Gallium-67 citrate scintigraphy and marginal zone lymphoma of the mucosa-associated lymphoid tissue. Ocular MALT

Olga Taşkaya Yaylalı[1],
Fatma Suna Kıraç[1],
Volkan Yaylalı[2],
Kaan Gündüz[3],
Ender Düzcan[4]

1. *Departments of Nuclear Medicine,*
2. *Eye Disease and*
3. *Pathology, Pamukkale University, School of Medicine Denizli, Turkey*
4. *Department of Eye Disease, Ankara University, School of Medicine, Ankara, Turkey*

Keywords: MALT lymphoma – Conjunctiva – ^{67}Ga scintigraphy – Radiotherapy

Correspondence address:
Dr. Olga Taşkaya Yaylali,
Pamukkale Universitesi Hastanesi,
Nükleer Tıp Anabilim Dalı,
Doktorlar cad. No:42 20100,
Denizli, Turkey.
E-mail: olgataskaya@yahoo.com and aylali@pamukkale.edu.tr
Tel: 0258 2410034 (157-163)
Fax: 0258 2517487

Received:
4 June 2007
Accepted revised:
27 September 2007

Abstract

We describe marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT) and especially MALT lymphoma occurring in the conjunctiva. Tumors of the conjunctiva and cornea are grouped into two major categories of congenital and acquired lesions. Lymphoid tumors of the conjunctiva are acquired tumors and can occur as an isolated lesion or can be a manifestation of systemic lymphoma. Primary lymphomas of the conjunctiva are extremely rare usually originate from extranodal marginal zone B-cell non-Hodgkin's lymphomas of MALT and occur among older adults with a mean age of 61 years. In the last decade it has been reported that MALT lymphomas may develop in various extraintestinal locations, sometimes even without the presence of a mucosa. Half of MALT lymphomas occur in the gastrointestinal tract. MALT lymphomas of the eye are rare and originate from the conjunctiva and the lacrimal glands. Studies evaluating the clinical impact of ^{67}Ga-C scintigraphy for MALT-type lymphomas imaging are rare, based on small numbers, heterogenous groups of patients. Clinical examination, excisional biopsy, histopathology and immunohistochemical studies, computerized tomography and magnetic resonance imaging are also used for the diagnosis of cunjunctival MALT disease. A case of ours gives reason for further discussion. Treatment and follow-up of MALT lymphoma is described.

Hell J Nucl Med 2007; 10(3): 160-163 • *Published online: 19 November 2007*

Introduction

The term MALT lymphoma was coined in early 1980s in order to describe a characteristic marginal zone lymphoma of mucosa associated lymphoid tissue (MALT) which is the most common ocular adnexal lymphoid proliferation [1]. Most of these lymphomas originate from B cells and rarely from T cells of non-Hodgkin's lymphoma (NHL) [2, 3]. MALT lymphomas of the eye are rare and originate from the conjunctiva or the lacrimal glands [4-6]. MALT lymphoma has been described in the conjunctiva in 1980 by Knowles and Jakobiec [7]. The MALT lymphoma incidence is approximately 5% of all NHL [8]. About 170 orbital MALT lymphoma patients have been reported in the different series [1, 3-7, 9-13].

Ocular involvement represents 1%-28% of the extranodal lymphomas [10, 14]. The majority of ocular lymphomas occur in the orbit (60%) while conjunctiva, eyelids and the lacrimal glands can also be involved [6, 14]. Half of MALT lymphomas occur in the gastrointestinal tract, specifically the stomach, the terminal ileum and the appendix, but they may develop even without the presence of a mucosa [4, 5]. They have also been described in the bronchi, salivary glands, thyroid and the thymus [11-13]. The incidence of gastric B-cells lymphomas in Germany was reported to be between 20%-80% of the patients with primary gastric lymphoma [15].

Tumors of the conjunctiva and cornea are grouped into two major categories of congenital and acquired lesions. Lymphoid tumors of the conjunctiva are acquired tumors and can occur as an isolated lesion or as a manifestation of systemic lymphoma. Primary lymphomas of the conjunctiva are extremely rare and occur among older adults with a mean age of 61 years [2, 9, 10]. Conjunctival MALT lymphoma is a rare, low-grade, B-cell, NHL [3].

