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Unusual Orbital Tumor Diagnosis and Management of Ocular Follicular Lymphoma: A Case Report

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Abstract

Orbital follicular lymphoma is a subtype of orbital lymphoma, which is a group of lymphoproliferative disorders affecting the orbit. Early diagnosis and intervention are crucial for preserving vision and preventing systemic spread. A 69-year-old Hispanic female presented with a one-month history of double vision. MRI revealed a 3.7 cm enhancing mass in the right superior oblique muscle. Biopsy confirmed low-grade follicular lymphoma. PET-CT showed localized and mild systemic involvement. Bone marrow biopsy indicated no lymphoma involvement. The patient is undergoing targeted therapy with bendamustine and rituximab every 28 days for 4 cycles, with regular follow-ups. This case underscores the importance of considering lymphoma in patients with unusual ocular symptoms and highlights the role of comprehensive imaging, biopsy, and bone marrow examination in diagnosis and treatment planning.

Keywords: Orbital lymphoma; Double vision; Proptosis; Follicular lymphoma; MRI; PET-CT; Ki-67; CD20; CD10; BCL6; BCL2; Bendamustine; Rituximab

Introduction

Orbital lymphoma is an uncommon cause of ocular symptoms but represents a significant portion of orbital malignancies. Timely diagnosis is essential to manage the disease effectively and preserve vision.

Case Presentation

Patient information and Clinical Findings

A 69-year-old Hispanic female presented to her primary care physician with complaints of double vision that began one month prior. The patient reported binocular diplopia without pain or other neurological symptoms. Physical examination revealed mild proptosis of the right eye.

Diagnostic Assessment

An MRI of the brain and orbits with and without contrast revealed a 3.7 cm enhancing mass with associated restricted diffusion in the right superior oblique muscle, contributing to mild right proptosis. These findings were highly suspicious for neoplasm, likely lymphoma.

An orbital mass biopsy revealed low-grade follicular lymphoma expressing CD20, CD10, BCL6, and BCL2. The Ki-67 showed a proliferation index of 10-20%.

A PET-CT scan of the whole body showed FDG uptake within the right

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medial orbital mass with an SUV max of 9.6, consistent with the patient's history of right orbital lymphoma. An unspecified FDG-avid right axillary lymph node measured 0.6 × 0.7 cm with an SUV max of 2.9. The spleen was not enlarged but exhibited slightly increased FDG uptake with an SUV max of 5.6, higher than the background physiologic FDG uptake in the liver. Bone marrow biopsy histopathology showed mildly hypercellular marrow with trilineage hematopoiesis and no involvement by lymphoma. The aspirate showed orderly maturation with no atypical lymphocytes. Flow cytometry was negative for lymphoma. Laboratory results showed WBC 7.8K, Hgb 14.2 g/dL, MCV 89.7, and PLT 193K.

Diagnosis and Treatment

Low-grade follicular lymphoma of the right orbit without bone marrow involvement. The patient was referred to oncology for treatment planning. She was started on bendamustine and rituximab every 28 days for 4 cycles, with regular monitoring.

Follow-up and Outcomes

The patient is undergoing regular follow-ups. Initial response to treatment is positive, with a reduction in mass size and symptom improvement.

Discussion

The diagnosis of systemic follicular lymphoma is made based on the evaluation of a lymph node biopsy, typically in a patient with a history of waxing and waning lymphadenopathy. Bone marrow examination is an important component of staging [1]. Orbital lymphoma, although rare, should be considered a key differential diagnosis for patients presenting with ocular symptoms such as diplopia and proptosis [1].

These lymphomas accounts for approximately 7–8% of all non-Hodgkin's lymphomas (NHLs). They can develop from B-lymphocytes, T-lymphocytes, or NK lymphocytic cells, and are recognizable by its morphological heterogeneous appearance with variable presence of germinal centers, plasma cells, and/or monocytic lymphocytes [2-5].

