Conjunctival Lymphoma

Miles F. Greenwald BS, Thomas M. Meirick BS, Lindsay K. McConnell MD (../bio/authors/McConnell-Lindsay.htm), Erin M. Shriver MD (https://www.medicine.uiowa.edu/eye/profile/erin-shriver)

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INITIAL PRESENTATION

Chief Complaint

"Bump in the middle corner of the left eye"

History of Present Illness

A 51-year-old male noticed a "raised bump" on the nasal portion of his eye a month prior to presentation. He associated the lesion with the onset of a red eye and episodic foreign body sensation. Additionally, he noticed that his left eyelid had been slightly "more droopy" over the past two months. He denied pain and had not experienced any photophobia, diplopia or decreased visual acuity.

Review of Systems

- He denied any recent fevers, chills, myalgias, arthralgias, unintended weight loss, or night sweats.

Past Ocular History

- Wears daily contact lenses and reported good hygiene
- Follows regularly with local optometrist, last eye exam was reportedly normal 9 months prior
- No history of ocular trauma or surgery

Past Medical History

- Hyperlipidemia

Medications

- Atorvastatin 10 mg daily

Allergies

- Sulfa

Family History

- No known family history of eye problems
- No family history of malignancies

Social History

- Non-smoker, drinks occasionally
- Works as an engineer

OCULAR EXAMINATION

Visual Acuity with correction (Snellen)

- Right eye (OD): 20/25
- Left eye (OS): 20/20-1

Ocular Motility/Alignment

- OD: Full ROM
- OS: Full ROM

Intraocular Pressure (Tonopen)

- OD: 13 mmHg
- OS: 14 mmHg

Pupils

- OD: 4 mm dark, 2 mm light, brisk reaction, no relative afferent pupillary defect (RAPD)
- OS: 4 mm dark, 2 mm light, brisk reaction, no RAPD

Confrontation visual fields (Counting fingers)

- OD: Full to confrontation in all four quadrants
- OS: Full to confrontation in all four quadrants

External

OD	OS (Figure 1a-b)

MRD1: 4mm	MRD1: 2mm
MRD2: 6mm	MRD2: 6mm
Levator Function: 14mm	Levator Function: 14mm
Exophthalmometry (base 94): 11mm	Exophthalmometry (base 94): 10mm

(../cases-i/case243/Fig1a-LRG.jpg)

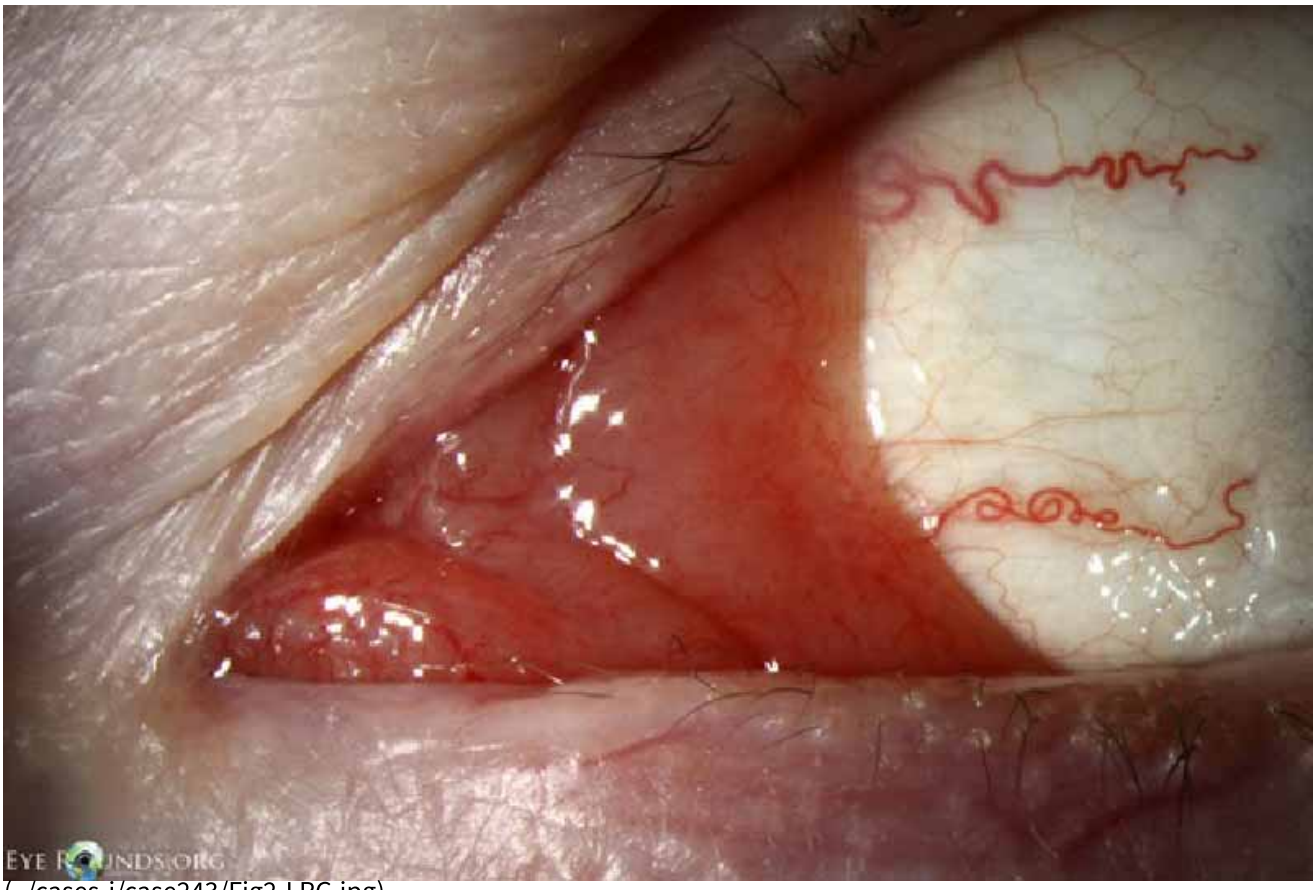
Figure 1a: External photo showing left lid ptosis and left caruncular lesion.

