PRIMARY INTRAORBITAL B-CELL LYMPHOMA. A CHALLENGING DIAGNOSIS. CASE PRESENTATION AND REVIEW OF THE LITERATURE

Case Report

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ABSTRACT

To describe and report a challenging case of primary intraorbital B cells lymphoma and to provide an update review of the literature, highlighting the importance of the clinical and multimodality imaging assessment and finding. A 52-year-old Indian male patient, known to have hypertension and type II diabetes presented to Emergency Department complaining of 4 days history of gradual onset blurring of vision, left eye pain and double vision. Clinical examination showed left eye proptosis. MRI Head and Orbit showed left infraorbital extraconal mass lesion along the inferior aspect of the left orbit; Positron emission tomography (PET CT scan) whole body showed intensive uptake left orbital cavity and Left testis/ epididymis uptake also compatible with suspected lymphoma activity. Under general anesthesia Incisional biopsy was done. Histopathological examination showed Diffuse large B-cell lymphoma, NOS (Not Otherwise Specified). Patient received total two cycles of Hyper-CVAD (cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride and dexamethasone) in addition of two cycles of R-CHOP (rituximab cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisolone) showing regression of the lesion on PET CT scan as well as regression of the symptoms. Orbital lymphoma can be easily mistaken for another ocular disease due to the slowly progressing nonspecific complaints of the patients. If unspecific orbital symptoms are present, adequate imaging studies followed by early surgical biopsy will contribute to the early diagnosis. We should always be suspicious of this diagnosis especially in patients over sixty years of age with slowly growing mass in the orbit or proptosis non-reacting to specific treatment.

Key Words: Orbital Tumors; Orbital Lymphoma; B-Cell Lymphoma; Immunohistochemistry; Positron emission tomography.

Oculo-Orbital non-Hodgkin's lymphoma is a rare presentation that accounts for 1 to 2% of all lymphomas, 1 to 8% of non-Hodgkin´s lymphomas, and 10% of extra-nodal non-Hodgkin lymphoma. However, it is most common malignant orbital tumor in adults [1,2,3]. It constitutes more than half of all orbital malignancies (55 percent) [4]. Orbital lesions include many pathological types with varying degrees of malignancy and may be difficult to distinguish from other ocular diseases such as retinal choroidal reactive lymphoid hyperplasia and orbital inflammatory pseudotumor. [5, 6]

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INTRODUCTION

A 52-year-old Indian male patient, known to have hypertension and type II diabetes presented to Emergency Department complaining of 4 days history of gradual onset blurring of vision, left eye pain and double vision. Clinical examination showed left eye proptosis, tense and hard to digital palpation, limitation to abduction gaze and binocular diplopia. Magnetic resonance image (MRI) Head and Orbit showed left infraorbital extraconal mass lesion along the inferior aspect of the left orbit displacing the inferior rectus muscle superiorly and pushing the eye globe forward extending to the left maxillary sinus. PET CT scan whole body showed Left testis/epididymis uptake along with additional foci at the ductus deferens also compatible with lymphoma activity. Under general anesthesia Incisional biopsy was done using left sub ciliary incision, mass was identified in the supraperiostal plane, and three main incisional biopsy specimens were harvested and sent for histopathology investigations. Histopathological examination showed multiple fragments of fibroconnective tissue infiltrated by diffuse sheets of atypical lymphoid cells.

The cells are composed of large Centro blasts with scant cytoplasm, high nuclear to cytoplasmic ratio, atypical irregular nuclei having a vesicular chromatin and prominent nucleoli. Apoptotic bodies and mitotic activity including atypical ones are increased. The final diagnosis was Diffuse large B-cell lymphoma, NOS (Not Otherwise Specified), activated B cell type and staged as Staged IV. Patient received total two cycles of Hyper-CVAD (cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride and dexamethasone) and two cycles of R-CHOP

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(rituximab cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisolone) showing regression of the lesion on PET CT scan as well as regression of the symptoms.

DISCUSSION

The etiology of Orbital lymphomas is unknown, and the optimal treatment regimens remain controversial among researchers [7]. Orbital lymphoma may be unilateral or bilateral. It has been known to present in patients between 15 and 70 years of age. Historically, a female preponderance has been noted. Geographically, the disease is most common in Asia and Europe. [8]

Ocular adnexal lymphomas account for approximately 11% of all ocular tumors and most often occur in the orbit, followed by the conjunctiva. The most common subtype of ocular adnexal lymphoma is extra nodal marginal zone B-cell lymphoma (60%–66%), followed by follicular lymphoma (10%–15%), diffuse large B-cell lymphoma (8%–13%), and mantle cell lymphoma (1%–5%). The prognosis of ocular adnexal lymphomas varies with each pathological type [9, 10, 11 ,12].

