Original Article

Lacrimal gland lymphoma: Role of radiation therapy

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Background: To report the clinical and treatment outcome of patients with lacrimal gland lymphoma (LGL) treated with radiation therapy (RT) at Fox Chase Cancer Center, Philadelphia, PA, USA.

Materials and Methods: Institutional review board approved retrospective chart review of eight patients and literature review.

Results: The study patients included six males and two females with a mean age of 70 years (range 58-88 years). The mean follow-up period was 23 months (range 3–74 months). Four patients had mucosa-associated lymphoid tissue (50%) lymphoma and four patients had other non-Hodgkin's lymphoma variants. Four patients had bilateral disease (50%). Four patients had primary LGL (stages I-IIAE, 50%) and four had LGL as part of systemic lymphoma (stage IVAE, 50%). The median RT dose was 2987 cGy (range 2880–3015 cGy). All patients had complete response to RT with symptomatic relief. Minimal dry eye was seen in all patients. There were no late effects such as corneal ulcer, radiation retinopathy, maculopathy, papillopathy, or secondary neovascular glaucoma.

Conclusions: RT alone is an extremely effective treatment in the curative management of localized LGL and provides durable, local control of secondary LGL.

Keywords: Lacrimal gland lymphoma, mucosa-associated lymphoid tumor, Non-Hodgkin's lymphomas, radiation therapy

Introduction

Non-Hodgkin's lymphomas (NHLs) are among the most common primary tumors occurring in the ocular adnexa. Primary lacrimal gland lymphoma (LGL) is relatively rare. The mucosa-associated lymphoid tumor (MALT) subtype of extranodal marginal zone lymphoma is the most frequent histological subtype. An association with Chlamydia psittaci infection is noted in many, but not all, published series.[1-3] Synchronous bilateral lacrimal gland involvement at presentation is seen in 20% of cases. MALT lymphoma in the lacrimal gland has a high rate of extraorbital involvement and usually presents as a localized disease in extranodal tissues or organs such as stomach, salivary gland, thyroid gland, and not infrequently in the orbital adnexa (stage IE). Biopsy is important for diagnosis. Imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) of the orbits are useful in determining the extent of disease. The condition is quite indolent with a relatively good prognosis.[4,5] Radiation therapy (RT) has an important role in the management.[5-11] Clinical course of localized MALT lymphomas is variable and firm evidence is lacking due to the rare incidence of these lymphomas. The role of RT and the outcome of therapy are discussed in eight patients with LGL treated at the Fox Chase Cancer Center (FCCC), Philadelphia, PA, USA between 1999 and 2011.

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Materials and Methods

The FCCC is a National Cancer Institute-designated comprehensive Cancer Center research facility and a cancer hospital. As a tertiary care facility, its patient population comes from around the region, from community physicians, smaller hospitals, and those lacking experience in treatment of rare cancer cases.

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Patients diagnosed as having LGL (biopsy-proven) were identified. All patients with LGL underwent workup including CT or MRI of the orbits [Figure 1]. Fluoro deoxy glucose positron emission tomography scan, serum lactate dehydrogenases, flow cytometry, and bone marrow biopsy were performed to rule out systemic involvement. Response to therapy was graded as remission, partial remission, stable, and relapsed. Clinical files from the identified patients were retrieved and reviewed to record the following data: Age, sex, tumor histology and stage, vision, and treatment-related characteristics (radiation and/or chemotherapy records). The study was approved by the institutional review board.

Radiotherapy

Patients were simulated using CT simulation with an Aquaplast mask (WFR/Aquaplast Corp., Avondale, PA) to improve daily reproducibility. Axial images were obtained every 3 mm from the top of the head down to 2 cm below the clavicle with intravenous contrast. The treatment regions included the lacrimal glands along with the tumor. RT was delivered with two oblique fields to cover the tumor [Figure 2]. Acute and late toxicity were recorded as per the Radiation Therapy Oncology Group (RTOG) toxicity criteria.[12]

Chemotherapy

Two patients received chemotherapy. The first patient received rituximab 375 mg/m^2 weekly for 4 weeks followed by three cycles of R-CHOP [rituximab, cyclophosphamide, daunorubicin, oncovin (vincristine), and dexamethasone] chemotherapy as treatment for NHL (MALT) of right palate. He subsequently experienced recurrence in both lacrimal glands for which he received RT only. Thus, he only received chemotherapy for the treatment of his primary site.

The second patient was initially diagnosed with mantle cell lymphoma of the tonsil and was on maintenance rituximab just before receiving RT for the mantle cell lymphoma recurrence in both lacrimal glands 3 years after RT for the primary lesion. The dose of rituximab therapy was 375 mg/m^2 every 8 weeks.

