

Orbital Lymphoid Lesions: Short Series with Cytohistological Correlation

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ABSTRACT

Orbit and ocular adnexae are common sites (10-15%) for developing lymphoid lesions but have diagnostic and staging difficulties similar to other extranodal sites. Out of 15 fine needle aspirates from orbital lesions received in last 5 years three female patients of age 56, 46 and 72 years presented to FNAC clinic with upper eyelid swellings of 2 years, 3 years and 3 months duration. Systemic examination was unremarkable. Hematological and Serum protein electrophoresis was normal. On MRI case 1 was suggestive of infective/neoplastic lesion. On CECT case 2 was suggestive of pseudotumor/lymphoma while case 3 was suggestive of pseudotumor. F.N.A.C of case 1 showed polymorphous population of lymphoid cells, without any significant mitosis. FNAC of case 2 showed a monotonous population of lymphoid cells and Case 3 showed a relatively monotonous population in a background of lymphoglandular bodies. Case 1: Responded to steroids. Case 2: was advised a biopsy for confirmation, Case 3: Excision done in view of the recurrent nature with no response to steroids. Histopathology in Case 2 showed a non encapsulated mass with proliferation of lymphoid cells forming nodules, IHC showed a monoclonal pattern while Case 3 showed a nonencapsulated mass with nodular proliferation of lymphoid cells involving the surrounding adipose tissue with formation of primary and secondary follicles and Immunohistochemistry (IHC) showed a polyclonal population. Three cases are being discussed to highlight the diagnostic dilemmas in orbital lymphoid lesions and relevance of IHC in such cases.

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Introduction

A total of 15 Fine needle aspiration cytology (FNAC) lesions of orbit having eyelid swellings were reviewed over a period of five years of which three patients diagnosed as having lymphoid lesions have been taken for the present study. Lymphoid proliferations comprise 10-15% of all space occupying lesions of the orbit and pose a diagnostic challenge for clinicians and diagnosticians alike.^[1] Delineation between benign and malignant orbital lymphoid lesions is difficult, in absence of clearcut architectural differentiating criteria as defined in a lymph node. This is due to presence of only few scattered lymphoid cells in the orbit.^[2,3]

There have been attempts to categorize orbital lymphoid lesions into different categories dividing them into Lymphoma, indeterminate lesions and reactive lymphoid hyperplasia.^[2,4] Few authors divided them as Lymphoma, Benign pseudolymphoma, Orbital pseudotumor, Orbital lymphoid hyperplasia and Chronic inflammatory lesions.^[1,5] Some authors divided them immunologically into monoclonal and polyclonal.^[4,5]

Further attempts have been made to extend the utility of Fine Needle Aspiration Cytology (FNAC) in orbital lesions,^[6,7] wherein overlaps between pseudolymphoma and lymphoma have been reported invariably, although 100% concordance has also rarely been reported.^[8] The cases where atypical features are present, one has to rely on Immunohistochemistry (IHC) or Polymerase chain reaction for further delineation.^[2,4,6,7,9] and through a short series of three cases we aim to highlight these diagnostic dilemmas.

Case Reports

Case 1: 58 year old female presented with a slowly progressive painless right upper eyelid mass of 2 years duration. Systemic and hematological examination revealed no abnormality. Serum electrophoresis showed mild increase in gamma globulins. B-scan orbit was normal. MRI showed a well defined soft tissue signal intensity lesion measuring 21 x 17 x 19 mm in the right upper quadrant of orbit inseparable from the right lacrimal gland and closely abutting the right lateral rectus muscle giving a probable diagnosis of ? neoplastic ?? infective lesion. F.N.A.C done showed polymorphous population comprising of mature and transformed lymphocytes along with occasional plasma cells. Mitosis was absent. A diagnosis of Orbital Lymphoid Hyperplasia was given and a biopsy was advised, however the patient responded to steroids.

Case 2: A 72 year old female presented with a gradually progressive protrusion of the left eyeball since three months.

Systemic, Hematological and Serum electrophoresis revealed no abnormality. B-scan and visual acuity was normal. The patient did not have any constitutional or other significant symptoms. However experienced slight eye pain and heaviness of head. CECT orbit showed a 27 x 21 x 20 mm ill defined homogenous intraconal mass in superior compartment of left orbit encasing the optic nerve with patchy enhancement, however sparing the surrounding muscles, fat and bones. F.N.A.C done showed highly cellular smears comprising of singly lying pleomorphic cells larger than the mature lymphocytes having round to oval vesicular nucleus with indistinct nucleoli and stripped off cytoplasm in most of the cells, however wherever preserved was scant and pale blue. Few cells showed irregular nucleus with lobulation and clefting along with binucleation. Infrequent mitosis and lymphoglandular bodies were noted in the hemorrhagic background. A diagnosis of high grade lymphoma was given and a biopsy advised.

