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Prognosis of orbital lymphoid hyperplasia

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Abstract ● Background: Orbital lymphoid hyperplasia can be associated with systemic non-Hodgkin lymphoma (NHL), even when polyclonal proliferation is found in the orbit. Although irradiation is recommended, some orbital lymphoid hyperplasias are treated by steroids (when inflammation is clinically presumed) or left untreated. ● Methods: The incidence of concurrent NHL and the incidence of future NHL after oral prednisone, radiotherapy, or no treatment were retrospectively evaluated in 33 cases of lymphoid hyperplasia (22 benign lymphoid hyperplasias, BLH, and 11 atypical lymphoid hyperplasias, ALH), after follow-up of 2–13 years. ● Results: NHL occurred in 12 of 33 cases (36.4%). In seven patients it was concurrent; in five patients it occurred 2–6 years later. In the actuarial curve, at 5 years 55% of patients were free of lymphoma, at 10 years, 46%. NHL was more commonly observed when the lacrimal gland was involved (57% vs 21%; $P=0.03$). Of the 13 patients treated with oral steroids, 46% had complete response, 39% partial response, and 15% future NHL. Of the seven irradiated patients, five (71%) had complete response, two (29%) partial response, and none future NHL. Of the eight untreated patients, five (63%) had partial response and three (37%) future NHL. Irradiated lacrimal gland BLHs only achieved partial response, one having radiation-induced orbital inflammation. ● Conclusion: Because of a high risk of NHL, in all orbital lymphoid tumors systemic staging and follow-up are mandatory. The advised management is irradiation, except for Sjögren syndrome, an initially inflammatory lacrimal gland BLH, where a course of steroid is suggested before considering radiotherapy.

Introduction

Orbital lymphoid tumors represent a continuous spectrum of lymphoproliferative disease, generally subdivided into three grades: benign (or reactive) lymphoid hyperplasia (BLH), atypical lymphoid hyperplasia (ALH), also called indeterminate lymphoid proliferation, and malignant non-Hodgkin lymphoma (NHL) [5, 7, 12]. Clinical and radiological differentiation of benign from malignant forms is impossible [13, 24], and even their histological characterization is challenging, often requiring immunohistochemical and molecular genetic studies [22, 23]. One of the most striking features of orbital lymphoid tumors is the possible association with systemic malignant lymphomas, even when polyclonal proliferation is found in the orbit [13]. Therefore, it would appear that all lymphoid tumors should be regarded as true neoplasms and treated as such, i.e. they should undergo systemic staging and subsequently radio- and/or chemotherapy [5]. Nevertheless, one exception is represented by Sjögren syndrome, in which an initially au-

toimmune inflammation may become hypercellular and then evolve into a lymphoid tumor [6]. Then, some early lymphoid tumors of the lacrimal gland may benefit by systemic steroid treatment rather than irradiation. However, the correlation between treatment and prognosis of lymphoid hyperplasia has never been investigated.

The purpose of this study was to evaluate: (1) the incidence of concurrent and future NHL in patients with orbital lymphoid hyperplasia; (2) the incidence of future NHL in patients with orbital lymphoid hyperplasia after treatment with oral prednisone, radiotherapy, or simple incisional biopsy (untreated); (3) the difference in terms of prognosis in patients with lacrimal gland involvement.

Patients and methods

Charts of patients with orbital lymphoid hyperplasia seen in our department since 1975 were reviewed. Patients with a known or suspected diagnosis of systemic malignant lymphoma at referral were excluded, as well as bilateral cases and those involving conjunctival and eyelid localizations, since they have a different prognosis [13]. Patients with incomplete systemic staging were also excluded. Orbital diagnosis was obtained in all cases by examination of an incisional biopsy specimen by means of histological, immunohistochemical and molecular genetic techniques (polymerase chain reaction, PCR) [3, 22, 23]. In no case was fine-needle aspiration biopsy used for diagnosis. Slides of earlier patients were reviewed and studied by immunohistochemistry and PCR in blinded fashion.