(../cases-i/case243/Fig1b-LRG.jpg)

Figure 1b: External photo of left eye showing raised, pink caruncular lesion

Slit Lamp Exam OS:

- Lids/Lashes: ptosis
- Conjunctiva: temporal papillae on palpebral conjunctiva upon eversion of eyelid, fleshy salmon colored lesion near caruncle measuring approximately 8x3cm in diameter (Figure 2)
- Cornea: Clear
- Anterior Chamber: Deep and quiet
- Iris: Normal shape and architecture
- Lens: Clear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> *Figure 2: Slit lamp photo showing salmon colored patch with telangiectatic vessels in caruncle of left eye.*

Differential Diagnosis

1. Reactive lymphoid hyperplasia
2. Conjunctival lymphoma
3. Conjunctival amyloid deposition
4. Squamous papilloma
5. Oncocytoma
6. Conjunctival squamous cell carcinoma
7. Conjunctival melanoma

Additional testing

Left eye caruncular lesion was biopsied the same day in clinic. Specimens sent for anatomic pathology and immunohistochemistry for flow cytometry evaluation.

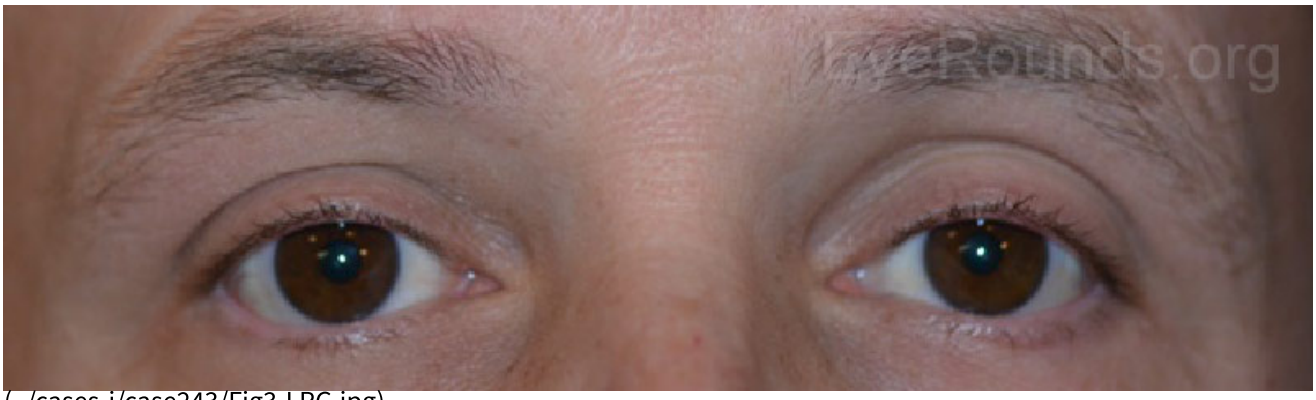
Diagnosis

Extranodal marginal zone B-cell lymphoma of the conjunctiva

CLINICAL COURSE

After diagnosis of extranodal marginal zone B cell conjunctival lymphoma, the patient was referred to an oncologist for evaluation of systemic involvement, including basic hematologic screening tests; magnetic resonance imaging (MRI) of the orbits; and computerized tomography (CT) of the chest, abdomen and pelvis.