An 80% of lymphomas involving ocular adnexa (conjunctiva, orbit, lacrimal gland, and eyelid) have mature B-cell origin [4] as a response to persistent antigenic stimulation in case of chronic inflammatory or autoimmune disorders [6,7]. Association with C. psittaci infection is also documented, especially in Eastern nations, even if there is no overall acceptance [5-8]. Extranodal marginal zone B cell lymphoma represents the most frequently reported subtype, followed by diffuse large B-cell lymphoma [4].

Follicular lymphoma is a less common subtype, representing about 9-11% of orbital lymphoma cases. Over the past 24 years (1994-2017), 2211 cases of orbital lymphoma with known subtypes have been reported. The vast majority of these lymphomas are of B-cell origin (97%), with extranodal marginal zone B-cell lymphoma (EMZL) being the most common subtype (59%), followed by diffuse large B-cell lymphoma (23%), follicular lymphoma (9%), and mantle cell lymphoma (5%). It has been postulated that varying sites of disease are prognostic indicators for developing systemic involvement. 20% of conjunctival, 35% of orbital, 67% of eyelid orbital adnexal lymphoma develop systemic lymphoma after four years. Mortality ranges from 0-20% for extranodal marginal zone B-cell lymphoma, 20-37% for follicular lymphoma, 38-100% for mantle cell lymphoma, and 14-100% for lymphoplasmacytic lymphoma. Relapse has been noted to be over five years [4,9-10].

Lymphoma occurs predominantly in elderly individuals [11] with an incidence peak amongst the fifth and seventh decade of life (median age 65 years), with a female predominance (male/female = 1:1.5/2) in the Western population [11].

Similar data was found by Ahmad Samir Alfaar et. al. [1], in a study among 87,543 patients with ocular and adnexal malignancies retrieved from the North American Association of Central Cancer Registries (NAACCR), that detected a 20.4% of patients affected with ocular and orbital lymphoma. The incidence was highest in the orbit, followed by the conjunctiva. The number of cases in females was higher than that in males. Patients aged between 60 and 79 years were the most affected group. In the same study, it was also found that Lymphoma occurred mainly unilaterally (90.7%), most patients presented with mature Non-Hodgkin B-cell lymphoma (78.1%), representing the highest rate among all lymphoma subgroups. Its subtypes, marginal zone lymphoma (MZL), diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma, were the most common subtypes, with 45.7, 12.3, and 11.0%, respectively [12].

Recent studies have reported an increased incidence of ocular and adnexal lymphomas in countries such as the USA, Canada, Denmark, and South Korea [13-14]. Coinciding with reviewed literature, our case was a 69 years old female.

Clinical Presentation and Diagnosis

Orbital and ocular adnexa lymphoma (OOAL) are often insidious, due to few and unspecific symptoms such as localized pain, conjunctival swelling, redness, and itching irritation, leading to a differential diagnosis with other benign pathologies, often masqueraded by the use of topical steroids, that can delay diagnosis. It has been estimated a median interval between onset symptoms and definitive diagnosis of 7 months ranging from 1 month up to 10 years.

Clinical presentations may vary depending on the primary localization. A palpable rubbery or firm mass can be observed with other compression symptoms such as periorbital

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edema, decreased visual acuity, and motility disorders; other uncommon symptoms are conjunctival hyperemia, blurry vision, chemosis, ectropion, pterygium, photophobia, and corneal symptoms. Lacrimal gland infiltration symptoms are dryness, pain, lacrimal duct discharge, epiphora, displacement of the globe, proptosis, and ocular motility reduction [15-17].

Overall, the most common symptom of orbital lymphoma is proptosis. Hence, patients presenting with proptosis, especially unilateral proptosis, should always be referred to a computed tomography scan or MRI [18,19].

Main symptom of the patient presented here was diplopia, with associated mild right eye proptosis on physical exam.