We had the option to study a 65 year old male with a marginal zone B-cell lymphoma of MALT which gives reason for further discussion: He had a history of stinging sensation and minimal irritation in the left eye for longer than 2 months and a nodal pink mass in the left upper palpebral conjunctival region (Fig. 1A, 1B). He had no history of conjunctivitis, no mucopurulan secretion or swelling. At the excisional biopsy of the conjunctival lesions, as much tissue as possible was removed. Histopathology and immunohistochemical studies revealed sheets of lymphoid cells with slightly indented nuclei and a sparse cytoplasm, confirming the

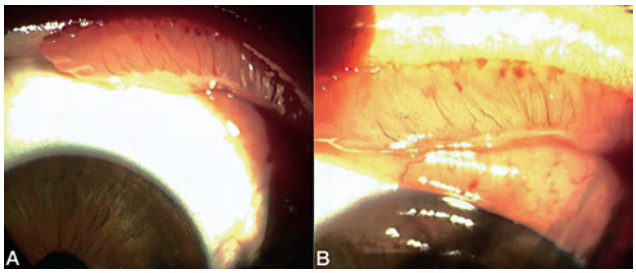

Figure 1. A: Picture of the left eye showing a nodal pink mass, "salmon-pink'' lesion arising from the left upper palpebral conjunctival region. B: Larger view of the upper palpebral conjunctiva, shows the conjunctival lesion overlying dilated blood vessels.

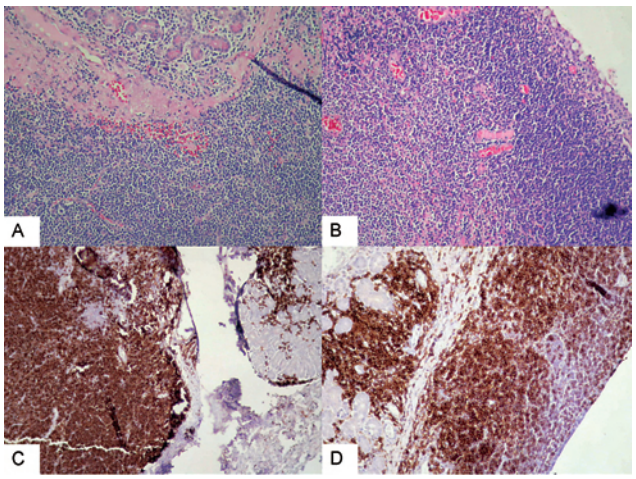

Figure 2. A: The haematoxylin and eosin (H and E) stain of the left eye conjunctival biopsy specimen demonstrating dense lymphoid infiltrate (magnification ×40). B: The H and E stain of the left conjunctival biopsy specimen (magnification ×400) showing conjunctival epithelium and underlying stroma infiltrated by small lymphoid cells. C: Immunohistochemical stain of conjunctival biopsy of left eye, CD-20 positive and CD-5 and CD-10 negative B cells were detected (magnification ×40). D: Immunohistochemical biopsy specimen showing CD-20 positive B cells (magnification ×400).

diagnosis (Fig. 2A-D). A computerized tomography (CT) scan of the brain and the orbita showed a soft tissue density superior to the left bulbus oculi connected with the superior rectus muscle, while no abnormal density or lesion was found in the opposite side of ocular region (Fig. 3A). CT scans of the head, chest, abdomen, and pelvis, were normal except for a focal area of abnormal uptake in the left orbit (Fig. 3B). Whole body CT and gallium-67 citrate (^{67}Ga-C) scans and physical examination confirmed localised disease. A dose of 370 MBq of ^{67}Ga-C was injected (Mallinckrodt Medical, The Netherlands) and planar γ-camera whole body images (GE, Genieacq-Entegra, USA) were obtained at 4, 24 and 48 h. No radiopharmaceutical related discomfort or side-effects were observed. Routine haematology, biochemistry, bone marrow and cerebrospinal fluid tests, were normal. The patient was given the option of either radiation treatment or follow-up without treatment. He chose to be treated with radiation and was given a total dose of 40 Gy to the remaining conjunctival lesions which

