ocular de células B da zona marginal: relato de caso e revisão da literatura

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ABSTRACT

Female patient, 70 years old, presented with complaints of left eye pruritus, tearing and redness, for 2 months. Physical examination revealed only mild conjunctival hyperemia. Biopsy was ordered, and suggested the hypothesis pseudo lymphoma by insufficient classification criteria. After a year, the patient returned with the same symptoms, and left ocular proptosis associated with lymphatic aspect of proliferation in bulbar conjunctiva, with the presence of blood vessels, occupying the entire upper region and most of the medial, extending into the limbo without occlusion the visual axis, extrinsic ocular motility preserved. Another biopsy and immunohistochemistry were compatible with a B cell marginal zone lymphoma. Tomographic studies of cranium, neck and orbits were performed, and the orbit showed enlargement of the left superior rectus muscle volume, with intense contrast uptake, affecting belly and tendon and blurring of adjacent fat. Six cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone, CHOP, were done every 21 days. There was improvement in ocular symptoms after the first cycle. After the fourth, new scans from the orbits revealed regression of thickening of the left superior rectus muscle, and even better after the sixth cycle. The MALT lymphomas account for 5-17% of all cases of NHL, accounting for over 90% of lymphomas affecting the eye attachments, but can originate in different tissues. Due to the rarity of the disease, there are no randomized prospective studies to define a therapeutic consensus. The literature suggests that treatment should be individualized.

Keywords: *Ocular lymphoma; non-Hodgkin's lymphoma; MALT lymphoma; Lymphoid hyperplasia; Pseudolymphoma; Case reports*

RESUMO

Paciente feminina, 70 anos, apresentou-se com queixas de prurido ocular à esquerda, lacrimejamento e hiperemia há 2 meses. Ao exame físico, apenas hiperemia conjuntival discreta. Foi solicitada biópsia, que sugeriu a hipótese de pseudolinfoma pela insuficiência de critérios classificatórios. Após um ano a paciente retornou com os mesmos sintomas e proptose ocular à esquerda, associado a proliferação de aspecto linfático em conjuntiva bulbar, com presença de vasos sanguíneos, ocupando toda região superior e maior parte da medial, se estendendo até o limbo, sem oclusão do eixo visual e mobilidade ocular extrínseca preservada. Nova biópsia e imuno-histoquímica, foram compatíveis com linfoma de células B da zona marginal. Foram realizadas tomografias computadorizadas (TC) de crânio, pescoço e órbitas, revelando aumento do volume do músculo reto superior esquerdo, com intensa impregnação pelo contraste, acometendo ventre e tendão, com borramento de gordura adjacente. Foram programados 6 ciclos de quimioterapia com ciclofosfamida, doxorrubicina, vincristina e prednisona, CHOP, a cada 21 dias. Houve melhora dos sintomas oculares após o primeiro ciclo. Após o quarto, nova TC de órbitas evidenciou regressão do espessamento do músculo reto superior esquerdo, ainda melhor na TC realizada após o sexto ciclo. Os linfomas MALT são responsáveis por 5-17% de todos os casos de LNH, respondem por mais de 90% dos linfomas que acometem os anexos oculares, mas podem se originar em diversos tecidos. Devido a raridade da doença, carecem estudos prospectivos randomizados que definam um consenso terapêutico. A literatura sugere que o tratamento deve ser individualizado.

Descritores: Linfoma ocular; Linfoma não-Hodgkin; Linfoma MALT; Hiperplasia linfoide; Pseudolinfoma; Relatos de casos

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Introduction

The orbital lymphoma is rare and comprises approximately 10% of all orbital neoplasms. Most of the non-Hodgkin's lymphomas (NHL) in the ocular adnexa are extranodal B-cell marginal zone lymphomas, also known as MALT lymphomas. [1-4]

Marginal zone lymphomas (MZL) originate from memory B lymphocytes normally present in a distinct micro-anatomic compartment called the marginal zone in the secondary lymphoid follicles. According to the site of origin and molecular characteristics, they can be classified into 3 subtypes according to the World Health Organization: extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), splenic marginal zone lymphoma and nodal marginal zone lymphoma.[5]

MALT lymphomas account for 5-17% of all NHL cases, depending on the series. [6] In relation to the sites of involvement, they account for 50% of all gastric lymphomas and more than 90% of lymphomas affecting the eye adnexa, but they may originate in many other epithelial tissues as salivary gland, thyroid, lung, breast, skin, liver, small intestine, urogenital system and dura mater. Most cases involve adults over 60 years old, with a slight predominance for women. [7-9]