After it was confirmed that there was no systemic disease involvement, the patient was treated with external beam radiation therapy (EBRT) (total dose of 24 Gy in 15 fractions) to the left eye without complication. Three months post-treatment, follow up laboratory evaluation and orbital CT demonstrated no recurrence. A new lesion was noted in the inferior fornix of the right eye at his 6 month post-treatment follow up appointment. The patient was asymptomatic and unaware of the growth of the forniceal lesion. Biopsy revealed a right conjunctival marginal zone B-cell lymphoma and imaging demonstrated localized disease. He received similar local radiation therapy (24Gy in 15 fractions) to the right eye and was disease free four months following completion of radiation to the right eye (Figure 3).



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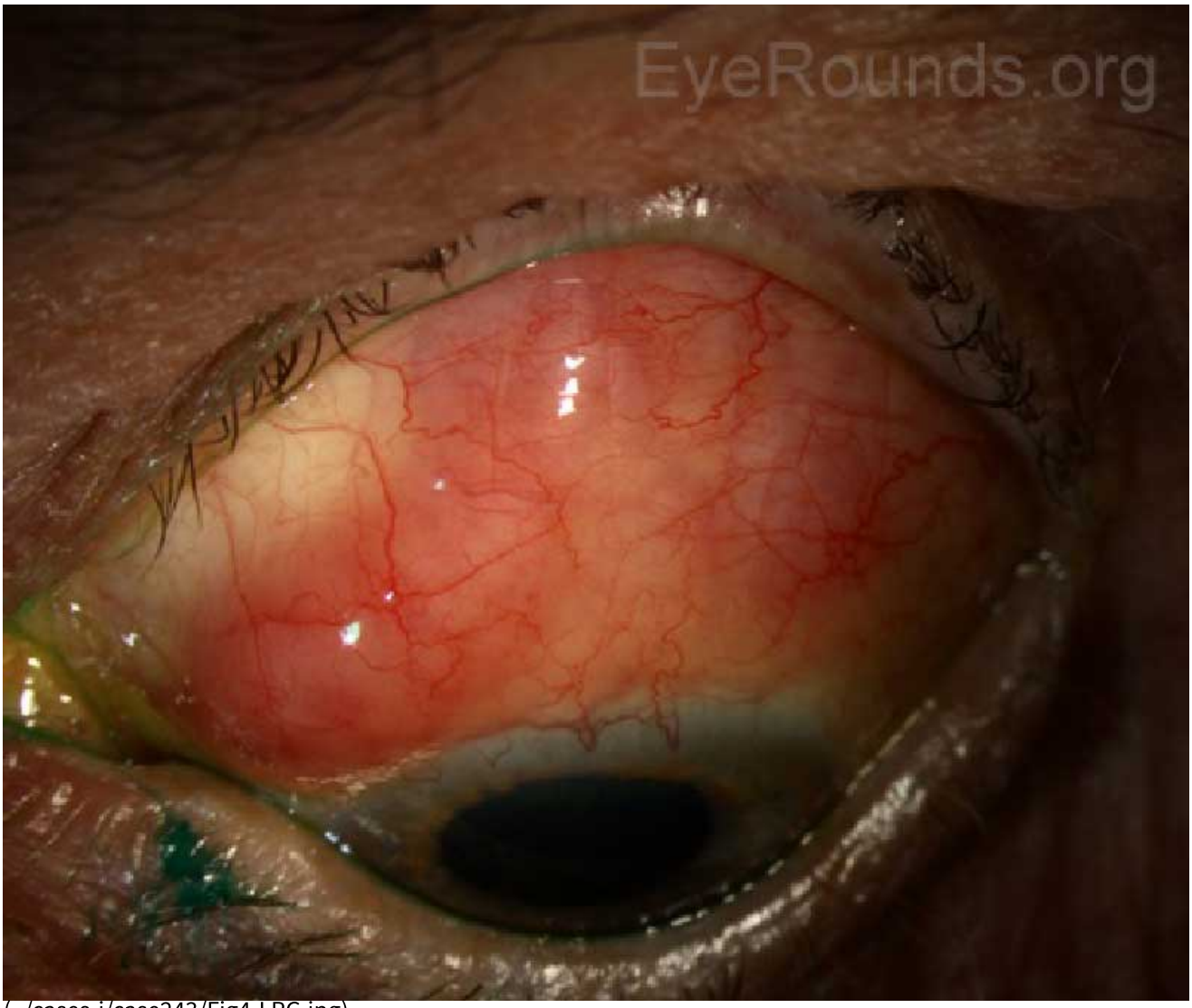
> *Figure 3: External photos showing resolution of ptosis four months following radiation treatment to the right eye lesion and eleven months after completing radiation to the left eye lesion.*