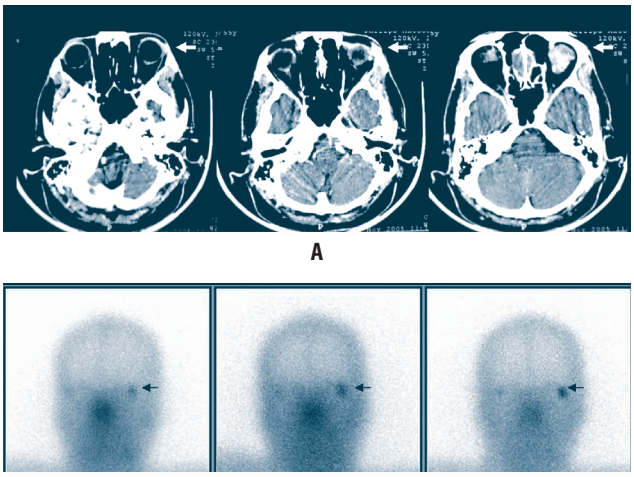

Figure 3. A: Orbital computed tomography proved an increased soft tissue density superior to the left bulbus oculi (white arrows) without an extraocular lesion. B: A sequential ^{67}Ga-C images was obtained at 4h, 24h, and 48 h after administration of 370 MBq tracer intravenously. The anterior cranium planar images showed accumulation of the tracer in the left orbital region (black arrows).

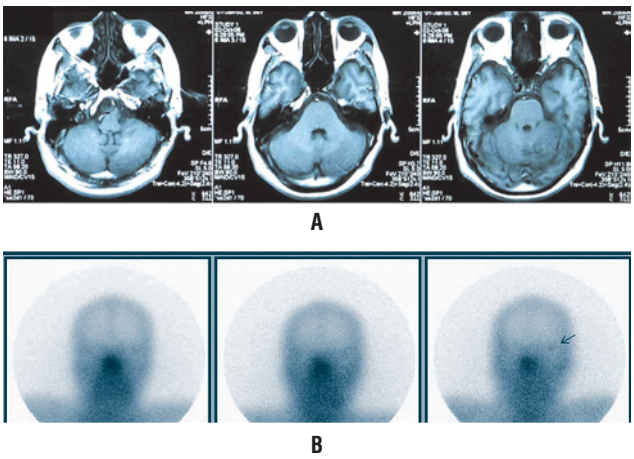

Figure 4. A: Orbital MRI images were obtained for the evaluation of therapy response. There was not any sign of recurrence and/or residual tumor in the left bulbus oculi. B: After radiotherapy, the anterior cranial planar images were acquired at 4h, 24h, and 48 hours. Little ^{67}Ga-C accumulation was observed in the tumoral region (arrow) compared to baseline planar ^{67}Ga-C images.

disappeared immediately following radiation. Three months later, orbital magnetic resonance imaging (MRI) was normal (Fig. 4A). Also, there was decreased ^{67}Ga-C uptake at the region of the tumor as compared to the baseline findings (Fig. 4B). During a 12 months follow-up period, no evidence of local recurrence or dissemination was detected by detailed physical examination, CT, MRI scans or routine laboratory tests and the patient had a complete tumor remission.

The diagnosis

Primary conjunctival low-grade lymphoma may share similar clinical features with allergic conjunctivitis [16]. Patients ex-

hibit symptoms such as irritation, epiphora, blurred vision, proptosis, and diplopia, but they can also be asymptomatic [7]. Clinically, lesions usually appear as diffuse, slightly elevated pink masses located in the stroma or deep to Tenon's fascia, most commonly in the forniceal region of the eye. This appearance is similar to that of smoked salmon; hence it is termed as the "salmon patch" [2, 12]. On ocular examination of our patient, a nodal pink mass was found in the left upper palpebral conjunctival region. Viral or bacterial infection was less likely because the clinical course was longer than 2 months, the patient had no history of allergic conjunctivitis, did not wear contact lenses, and had no related clinical findings. Although simultaneous presentation of lymphoma affecting the conjunctiva in one eye and the orbit in the opposite side is rare, any patient with an isolated conjunctival lymphoma should be carefully examined at the contralateral eye and orbit, if necessary with an orbital CT, in order to rule out bilateral involvement [17].

Although most conjunctival lymphoid tumors are acquired tumors, arising from a long-standing antigenic stimulation against viral infection, MALT lymphomas are considered indolent tumors, usually occurring in the older age groups (50-70 years old) [12, 18]. It has been suggested that this distribution when compared with other low-grade small B-cell NHL shows a lower propensity to dissemination and to bone marrow infiltration [19]. Systemic disease at presentation or during the course of the disease can be found in up to one-third of patients with local MALT lymphomas [4, 9].

