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LOCALIZED ORBITAL LYMPHOMA

PIERO GALIENI,* ENNIO POLITO,° ANTONIO LECCISOTTI,° GIUSEPPE MAROTTA,* STEFANO LASI,#
CATIA BIGAZZI,* ALESSANDRO BUCALOSSI,* GIAMPIERO FREZZA,@ FRANCESCO LAURIA*

**Divisione e Cattedra di Ematologia; °Istituto di Clinica Oculistica; #Istituto di Anatomia Patologica, Università degli Studi di Siena; @Istituto di Radioterapia, Università degli Studi di Bologna, Italy*

ABSTRACT

Background and Objective. Localized orbital non Hodgkin's lymphoma is a rare event which has not been reported much in the literature. The aim of this study was to evaluate the clinical features, histology, treatment and clinical outcome of patients with localized orbital lymphoma.

Methods and Results. Fifteen patients with stage I-E orbital lymphoma diagnosed between 1975 and 1992 were reviewed. Diagnosis was formulated from 3-84 (median 23) months after the appearance of symptoms. Eight patients were males and 7 were females; median age was 55 years. The lacrimal gland was involved in 8 cases, the orbit in 7. Bilateral orbital localization was observed in only one patient. All cases were diagnosed as low-grade MALT lymphoma. Chemotherapy was administered in 7 patients, radiotherapy was employed in 7 and surgical excision was performed in the remaining case. Almost all the patients (14/15; 93%) achieved a complete remission (CR). Local relapse (LR) was observed in 3 cases but disease spread was never recorded.

Interpretation and Conclusions. Correct histological diagnosis and careful staging are very important for the treatment and outcome of localized low-grade orbital lymphoma. These patients show a very good prognosis and radiation therapy alone is very effective in the treatment of this malignancy.

Key words: orbital lymphoma, clinical outcome, chemotherapy, radiotherapy

Orbital lymphoma is a rare tumor which comprises about 10% of all orbital neoplasms.[1] Its incidence among all extranodal lymphomas has not yet been assessed exactly.[1] It has been reported that orbital localization amounts to two-thirds of all cases of ocular adnexal lymphomas in which lacrimal gland and orbital soft tissue involvement are almost equal.[2]

This group of lymphomas comprises mostly low-grade B-cell lesions,[1] and Isaacson in particular has underlined that this type of lymphoma seems to be of MALT origin.[3]

Clinical presentation is frequently characterized by slow painless onset of a mass scarcely associated with inflammatory or functional signs, which on computed tomography appears to be molded to adjacent normal orbital structures.[4] Although in most patients the disease appears to be indolent and localized, it may also represent the extranodal localization of a disseminated form.[1,4]

The management, long-term survival and outcome of the disease are correlated to histology and extension, as demonstrated by the poor clinical course observed in patients with a high-grade histological pattern and stage III-IV.[2,5]

The aim of our study was to evaluate the clinicopathological aspects, treatment, and outcome of patients presenting with a localized form of orbital lymphoma.

Patients and Methods

The records of 15 patients with orbital lymphoma stage I-E diagnosed between June 1975 and March 1992 were carefully reviewed.

Diagnosis and staging of the disease were carried out, respectively, at the Orbital and Adnexal Service (Department of Ophthalmology and Neurosurgery) and Department of Hematology of the University of Siena.

Histological diagnosis, obtained only with an incisional biopsy in all cases, was formulated on hematoxylin-eosin and Giemsa-stained specimens, supported by immunohistochemical analysis, and recategorized according to the criteria established by the REAL classification.[6]

Diagnosis was followed by staging procedures that included complete blood count, chemical and physical examination, chest x-ray or CAT scan, abdominal ultrasonography and CAT scan, gastrointestinal contrast X-ray or gastroduodenoscopy, ENT examination plus biopsy where necessary, and bone marrow biopsy.

The therapeutic approach varied and was closely connected with the time of diagnosis: 7 patients were treated with chemotherapy (COP-CHOP regimens), 1 with surgery, and 7 (diagnosed after 1988) with radiotherapy. Radiotherapy was applied through convergent oblique 6 MV γ-photon or χ-photon fields to the entire content of the orbital cavity. Wedge-

Correspondence: Dott. Piero Galieni, Divisione di Ematologia, Ospedale "A Sclavo", via Tufi 1, 53100 Siena, Italy. Tel. international +39.577.586745. Fax. international +39.577.586185.
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Table 1. Clinical characteristics of 15 patients with localized orbital lymphoma.