Soon after the diagnosis of lymphoid hyperplasia, all patients had undergone systemic staging, consisting of physical examination, clinical lymph node evaluation, complete blood count, chest radiograph, abdominal ultrasonography, gastrointestinal contrast X-ray, bone marrow aspiration, and biopsy. Patients were re-examined after 6 months and then staged every year. Lymphomas were classified according to the Working Formulation [21]. Ultimately, 33 patients were included in the study (22 BLH and 11 ALH).

In the group of BLH, the disease was located in the lacrimal gland in 11 of 22 cases (50%), while in the ALH group lacrimal gland was involved in 3 of 11 cases (27%). In the whole series, lacrimal gland involvement was found, therefore, in 14 of 33 cases (42%).

Treatment consisted of oral steroids (prednisone, 80 mg per day, slowly tapered when a response was obtained) or external beam orbital radiotherapy (2000–2900 cGy). In recent years, when the concept of a potential neoplasm was recognized, radiotherapy was generally preferred to steroids. Some patients did not receive any treatment because they had minor symptoms and refused treatment or failed to attend for initial follow-up. Evidence of NHL was the endpoint of follow-up, which ranged from 2 to 13 years (mean 4.5 years). Of the 28 patients without NHL at the time of diagnosis, 13 were treated with oral prednisone, seven with irradiation (in two cases after unsuccessful steroid therapy) and eight received no treatment.

Results

Incidence of concurrent or future lymphoma

In the whole series, malignant lymphoma occurred in 12 of 33 cases (36.4%), with the same proportion found in each group: 4 of 11 cases in the ALH group and 8 of 22 cases in the BLH group. In 7 of 33 patients (21.2%) a systemic lymphoma was discovered at the time of the diagnosis of the orbital lesion (stage II, three patients; stage III, three patients; stage IV with high grade, one patient). In 2 of 33 patients (6%) a systemic lymphoma was diagnosed 4 and 5 years later (stage II and stage IV, respectively). In 3 of 33 patients (9%), an orbital NHL (stage I_E=I extranodal) occurred 2, 2 and 6 years later, in the same location as the primary tumor. All NHL were of a low grade, except for the one high-grade lesion mentioned.

NHL occurred in 8 of 14 patients (57%) with lacrimal gland location and in 4 of 19 patients (21%) with uninvolved lacrimal gland (χ^2=4.53, P=0.03).

The Kaplan-Meier actuarial curve [9] showed that 55% of patients were free of lymphoma after 5 years and 46% after 10 years (Fig. 1). The log-rank rest [15], comparing the separate curves of ALH and BLH, found no statistically significant difference.

Outcome in untreated patients (biopsy only)

Five patients with BLH received no treatment. Three patients with a small mass had no signs or symptoms after a partially excisional biopsy. In the remaining two cases (one with lacrimal gland involvement) stage I_E NHL occurred 2 and 6 years later.

Three patients with ALH received no treatment. As in the BLH group, two patients with a small mass had no

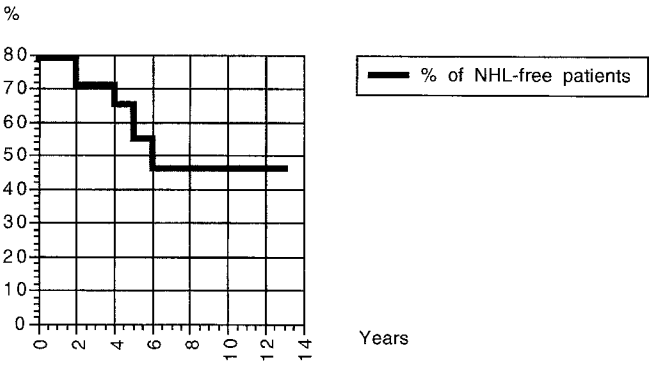

Fig. 1 Non-Hodgkin lymphoma (*NHL*)-free survival (Kaplan-Meier actuarial curve) in 33 patients with orbital lymphoid hyperplasia