Conjunctival biopsy allows early diagnosis and early treatment [11, 16, 20]. Biopsy is necessary to establish the diagnosis and systemic evaluation is necessary to exclude the presence of a systemic lymphoma. Excisional biopsy supports the diagnosis and the evaluation of conjunctival MALT lymphomas. Other diagnostic modalities such as physical examination, CT, MRI and bone marrow biopsy are used to study eye MALT lymphomas.

The use of ^{67}Ga-C scan for the evaluation of disease activity in patients with diffuse aggressive NHL was highly predictive of eventual outcome more predictive than the CT scan [21]. ^{67}Ga-C scintigraphy has been used extensively and effectively in patients with conjuctival MALT lymphomas for the detection of local or systemic disease, for staging, and for the assesment of treatment effect [1, 22]. The ^{67}Ga-C whole body scintigraphy can detect small lymphoid lesions in the mucosal tissue and provide early treatment of these lesions [23-25].

Although NHL are the most frequent malignant tumors of the eye and ocular adnexae, representing up to 55% of all orbital tumors [26] and have been successfully studied with ^{67}Ga-C imaging, MALT lymphomas of the conjunctiva have been rarely studied with ^{67}Ga-C [1]. These studies are based on small numbers and heterogenous groups of patients [23-25, 27, 28]. ^{67}Ga-C uptake is seen only in avid and viable lymphoma tissue [28]. ^{67}Ga-C scintigraphy has been successfully used for the differentiation of gastric MALT lymphomas [24, 25], however, the mechanism of the uptake of ^{67}Ga-C in MALT lymphoma is not clear [23-25, 28].

The ^{67}Ga-C scintigraphy has an important role in defining complete remission after treatment and therefore in planning subsequent treatment [29]. Following treatment, ^{67}Ga-C scintigraphy has a clinical impact when radiological abnormalities persist because it can either avoid unnecessary complementary treatment or confirm the need to change treatment modalities [30]. It has been reported that ^{67}Ga-C is superior to CT scan and equivalent to MRI in detecting true negative patients during restaging (specificity: 98%, 45% and 92%, respectively) [29]. Conventional diagnostic radiology and CT are generally unable to differentiate tumor tissue from fibrosis. However, ^{67}Ga-C scan and MRI can potentially differentiate residual active tumor tissue from fibrosis [31]. Especially in lymphoma patients, the ^{67}Ga-C scan remains the imaging technique for monitoring and differentiating the eventual active residual tumor. MRI could probably be considered a second choice technique to be used only in selected cases such as with intraabdominal lesions because of its lower specificity as opposed to the ^{67}Ga-C scan, in evaluating potentially active residual disease [29-31].

Treatment

Although different types of treatment have been employed for patients with local conjuctival MALT lymphomas, surgery is considered as the first choice [4]. Because these lesions are usually indolent and localised (stage I), radiotherapy is also applied [1]. Carefully planned radiotherapy with lens shielding is an effective and safe method in the management of conjunctival MALT lymphomas [5, 10, 18, 32, 33]. The optimal dose for obtaining a local tumor control with minimal complications remains unclear. Complications are more releated to the technique than to the dose. Doses of 30-35 Gy are recommended for conjunctival lymphomas [10, 33]. Due to lense sensitivity characteristic radiation-induced cataract may appear, especially when lens shielding is absent. Dry eye and corneal damage may also result after radiation. Radiation-induced retinopathy is usually a complication of doses higher than 45 Gy, although even smaller doses of 30-40 Gy have been reported to induce radiation retinotherapy. Thus, long term follow-up after radiation treatment is necessary [10]. Radiotherapy treatment planning must be individualized, based upon the extent of the disease assessed by both clinical examination and imaging modalities [10].

Combined radiotherapy with chemotherapy have been applied as these tumors have the potential of relapsing locally or rarely systematically or if the patient has a systemic lymphoma [4]. In cases of low-grade MALT lymphomas of conjunctival origin, aggressive chemotherapy is not justified.

Other treatment options include excisional biopsy, cryotherapy and local interferon injections [10, 19, 34, 35]. Follow-up without radiation is an option for patients with conjuctival MALT lymphoma after excisional biopsy since many patients show spontaneous regression of the tumour after excisional biopsy [1]. Our patient was free from symptoms after 12 months follow-up.