Number	15
Males/females	8 / 7
Median age (range) (yrs)	55 (28-82)
Mean duration of symptoms before diagnosis (months)	23
Localization:	
orbit	7
lacrimal gland	8
Histology:	
MALT	15
Therapy:	
radiotherapy	7
chemotherapy	7
surgery	1
Number of patients still alive	14

shaped filters were always employed in order to homogenize dose distribution, and the fields were placed at such an angle that irradiation of the controlateral orbital cavity was contained within 5%. Daily fractions of 180-200 cGy were administered, with the total dose ranging between 3600-4000 cGy. The lenses were never shielded and the patients were warned about the possibility of cataracts developing.

Complete regression of the tumor mass after treatment, as evaluated by an instrumental exam (CAT or NMR), was considered complete remission (CR). Partial remission (PR) consisted of incomplete disappearance of the orbital mass.

Survival curves were estimated by the Kaplan and Meier method.[7]

Results

The clinical characteristics of the 15 patients considered in this study are reported in Table 1.

The median interval between initial symptoms and diagnosis was 23 (range 3-84) months, and the symptoms most frequently observed were swelling, alone or associated to exophthalmus, lacrimation, burning and diplopia. The lacrimal gland was involved in 8 cases while the orbit was involved in the remaining 7. In almost all cases the tumor was unilateral. One case presented concomitant gastric involvement. In all cases the histological diagnosis was marginal zone, low-grade B-cell lymphoma.

The values of LDH and β2 microglobulin, the latter being determined when that laboratory procedure became available, always fell within the normal ranges. A serum monoclonal component was never found.

Seven patients were treated with radiotherapy and all of them achieved a CR, with a median duration of 51 (range 33-93) months, which is still maintained in all cases. Seven patients were treated with 6-8 courses of COP (3) or CHOP (4) chemotherapy and 6 of them achieved a CR. Two patients (1 in PR and 1 in CR) experienced a local relapse 48 and 84 months, respectively, after completion of

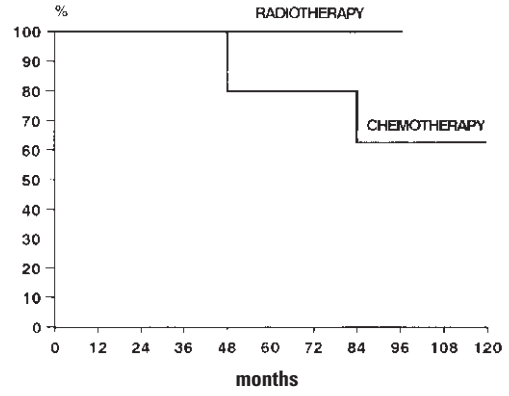

Figure 1. Actuarial freedom from local relapse curve of the patients with localized orbital lymphoma treated with chemotherapy or radiotherapy.

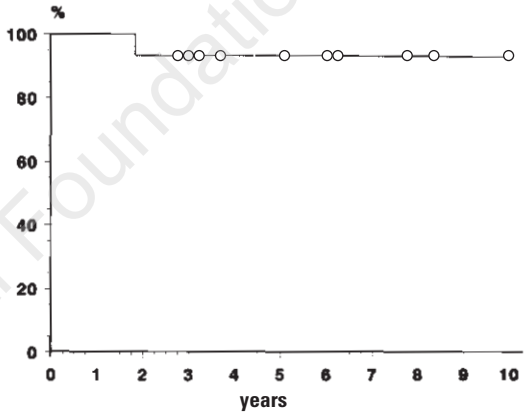

Figure 2. Kaplan-Meier survival curve of 15 patients with localized orbital lymphoma.

chemotherapy (Figure 1). Both were treated with local irradiation (3600 cCy) and achieved CR. In the last patient treated with surgerical excision of the orbital mass, a local relapse occurred after 5 years. Treated subsequently with radiotherapy (5000 cCy), the patient achieved a CR which lasted 3 years. Thereafter the patient experienced a second local relapse and was again treated with radiotherapy (3000 cCy), but 15 months later developed cheratitis which led to bulbar enucleation.

