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

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. MALT lymphomas 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 67Ga-C citrate 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 conjunctival MALT disease. A case of ours gives reason for further discussion. Treatment and follow-up of MALT lymphoma is described.

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

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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. MALT lymphomas 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 mucopurulent secretion or swelling. At the excisional biopsy of the conjunctival lesions, as much as possible was removed. Histopathology and immunohistochemical studies revealed sheets of lymphoid cells with slightly indented nuclei and a sparse cytoplasm, confirming the...
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 \(\gamma\)-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 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-
habit 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 fornical 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 scintigraphy 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 conjunctival MALT lymphomas for the detection of local or systemic disease, for staging, and for the assessment 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 conjunctival MALT lymphomas, surgery is considered as the first choice [4]. Because these lesions are usually indolent and localized (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 related to the technique than to the dose. Doses of 30-35 Gy are recommended for conjunctival lymphomas [10, 33]. Due to dense 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 retinopathy. 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 conjunctival 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. 67Ga-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