Table 1 Outcome in eight untreated cases (partial excision) of orbital lymphoid hyperplasia (*ALH* atypical lymphoid hyperplasia, *BLH* benign lymphoid hyperplasia, *NHL* non-Hodgkin lymphoma)

	Complete response	Partial response	Future NHL
BLH (n=5)	0	3 (60%)	2 (40%)
Lacrimal gland (1)	0	0	1 (100%)
Non-lacrimal gland (4)	0	3 (67%)	1 (33%)
ALH (n=3, all non-lacrimal gland)	0	2 (67%)	1 (33%)
BLH+ALH (n=8)	0	5 (63%)	3 (37%)
Lacrimal gland (1)	0	0	1 (100%)
Non-lacrimal gland (7)	0	5 (71%)	2 (29%)

signs or symptoms after biopsy. In the remaining case, a stage IV NHL occurred 5 years later.

Data are summarized in Table 1.

Outcome after oral prednisone

Ten patients with BLH were treated with oral steroids. Six (two with lesions located in the lacrimal gland) had a complete and permanent response. One patient experienced a partial regression of symptoms, but the orbital mass was unchanged. One BLH, located in the lacrimal gland, recurred each time steroids were tapered, and was therefore irradiated. After a dose of 2800 cGy, the patient experienced cutaneous and orbital inflammation, which had to be treated with steroids again; finally, partial mass reduction was observed. Two lesions (both in the lacrimal gland) had a complete response, but recurred 2 and 4 years later as NHL (stages I_E and II).

Three patients with ALH were treated with oral steroids; they all had partial regression of symptoms, but the orbital mass was unchanged. One mass (located in the lacrimal gland) was subsequently treated by irradiation, achieving a complete and permanent response.

Data are summarized in Table 2.

Outcome after radiotherapy

Four patients with BLH were irradiated. Two patients achieved a complete and permanent response. Two masses (both located in the lacrimal gland, one of which had been unsuccessfully treated by steroids) had a partial response.

Three patients with ALH (two in the lacrimal gland) were irradiated, all experiencing a complete and permanent response.

Comparing irradiated patients with non-irradiated patients (steroid+untreated), it appears that radiotherapy may protect against the occurrence of NHL (χ^2 2.03, P=0.1).

Data are summarized in Table 3.

Table 2 Outcome of oral prednisone treatment in 13 cases of orbital lymphoid hyperplasia

	Complete response	Partial response	Future NHL
BLH (n=10)	6 (60%)	2 (20%)	2 (20%)
Lacrimal gland (5)	2 (40%)	1 (20%)	2 (40%)
Non-lacrimal gland (5)	4 (80%)	1 (20%)	0
ALH (n=3)	0	3 (100%)	0
Lacrimal gland (1)	0	1 (100%)	0
Non-lacrimal gland (2)	0	2 (100%)	0
BLH+ALH (n=13)	6 (46%)	5 (39%)	2 (15%)
Lacrimal gland (6)	2 (33%)	2 (33%)	2 (33%)
Non-lacrimal gland (7)	4 (57%)	3 (43%)	0

Table 3 Outcome of radiotherapy in seven cases of orbital lymphoid hyperplasia

	Complete response	Partial response	Future NHL
BLH (n=4)	2 (50%)	2 (50%)	0
Lacrimal gland (2)	0	2 (100%)	0
Non-lacrimal gland (2)	2 (100%)	0	0
ALH (n=3)	3 (100%)	0	0
Lacrimal gland (2)	2 (100%)	0	0
Non-lacrimal gland (5)	1 (100%)	0	0
BLH+ALH (n=7)	5 (71%)	2 (29%)	0
Lacrimal gland (4)	2 (50%)	2 (50%)	0
Non-lacrimal gland (3)	3 (100%)	0	0