It is theorized that the lymphoid hyperplasia occurs in response to stimulation by antigens, followed by additional oncogenic events including chromosome abnormalities perpetuating the disease development. [10] Four recurrent chromosomal translocations were found: t(11;18) (q21;q21), t(14;18)(q32;q21), t(1;14)(p22;q32) e t(3;14)(p13;q32) resulting in the activation of NF-kappa B, a factor involved in the survival of these cells.[11-13]

A variety of autoimmune diseases have been associated to the development of MZL, like rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, Wegener's granulomatosis, and Hashimoto's Thyroiditis, and autoimmune mechanisms may play a role in pathogenesis. [14]

This study aims at describing a case of ocular marginal zone B cells, emphasizing the clinical epidemiological characteristics and treatment options described in the literature, since there are no prospective randomized studies comparing the therapeutic options.

Case Report

Female patient, 70 years old, sought treatment in February 2012, complaining of itchy left eye, with tearing and redness for 2 months. The physical examination showed only a discreet conjunctival hyperemia. The left eye biomicroscopy showed decreased endothelial density to the age. Biopsy was requested, and the sample represented tenon of limbal region, mucous and intermuscular membrane, in which immunohistochemistry was performed and identified lymphoepithelial infiltration, suggesting the hypothesis of pseudolymphoma due to insufficient classification criteria. There was follow-up discontinuity, so that in September 2013 the patient returned with the same symptoms and eye left proptosis associated to extensive proliferation of the lymphatic aspect in bulbar conjunctiva (Figures 1A and 1B), with the presence of blood vessels occupying the entire superior region and most of the medial region, extending into the limbo, but without occlusion of the visual axis and extrinsic ocular motility preserved. We opted for a new biopsy (Figures 2-4) and immunohistochemistry (Table 1), which was compatible with B-cell lymphoma of extra nodal marginal zone. Studies were carried out with computed tomography (CT) of skull, neck and orbits, revealing an isolated finding of increased volume of the left superior rectus muscle, with intense impregnation by contrast, affecting the womb and tendon, with blurring of adjacent fat (Figures 5A and 5B). Once identified the nature of the disease, stage IE (Ann Arbor System), and considering the location of the lesion, 6 cycles of were programmed with cyclophosphamide, doxorubicin, vincristine and prednisone, CHOP, every 21 days. The patient developed with improvement of ocular symptoms and regression of proliferation in the bulbar conjunctiva right after the first cycle. After the fourth cycle, a new CT of the orbits showed regression of the thickening of the left superior rectus muscle, which was even better in the CT carried out after the sixth cycle (Figures 6A and 6B).

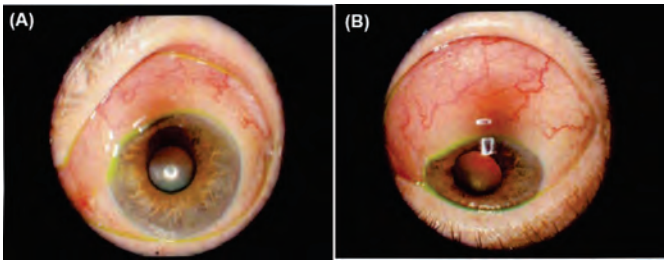

Figure 1: Extensive proliferation of lymphatic aspect in the bulbar conjunctiva, observed in neutral position (A) and infraduction (B) located in the left eye.

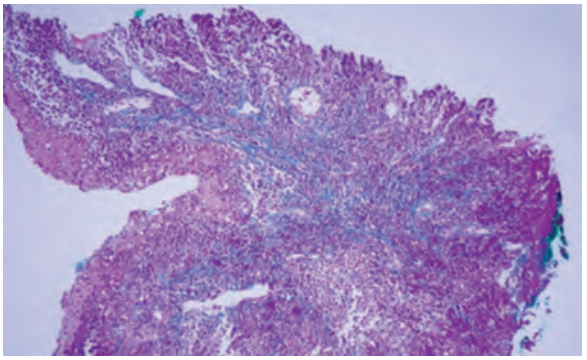

Figure 2: Small lymphocytes infiltrating diffusely the stroma and epithelium of the conjunctiva (H&EX 100).