Almost 80 percent of orbital and adnexal lymphomas are of low-grade variety, with B-cell lymphomas and extra nodal marginal zone lymphoma of the mucosa-associated lymphoid tissue type being the most common histological diagnoses [13].

Patients typically demonstrate a pink or red "salmon patch" of swollen conjunctiva or conjunctival hyperemia commonly observed as a painless palpable mass in the superolateral quadrant. It may lead to proptosis, ptosis, diplopia, or abnormal ocular movement. The enlarged Lacrimal gland displaces the eyeball inferomedial. In regards of eyelids swelling and prolapse may occur [14].

A systematic approach and evaluation of the patient is necessary to proper diagnose and exclude common and benign orbital disorders such as, pseudotumor, lymphangioma, hemangioma, lymphoid hyperplasia, tumor arising from the maxillary sinus invading the orbits and in advanced stages orbital metastasis:

• Full medical history and top to bottom physical examination

• Complete ophthalmology assessment and examination including the opposite orbit as well as the oral cavity and oro-pharynx

• Complete blood works

• Tissue sampling for histopathology investigation such as Fine-needle aspiration and biopsy

• With a confirmed lymphoma diagnosis patient must be scanned for possible metastasis (Chest x-ray, Computed tomography (CT) and magnetic resonance imaging (MRI) of orbit, abdomen, thorax, and pelvis

Both computed tomography (CT), magnetic resonance imaging (MRI), are considered gold standard. CT is useful for visualization of bony structures and identification of tumor erosion or hyperostosis of bone. Jin et all [15] found that the isodense soft tissue masses characterized primary orbital lymphoma with clear demarcation on CT images; the lesions showed homogeneously marked enhancement when contrast medium was used. Simon et al [16] discovered that benign lesions were more likely hyperdense or hypodense on CT in comparison with inflammatory and malignant tumors. Briscoe et al. [17] suggested that bone changes were more common on CT images when orbital lymphomas were suspected.

MRI is preferred for characterization a detail imaging soft-tissue structures and orbital apex tumors. The following items should be evaluated: 1) the laterality (unilateral/bilateral), 2) the characteristic of the margins (well-defined, ill-defined [infiltrative], and lobulated) and signal intensity on T1-weighted, T2-weighted, and diffusion-weighted images relative to cerebral cortex (hypo, iso or hyper- intense), 3) the homogeneity and degree of contrast enhancement relative to extraocular muscles, 4) the presence of a signal void from a vessel in the lesion on T2-weighted images, referred to as the "flow void sign," and 5) findings indicative of sinusitis. [18-19]

Similar to intracranial lymphoma, the densely cellular nature of these tumors with high nucleus-to-cytoplasm ratio results in relatively specific appearances:

Signal characteristics include:

• T1: iso- to hypointense to muscle

• T2: iso- to hyperintense to muscle

• T1 C+ (Gd): homogeneous enhancement

• DWI: increased signal intensity - restricted diffusion

• ADC: reduced values - restricted diffusion [20-21]

Thus, combining CT and MRI imaging could be useful for accurate diagnosis.

Multimodality treatment including surgery, chemotherapy, and radiation or a combination have been advocated in the management of orbital lymphomas. Staging of tumor is an important guide to selection of an appropriate treatment strategy. Surgery is usually utilized as a diagnostic tool. Complete remission without significant complications has been reported with radiation alone. Radiotherapy alone has been reported to provide excellent local control and survival in patients having localized mucosa-associated lymphoid tissue lymphoma.

Numerous reports confirm the efficacy of conventional treatment strategies such as surgery, radiotherapy, or chemotherapy, alone or in combination, with no significant survival difference [22 23 24]. Surgery as the only treatment modality should not be administered, because there is obviously a high likelihood of local relapse after surgery according to previous reports. The difficulty of complete resection with preservation of function in the orbit may explain the high relapse rate [25].

Combination chemotherapy is effective in orbital lymphoma. Most often, chemotherapy was administered after either surgery or radiotherapy or was reserved for patients with advanced disease stages [26].