Imaging and Histopathology

Characteristically, the tumor cells express monotypic immunoglobulin light chain, CD19, CD20, CD10, and BCL6, and are negative for CD5 and CD23. The vast majority (>85 percent) of tumors express BCL2 as a result of the t(14;18), which can be detected by fluorescence in situ hybridization (FISH) or by polymerase chain reaction (PCR) [1].

Our patient biopsy of the orbital revealed low-grade follicular lymphoma expressing CD20, CD10, BCL6, and BCL2. The Ki-67 showed a proliferation index of 10-20%.

Staging

The initial evaluation of patients is a milestone. It is important to define if the neoplasm has systemic extension or is locally confined. A complete ophthalmologic examination followed by an adequate tissue sampling for histopathologic diagnosis is mandatory. Staging workup must include: physical examination, bone marrow biopsy, MRI, CT of head and neck, chest, abdomen, and pelvis, and 18-fluorodeoxyglucose-positron emission tomography-CT (FDG-PET-CT) to complete staging of the patient. CT and MRI studies of the facial district are important to evaluate localization, size, and local infiltration of the mass, which helps identify the correct staging and also the following treatment strategy (i.e., choosing between intralesional or systemic therapy, radiotherapy planning, etc.) [20-21].

The Ann Arbor staging system was originally developed for clinical staging of HL, but it has long been used for clinical staging of NHL as well. The staging system includes 4 stages taking the following features into account: nodal and extranodal lymphoma sites, lymph node involvement differentiating between lymph node involvement on one or both sides of the diaphragm, and metastatic spreading [18].

Approximately 85–90% of patients with a diagnosis of OOAL have stage I disease; nodal involvement is reported in 5% of patients; only 10–15% of patients have disseminated disease [6] (Table 1).

In accordance with the reviewed literature, the patient presented with an Ann Arbor stage IAE.

The PET-CT findings in this case were significant for localized FDG uptake in the right orbital mass and a small right axillary lymph node, with no widespread systemic involvement. The slight increase in FDG uptake in the spleen, without enlargement, suggested possible low-level involvement, which is not uncommon in lymphoma cases.

The bone marrow biopsy ruled out marrow involvement by lymphoma, which has important prognostic implications. The absence of atypical lymphocytes and negative flow cytometry for lymphoma further supported the localized nature of the disease.

Treatment and Prognosis

Various strategies of treatment are available depending on the initial stage of the neoplasm: surgical excision, radiotherapy, chemotherapy, and immunomodulating therapy or combination therapy. Tailoring the treatment requires a multidisciplinary approach which should consider extensions, patient comorbidities, disease-related prognostic factors, short and long-term efficacy, and toxicities impact on a patient's quality of life. Radiotherapy alone is usually the treatment of choice, in early stage and indolent OOAL (stage I–IIE). Patients with stage III or IV or with aggressive OOAL's histotypes need a systemic treatment chemotherapy/immunotherapy combined with local radiotherapy [6,8,24].

OOALs are characterized by high radiosensitivity. External beam radiation therapy (EBRT) is the gold standard treatment in OOAL classified as Ann Arbor Stage IE-IIE thanks to high response rates and outstanding local control. It has been considered the standard treatment for low-grade, isolated OOALs for the past decades. Radiotherapy can be administered as a solo treatment, with adjuvant systemic therapy, or as salvage therapy after partial or incomplete response or in case of relapse [15,25,31-32]. The typical radiation dose is around 30 Gy. For more advanced stages (IIIE or IV), chemotherapy is often employed, sometimes in combination with radiation therapy. For managing solitary low-grade lymphomas, radiotherapy is the treatment of choice. Chemotherapy, with or without radiotherapy, should be selected for disseminated and high-grade lymphomas [9-10,26].

"Watch and wait" is not recommended due to the high incidence of local and systemic recurrence, but it can be taken under consideration in the setting of frail elderly patients with low-grade, asymptomatic, and unilateral disease with severe comorbidities that preclude other and more aggressive therapeutic approaches [27-28].