Results

Eight patients with LGL (six males and two females) were identified. The mean age was 70 years (range 58–88 years). Patient, tumor, and the treatment characteristics are shown in Table 1. Proptosis was the most common presenting symptom in addition to diplopia (*n*=2), irritation of the eye (*n*=1), and limitation of ocular movements (*n*=4). None of the patients had B symptoms such as night sweats, loss of over 10% or more of body weight, and fevers of unknown origin. Four patients had primary LGL (stages I-IIAE, 50%) and four had LGL as part of systemic involvement (stage IVAE, 50%). Four patients had bilateral disease (50%).

Biopsy was done in seven patients: Two patients had biopsy by fine needle aspiration, four patients had an incisional biopsy, and one patient had an excisional biopsy. The eighth patients had clinical and radiographic recurrence of lymphoma involving both lacrimal glands (1.5 years after a primary diagnosis and treatment of tonsil mantle cell lymphoma) and refused biopsy. Four patients had MALT lymphoma (50%) and four NHL variants. Eight patients had cluster differentiation (CD) 20 positive on immunohistochemistry or flow cytology analyses. All patients underwent RT. The median RT dose was 2987 cGy (range 2880–3015 cGy) with a dose per fraction of 150–200 cGy over 3–4 weeks duration, 5 days a week. All patients had complete response with RT with symptomatic relief at a mean follow-up of 23 months. Toxicity included acute radiation dermatitis (grades 1 and 2) in the radiation fields (*n*=5), conjunctivitis (*n*=2), and minimal dry eye in all patients. There were no late effects such as corneal ulcer, radiation retinopathy, maculopathy, papillopathy, or secondary neovascular glaucoma.

Chemotherapy is indicated for widespread disease, as RT is only effective locally. Chemotherapy is usually received first unless there are significant symptoms present that need to be palliated with RT. Two patients received chemotherapy. The first patient received rituximab 375 mg/m^2 weekly for 4 weeks followed by three cycles of R-CHOP [rituximab, cyclophosphamide, daunorubicin, oncovin (vincristine), and dexamethasone] as part

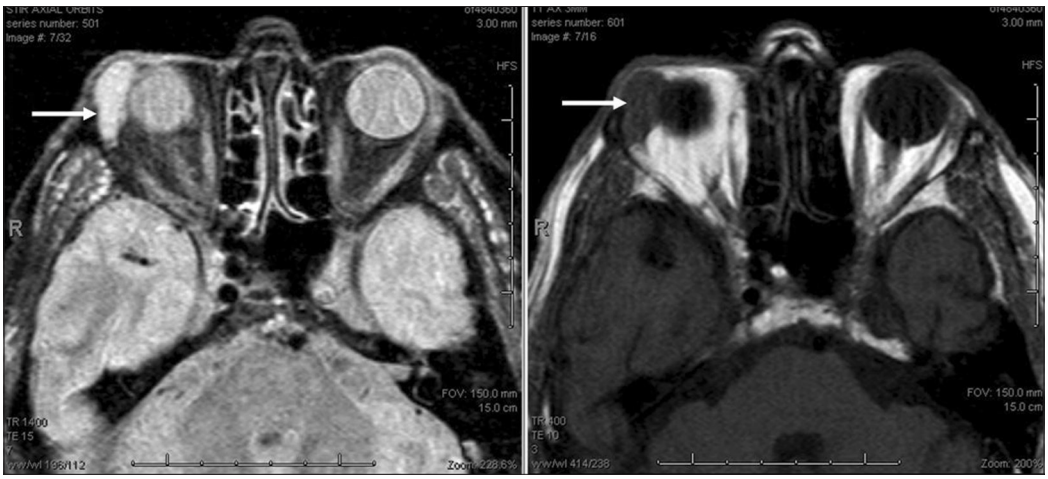

Figure 1: Pretreatment magnetic resonance imaging. Right lacrimal gland (arrow) is enlarged and clearly visible

Table 1: Demographic data of eight cases of lacrimal gland lymphoma

Case No.	Age	Gender	Histology	Laterality	Radiotherapy details TD, dose/fraction, no of fractions	Stage	Status at last visit
1bm	88	Female	MALT	Unilateral	3000 cGy, 200 cGy, 15 fractions	IAE	NED
2bg	64	Male	NHL	Bilateral	3000 cGy, 150 cGy, 20 fractions	IIAE	NED
3al	70	Male	B cell NHL	Bilateral	3000 cGy, 150 cGy, 20 fractions	IVAE	NED
4ca	84	Male	MALT	Unilateral	3000 cGy, 150 cGy, 20 fractions	IAE	NED
5jj	67	Male	NHL	Unilateral	3000 cGy, 150 cGy, 20 fractions	IVAE	NED
6fd	67	Female	MALT	Unilateral	2880 cGy, 180 cGy, 16 fractions	IAE	NED
7sj	58	Male	MALT	Bilateral	3015 cGy, 175 cGy, 15 fractions	IVAE	NED
8hw	69	Male	NHL	Bilateral	3000 cGy, 150 cGy, 20 fractions	IVAE	NED