Histopathology showed a nonencapsulated mass with proliferation of lymphoid cells forming nodules at places. The lymphoid cells were larger than the mature lymphocytes with irregular nuclear contours with scant to moderate cytoplasm and vesicular nuclear chromatin. Fine fibrosis with focal areas of necrosis was noted. Mitosis was infrequent. Amongst IHC markers CD 20 positivity was seen mainly in the larger cells with no T cell positivity and thereby confirming the diagnosis.

Case 3: 46 year old female a native of Arunachal Pradesh presented with a progressive, painless and recurrent left upper eyelid swelling since 3 years. Systemic, hematological examination and serum electrophoresis revealed no abnormality. B-scan and visual acuity was normal. CECT showed 27 x 14 x 12 mm extraconal soft tissue density in upper outer aspect of left orbit, in periorbital location in continuity with lacrimal gland with minimal surrounding infiltrates sparing extraocular muscles, fat, optic nerves and bony margins with a likely diagnosis of pseudotumor. F.N.A.C showed a relatively monotonous population in a background of lymphoglandular bodies and very very occasional plasma cells. A diagnosis of Orbital lymphoid hyperplasia was given. However biopsy was advised to rule out lymphoma.

On Histopathology variable sized nodules separated by fibrous bands showing polymorphous lymphoid proliferation along with formation of germinal centres in many of the nodules was seen. Peripheral areas showed a diffuse pattern with entrapped adipose tissue. The lymphoid cells were larger than mature lymphocytes showing angulated nuclear borders and scanty cytoplasm

along with interspersed larger cells having abundant pale cytoplasm. Very occasional plasma cells and infrequent mitosis was noted. No residual lacrimal gland identified. A diagnosis ? atypical orbital lymphoid hyperplasia/pseudolymphoma was given supplemented by IHC which revealed a polyclonal population of lymphoid cells. The IHC panel comprised of the markers available in our set up and included both B and T cell markers. T cell markers included CD 3 and CD8 showing mainly interfollicular area positivity, CD4 positive cells were randomly distributed throughout the nodule. Amongst B cells CD 20 positivity was seen with in the nodule in germinal center and scattered positivity in the interfollicular area. BCL2 showed non germinal centre positivity, CD 10 was negative and Lambda/kappa showed polyclonal pattern with no light chain restriction. Pancytokeratin was negative indicating absence of any epithelial component and residual lacrimal gland while Ki 67 showed < 1% positivity. Post Operative follow up for 3 months with steroids was uneventful, however patient came back with a recurrence and was advised radiotherapy.

Discussion

Localised lymphocytic proliferation within the orbit is commonly seen as causing swelling/proptosis and poses a challenging problem as their benign or malignant nature cannot usually be determined by clinical and radiological

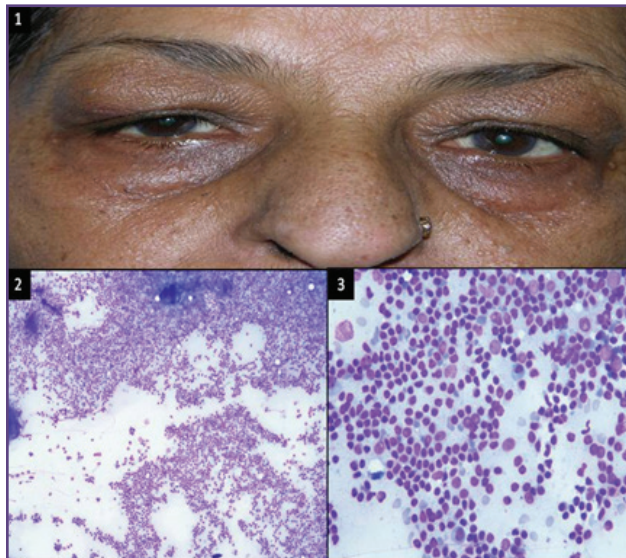


Fig. 1: (1) 56 years female showing a firm, mobile right upper eyelid swelling measuring 2x1cm (Case 1). (2,3) Cytosmear showing polymorphous population comprising of mature and transformed lymphocytes along with occasional plasma cells. (Giemsa 10X, 40X)

criteria.^[4] Lymphoid tumors are most commonly seen in the orbit (52%) followed by conjunctiva (29%).^[4] These tumors also known as lymphoproliferative lesions are the most common primary orbital tumors in adults comprising of reactive lymphoid lesions and lymphoma which are often difficult to differentiate.^[2,4,10,11]