Survivals rates depend on several factor such as, age of the patient, histopathology of the lesion and clinical course. Deliang L Liu et all [27] performed a large retrospective cohort of patients with B-cell primary ocular lymphoma (POL) from the Surveillance, Epidemiology, and End Results database where 2778 patients with B-cell POL whose complete clinical information were listed in the Surveillance, Epidemiology, and End Results database between 1997 and 2014. In this study, the overall survival was 181 months, and the median tumor-related mortality has not yet been reached. Patients with ocular B-cell lymphoma, if treated properly, have a greater chance of surviving for longer periods than patients with other B-cell lymphomas. This previous study, 516 of 2778 patients were diagnosed with invasive lymphoma, and the median survival was only 103 months.t

In contrast, the median survival has not yet been determined for patients with indolent lymphomas, suggesting that patients with invasive lymphoma, as with other B-cell lymphomas, require more aggressive treatments. Among those with invasive lymphoma, patients who received both chemotherapy and radiotherapy had the longest survival time, whereas the survival time was similar between patients who received radiotherapy alone and those who received chemotherapy alone.

The survival time was shortest in patients who received neither radiotherapy nor chemotherapy. For indolent lymphomas, the survival time was shortest in patients (≥60 and <60 years old) who received chemotherapy alone. Among all patients, the patients aged 60 years or over with invasive lymphoma had the highest mortality rate, with a median survival of only 76 months; the survival time was longer in patients who received both radiotherapy and chemotherapy.

Regarding our histopathology diagnosis diffuse large B cell lymphoma (DLBCL) is an aggressive B-cell lymphoma, histologically characterized by diffuse proliferation of large neoplastic B lymphoid cells with a nuclear size equal to or exceeding normal histiocyte nuclei. DLBCL, NOS is the most common category of DLBCL. It is a diagnosis of exclusion, applying to DLBCL cases that do not fit into any specific disease subgroups. DLBCL is more common in the elderly but may be seen in any age group. It can arise de novo or as a progression or transformation from low grade B-cell malignancy, such as follicular lymphoma or chronic lymphocytic leukemia (CLL)

Orbital lymphoma can be easily mistaken for another ocular disease due to the slowly progressing nonspecific complaints of the patients. If unspecific orbital symptoms are present, adequate imaging studies followed by early surgical biopsy will contribute to the early diagnosis. We should always be suspicious of this diagnosis especially in patients over sixty years of age with slowly growing mass in the orbit or proptosis non-reacting to specific treatment

Figure 1: Pre-operative clinical pictures reflecting clinical examination findings.

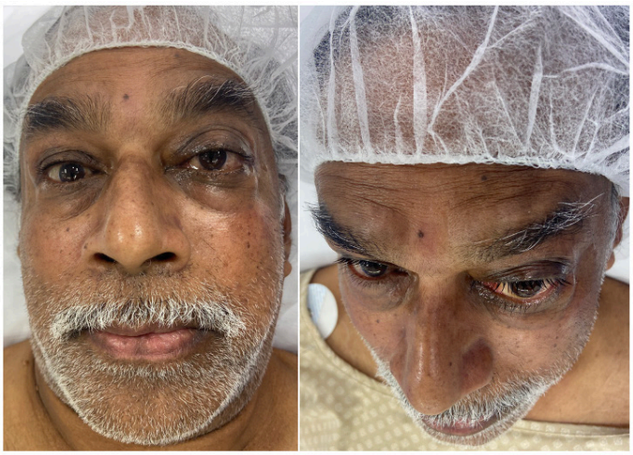


Figure 2: Coronal and sagittal MRI views which showed extension of the infraorbital tumor to adjacent spaces.

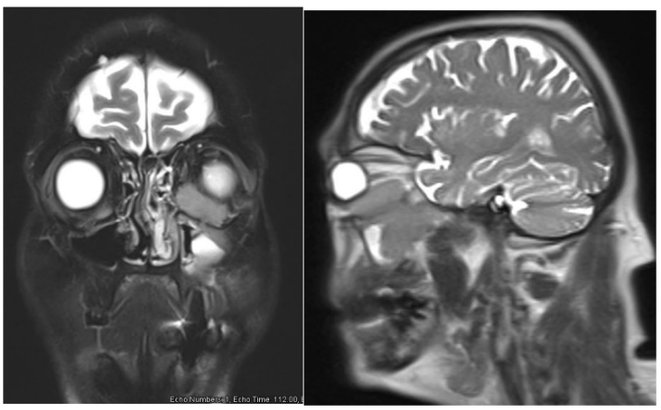


Figure 3: Intraoperative picture showing dissection of the tumor and specimen that was sent to histopathology laboratory.

