ABSTRACT

Purpose: To report nine cases of orbital lymphomas.

Methods: We reviewed the clinical records of nine patients diagnosed with orbital lymphoma and performed a literature search related to this condition.

Results: We present a series of five women and four males with orbital lymphoma involving the orbital region. In our cases, most patients presented concurrent extraorbital lymphoma when the orbital disease was first noticed (seven out of nine patients). We found three MALT lymphomas, two follicular lymphomas, two non-Hodgkin large B cell lymphomas, one low grade B cell lymphoma, and one mantle cell lymphoma. Eight patients were alive and one had died as a consequence of his lymphoma at the time this report was written.

Conclusions: An increase in the incidence of non-Hodgkin orbital lymphomas has been observed over the last three decades. The most common type in the orbital region is the MALT lymphoma. The clinical features observed in our series are similar to those reported in the literature. Since lymphomas are the most frequent malignant tumours in the orbit, usually with extraorbital involvement, and

RESUMEN

Objetivo: Describir nueve casos de linfomas orbitarios.

Métodos: Revisión de historias clínicas de nueve pacientes diagnosticados de linfoma orbitario y consulta de la bibliografía relacionada con esta patología.

Resultados: Se presenta una serie compuesta por cinco mujeres y cuatro varones con linfoma en la región orbitaria. En nuestros casos, la mayoría de los pacientes presentaron linfoma extraorbitario concurrente en el momento en el que el proceso orbitario fue detectado por primera vez (siete de los nueve pacientes). Tres de los pacientes presentaron linfoma MALT, dos linfomas foliculares, dos linfomas no Hodgkin de células B grandes, un linfoma de células B de bajo grado y un linfoma de células del manto. Ocho pacientes se mantienen vivos y uno ha fallecido a consecuencia de su linfoma en el momento de escribir este artículo.

Conclusiones: Se ha observado un incremento de la incidencia de los linfomas no Hodgkin orbitarios durante las últimas tres décadas. El tipo más común en la región orbitaria es el linfoma MALT. La forma
Lymphomas are the most frequent orbital malignant tumors. According to recent publications, these tumors account for 11% of all orbital tumors (1) and 55% of malign tumors (2). This high prevalence and the possibility of providing effective treatment for their healing increases the importance of these neoplasm for the ophthalmologist. In this article we present nine cases of orbitary lymphomas together with a bibliographic review related to this pathology.

**INTRODUCTION**

Lymphomas are the most frequent orbital malignant tumors. According to recent publications, these tumors account for 11% of all orbital tumors (1) and 55% of malign tumors (2). This high prevalence and the possibility of providing effective treatment for their healing increases the importance of these neoplasm for the ophthalmologist. In this article we present nine cases of orbitary lymphomas together with a bibliographic review related to this pathology.

**SUBJECTS, MATERIAL AND METHODS**

Nine cases of orbitary lymphomas are presented, comprising five females and four males. All were attended in the Ophthalmology Service of our hospital between July 2002 and September 2006. The bibliographic information was obtained by searching medical literature, mainly the PubMed database (National Library of Medicine, USA) for analyzing and verifying our findings. The clinical characteristics and evolution of the cases of this series are described below.

**RESULTS**

**Case 1**

Female, aged 69, who referred right palpebral ptosis since September 2002 without any other symptoms (fig. 1A). She came to the internal medicine and neurology practice between 15 and 20 days after its appearance. A CAT scan performed one month later revealed an injury of approximately 1.5 x 1.8 cm in the central area of the upper right eyelid (fig. 1B). At that point she was referred to our Ophthalmology Service. The NMR (fig. 1C) showed an injury of the same size located behind the septum and above the eyelid elevator muscle. When surgically accessing the injury, it was noticed that it infiltrated the tendon of the elevator muscle and it was removed. The anatomic diagnostic was of MALT lymphoma. The patient was referred to the Hematology Service where the extension study was carried out which determined a single location in the right orbit. Radiotherapy treatment was indicated and at present the patient is stable without relapses.