Most MALT lymphomas of the orbit are localized at the time of diagnosis and extraorbital relapse occurs only in 10%-20% of the patients, after treatment [1, 5, 6, 11, 32]. The contralateral eye is a potential site of relapse. Local and systemic recurrence of MALT lymphomas occur within 3 months to 10 years, after the first treatment, thus a long-term follow-up period with detailed clinical examination is required [1, 10, 15, 36, 37].

In conclusion, conjunctival MALT lymphoma is a rare cause of unilateral red eye. ^{67}Ga-C scintigraphy is important to support the diagnosis treatment and follow-up of these patients since recurrence may occur up to 10 years after the initial diagnosis.

Bibliography

1. Matsuo T, Yoshino T. Long-term-follow up results of observation or radiation for conjunctival lymphoma. *Ophtalmology* 2004; 111: 1233-1237.
2. Shields CL, Shields JA. Tumors of the conjunctiva and cornea. *Surv Ophthalmol* 2004; 49: 3-24.
3. Isaacson P, Wright DH. Extranodal malignant lymphoma arising from mucosa-associated lymphoid tissue. *Cancer* 1984; 53: 2515-2524.
4. Tiemann M, Häring S, Heidemann M et al. Mucosa-associated lymphoid tissue lymphoma in the conjunctiva of a child. *Virchows Arch* 2004; 444: 198-201.
5. Nedeljkov-Jancic R, Mihaljevic B, Bakrac M et al. Mucosa-associated lymphoid tissue lymphoma of the lacrymal gland-a case report. *Srp Arh Celok Lek* 2005; 133: 272-275.
6. Ling Y, Yeou-Ping T, Phil Yeong-Fong C et al. Combination of an adult inclusion conjunctivitis and mucosa associated lymphoid tissue (MALT) lymphoma in a young adult. *Cornea* 2004; 23: 71-75.
7. Knowles DM, Jakobiec FA. Orbital lymphoid neoplasms. A clinicopathologic study of 60 patients. *Cancer* 1980; 46: 576-589.
8. Au WY, Gascoyne RD, Le N et al. Incidence of second neoplasms in patients with MALT lymphoma: no increase in risk above the background population. *Ann Oncol* 1999; 10: 317-321.
9. Shields CL, Shields JA, Carvalho C et al. Conjunctival lymphoid tumours. Clinical analysis of 117 cases and relationship to systemic lymphoma. *Ophthalmology* 2001; 108: 979-984.
10. Xicoy B, Ribera JM, Arellano A et al. Effectiveness of local radiotherapy in primary extranodal marginal zone B-cell lymphoma of MALT or MALT lymphoma of conjunctiva: study of four cases. *Leuk Lymp* 2002; 43: 1975-1977.
11. Minasian MC, Sharma A, Richman PI et al. Conjunctival MALT lymphoma: an unusual cause of red eye. *Postgrag Med J* 1999; 75: 423-424.
12. Ramulu P, Iliff NT, Green WR et al. Asymptomatic conjunctival mucosa-associated lymphoid tissue-type lymphoma with presumed intraocular involvement. *Cornea* 2007; 26: 484-486.
13. Yu CS, Chiu SI, Ng CS et al. Localized conjunctival mucosa-associated lymphoid tissue (MALT) lymphoma is amenable to local chemotherapy. *Int Ophthalmol* 2007; Jun 23: (electronic only)
14. World Health Organisation (1999) Classification of neoplastic diseases of hematopoietic and lymphoid tissues: report of the clinical advisory committee meeting-airlie house, Virginia, November, *J Clin Oncol* 1997; 17: 3835-3849.
15. Ullrich A, Fischbach W, Blettner M. Incidence of gastric B-cell lymphomas: a population-based study in Germany. *Ann Oncol* 2002; 13: 1120-1127.
16. Lee DH, Sohn HW, Park SH et al. Bilateral conjunctival mucosa-associated lymphoid tissue lymphoma misdiagnosed as allergic conjunctivitis. *Cornea* 2001; 20: 427-429.
17. Mamalis N, Mackman G, Holds JB et al. Simultaneous bilateral conjunctival and orbital lymphoma presenting as a conjunctival lesion. *Ophtalmic Surg* 1988; 19: 662-663.