Prognosis in patients with concurrent or future NHL

NHL was diagnosed in 11 patients (seven at the time of orbital presentation, four later). Patients at stage I_E received orbital radiation therapy (2000–3500 cGy); other stages (II-IV) were treated with chemotherapy, possible associated with radiotherapy [16]. Follow-up ranged from 2 to 6 years. Complete remission was obtained in both patients with stage I_E tumors. Of the four patients with stage II lesions, two achieved complete remission and two a partial response (reduction greater than 50% of the sums of the greatest tumor diameter and its perpendicular). All three patients with stage III experienced a partial response. Of the two patients with stage IV, the first (high grade) died 2 years after the diagnosis, while the second achieved a complete response at 4 years of follow-up.

Discussion

The present study shows that, in both BLH and ALH, the incidence of concurrent or future lymphoma is high (45% after 5 years). The majority of associated lymphomas occur at the time of orbital diagnosis, and most of the remainder within 6 years from that time. These findings are in agreement with those of previous studies [13], in which, however, actuarial analysis was not performed. Moreover, our analysis showed a statistically significantly higher occurrence of NHL (57%) in lacrimal gland lymphoid hyperplasia. The prognosis of concurrent and future NHL is closely related to Working Formulation grade, as noted in previous series [16].

In addition, our study appears to show that radiotherapy may protect against the occurrence of lymphoma ($P=0.1$), though a larger sample would be required to confirm our impression. In our series, none of the irradiated patients was later affected by NHL, while three of the untreated cases (37%) and two of the patients treated with steroids (15%) were affected. Prednisone was ineffective in ALH.

The problem of treatment becomes more challenging when considering lacrimal gland lymphoid tumors. Indeed, true inflammatory conditions ("pseudotumors" or idiopathic dacryoadenitis) cannot readily be distinguished clinically and radiologically from lacrimal gland BLH and ALH [8, 14, 18]. Lacrimal gland lymphoid tumors are therefore often first treated with oral steroids, and undergo biopsy only when unresponsive or recurrent, or when they have a chronic presentation [11, 17, 19]. Furthermore, it must be considered that at least some lymphoid tumors may descend from a hypercellular autoimmune inflammation (Sjögren syndrome) [6], and that ocular and non-ocular lymphomas are not uncommon in Sjögren syndrome [2, 10] and Mikulicz syndrome [4]. Immature lymphoid cells, necrosis, and reactive clusters of histiocytes in a lymphoid proliferation have been pointed out as premalignant features in Sjögren syndrome [1], as well as immunoblastic and lymphoplasmacytoid "proliferation areas" [20]. In our series, two patients presented with a sicca syndrome with parotid and lacrimal swelling, but biopsies revealed a lacrimal gland lymphoma associated with a parotid benign lymphoepithelial lesion. It is questionable whether a patient with keratoconjunctivitis sicca should undergo radiotherapy, with the danger of worsening of symptoms. In our experience, lacrimal gland irradiation seems more effective and more justified in ALH than in BLH (Table 3). A 41-year-old woman with inflammatory features at presentation was treated with steroids and experienced several recurrences. A biopsy was therefore performed, revealing a lacrimal gland BLH, which was then treated with radiotherapy. Soon after irradiation, an acute orbital inflammation was observed, requiring high-dose steroids, and finally only a partial response was obtained.

The present study confirms that all patients with an orbital lymphoid tumor should undergo systemic staging in order to rule out extra-orbital involvement. The next step in management is definitely represented by irradiation if the lacrimal gland is not involved and in cases of lacrimal gland ALH. Some lacrimal gland BLH and so-called benign lymphoepithelial lesions represent intermediate situations between true inflammation and a lymphoid tumor. Since their discrimination is often impossible (especially when recent onset and external inflammatory features are observed and biopsy is not indicated), a short steroid course seems a reasonable first approach. Systemic staging and even biopsy can be repeated in order to recognize early lymphomatous changes, which require irradiation. Steroids are effective in treating the inflammatory status, and even in reducing lymphoid tumor volume, but not in preventing malignant lymphomatous transformation.

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