**Case 2**

Female, aged 60, who was admitted to the internal medicine service in November 2004 for assessing upper right eyelid tumefaction and multiple cervical adenopathies which had increased in size in the past seven months, with progressive appearance of asthenia, anorexia, weight loss and night sweating. A medullar and ganglionary biopsy allowed for the diagnosis of non-Hodgkin mantle cell lymphoma, stage IVB. The patient was treated with chemotherapy which produced a partial remission. In August 2005 a CAT scan was carried out which revealed a relapse of the palpebral tumor (fig. 2). Accordingly, she was referred to our service in September 2005. Due to the rapid growth of the tumor, an additional chemotherapy and immune therapy was initiated which produced a rapid response. In March 2006 she exhibited a new relapse.
again treated with chemotherapy with a discrete response. At present the development process of the tumor continues.

Case 3

Male, aged 50, who was attended at another hospital for a discrete exophthalmos in the left eye which started one month earlier (fig. 3A). His relevant history included infra-orbital and supra-orbital masses which moved with palpation, with an exophthalmos of about 3 mm vis-à-vis the other eye. The rest of the ophthalmological exploration was normal. A previous CAT scan carried out in June 2002 revealed a left retro-ocular mass classified as a probable inflammatory pseudo-tumor. An orbitary NMR carried out in June 2002 (fig. 3B) gave rise to the first diagnostic possibility of an orbitary lymphoma or metastasis and accordingly the patient was referred to our Ophthalmology Service in July 2002, where a PAAF was carried out, the result of which was compatible with a non-Hodgkin lymphoma. Subsequently, a biopsy confirmed the diagnostic of low positive B lymphoma for CD20 and Bcl-2 (without specifying the type). The extension study revealed the absence of additional tumor locations. Radiotherapy was indicated. To this date the patient continues in full remission.

Case 4

Male, aged 53, who attended our ophthalmology practice in April 2004 due to a soft, compressible
bulge of approximately 1 cm diameter in the medial portion of the right upper eyelid (fig. 4). The patient history did not include relevant data. One month later the tumoration was removed and its consistency was semi-soft, with pseudo-capsula and multiple lobes, extending through the internal wall of the orbits up to the apex without involving bone tissue. The anatomic and pathological diagnostic was of MALT lymphoma. The patient was referred to Hematology where a possible cervical involvement was detected due to PET. Treatment was established with radiotherapy in the orbit and neck. To date, the patient continues in remission.

Case 5

Male, aged 71, diagnosed in October 2001 with nasopharyngeal large B-cell lymphoma with involvement of the middle ear, right maxillary sinus, right cervical adenopathies and possible pleural and bone marrow involvement as per flow cytometry. Loco-regional chemo- and radiotherapy treatment was initiated, with a full response. In March 2004, the patient exhibited a right inferior eye lid edema, which two months later made it difficult for the patient to open the eye (fig. 5A). The patient did not exhibit relevant symptoms. An orbital CAT scan carried out in May 2004 revealed a soft tissue density mass in the lower internal area of the right orbit (fig. 5B) which, by means of a PAAF, confirmed the suspected lymphoma relapse. The extension study revealed infiltration in the bone marrow. The patient received systemic chemo- and radiotherapy on the right orbit. Two years later, the patient exhibited a new relapse in the facial region (an adenopathy below the right side of the chin) for which he was given radiotherapy treatment. At present, he remains without symptoms.