Subsequently these lymphoproliferative lesions have been categorized by Knowles and Gaag et al into :

1. Lymphoma - Malignant end of spectrum
2. Benign pseudo lymphoma
 - Orbital pseudotumor
 - Orbital lymphoid hyperplasia
3. Orbital inflammatory diseases (OID)

An inflammatory presentation is not uncommon in orbital lymphoid tumors which accounts for up to 6% of orbital diseases.^[12] Differential diagnosis of OID ranges from idiopathic inflammatory disease to systemic or local inflammatory conditions to other associated conditions such as neoplasm, infection, congenital malformation, or trauma.

It is divided into primary and secondary . Primary lesions being infectious (bacterial, fungal , parasitic), non infectious (thyroid associated) and idiopathic (which is the third most common orbital disease after thyroid associated

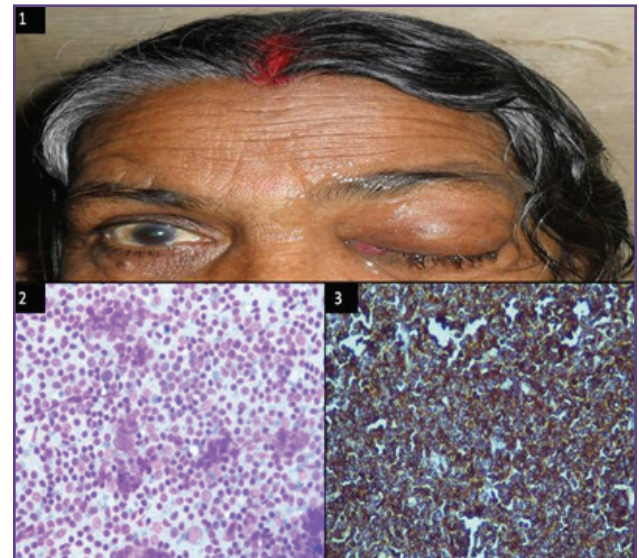


Fig. 2: (1) 72 years female with a firm left upper eyelid swelling measuring 2.7x 2.1 cm (Case 2). (2) Cytosmears showing highly cellular smears comprising of singly lying pleomorphic cells larger than the mature lymphocytes. (Giemsa 40X) (3) CD 20 positivity seen mainly in the larger cells with no T cell positivity. (IHC 40X)

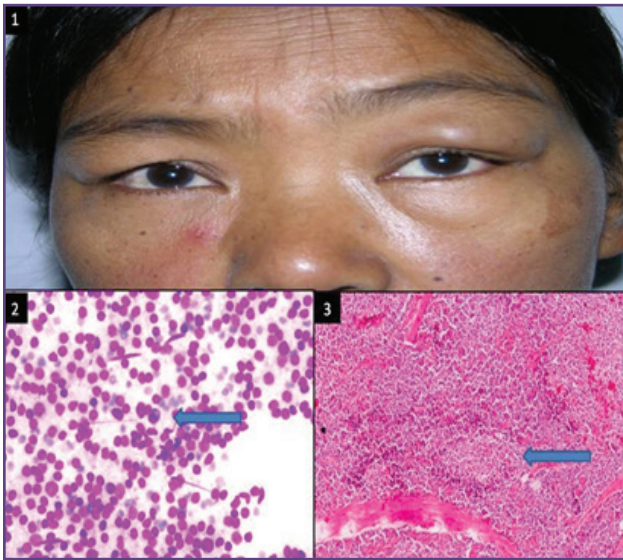


Fig. 3: (1) 46 years female showing a firm, oval swelling measuring 2x1x1cm in size located in upper lateral angle of left orbit (Case 3). (2) Cytosmear showing a relatively monotonous population of lymphoid cells in a background of lymphoglandular bodies and very occasional plasma cells. Arrow showing a plasma cell. (Giemsa 40X) (3) Histopathology showing a nonencapsulated mass with nodular proliferation of lymphoid cells involving the surrounding adipose tissue with formation of primary and secondary follicles. Arrow shows a follicle with surrounding mantle zone. (H&E 10X).