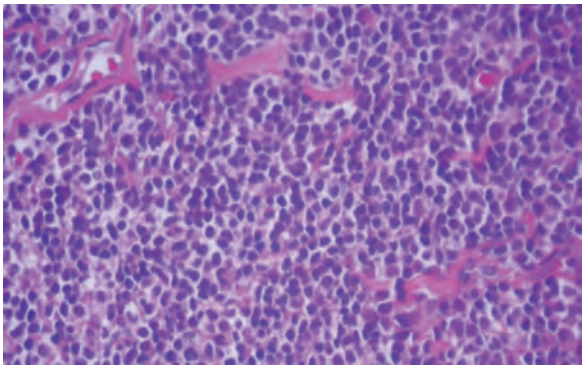

Figure 3: Detail of the small, rounded neoplastic lymphocytes showing chromatin condensation and diffuse infiltration between the septa of the conjunctival stroma (400 H&EX).

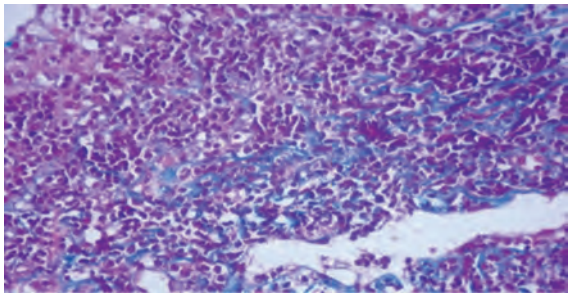

Figure 4: Detail of the lymphocyte population consisting of small rounded lymphocytes that infiltrate the conjunctive beams and the conjunctival mucosa epithelium on the left of the photo.

Table 1
Immunophenotypic markers analyzed in the clinical case

CD20	+	
CD45 LAC	+	
PAX-5	+	
BCL-2	+	
MUM-1	+	
CD43	+	
CD79A	+	
IgM	+	
MIB-1 (Ki-67)		+<5% of lymphoid cells
CD23	-	
CD5	-	
CD22	-	
BCL-6	-	
CD10	-	
CD15	-	
CD30	-	
Cd30	-	
Cyclin D1	-	

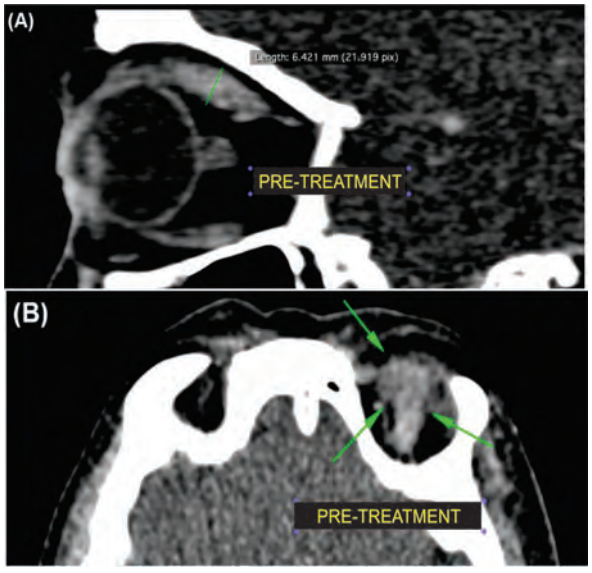

Figure 5: Orbit computed tomography showing an increase in the volume of the left superior rectus muscle demonstrated in sagittal (A) and axial (B) sections.

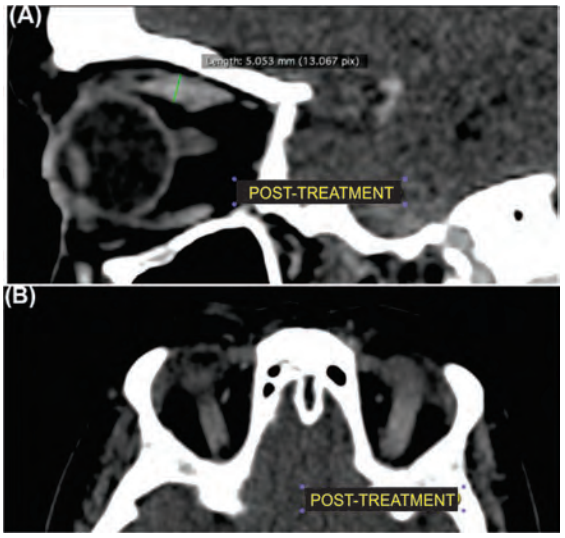

Figure 6: Orbital computed tomography showing thickening regression of the left superior rectus muscle, in sagittal (A) and axial (B) sections after six cycles of CHOP.