Case 6

Female, aged 55, who visited our Ophthalmology Service in January 2002 for a tumoration in the left lachrymal fossa which produced palpebral ptosis and inferior displacement of the globe (fig. 6A). An orbital CAT confirmed the existence of a mass in the left lachrymal fossa which was removed in February 2002. The diagnostic was of low degree lymphoma B. The patient did not return until September 2003 exhibiting a left pre-auricular tumoration (fig. 6B) for which a biopsy confirmed the diagnostic of follicular lymphoma. An extension study determined stage 4. Chemotherapy treatment was initiated and the patient is at present free of symptoms.
Case 7

Female, aged 64, diagnosed in May 2002 with pulmonary MALT lymphoma after a trans-bronchial biopsy and an extension study which revealed a minimum infiltration in the bone marrow with flow cytometry. She received chemotherapy treatment with partial response. In October 2002 progression at the pulmonary level and infiltration of the bone marrow was detected. An additional chemotherapy and immune therapy treatment was prescribed, which gave a partial response. In February 2006 a new extension study was performed which revealed a mass in the medium straight muscle of the right eye (fig. 7B), for which she was referred to our Ophthalmology practice. A PAAF did not allow for a diagnostic and accordingly the tumor was biopsied. During the intervention a mass compatible with lymphoma was evidenced in the medium muscle. The diagnosis of the biopsy was of MALT lymphoma. Chemotherapy treatment was established with partial response. At present, the patient remains stable.

Case 8

Male, aged 41, without relevant history. In September 2004 he was attended in our ophthalmology practice for pain in the right jawbone which irradiated towards the orbit, with palpbral ptosis and 4mm exophthalmos in the RE (fig. 8A). A NMR revealed a tumoration in the right cavernous sinus which produced a syndrome of the orbitary apex (fig. 8B). As a biopsy was not feasible, a systemic study was carried out which revealed a cecal tumor which, when biopsied, was diagnosed as large B-cell lymphoma. Therefore the mass in the cavernous sinus was taken to be a metastasis of this tumor. The patient’s condition involved unfavorably in a short time with peritoneal metastasis, ascitis and pleural hemorrhage, with demise occurring three weeks after the first visit.

Case 9

Female, aged 78, who attended our practice in August 2006 due to exophthalmos and pain in the right eye which began approximately 1 year earlier (fig. 9A). An orbital CAT (fig. 9B) revealed the
existence of a solid, contrast-capturing dense mass occupying the lower external quadrant of the right orbit. A PAAF performed in September 2006 was compatible with non-Hodgkin lymphoma. Accordingly, the patient was referred to hematology. A biopsy of a right supra-clavicular adenopathy and an extension study confirmed the diagnostic of follicular lymphoma grade 2 stage 4. Chemotherapy and immune therapy treatment was established leading to a remission of the condition. At present, the patient remains stable and free of symptoms.

DISCUSSION

The lymphomas affecting the conjunctiva, lachrymal gland, orbit and eyelids are usually low degree tumors (2). Recent studies show that lymphomas represent approximately 11% of all tumors of these structures and 55% of malign tumors in these areas (1,2). According to our own statistics, lymphomas constitute one of the most frequent orbital tumors, accounting for approximately 15%.

Published series show that the large majority of orbital lymphomas (91%) (2) begin with ophthalmological symptoms consisting of pink-colored conjunctival masses or conjunctival hyperemia in 32% of cases, exophthalmos in 27%, palpable or orbital mass in 19%, visual acuity reduction and ptosis in 6% and diplopia in 2% (2). In our series, the most frequent clinical presentation was palpebral or orbital mass (four cases) followed by exophthalmos (two cases), palpebral ptosis (one case), ptosis with exophthalmos (one case) and ptosis with palpebral mass (one case). In spite of the frequency with which the conjunctival seems to be affected (32% of cases) (2), we did not observe that in any of our patients.

The mean interval between the onset of symptoms and the diagnostic date is 4 to 6 months (2-5). In our series we observed that in most cases the interval was between one and two months. In one case (case 8), considering the aggressive evolution of the neoplasia, the diagnostic was established
approximately 15 days after the first symptoms. In two cases (cases 2 and 9), due to the patient’s delay in visiting the practice, the diagnostic was made with an interval of over one year since the appearance of the symptoms. In one case (case 7) we were unable to determine the time which elapsed between the appearance of the symptoms and the diagnostic because the initial lymphoma diagnostic had been made six years before he attended our Ophthalmology Service.