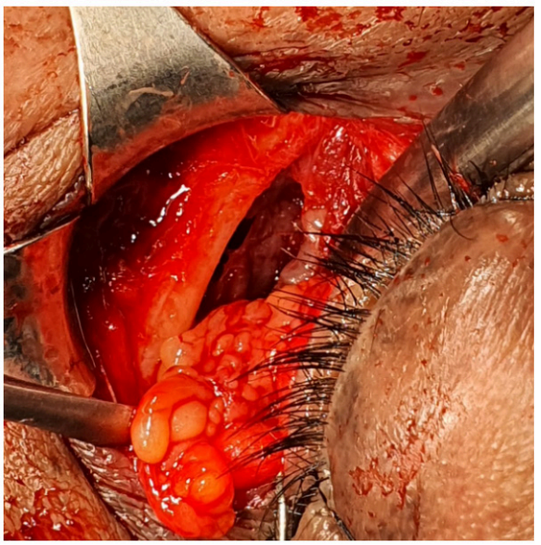


Figure 4: Left: PET CT scan performed prior treatment reflecting increased intake left orbital cavity. Right: PET CT scan performed after chemotherapy treatment reflecting total regression of the prior intake in the left orbital cavity.

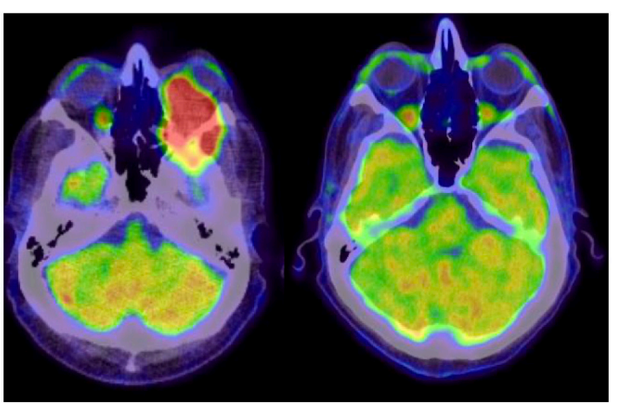


Figure 5: Post chemotherapy clinical pictures that showed regression of clinical findings upon patient evaluation.

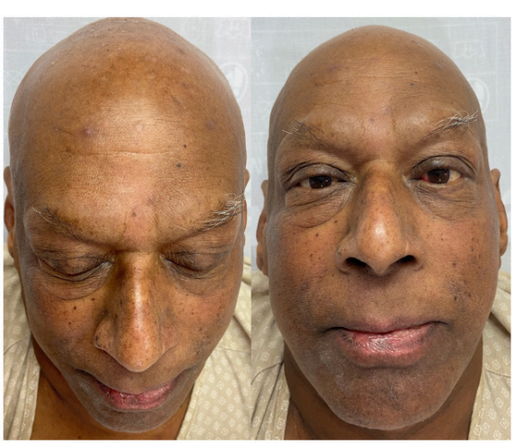
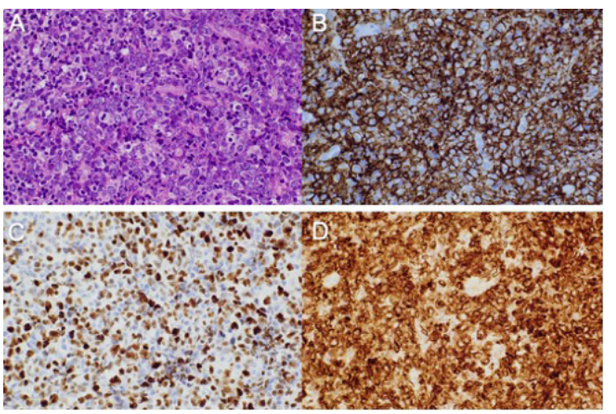


Figure 6: Immunohistochemistry (Figure B-D) showed that atypical cells are B lymphocytes that are positive for CD45, CD20, PAX 5, BCL-6, BCL-2, MUM-1 and C-MYC with Ki67 staining 85% of lymphoid cellular nuclei. CD3 and CD5 are positive in small reactive/residual lymphocytes only. These findings diagnose diffuse large B cell lymphoma, not otherwise specified. FISH for C-MYC is negative.



PATIENT CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images including clinical pictures and investigations. A copy of the written consent and approval by ethics committee from our institution are available for review by the Editor of this journal.

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DECLARATION OF COMPETING INTEREST

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AUTHORSHIP

All authors attest that they meet the current ICMJE criteria for Authorship.

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