Discussion

The clinical presentation depends on the site involved; in the case of ocular adnexa, the patient may have Sjögren's syndrome, conjunctival hyperemia, proptosis, chemosis or palpable mass of indolent growth. [15,16]

The natural history of the disease has indolent character, and differs in clinical and biological aspects when compared to MALT lymphomas of the gastrointestinal tract. An example is the strong association of chronic antigenic stimulation for H pylori, well established in the development of gastric MALT lymphoma. Although there are theories explaining the pathogenesis of the disease involving autoimmune or infectious stimuli, extra gastric lymphomas did not regress after eradication of H pylori, but in some countries, the ocular lymphoma adnexa have been associated to infection by Chlamydia psitacci and regressed after antibiotic therapy.[17]

Histological findings consist of poorly defined follicular areas consisting of monocytoid B cells with large nuclei. An important feature is the lympho-epithelial lesions, defined by the distortion of the epithelial structures by neoplastic lymphoid cell aggregates.[18] An histologic transformation for large-cell lymphoma is reported in approximately 10% of cases.[19,20]

On immunohistochemistry, the presence of an intraepithelial lymphocyte population positive for antigens associated to cells B CD20, CD19, CD22, CD79a and negative for CD3, CD21, CD35, and which is generally negative for CD5 CD10, CD23, support the diagnosis of MALT lymphoma. [21]

The management of non-gastric disease is not clearly defined, and retrospective studies showed that patients treated with radiation therapy, surgery and chemotherapy, alone or in combination, resulted in excellent control of the disease and survival rates, and no modality proved to be superior to another. [16,19,20,22]

Currently the guidelines recommend that the therapeutic decision is based on the stage of the disease, determined by the Ann Arbor system (Table 2), the site of the tumor and the clinical and individual characteristics of the patient. [21]

Imaging studies should include a tomography without contrast of the thorax, abdomen and pelvis to exclude distance

Table 2
Ann Arbor staging system also used for MZL

Stage I:
• I: Involvement of a single lymph node chain
• IE: Isolated involvement of organ or extralymphatic site
Stage II:
• II: Two or more lymph node chains on the same side of the diaphragm
• IIE: Involvement of organ or extralymphatic site and one or more lymph node chains on the same side of the diaphragm
Stage III:
• III: Involvement of lymph node chains on both sides of the diaphragm
Additional criteria:
• IIIS: Involvement of the spleen
• IIIE: Involvement of the extralymphatic site
Stage IV:
• IV: Diffuse or disseminated involvement of one or more extralymphatic organ /tissues, associated to lymph node involvement or not
Extranodal sites:
M:bone marrow; L:Lung; H:liver; P:pleura; O:bone; D:skin and subcutaneous tissue

disease. Furthermore, patients with multifocal disease should have aspirate and bone marrow biopsy. [23]

Patients with limited disease, stages IE and IIE, should consider locoregional radiotherapy with doses between 25-30 Gy. [14,24] This lymphoma is very sensitive to radiation, and the dose should not exceed 30Gy due to the risk of damage to the ocular structures. Studies have demonstrated complete response in more than 90% of cases with this approach. [25] However, radiotherapy is not universally accepted for patients with MZL of ocular adnexa. [26-28] Bennett et al. reported that the chemotherapy regimen was effective in the primary high-grade orbital lymphoma or with distance disease. [29]

Alkylating agents such as cyclophosphamide and chlorambucil result in a high rate of disease control, and can be used alone or in combination. [30-32] Phase II studies using monoclonal antibodies anti-CD20, Rituximab, showed a response rate of 70%, representing one more option in the treatment of systemic disease. [33]

Chemotherapeutic drugs used for the treatment of indolent NHL have also demonstrated high effectiveness. In retrospective analysis, 26 patients with MALT lymphoma in recurrence have received rituximab and cyclophosphamide, doxorubicin/ mitoxantrone, vincristine and prednisone (R-CHOP/R-CNOP), 77% of which achieved complete remission and 23% partial remission. Primarily hematologic toxicity was reported with these schemes.[34]