DISCUSSION

Epidemiology

Approximately 2-8% of extranodal lymphomas occur within the adnexa of the eye [1]. Of these, approximately 25% occur within the conjunctiva [2]. Estimated incidence of conjunctival lymphoma is 2-4/1,000,000 [1]. Conjunctival lymphoma is most commonly a primary neoplasm, although 10 to 30 percent are secondary tumors in patients with disseminated lymphoma [3]. The most classic location for conjunctival lymphoma is the inferior fornix, although involvement in the superior fornix or elsewhere is not uncommon (Figure 4).



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> *Figure 4: Slit lamp photo showing the salmon-pink appearance classically associated with conjunctival lymphoma.*

Four pathological subtypes constitute the large majority of reported cases of conjunctival lymphoma, all of which are classified as non-Hodgkin's B-cell lymphomas [1]. Extranodal marginal zone lymphoma (68-81% of reported cases) is the most common subtype, followed by follicular lymphoma (8-16%). Both are histologically considered low-grade malignancies. Less common subtypes include mantle cell lymphoma (3-7%) and diffuse large B-cell lymphoma (3-4%) which are considered high-grade malignancies [1-2]. Conjunctival lymphoma is most common in the 5th to 7th decades, with a slight female predominance [1,3]. It is the third most common malignancy involving the conjunctiva, behind squamous cell carcinoma and melanoma [4].

Pathophysiology and Natural History

Conjunctival lymphoma can appear clinically identical to reactive lymphoid hyperplasia. Both conditions are examples of lymphoproliferative neoplasms and must be carefully distinguished. Reactive lymphoid hyperplasia results from antigen stimulation of the conjunctival lymphoid system and is more common in younger patients. Lymphoma also arises from the conjunctival lymphoid system, although the link with chronic antigen stimulation is controversial in the literature [3,5-9] Risk factors for lymphoma development include chronic exposure to bioactive solvents and reagents, chronic autoimmune conditions, and increasing age [10].

Signs/Symptoms

The most common symptoms include foreign body sensation, ptosis and epiphora. The most common sign is a painless enlarging mass, which classically takes on a salmon-pink, flesh-colored appearance when deep to the conjunctiva [1]. The average delay between clinical onset and diagnosis is 6-8 months secondary to lack of significant symptoms [1,3]. Constitutional B-symptoms, including fever, night sweats, malaise and unintended weight loss are all rare in the low-grade subtypes (4-8%) [1].

Diagnosis and Staging

Diagnosing conjunctival lymphoma after biopsy is complex as it depends on morphologic and cytometric analysis. Clinically, two samples are needed, one fixed for morphologic examination and one fresh specimen for flow cytometry. Histological heterogeneity can create diagnostic and prognostic challenges and thus flow cytometry has become critical for diagnosis. This technique gives not just clarity differentiating lymphoma from reactive lymphoid hyperplasia, but it can also define the specific subtype of lymphoma. For example, marginal zone B-cell lymphomas are positive for CD20, BCL2, PAX5, and CD79A but typically do not express CD5, CD10 or CD23 [4].

After the diagnosis of conjunctival lymphoma is made, systemic involvement of the lymphoma must be ruled-out [9]. This is particularly important because patients can have asymptomatic regional lymph node involvement and/or systemic involvement at the time of diagnosis [9]. Evaluation for systemic involvement includes orbital CT and/or MRI, basic hematologic screening tests (complete blood count, white blood cell differential, serum immunoprotein electrophoresis), CT chest/abdomen/ pelvis, and bone marrow biopsy. The most common stage at initial diagnosis was stage IE using Ann Arbor staging and stage T1 using the AJCC TNM staging system (Table 1a-b). Both of these stages indicate only local involvement.

Table 1a. TNM-based orbital lymphoma staging system [11].