NHL: Non-Hodgkin's lymphoma, MALT: Mucosa-associated lymphoid tissue, TD: Total dose, E: Extranodal, NED: No evidence of disease

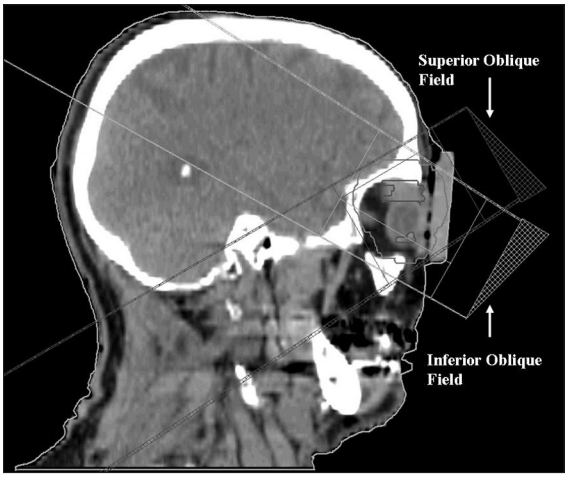

Figure 2: Treatment fields and the gross tumor volume for the patient in Figure 1. Treatment was with two oblique portals

of treatment for his original diagnosis of MALT of right palate. He subsequently experienced recurrence in bilateral lacrimal glands for which received RT only. Thus, he received chemotherapy only for the treatment of his primary site. The second patient was initially diagnosed with mantle cell lymphoma of the tonsil and was on maintenance rituximab just before receiving RT for the mantle cell lymphoma recurrence in bilateral lacrimal glands 3 years after RT for the primary lesion. The dose of rituximab therapy was 375 mg/m^2 every 8 weeks.

Discussion

Primary lymphoma of the lacrimal gland is a rare tumor. The MALT subtype of B-cell NHL,[2,3,8] is the most common histological subtype affecting the lacrimal gland. Its incidence increases with age.[4,5,13] Usually, the MALT subtype of NHL affects other mucosal or epithelial tissues, such as the stomach, salivary gland, and thryroid gland and has an indolent course. The MALT lymphoma of the ocular adnexa usually affects women. A large proportion of the primary orbital lymphomas are of the MALT subtype and mostly have a favorable prognosis; however, patients with bilateral lacrimal gland involvement at presentation and non-MALT lymphoma tend to have a worse prognosis, as bilateral lacrimal gland involvement usually constitutes larger burden of disease. Secondary LGL by definition represents more diffuse and widespread disease and therefore may have a worse prognosis.[4,5,14] The MALT lymphoma is frequently associated with genetic translocations t(11;18(q21;q21),[15] t(14:18)(q32:q31),[16] and trisomy 3. Some of the literature demonstrates an association with *Chlamydia psittaci* infection, although a study from south Florida has not found a great incidence of *C. psittaci* infection in their patient cohort.[1]

Following lacrimal gland enlargement, the most common presenting symptoms are proptosis, eyelid swelling, and vision changes. In our series, all but two patients presented with these symptoms; the other two patients presented with a lacrimal gland mass found on surveillance imaging for other conditions.

Due to its rare histology, there is no standardized treatment strategy and most reported series are retrospective single-institution or case report studies. The treatment approach for these patients was based on prior published literature. Many of those reports also included other types of lymphoma, such as diffuse large B-cell lymphoma, follicular lymphoma, and small lymphocytic lymphoma, all of which may have a more aggressive behavior than MALT lymphoma. The mainstay of the treatment is RT, with a potential added benefit from chemotherapy. Surgery is usually avoided for the sake of eye function preservation. Six of our patients were treated with radiation alone and two of the patients had received rituximab before receiving radiation. Both of these cases were lymphoma recurrences in both lacrimal glands, with primary sites of disease being in oral palate and tonsil, respectively.

Rituximab is a murine/human monoclonal antibody which binds specifically to the antigen CD20 that is located on pre-B and mature B lymphocytes. The antigen is expressed on more than 90% of B-cell NHLs. It is administered intravenously in usual doses of 375 mg/m^2 either in combination with other chemotherapeutic agents or by itself as maintenance therapy for the treatment of NHL. Its contraindicated in hepatitis B-positive patients secondary to potential hepatitis virus reactivation. Typical side effects are hematologic (decreased blood counts) and fever; a serious side effect encountered about 20% of time is a hypersensitivity reaction. There is also a risk of development of peripheral ulcerative keratitis. In our series, the two patients who received rituximab were hepatitis B negative, had a very minor (grade 1) decrease in blood counts, and had no ophthalmologic complications.