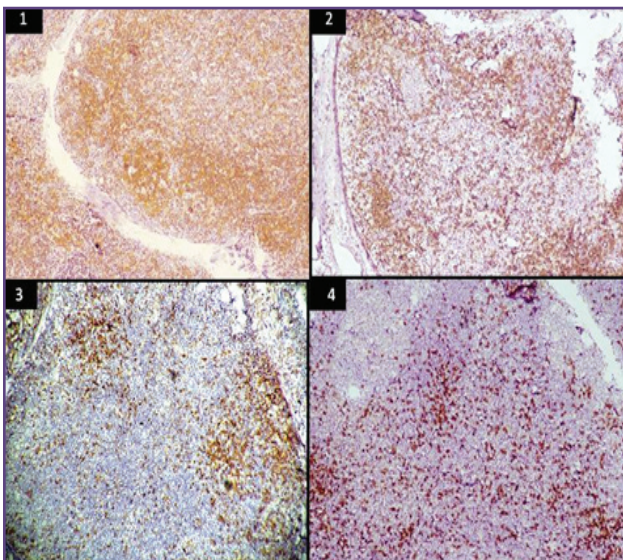


Fig. 4: (1) CD 20 positivity with in the nodule in germinal center and scattered positivity in the interfollicular area (10X) (2) CD 3 showing interfollicular area positivity. (10X) (3) CD4 positive cells randomly distributed throughout the nodule. (10X) (4) CD8 showing mainly interfollicular area positivity. (10X)

ophthalmopathy and lymphoproliferative diseases) . Secondary lesions occur in response to inflammation due to some orbital condition like lymphoproliferative disease, foreign body , trauma , hemorrhages etc. [10,12]

The last two groups in the classification are characterized morphologically by a relatively monomorphous, hypercellular, reactive lymphoid hyperplasia, or by a heterogenous cell population with small and large lymphocytes, plasma cells, eosinophils, histiocytes and by lymphofollicles with germinal centres and fibrosis.

Excluding lymphoma all are interchangeable terms, used to describe orbital mass lesions in which mature lymphocytes are noted to infiltrate orbital structures.[14]

On the other hand Ghasemi [2] et al have categorized them into :

1. **Reactive lymphoid hyperplasia (RLH)** - Composed of dense polymorphous population of well differentiated lymphocytes, other inflammatory cells and occasional lymphoid follicles with germinal centers. Mitosis if present is restricted only to the germinal centers and tingible body macropahges can also be seen. However dutcher bodies are absent. Immunohistochemically the tumors consist of mixed population of T- and B-lymphocytes and show polyclonality for Kappa/lambda. BCL-2 positivity is seen in interfollicular zones only.
2. **Atypical lymphoid hyperplasia (indeterminate lesions)** - Represent between 3-12% of the lymphoproliferative lesions in the ocular adnexa.[4] It does not reveal overt benign or malignant features and lie in a gray zone .This group consists of those borderline cases in which the diagnosis of the lesions cannot be determined with certainty using conventional histological techniques. These lesions can have a diffuse/follicular pattern and cells manifest borderline maturity or contain atypical cells with large hyperchromatic nuclei. Often requires IHC to categorize and gives polyclonal pattern.
3. **Lymphoma** – Ocular lymphomas represent 8 % of all the extranodal lymphomas and show classic cellular atypia or immunophenotypically, express monoclonality. Most of them are primary extranodal lymphoma of the marginal zone of mucosa associated with lymphoid tissue (MALT type lymphoma). Important histomorphologic features of ocular adenexal lymphomas is cytologic atypia and dutcher bodies though immunohistochemistry is required in one third of the cases.[13] Germinal centre formation, polyclonality and lack of cellular atypia indicate benign lesions however some polyclonal tumours

may become malignant and some monoclonal tumors may remain benign. 27-29% of patients with RLH and 45% with indeterminate lesions are known to develop disseminated disease.^[4]

Some authors have attempted to distinguish orbital pseudotumor from orbital lymphoid hyperplasia, but these distinctions are difficult and of uncertain prognostic or therapeutic importance.^[14]

Case 1 in our study was categorized as orbital lymphoid hyperplasia as per both the classifications. Case 2 occupies the extreme malignant end of the spectrum as per the classifications and immunologically being monoclonal. However case 3 was categorized as Benign pseudolymphoma and atypical lymphoid hyperplasia respectively, though polyclonal immunologically.