Lymphoid proliferations in the ocular region can occur at any age, but more frequently in the fifth or seventh decade of life (2-9) and involve 1.75 females for every male (4-6,10). In our cases the mean age was of 60 years at diagnostic time, with the youngest patient being 41 and the oldest 78. These numbers match the data published in literature. Our statistics comprise 5 females and 4 males, which reflects a similar tendency to that shown in larger series.

Approximately 50% of ocular region lymphomas are located in the lacrimal gland and other intra-orbital areas, particularly the anterior-superior orbit (2,9,11,12). The conjunctiva is affected in a third of patients and in 96% of cases it involves a low grade tumor (2). Palpebral involvement varies in different series between 0% and 44%, with the mean value of published studies being close to 10% (2). In approximately 10-17% of cases the lymphoma appears bilaterally (3-5), while it appears simultaneously in both orbits in approximately 80% of bilateral cases and subsequently in 20% of cases (13). Other publications broaden the bilaterality percentage ranges from 7 to 24% of cases (2,9).

Between 20 and 40% of patients have extra-orbital lymphoma histories when diagnosing orbital lymphoma (4,5,14). The lymphomatous diffuse disease is found mainly in patients with high-degree non-Hodgkin lymphoma. Twenty-six percent of low degree lymphoma patients reach stage 4 while 56% of patients with high degree lymphoma reach said stage (2,9).

In our study the lymphoma was localized inside the orbit in 3 cases (in the lower external, inferior and medial areas) in the lacrimal fossa in 1 case, sharing eyelid and part of the orbit in 3 cases, only in the eyelid in 1 case and in the cavernous sinus in 1 case. We did not find conjunctival involvement or bilaterality in any case. In 7 out of the 9 cases there was a lymphoma with extra-orbital location. In 1 case (case 6) we found an extra-orbital disease in the follow-up because the patient delayed treatment and follow-up visits. Even though we have very few cases to consider this as significant, our series exhibits an occurrence of extra-orbital lymphoma greater than expected.

In their 112-patient statistics on ocular region lymphomas, Coupland et al (4) found 64% of B-cell lymphoma in the extra nodal marginal area (MALT), 10% of centre follicular lymphomas, 9% of large diffuse B-cell lymphomas, 6% of plasmocytomes, and 5% lymphplasmocytic lymphoma. On the other hand, in a series of 73 ocular region lymphoma cases, McKelvie et al (15) found 63% of MALT lymphomas, 17% of follicular lymphomas, 11% of large diffuse B-cell lymphomas, 3% of mantle cell lymphomas, 3% of chronic lymphocytic leukemia of B cells/small lymphocytic lymphoma, 1.5% of peripheral T-cell lymphomas and 1.5% of Natural killer cell lymphoma.

Nearly all studies agree in that the most common type of non-Hodgkin orbital and ocular region lymphoma is the MALT (4,15,16). In our statistics we found 3 MALT lymphomas, one low degree B lymph-
homa, two large B-cell non-Hodgkin lymphomas, 2 follicular lymphomas and one mantle lymphoma, which matches the results of other published studies.

Recent publications refer to the possibility of association between MALT lymphomas with infection by Chlamydia Psittachi (2,16,17). This means that, even though radiotherapy was the standard treatment for localized ophthalmological lymphomas, we are witnessing the emergence of other options with likely therapeutic value such as antibiotic therapy for Psittaci. In addition, CD20 monoclonal antibody therapy can constitute a promising alternative for external irradiation and its potential toxicity (2).

In general terms, the findings of our series are very similar to those described in literature. It is important for the ophthalmologist to be familiar with this type or orbitary pathology because on many occasions we are the first specialists to examine the patients who suffer it. Early detection is very important because it is a potentially curable disease. A comprehensive medical history is particularly relevant because, when ophthalmological symptoms appear, the presence of extra-orbitary involvement is quite frequent. Recent studies have observed an increased prevalence of orbitary non-Hodgkin lymphomas and therefore it is important to identify this entity to avoid it going unnoticed (18).

REFERENCES