CASE REPORT

More than meets the eye: the 'pink salmon patch'

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SUMMARY

Ocular adnexal lymphomas account for 1–2% of all non-Hodgkin's lymphomas. Conjunctiva is the primary site of involvement in one-third of cases. We present a case of a 47-year-old Hispanic woman who presented with left eye itching and irritation associated with a painless pink mass. Physical examination revealed the presence of a 'pink salmon-patch' involving her left medial conjunctiva. Orbital CT showed a subcentimeter left preseptal soft tissue density. Biopsy revealed a dense subepithelial lymphoid infiltrate comprised predominantly of B cells that did not coexpress CD5 or CD43. These findings were consistent with B-cell marginal zone lymphoma. Further staging assessment did not reveal disseminated disease. She had stage 1E extranodal marginal zone lymphoma as per Ann Arbor staging system. She received external beam radiotherapy to her left eye with complete resolution of the lymphoma in 2 months and continues to remain tumour free at 8-month follow-up. She will be followed up closely for development of any local (unilateral or contralateral eye) or systemic recurrence in the long run.

BACKGROUND

This paper reports about ocular marginal zone lymphoma. Although this entity is uncommon, its presenting features are similar to the more commonly seen conditions. Hence, its early diagnosis may be missed. Since this tumour has very good response to radiation, especially when it is localised, early recognition and prompt treatment is imperative. Clinicians should be aware of this condition and request a conjunctival biopsy when in doubt. Also, since there remains a high risk of progression to systemic lymphoma in the long run, these patients should be monitored closely.

CASE PRESENTATION

A 47-year-old Hispanic woman was seen in the ophthalmology clinic for a 3-week history of a painless pink mass on the inner aspect of her left eye associated with itching and irritation.

There was no headache, painful eye movements, blurry vision or double vision. She did not have watering of the eye, redness or photophobia. There was no history of use of topical ophthalmic medications. She had no systemic complaints. She had no history of sexually transmitted diseases. Her medical history was significant for poorly controlled diabetes mellitus and migraine. She denied smoking, alcohol or illicit drug abuse. Her family history was significant for the presence of diabetes mellitus in her mother. On examination, her visual acuity was 20/20 in each eye. Pupils were normal in size and bilaterally equal reacting to light. Ocular

motility and intraocular pressures were normal. Physical examination of the left eye showed an irregular 'pink salmon-patch' involving the superomedial aspect of the conjunctiva with extension into the inferior fornix (figure 1A,B). Right eye examination was normal. Dilated fundus examination showed normal macula, vessels and periphery bilaterally. There were no preauricular, submandibular or cervical lymph nodes palpable. Rest of the physical examinations was unremarkable.

INVESTIGATIONS

CT of the orbit with contrast showed a subcentimeter left preseptal soft tissue density (figure 2). Brain CT was unremarkable. Biopsy of the conjunctival mass showed a dense subepithelial lymphoid infiltrate comprised predominantly of B cells (figure 3A–C) that did not coexpress CD5 or CD43. Clonal rearrangement of immunoglobulin heavy chain gene was detected by PCR. These findings were consistent with a B-cell type, marginal zone lymphoma. Results of laboratory tests were normal including a complete blood count and serum lactate dehydrogenase (LDH) level. Chest,

Figure 1 (A and B) Left eye examination reveals a pink salmon patch over the inferior fornix and the nasal bulbar conjunctiva.

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Figure 2 Orbital CT with contrast (axial view) showing a left preseptal soft tissue density.

abdomen and pelvis CTs were unremarkable. 18-Fluorodeoxyglucose-positron emission tomography (PET)/CT revealed enhanced metabolism in the left medial conjunctiva. There was no evidence of disseminated disease. Bone marrow examination did not reveal any evidence of lymphoma. The patient tested negative for *Chlamydia psittaci*. The patient was thus diagnosed with left conjunctival extranodal marginal zone lymphoma (EMZL), stage 1E according to the Ann Arbor classification.

DIFFERENTIAL DIAGNOSIS

The key clinical feature is evaluation of a salmon pink mass over the bulbar conjunctiva. Differential diagnoses include nodular scleritis, chronic follicular conjunctivitis, fibrovascular pterygium, benign tumours such as squamous papilloma, reactive lymphoid hyperplasia and malignant tumours such as ocular adnexal lymphomas (OALs) and amelanotic melanoma.

Nodular scleritis is associated with systemic diseases in 50% of cases.¹ These include systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, Wegener's granulomatosis and spondyloarthropathies. It usually presents with redness and a severe constant boring pain that radiates to the face, worsens at night and with eye movement. This patient had a painless mass which would make this diagnosis less likely. However, autoimmune workup including ANA, ds-DNA, RA factor, Anti-CCP, c-ANCA, p-ANCA, SS-A, SS-B and Anti-RNP may be sent if in doubt.