Similar to the reported age/sex distribution; out of three cases, two of benign nature were seen in patients in their fourth decade while case no.2 being malignant was seen in elderly with all being females.^[1,11] though few authors observed no significant gender and age correlation.^[2,4]

These patients presented with palpable mass/swelling, pain and diplopia as also seen in 65% of cases, with symptoms being less acute in lymphoma.^[1,2,4,1] Time duration of complaints were much longer in cases with lymphoma versus pseudolymphoma /chronic inflammation, similar to as seen in our study.^[1]

Case no.3 was chosen to illustrate how difficult and dilemmatic the diagnosis and management of orbital lymphoid tumors can be. In view of recurrent nature of the swelling even after course of steroids in this case, a biopsy was advised to rule out lymphoma. Also because the patients origin was from north eastern india, where the incidence of lymphomas is more.^[15] Morphologically infiltration of lymphoid cells into the surrounding adipose tissue was insignificant, as the site is extranodal. Presence of primary and secondary follicles with germinal centres along with fibrosis favoured benignity in Case 3 however the peripheral diffuse pattern even in absence of atypia favoured indeterminate category, and therefore IHC was used as an adjunct to rule out lymphoma^[2], which showed both B and T cell positivity with no light chain restriction. Also no histological atypia was seen, and therefore a diagnosis of pseudolymphoma was given. The low ki 67 labelling index also suggested the diagnosis. Low grade B cell lymphomas were ruled out by absence of bcl-2 positivity as seen in follicular lymphoma and Kappa/lambda being monoclonal while Extranodal marginal zone lymphomas (MALT) were excluded due to the absence of atypical monocytoid B cells and CD 5 as also noted by other workers.^[1,2,6,7,9]

All the authors had to face diagnostic challenges in the form of indeterminate cases. In our study the lesions were divided into two groups reactive lymphoid hyperplasia and lymphoma; with a gray zone of so called histologically indeterminate tumor was observed in case 3, as also reported by others.^[1,2,4]

However immunohistochemical studies along with other molecular studies helped in decreasing the number of indeterminate cases. IHC was a helpful tool in our study used for confirmation, diagnosis and categorization. Also used to determine the clonality of indeterminate cases with evaluation of clonal immunoglobulin light chains (kappa/lambda) expression to find neoplastic cells.^[1,2,4]

Panel of monoclonal antibodies like CD45, CD30, CD20, CD5, CD8, CD21, CD23, ki67, p53, bcl2, ki67, p53 and pan cyto keratin were used. Polyclonal antibodies were used to test the expression of CD 3 antigens and of the immunoglobulin chains kappa, lambda, gamma etc. Proliferative markers like p53, ki 67 also correlate with the prognosis and divide the tumor accordingly into low and high grade.^[4]

Other sophisticated methods which can be applied are electron microscopy, immunofluorescence and molecular diagnostic tests like PCR.^[1,2,4] Recent development of these techniques have made it easier to differentiate benign from malignant orbital lymphoid disorders.^[14]

Few authors suggested that 27%-29% of RLH and upto 45% indeterminate lesions ultimately develop disseminated disease and therefore accurate and prompt diagnosis with a close follow up of the lymphoid proliferations in the orbit results in better adjusted treatment for each group of patients.^[1,4]

Most cases of pseudotumors respond well to steroids which are used as first line therapy, with durable complete response in 50% of the cases. However radiation therapy gives a 75%-100% response with almost rare relapse rates.^[14]

Rituximab which is a chimeric monoclonal antibody directed against CD20 receptors is being used as a latest targeted therapy. Since benign lymphoid hyperplasia of the orbit predominantly consists of B-cells bearing the CD20 surface marker, rituximab is a treatment alternative for refractory benign lymphoid hyperplasias along with other lymphoproliferative disorders and when used in combination with radioimmunotherapy or standard chemotherapy gives a more durable response with lesser side effects than radiation therapy.^[16]

BLH can be left untreated if the associated symptoms are minimal. There is evidence, however, that BLH can

undergo malignant transformation especially in lesions involving the lacrimal gland and therefore a careful follow up of the pseudolymphoma patients and patients with a chronic inflammatory disease is mandatory in order to study whether a neoplastic disorder can arise locally from a reactive process. ^[1]

Summary

Differentiation between benign and malignant lymphoid proliferations of the ocular adnexa creates a diagnostic dilemma. We endorse that relying purely on FNAC is not recommended and often requires a good histomorphologic correlation keeping in mind the similarity in clinical presentation of indeterminate cases to lymphomas. Majority recommend a biopsy if this can be performed without significant morbidity due to the unusual nature of lymphoproliferative disorders. Though histopathology is considered confirmatory in diagnosis of these lesions, immunohistochemistry with other molecular techniques is required for a more refined diagnosis of lymphoid proliferations.