(A) TNM-based AJCC staging system* for ocular adnexal lymphomas	
Primary tumor (T)	
TX	Lymphoma extent not specified
T0	No evidence of lymphoma
T1	Lymphoma involving the conjunctiva alone without orbital involvement
T1a	*Bulbar conjunctiva only*
T1b	*Palpebral conjunctiva ± fornix ± caruncle*
T1c	*Bulbar and nonbulbar conjunctival involvement*
T2	Lymphoma with orbital involvement ± any conjunctival involvement
T2a	*Anterior orbital involvement but no lscrimal grand involvement (± conjunctival disease)*

T2b	*Anterior orbital involvement with lacrima gland involvement (± conjunctival disease)*
T2c	*Posterior orbital involvement (± conjunctival involvement ± any extraocular muscle involvement)*
T2d	*Nasolacrimal drainage system involvement (± conjunctival involvement but not including nasopharynx)*
T3	Lymphoma with preseptal eyelid involvement ± orbital involvement ±
T4	Orbital adnexal lymphoma extending beyond orbit to adjacent structures, such as bone and brain
T4a	*Involvement of nasopharynx*
T4b	*Osseous involvement (including periosteum)*
T4c	*Involvement of maxillofacial, ethmoidal, ± frontal sinuses*
T4d	*Intracranial spread*
Lymph node involvement (N)	
NX	Involvement of lymph nodes not assessed
N0	No evidence of lymph node involvement
N1	Involvement of ipsilateral regional lymph nodes
N2	Involvement of contralateral or bilateral regional lymph nodes
N3	Involvement of peripheral lymph nodes not draining ocular adnexal region
N4	Involvement of central lymph nodes
Distal metastasis (M)	
MX	Dissemination of lymphoma not assessed
M0	No evidence of involvement of other extranodal sites
M1	Lymphomatous involvement in other organs recorded either at first diagnosis or subsequently
M1a	*Noncontiguous involvement of tissues or organ external to the ocular adnexa (e.g. parotid gland, submandibular gland, lung, liver, spleen, kidney, breast)*
M1b	*Lymphomatous involvement of the bone marrow*

M1c	*Both M1 and M1b involvement*

Table 1b. Ann Arbor staging classification specific to lymphoma [11].

(B) Ann Arbor staging classification for Hodgkin and non-Hodgkin lymphomas	
Stage I	Involvement of a single lymph node region or extralymphatic region/organ (IE)
Stage II	Involvement of 2 or more lymph node regions or lymphatic structures on teh same side of the diaphragm alone or extralymphatic regions on the same side of the diaphragm (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm with localized extralymphatic (IIIE) or splenic (IIIS) involvement or both (IIIES)
Stage IV	Involvement of one or more organs or tissues outside the lymphatic system, with or without involvement of nearby lymph nodes
	A: Without B symptoms **B:** Fever, night sweats, weight loss >10% body weight over the last 6 months

Treatment, Surveillance and Prognosis

Localized disease is most commonly treated with external beam radiation therapy (ERBT) with or without chemotherapy [1,10]. ERBT dose normally ranges between 15-45 Gy [1]. The complete remission rate of localized lymphoma is over 90 percent [3-4]. Radiation therapy can also prevent systemic spread in some cases if the lesion is isolated [10]. Other options include excision only, excision and topical chemotherapy, and intralesional chemotherapy [9]. Agents used include interferon alfa-2b and rituximab [3]. For disseminated disease, a single agent or combination chemotherapy is commonly used [3].

Disease recurrence has been shown to be significant, as one recent study showed 38% of patients with extranodal marginal zone conjunctival lymphoma had recurrence with a median recurrence of 24 months [1]. It is therefore recommended to continue surveillance indefinitely with follow up every 3 months for the first year, followed by every six months to a year thereafter [3].

Tumor histology is the most significant prognostic factor, as survival is much longer for low grade malignancies like marginal zone and follicular lymphoma compared to high grade malignancies like mantle cell lymphoma [1]. The location of lymphoma within the orbit also carries prognostic value, as conjunctival lymphoma carries the lowest risk of systemic lymphoma while lymphoma of the eyelids carries the highest risk [10]. Bilateral involvement has a significant impact on survival, with one study finding the 10-year progression free survival to be 72% for those with unilateral disease compared to 48% in bilateral disease [12].

EPIDEMIOLOGY	SIGNS
1. Incidence: 0.2 per 100,000 person-years 2. Most common age: 50-70 years 3. 80% primary malignancy 4. 80% local involvement only on diagnosis	1. Salmon-pink colored mass on the conjunctiva 2. Painless mass 3. Chemosis 4. Exophthalmos 5. Ptosis

SYMPTOMS	TREATMENT/MANAGEMENT
1. Foreign body sensation and eye irritation 2. Diplopia 3. Constitutional B-symptoms if systemic involvement	1. Radiation therapy and/or excision for local involvement 2. Single or multiple agent chemotherapy for systemic disease

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University of Iowa Carver College of Medicine
Department of Ophthalmology & Visual Sciences
200 Hawkins Dr.
Iowa City, IA 52242