The median dose of RT received by our patient cohort was 2900 cGy in 15–20 fractions. Published literature demonstrates 24-month local control rates of 98% and up to 52% of patients achieving complete response using RT doses between 30 and 36 Gy in 2-Gy fractions[6,7] In a case report by Saka *et al*., a 72-year-old female with LGL was treated by radiotherapy alone to a dose of 30 Gy in 15 fractions, with the results of complete clinical remission 1.5 years after treatment.[17] Another study from Japan by Sasai *et al*. reported outcome in 32 patients with NHL (26 with marginal zone B-cell lymphoma) treated with RT with or without chemotherapy and had 3 patients with marginal zone B-cell lymphoma and 4 patients with other types of NHL who relapsed.[2] The outcomes were better with the four patients who had marginal zone B-cell lymphoma; all the patients with other types of NHL (four patients) died of recurrent disease. A study by White *et al*. (1995) published a report on treatment results of MALT lymphoma of the orbit involving 16 patients, 3 (20%) of whom had lacrimal gland involvement. Eleven patients had radiation alone, nine of whom went into complete remission.[3] Galieni *et al*. reported treatment results for 15 patients with localized orbital MALT (8 of which had lacrimal gland involvement) treated with RT or chemotherapy with long-term disease control in 12 of 15 patients.[18] Another case report by Agulnik *et al*. reported a 3-year complete clinical remission after 25 Gy in 15 fractions.[8]

Expected side effects from RT treatment to the lacrimal gland can vary based on the radiation dose received but can typically manifest as skin toxicity (redness, dryness, and itchiness), radiation retinopathy, papillopathy, maculopathy, cataract, corneal ulcers, secondary glaucoma, dry eye, or lash loss. In our case series with a median follow-up of 24 months, all patients experienced RTOG grade 1 skin toxicity. None of the patients experienced radiation retinopathy, papillopathy, or maculopathy. Three patients, one of whom had bilateral tumor involvement, developed a cataract after RT. The cataracts were not severe and none of them required surgical intervention as the visual acuities remained unchanged from pretreatment level. The patient with a pretreatment visual acuity of 20/90 required surgical management for the cataracts. It is likely that RT only contributed slightly to cataract progression in this patient as the visual acuity before treatment was already low. We attribute the low incidence of cataract in our series due to the use of a "lens-sparing technique"[19] (avoidance of lens by radiation beam and/or using a lead shield). There are reports of a higher incidence of postradiation cataract formation in cases without a lens-sparing technique;[11] however, another source mentions cataract formation even with the lens-sparing technique.[9] All other patients experienced only mild dry eye symptoms, while three patients had loss of lashes. Another potential side effect of RT is a decrease in visual acuity. This is usually a result from changes in corneal refraction secondary to ulcer formation. There was only one patient who developed a corneal ulcer; however, the patient did not experience any change in visual acuity. None of the other patients experienced decrease in visual acuity. The tolerance dose of the cornea has been reported to be on the order of 50 Gy in conventional fractionation, and none of the patients in this series received dose higher than 30 Gy. There were no injuries to the optic nerve. Our median follow-up was not long enough to report on the late toxicities. All of our patients were treated with wedge pair technique using either lateral or oblique fields. Goyal *et al*. published minimal side effect profile to the contralateral orbit using intensity-modulated RT,[20] suggesting that this technique minimizes toxicity to surrounding tissues.

Our patient series reports four of eight patients with bilateral lacrimal gland involvement. Other studies on orbital lymphoma, such as the study by Bolek *et al*.,[11] reported 10% incidence of bilateral disease, and the University of Florida[10] study by Smitt *et al*. reports 20% of patients developing metachronous bilateral involvement.

These tumors usually have a tendency to progress slowly. There was a case report by Zimpfer *et al*., who reported spread of the tumor to lung and bone 11 years after first symptoms.[21] Therefore, given the natural tendency of indolent lymphoma to progress slowly and recur late, ongoing long-term follow-up is warranted for these patients.

Conclusion

Orbital or adnexal involvement or both by NHL may appear at any time during the course of the disease. RT has an important role in the management. MALT lymphoma responds well to low dose of RT with prolonged local remission and would be the treatment of choice for stage IAE disease. The results of this study strongly suggest that every patient with NHL in whom any periorbital or orbital mass, ptosis, proptosis, or lid edema develops should be suspected of having orbital lymphoma involvement until proven otherwise. We recommend long-term follow-up for these patients as late relapses were seen in published data.

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