Surgery alone showed a high risk of recurrence if not associated with adjuvant chemotherapy or radiotherapy. If

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infection with C. psittaci is detected, especially in Eastern countries, antibiotics, such as Doxycycline can be used [6-8].

Rituximab is a monoclonal chimeric anti-CD20 antibody that targets the surface antigen CD20, overexpressed on CD20-positive NHL B cells. It can be administered intralesionally in case of recurrence and local relapse or intravenously for bilateral or systemic involvement. It can be used alone or in combination with other chemotherapy drugs. Monoclonal antibodies can be used to deliver radioisotopes to the site of OOAL, with the same or better outcome compared to rituximab [6,29-30].

The standard treatment for low-grade follicular lymphoma includes chemotherapy and immunotherapy. Bendamustine combined with rituximab has been shown to be effective in inducing remission in follicular lymphoma patients. This regimen is typically well-tolerated and associated with a favorable response rate and progression-free survival.

For localized high-grade lymphomas (Stage I or II), a combination of chemotherapy and radiotherapy is often preferred to maximize local control of the tumor and reduce the risk of recurrence. Radiotherapy targets the primary tumor site, while chemotherapy addresses potential microscopic disease spread. Large tumor masses, or bulky disease, may particularly benefit from this combined approach, as radiotherapy can shrink tumors, making them more responsive to subsequent chemotherapy. Additionally, if the tumor responds well to initial cycles of chemotherapy, radiotherapy may be added to consolidate the response and reduce the risk of local recurrence.

In advanced disease (Stage III or IV), chemotherapy alone is typically the mainstay of treatment, as systemic therapy is needed to target widespread disease. However, radiotherapy may still be used in certain situations, such as to treat bulky disease or symptomatic sites. Patient factors, such as age and performance status, play a significant role in treatment decisions. Older patients or those with significant comorbidities may not tolerate aggressive combined treatments well, often necessitating a less intensive regimen. Patient preferences, symptoms, and disease burden also influence the choice of therapy, particularly in achieving rapid symptom relief and managing high tumor burden. This case exemplifies the complexity of treatment planning, highlighting the need for a tailored, multidisciplinary approach.

Orbital follicular lymphoma generally has a favorable prognosis, particularly for localized disease treated with external beam radiation therapy (EBRT). The 10-year disease-specific survival rate for patients treated primarily with EBRT is reported to be as high as 94%. The histopathological subtype and clinical stage of the disease are the most significant indicators of prognosis and patient outcome. Low-grade lymphomas, such as extranodal marginal zone B-cell lymphoma and follicular lymphoma, typically have a good prognosis. In contrast, high-grade lymphomas, such as diffuse large B-cell lymphoma and mantle cell lymphoma, are associated with a poorer prognosis [4,9].

The patient's positive initial response to treatment, with a reduction in mass size and improvement in symptoms, is encouraging. Regular follow-up is necessary to monitor for potential recurrence or progression of the disease.

Implications for Clinical Practice

This case underscores the importance of a multidisciplinary approach in the management of orbital lymphoma. Early recognition, comprehensive diagnostic workup, and timely initiation of appropriate therapy are critical for optimizing patient outcomes.

Given the rarity of orbital lymphoma, this case also contributes to the broader understanding of its presentation and management. Clinicians should maintain a high index of suspicion for lymphoma in patients presenting with atypical ocular symptoms and pursue thorough diagnostic evaluations accordingly.

Conclusion

This case report emphasizes the need for vigilance in diagnosing orbital lymphoma in patients presenting with unusual ocular symptoms. A multidisciplinary approach, including imaging, biopsy, bone marrow examination, and targeted therapy, is critical for accurate diagnosis and effective treatment. The patient's favorable initial response highlights the potential for positive outcomes with timely and appropriate intervention. Continued follow-up and monitoring are essential to ensure sustained remission and to address any recurrence promptly. This case contributes valuable insights to the limited body of knowledge on orbital follicular lymphoma, reinforcing the importance of early detection and comprehensive management strategies in improving patient prognosis.

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