The treatment of patients with advanced stage extranodal LMZ is not clearly defined, and most of the data in this population comes from a retrospective series or extrapolation of data from other indolent NHL. These patients are usually treated similarly to those with advanced stage follicular lymphoma, including immunotherapy with rituximab, with or without chemotherapy.[19]

References

1. Fung CY, Tarbell NJ, Lucarelli MJ, Goldberg SI, Linggood RM, Harris NL, et al. Ocular adnexal lymphoma: Clinical behavior of distinct World Health Organization classification subtypes. Int J Radiat Oncol Biol Phys. 2003;57(5):1382–91.
2. Galieni P, Polito E, Leccisotti A, Marotta G, Lasi S, Bigazzi C, et al. Localized orbital lymphoma. Haematologica. 1997;82(4):436–9.
3. Hasegawa M, Kojima M, Shioya M, Tamaki Y, Saitoh J, Sakurai H, et al. Treatment results of radiotherapy for malignant lymphoma of the orbit and histopathologic review according to the WHO classification. Int J Radiat Oncol Biol Phys. 2003;57(1):172–6.
4. Uno T, Isobe K, Shikama N, Nishikawa A, Oguchi M, Ueno N, et al. Radiotherapy for extranodal, marginal zone, B-cell lymphoma of mucosa-associated lymphoid tissue originating in the ocular adnexa: A multiinstitutional, retrospective review of 50 patients. Cancer. 2003;98(4):865–71.
5. Zinzani PL. The many faces of marginal zone lymphoma. Hematology. 2012;2012(1):426-32.
6. Cervetti G, Galimberti S, Sord E, Buda G, Orciuolo E, Cecconi N, *et al*. Significant efficacy of 2-CdA with or without rituximab in the treatment of splenic marginal zone lymphoma (SMZL). *Ann Oncol.* 2010;21(4):851–4.
7. Radaszkiewicz T, Dragosics B, Bauer P. Gastrointestinal malignant lymphomas of the mucosa-associated lymphoid tissue: factors relevant to prognosis. Gastroenterology. 1992; 102(5):1628-38.
8. White WL, Ferry JA, Harris NL, Grove AS Jr. Ocular adnexal lymphoma. A clinicopathologic study with identification of lymphomas of mucosa-associated lymphoid tissue type. Ophthalmology. 1995; 102(12):1994-2006.
9. Rosado MF, Byrne GE Jr, Ding F, Fields KA, Ruiz P, Dubovy SR, et al. Ocular adnexal lymphoma: a clinicopathologic study of a large cohort of patients with no evidence for an association with Chlamydia psittaci. Blood. 2006; 107(2):467-72.
10. Kahl B, Yang D. Marginal zone lymphomas: management of nodal, splenic, and MALT NHL. Hematology Am Soc Hematol Educ Program. 2008:359-64.
11. Ott G, Katzenberger T, Greiner A, Kalla J, Rosenwald A, Heinrich U, et al. The t(11;18)(q21;q21) chromosome translocation is a frequent and specific aberration in low-grade but not high-grade malignant non-Hodgkin's lymphomas of the mucosa-associated lymphoid tissue (MALT-) type. Cancer Res. 1997; 57(18):3944-8.
12. Auer IA, Gascoyne RD, Connors JM, Cotter FE, Greiner TC, Sanger WG, Horsman DE. t(11;18)(q21;q21) is the most common translocation in MALT lymphomas. Ann Oncol. 1997; 8(10):979-85.