18. Cauvain A, Delmer A, Godeau MJ et al. MALT (Mucosal Associated Lymphoid Tissue) lymphoma of the palpebral conjunctica. *Ann Dermal Venerol* 2006; 133: 168-170.
19. Wotherspoon AC, Dogan A, Du MQ. Mucosa-associated lymphoid tissue lymphoma. *Curr Opin Hematol* 2002; 9: 50-55.
20. Amstutz CA, Michel S, Thiel MA. Follicular conjunctivitis caused by a mantle cell lymphoma. *Klin Monatsbl Augenheilkd* 2004; 221: 398-400.
21. Vose JM, Bierman PJ, Anderson JR et al. Single-photon emission computed tomography gallium imaging versus computed tomography: predictive value in patients undergoing high-dose chemotherapy and autologous stem-cell transplantation for non-Hodgkin's lymphoma. *J Clin Oncol* 1996; 14: 2473-2479.
22. Khoury J, Nassrala S, Loberant N et al. Gamut: unilateral orbital uptake on ^{67}Ga scintigraphy. *Sem Nucl Med* 2003; 33: 331-333.
23. Hsu CH, Sun SS, Kao CH et al. Differentiation of low grade gastric MALT lymphoma and high grade gastric MALT lymphoma: the clinical value of ^{67}Ga citrate scintigraphy-a pilot study. *Cancer Invest* 2002; 20: 939-943.
24. Li S, Kurtaran A, Li M et al. ^{111}In-DOTA-dPhe1-Tyr3-octretide, ^{111}In-DOTA-lantreotide and ^{67}Ga citrate scintigraphy for visualisation of extranodal marginal zone B-cell lymphoma of the MALT type: a comperative study. *Eur J Nucl Med Mol Imaging* 2003; 30: 1087-1095.
25. Ben-Haim S, Bar-Shalom R, Israel O et al. Utility of gallium-67 scintigraphy in low grade non-Hodgkin's lymphoma. *J Clin Oncol* 1996; 14: 1936-1942.
26. Margo CE, Mulla ZD. Malignant tumors of the orbit. Analysis of the Florida Cancer Registry. *Ophthalmology* 1998; 105: 185-190.
27. Mansberg R, Wadhwa SS, Mansberg V. ^{201}Tl and ^{67}Ga scintigraphy in non-Hodgkin's Lymphoma. *Clin Nucl Med* 1999; 24: 239-242.
28. Gasparini M, Bombardieri E, Castellani M et al. Gallium-67 scintigraphy evaluation of therapy in non-Hodgkin's lymphoma. *J Nucl Med* 1998; 39: 1586-1590.
29. Devizzi L, Maffioli L, Benfante V et al. Comparison of gallium scan, computed tomography, and magnetic resonance in patients with mediastinal Hodgkin's disease. *Ann Oncol* 1997; 8: 53-56.
30. Delcambre C, Reman O, Henry-Amar M et al. Clinical relevance of gallium-67 scintigraphy in lymphoma before and after therapy. *Eur J Nucl Med* 2000; 27: 176-184.
31. Zinzani PL, Zompatori M, Bendandi M et al. Monitoring bulky mediastinal disease with gallium-67, CT-scan and magnetic resonance imaging in Hodgkin's disease and high-grade non-Hodgkin's lymphoma. *Leuk Lymphoma* 1996; 22: 131-135.
32. Suh CO, Shim SJ, Lee SW et al. Orbital marginal zone B-cell lymphoma of MALT: Radiotherapy results and clinical behavior. *Int J Radiat Oncol Biol Phys* 2006; 65: 228-233.
33. Monzen Y, Hasebe H. Radiotherapy for localized orbital mucosa-associated lymphoid tissue lymphoma. *Ophthalmologica* 2007; 221: 233-237.
34. Fuentes-Paez G, Saornil MA, Herreras JM et al. CHARGE Association, Hyper-Immunoglobulin M Syndrome, and Conjunctival MALT lymphoma. *Cornea* 2007; 26: 864-867.
35. Lucas RS, Mortimore R, Sullivan TJ et al. Interferon treatment of childhood conjunctival lymphoma. *Br J Ophthalmol* 2003; 87: 1191.
36. Hardman-Lea S, Kerr-Muir M, Wotherspoon AC et al. Mucosal-associated lymphoid tissue lymphoma of the conjunctiva. *Arch Ophthalmol* 1994; 112: 1207-1212.
37. Meunier J, Lumbroso-Le Rouic L, Vincent-Salomon A et al. Ophthalmologic and intraocular Non Hodgkin's lymphoma: A large single center study of initial characteristics, natural history, and prognostic factors. *Hematol Oncol* 2004; 22: 143-158.