Pterygium typically starts medially on the nasal conjunctiva and extends laterally onto the cornea in a wedge-shaped fashion that is its distinguishing feature. It is usually soft in consistency, regular in shape and bilateral. This is in contrast to neoplastic lesions that are often more vascular, irregular and unilateral. The mass in this case was irregular and did not involve the cornea making pterygium less likely. Treatment involves primary excision of the mass with conjunctival autograft.

Chronic follicular conjunctivitis occurs most commonly due to *Chlamydia trachomatis* infection. It is a sexually transmitted disease. Clinical features include mucous discharge, crusting of lashes, conjunctival hyperaemia and chemosis. Follicular reaction (cobblestone appearance) is a key feature and typically involves the bulbar conjunctiva and semilunar folds, which was not seen in this patient. Owing to the high prevalence of associated genital tract disease, systemic therapy is preferred.

Figure 3 Left inferior conjunctival mass biopsy: dense infiltration of monotonous cells beneath the conjunctival epithelium and even in perivascular areas. Cells are arranged in nodular pattern (H&E stain $\times 40$). Dense infiltration of monotonous cells beneath the conjunctival epithelium (H&E stain $\times 100$). Small to intermediate-sized lymphocytes with dispersed cytoplasm without nucleoli (H&E stain $\times 400$).

Confirmed cases may be treated with doxycycline 100 mg twice daily for 10 days or azithromycin 1 g single dose.²

It is thus clear based on the above discussion that initial differential diagnosis of a conjunctival mass is broad and biopsy is essential to rule out malignant aetiologies.

TREATMENT

The patient was treated with localised external beam radiotherapy (EBRT). The total dose given was 3060 cGy with fractions of 180 cGy/day. A tungsten eye shield was used to cover the patient's eye (except for the area of interest) during therapy to reduce the risk of radiation keratopathy, cataract and retinopathy.

OUTCOME AND FOLLOW-UP

On follow-up after 2 months, the patient did not report any itching or irritation of her left eye. Slit-lamp examination revealed complete resolution of the salmon-patch seen previously. A repeat CT of the orbits demonstrated complete resolution of the left conjunctival lesion (figure 4). The patient continues to follow-up without any visual complaints and remains tumour free at 8-month follow-up now. She will have long-term follow-up and will be monitored for development of any local (unilateral or contralateral eye) or systemic recurrence. Previous studies have shown that the rate of progression to systemic lymphoma is 38% at 5 years and 79% at 10 years of the initial diagnosis.³

DISCUSSION

OALs account for 1–2% of all non-Hodgkin's lymphomas.⁴ Conjunctiva is the primary site of involvement in 20–33% of cases followed by orbit in 46–74%, eyelid in 5–20%, lacrimal sac in 7.5% and caruncle in 2.5%.⁵ Multiple site and bilateral involvement is seen in 10–20% of patients.⁵ Ocular adnexa may also be the site of relapse in otherwise systemic lymphomas. EMZL of mucosa-associated lymphoid tissue (MALT) type is the most common subtype, followed by follicular and diffuse large B-cell lymphoma. *C. psittaci*, *Helicobacter pylori*, *Borrelia burgdorferi* and hepatitis C virus have been linked to MALT lymphomas.⁶ EMZL usually occurs in fifth to seventh decade and has a female predominance.⁶

Clinical features are often non-specific. It usually presents as a salmon-pink nodular patch involving the bulbar conjunctiva. Features such as rapid growth, invasion of surrounding tissues, ulceration and presence of feeder vessels support a diagnosis of lymphoma. In a review by White *et al*,⁷ common presenting symptoms included mass in 48%, swelling in 45%, followed by diplopia, ptosis and proptosis. Imaging plays an important role in detecting small, occult or multifocal lesions. CT and/or MRI of the brain and orbit help to assess size and location of the tumour. They, however, do not differentiate benign from malignant lesions. They also help in assessing patient's response to therapy as described in the present case. B-scan ultrasonography is more sensitive in detecting small extrascleral lesions. However, clinical presentation and imaging do not help with the definitive diagnosis. Confirmation depends on histopathology, immunophenotype and molecular genetics. Immunophenotypic analysis for B-cell and T-cell markers, heavy

and light chain restriction, CD5, CD10, CD23, cyclin D1 and bcl-2 should be performed. Flow cytometry helps with assessing quantitative data. Mantle cell and marginal cell tumours appear to be histologically similar but can be distinguished based on their differential expression of CD5. Molecular genetic analysis for gene rearrangements of the IgG heavy chain can determine clonality. Additional staging should follow including laboratory workup (complete blood count and LDH level), chest X-ray, CT of the chest, abdomen and pelvis, and a bone marrow biopsy. A PET scan is more sensitive than CT in determining distant disease.