At the present time, all the patients are alive and in CR, except one who died because of respiratory failure (Figure 2).

Discussion

In the present study we evaluated the clinicopathologic presentation, clinical course and results of treatment in a relatively large series of patients with a true localized orbital lymphoma observed for a mean period of about 7 (range 2.5-15) years.

Our results are in agreement with those described by Knowles:[2] e.g. male to female ratio close to one, median age 55 (range 28-82) years, approximately equal right and left orbital involvement, and the rare incidence of bilateral localization among our patients occurring in only one case.

Very often the slow appearance of a palpable mass in the orbit was the initial and the only sign of onset of the disease, as witnessed by the long time interval between symptoms and diagnosis, which lasted 23 (range 3 to 84) months. Despite this non negligible delay before diagnosis, these lymphomas remain confined to the orbit probably because they share features of homing to their tissue of origin,[8] or because there are no lymphatic drainage channels in the orbit and this prevents the dissemination of the neoplastic cells.[9] It has also been suggested that orbital lymphoma may be preceded by a reactive or inflammatory lesion before becoming neoplastic.[10-12] However, this hypothesis seems unlikely since no other disorder preceded the onset of lymphomas in these patients.

In keeping with the localized form of the disease and its low-grade histology, LDH and β2 microglobulin levels were always normal, as reported by other investigators.[13]

The histological diagnosis was reviewed and in all cases was low-grade mucosa-associated lymphoid tumor (MALT). This is in agreement with the findings reported by other investigators, suggesting further that localized lymphomas in extranodal sites are of MALT origin in almost all cases.[3,8] In fact, the contemporary involvement of the orbit and the stomach in one of our cases provides evidence that MALT lymphomas involve mucosal sites rather than lymph nodes.[8] However, in their work on localized orbital lymphoma, other authors reported the presence of intermediate-grade histology in about 30% of cases and some rare high grade forms.[14,15] This could be mainly due to the fact that many low-grade MALT lymphomas of the REAL classification were categorized as intermediate grade when histologic diagnosis and subtype were based on the working formulation for non-Hodgkin's lymphoma.[16] Furthermore, these reports[14,15] also contain ocular adnexal localizations (conjunctiva and eyelid) and some cases of diffuse disease that are not included here. Lastly, while it is very easy to find low-grade MALT lymphoma in this form of disease, other histologic patterns cannot be excluded.

Therapeutic results were impressive and both radiotherapy and chemotherapy may be considered effective in the treatment of these lymphomas. In fact, almost all patients achieved CR and all of them are still in CR, except for two who relapsed after chemotherapy (1 after COP and 1 after CHOP). These two patients were retreated with radiotherapy and both experienced a complete regression of the disease that still persists to date. These data confirm the effectiveness of radiotherapy in the management of low-grade orbital lymphomas both as primary treatment[5,14,15] and in the case of local relapse after chemotherapy. Moreover, the absence of important side effects such as cataracts, not yet observed in this series of patients treated at a dosage of 3600-4000 cGy, further confirms the primary role of radiotherapy in the treatment of this disease.[5,14,15,17] The absence of this typical side effect can only be partially explained by the exclusive use of megavoltage therapy in all cases together with the relatively young age of the patients treated (median 53; range 28-63 years). It is well known that the process of cataract development is also related to age and linked to many factors.[18] Besides, the median follow-up of the cases treated with radiotherapy is not yet long enough to exclude the possibility of cataract development.[14]

Several studies reported a high incidence of systemic progression of the lymphoma after successful primary local control with radiotherapy.[2,19,20] The absence of disease diffusion, never observed in this study either in the cases treated with radiotherapy or in those given chemotherapy, could be due to the indolence and the tendency of low-grade MALT lymphoma to remain localized, as well as to the fact that these lymphomas were truly localized diseases.

In conclusion, correct histological diagnosis and careful staging are very important for the treatment and outcome of localized low-grade orbital lymphoma, since both chemotherapy and mainly local radiotherapy at a dosage of 3600-4000 cGy over the entire content of the orbital cavity yield excellent results, long-lasting survival and few side effects in the short term. Further follow-up is necessary in order to better evaluate the clinical course of the disease and the incidence of cataracts in patients treated with radiotherapy without lens shielding.

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