13. Rinaldi A, Mian M, Chigrinova E, Arcaini L, Bhagat G, Novak U, et al. Genome-wide DNA profiling of marginal zone lymphomas identifies subtype-specific lesions with an impact on the clinical outcome. Blood. 2011; 117(5):1595-604.
14. Zucca E, Gregorini, A, Cavalli, F. Management of non-hodgkin lymphomas arising at extranodal sites. *Ther Umsch. 2010;* 67(10): 517–25.
15. Traweek ST, Sheibani K, Winberg CD, Mena RR, Wu AM, Rappaport H. Monocytoid B-cell lymphoma: its evolution and relationship to other low-grade B-cell neoplasms. Blood. 1989; 73(2):573-8.
16. Zucca E, Conconi A, Pedrinis E, Pedrinis E, Cortelazzo S, Motta T, Gospodarowicz MK, et al. Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. Blood 2003; 101(7):2489-95.
17. Ferreri AJ, Guidoboni M, Ponzoni M, De Conciliis C, Dell'Oro S, Fleischhauer K, et al. Evidence for an association between Chlamydia psittaci and ocular adnexal lymphomas. J Natl Cancer Inst. 2004;96(8):586–94.
18. Lim SH, Kang M, Song J. Extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue type of the ocular adnexa: Retrospective single instituition review of 95 patients. Indian J Ophthalmol. 2011;59(4):273-7.
19. Berger F, Felman P, Thieblemont C, Pradier T, Baseggio L, Bryon P, *et al*. Non-MALT marginal zone B-cell lymphomas: a description of clinical presentation and outcome in 124 patients. *Blood. 2010;* 95(6): 1950–6.
20. De Boer J, Hiddink R, Raderer M, Antonini N, Aleman B, Boot H, *et al*. Dissemination patterns in non-gastric MALT lymphoma. *Haematologica. 2008;* 93(2): 201–6.
21. Joshi M, Sheikh H, Abbi K, Long S, Sharma K, Tulchinsky M, et al. Marginal zone lymphoma. Ther Adv Hem. 2012; 3(5):275-90.
22. Tsang R, Gospodarowicz M, Pintilie M, Wells W, Hodgson D, Sun A, *et al*. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. *J Clin Oncol.2003;* 21(22): 4157–64.
23. Harada K, Murakami N, Kitaguchi M, Sekii S, Takahashi K, Yoshio K, et al. Localized ocular adnexal mucosa-associated lymphoid tissue lymphoma treated with radiation therapy: a long-term outcome in 86 patients with 104 treated eyes. Int J Radiat Oncol Biol Phys. 2014; 88(3):650-4.
24. Tsang R, Gospodarowicz M. Radiation therapy for localized low-grade non-Hodgkin's lymphomas. *Hematol Oncol. 2005;* 23(1):10–7.
25. Son SH, Choi BO, Kim GW, Yang SW, Hong YS, Choi IB, Kim YS. Primary radiation therapy in patients with localized orbital marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT Lymphoma). Int J Radiat Oncol Biol Phys. 2010; 77(1):86-91.
26. Smitt MC, Donaldson SS. Radiotherapy is successful treatment for orbital lymphoma. Int J Radiat Oncol Biol Phys. 1993;26(1):59–66.
27. Lee SW, Suh CO, Kim GE, Yang WI, Lee SY, Hahn JS, et al. Role of radiotherapy for primary orbital lymphoma. Am J Clin Oncol. 2002;25(3):261–5.
28. Yahalom J. MALT lymphomas: A radiation oncology viewpoint. Ann Hematol. 2001;80:B100–5.
29. Bennett CL, Putterman A, Bitran JD, Recant W, Shapiro CM, Karesh J, et al. Staging and therapy of orbital lymphomas. Cancer. 1986; 57(6):1204–8.
30. Levy M, Copie-Bergman C, Traulle C, Lavergne-Slove A, Brousse N, Flejou, J, *et al*. Conservative treatment of primary gastric low-grade B-cell lymphoma of mucosa-associated lymphoid tissue: predictive factors of response and outcome. *Am J Gastroenterol. 2002;* 97(2): 292–7.
31. Zinzani P, Stefoni V, Musuraca G, Tani M, Alinari L, Gabriele A, *et al*. Fludarabinecontaining chemotherapy as frontline treatment of nongastrointestinal mucosa-associated lymphoid tissue lymphoma. *Cancer. 2004;*100(10): 2190–4.
32. Simon B, Cheung N, McKelvie P, Fox R. McNab, A. Oral chlorambucil for extranodal, marginal zone, B-cell lymphoma of mucosa-associated lymphoid tissue of the orbit. *Ophthalmology. 2006;* 113(7):1209–13.
33. Martinelli G, Laszlo D, Ferreri A, Pruneri G, Ponzoni M, Conconi A, *et al*. Clinical activity of rituximab in gastric marginal zone non- Hodgkin's lymphoma resistant to or not eligible for anti-*Helicobacter pylori* therapy. *J Clin Oncol. 2005;* 23(9):1979–83.
34. Raderer M, Wohrer S, Streubel B, Drach J, Jage U, Turetschek K, *et al*. Activity of rituximab plus cyclophosphamide, doxorubicin/mitoxantrone, vincristine and prednisone in patients with relapsed MALT lymphoma. *Oncology. 2006;* 70(6): 411–7.

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