All patients should be appropriately staged using the conventional Ann Arbor or the recent American Joint Committee on Cancer Tumor-Node-Metastasis (TNM-AJCC) staging system. According to Ann Arbor staging, patients can be classified as stage I, II, III or IV. Stage I denotes OAL in a localised area. Stage II indicates lymphoma in two separate areas, an affected lymph node or organ and a second affected area, and both affected areas are confined to above or below the diaphragm. Stage III refers to lymphomas that have spread to involve both sides of the diaphragm (including 1 organ or area near the lymph nodes or the spleen). Stage IV indicates disseminated involvement of extralymphatic organs and includes lymphoma with liver, bone marrow or nodular pulmonary disease. Modifiers may be used for stage subclassification. 'E' denotes extranodal disease, 'A' or 'B' refers to absence or presence of B symptoms, 'S' refers to splenic involvement and 'X' is used if the largest deposit is >10 cm, that is, bulky disease. The major pitfall associated with the Ann Arbor staging is that it does not differentiate among different OALs based on anatomic location, bilaterality, multicentricity and extent of infiltration of the primary tumour. Hence, it cannot determine prognosis in these cases. Aronow *et al* did a retrospective clinical review of 63 patients with primary OAL who were staged according to the AJCC-TNM clinical staging system. They determined that the TNM system was indeed useful for precise characterisation of the extent of local disease. Although the T stage did not predict relapse or survival, N1-4 and M1 stages were able to determine less favourable survival outcomes.⁸

Localised conjunctival lymphoma has a good prognosis. It usually has normal serum LDH levels, absence of B symptoms and follows an indolent course. Twenty per cent of patients with localised disease will develop disseminated disease. Less than 5% of patients die from the lymphoma. Unfavourable prognostic indicators previously identified include advanced age at diagnosis, female, prior history of lymphoma, higher disease stage, elevated international prognostic index score, nodal involvement, non-conjunctival primary site, bilaterality at presentation, age older than 60 years, B symptoms and elevated LDH levels.⁹ Relapses usually involve the contralateral orbit. High-grade transformation may occur in 1–3% of cases.

Treatment depends on whether the disease is localised or disseminated. Localised disease may be treated with EBRT, intralesional injections of interferon alpha 2b or rituximab, or local excision.⁵ Surgical resection may be associated with a high risk of recurrence due to presence of tumour microinvasion in the surrounding tissues.⁵ Elderly and frail patients or those with significant comorbidities and asymptomatic disease may be offered a 'wait-and-watch' strategy. EBRT has a high response rate, good local control and a 4-year relapse rate of 20–25%. Russell *et al*¹⁰ showed that a median radiation dose of 30 Gy led to excellent local control and was well tolerated with expected cataractogenesis. Patients with recurrence were also salvaged successfully. The entire conjunctiva on the involved site should be

Figure 4 Orbital CT with contrast (axial view) now showing complete resolution of the previously seen left preseptal soft tissue density.

irradiated. This is because conjunctiva is a lymphoid-rich tissue compared with other structures in the orbit. If it is not completely included in the radiation field, it may lead to local relapses. Complications of EBRT include dry eye, cataract, glaucoma, retinal bleeding and retinopathy. Radiation-induced retinopathy and retinal bleeding usually occur with radiation doses above 40 Gy. Disseminated disease is treated with either chemotherapy (eg, cyclophosphamide, doxorubicin, vincristine and prednisone, ie, CHOP with or without rituximab), immunotherapy (rituximab) or radioimmunotherapy (using ^{90}Y -ibritumomab tiuxetan).⁶ Rituximab is a chimeric monoclonal antibody targeted against the CD20 antigen on B lymphocytes. ^{90}Y -ibritumomab tiuxetan as a modality of targeted radiotherapy offers the advantage of delivering a lower radiation dose than EBRT and at the same time targeting malignant cells throughout the body. It can be used for rituximab refractory

disease. This is because the two of them have different mechanisms of action. While rituximab utilises host effector mechanisms to kill tumour cells, ^{90}Y -ibritumomab tiuxetan acts directly through emission of beta particles. The eradication of *C. psittaci* infection with doxycycline (100 mg administered orally twice a day, for 3 weeks) has been proposed as an effective strategy but remains controversial.⁶

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Learning points

- Conjunctival extranodal marginal zone lymphoma is rare but should be considered in the differential diagnosis of a 'pink salmon patch'. Superior and inferior fornices should be carefully examined to detect occult lesions.
- If misdiagnosed as chronic conjunctivitis initially, biopsy should be considered if unresponsive to conventional therapies.
- Although most commonly a primary extranodal malignancy, it may be associated with systemic disease and needs proper staging evaluation to determine the type of therapy.
- Localised disease has excellent response to EBRT whereas systemic disease may need chemotherapy.
- Patients need long-term follow-up after treatment to detect relapses and for management of post-radiation ocular complications.

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