Multidisciplinary cooperation and a prompt follow up leads to further improvement of diagnosis and treatment of ocular adnexal lymphoproliferative disease with a need to work up all patients regardless of histopathologic diagnosis.

Bibliography

- Gaag R, koornneef L, Heerde P, Vroom T, Pegels J, Feltkamp S et al. Lymphoid proliferations in the orbit: malignant or benign? *British Journal of Ophthalmology* 1984; 68:892-900.
- Ghasemi M, Amoli AF, Gransar A. A clinicopathologic study of orbital and ocular adnexal lymphoproliferative lesions with immunohistochemical staining of indeterminate cases. *Acta Medica Iranica* 2003;41(1):11-14.
- Ulivieri S, Motolese PA, Motolese I, Motolese E, Menicacci F, Gennari P. Benign orbital pseudolymphoma. Case report. *Giugno-Luglio* 2009; 30: 299-301.
- Coupland SE, Krause L, Delecluse HJ, Anagnostopoulos I, Foss DH, Hummel M, Bornfels N et al. Lympho-proliferative lesions of the ocular adnexa. Analysis of 112 cases. *Ophthalmology* 1998;105:1430-1441.
- Knowles DM, Jakobiec FA. Ocular adnexal lymphoid neoplasms. *Hum Pathol* 1982; 13: 148-162
- Subramanian R, Solo S, Mishra MM, Murugan P, Siddaraju N, Basu D, Srinivasan R. Fine needle aspiration cytology of primary lymphoid lesions of the orbit: report of four cases. *Acta Cytol.* 2007;51(3):417-420.
- Tani E, Seregard S, Rupp G, Söderlund V, Skoog L. Fine-needle aspiration cytology and immunocytochemistry of orbital masses. *Diagn Cytopathol.* 2006;34(1):1-5.
- Singhal N, Mundi IK, Handa U, Punia RP, Mohan H. FNA in diagnosis of orbital lesions causing proptosis in adults. *Diagnostic Cytopathology.* 2012; 40(10) : 861-864.
- Lowen MS, Saraiva VS, Martins MC, Burnier Jr MN. Immunohistochemical profile of lymphoid lesions of the orbit. *Can J Ophthalmol* 2005; 40(5): 634-639.
- Choi VBL, Yuen HKL, Biswas J, Yanoff M. Update in pathological diagnosis of orbital infections and inflammations. *Middle East Afr J Ophthalmol* 2011; 18(4) : 268-276.
- Mannami T, Yoshino T, Oshima K, Takase S, Kondo E, Ohara N et al. Clinical, Histopathological, and Immunogenetic Analysis of Ocular Adnexal Lymphoproliferative Disorders: Characterization of MALT Lymphoma and Reactive Lymphoid Hyperplasia. *Mod Pathol* 2001;14(7):641-649.
- L K Gordon. Orbital inflammatory disease: a diagnostic and therapeutic challenge. *Eye* 2006; 20:1196-1206.
- Medeiros LJ, Harris N. Lymphoid infiltrates of the orbit and conjunctiva. A morphologic and immunophenotypic study of 99 cases. *Am J Surg Pathol.* 1989 Jun;13(6):459-71.
- Chesbro AC, Quivey JM. Cancer and benign diseases of eye and orbit. In: Leibel SA, Phillips TL, editors. *Textbook of radiation oncology*, 2nd ed. Philadelphia: Saunders; 2004: 1443-1461.
- Das D, Deka P, Bhattacharjee k, Das JK, Kuri G, Deka AK, Bhattacharjee H. Ocular adnexal lymphoma in the Northeast Indian population. *Indian J Ophthalmol* 2008 ; 56(2): 153-155.
- Ho HH, Savar A, Samaniego F, Manning J, Kasyan A, Pro B et al. Treatment of Benign Lymphoid Hyperplasia of the Orbit with Rituximab. *Ophthal Plast Reconstruct surgery* 2010; 26:11- 13.