

# A CLINICOPATHOLOGIC STUDY OF ORBITAL AND OCULAR ADNEXAL LYMPHOPROLIFERATIVE LESIONS WITH IMMUNOHISTOCHEMICAL STAINING OF INDETERMINATE CASES

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**Abstract-** The histopathologic diagnosis of orbital and ocular adnexal lymphoproliferative lesions is difficult, resulting controversy in classification, determining benignity or malignancy of them and treatment modality selection. We designed the following study to evaluate clinical, histopathologic and if necessary immunochemical features of them in decreasing indeterminate cases. The study includes 51 subjects of biopsy-proven orbital lymphoid lesions and inflammatory pseudotumors from pathologic practices of Farabi and Iman Khomeini Hospitals, from April 1994 to March 2000. We reviewed H&E stained slides. Then we examined clonality of indeterminate cases with evaluation of clonal immunoglobulin light chains ( $\kappa$  or  $\lambda$ ) expression to find neoplastic cells. CD markers were used for excluding other closed morphologic differential diagnosis. In conclusion we determined 40 cases of lymphoproliferative lesions, divided to the following three groups: malignant lymphoma with sixty-five percent frequency were the most common type of them, reactive lymphoid hyperplasia with twenty percent was the second one and atypical lymphoid hyperplasia with fifteen percent was the third one. The most common site of involvement was orbit (57.5%). Males were affected slightly higher than females. Median age at diagnosis was 62 years. The most common type of lymphoma group was low grade small lymphocytic lymphoma. It is necessary to note that 11 out of total 51 subjects were excluded under other pathologic diagnosis. On the other hand 4 cases of already diagnosed pseudo-tumors were reclassified into three lymphoid lesion categories above.

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**Key Words:** Orbit, ocular adnexae, lymphoproliferative lesion

## INTRODUCTION

Orbit and ocular adnexae are common sites for developing lymphoid lesions and like other extranodal sites have diagnostic and staging difficulties (1-3). Histologically these lesions are divided into three groups including: reactive lymphoid hyperplasia which is composed of polymorphic population of well differentiated lymphocytes, other cells and occasional lymphoid follicles with germinal centers. Immunophenotyping of this group shows polyclonal cells. Malignant lymphoma group show classic cellular Atypia or immunophenotypically, express monoclonal light chain of immunoglobulin or genetically reveal immuno-

globulin light chain genes rearrangement.

Atypical lymphoid hyperplasia (indeterminate) histologically, does not reveal overt benign or malignant features and lie in gray zone (3,4). Because normally, lymphoid tissue could not be found in orbits, is restricted in conjunctiva and lacrimal glands to only scattered lymphocytic infiltration, there for any lymphoid lesions in these regions is abnormal (4). Furthermore, due to absence of lymph nodes, the conventional histomorphologic criteria for determining their behavior does not have any benefit. Hence their definite diagnosis is based on cytomorphology and clonality of cells. The purpose of this study was to determine and classify lymphoproliferative lesions of orbit and to assess their clinical features. Moreover in order to reduce indeterminate cases, immunohistochemical staining of paraffin blocks was done. Because many clinicians and pathologists falsely believe on pseudotumors as lymphoid lesion, we reevaluated already diagnosed inflammatory pseudo tumors.

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## MATERIALS AND METHODS

We examined 51 cases of biopsy- proven orbital and ocular adnexal lymphoid lesions and pseudotumors in pathology departments of Farabi and Imam Khomeini Hospitals of Tehran from April 1994 to March 2000. We recorded clinical information including age gender, site (orbit, eyelids, conjunctiva or lacrimal glands), side, signs and symptoms presentation, extraocular manifestation and past lymphoma history of each case.

The hematoxylin and eosin-stained slides of all patients were reviewed by three pathologists. We described their histomorphologic features including cellular atypia polymorphism of cell population and presence of lymphoid follicles, germinal center and lymphoepithelial lesion. In controversial or indeterminate cases and to exclude other closed morphologic differential diagnosis, immunohistochemical staining for clonal immunoglobulin light chain ( $\kappa$  or  $\lambda$ ) expression, CD3, CD20, and CD45 markers were done. Then we classified the diagnosed lymphoid lesions to three groups described above. Malignant lymphoma was classified according to working formulation. We also classified the lymphoma according to real system, based on histologic and immunophenotyping with CD markers. In some cases that immunophenotyping had not been done, we defined them as low grade lymphomas.

## RESULTS

Eleven out of total 51 subjects histologically and immunophenotypically did not correlate with lymphoid lesions which as pseudotumor, myeloid leukemia and carcinoma were excluded, on the other hand 4 already diagnosed pseudotumors were reclassified as one of three lymphoid groups. Final frequency of orbital and ocular adnexal lymphoproliferative lesions after morphologic and immunophenotyping review is shown (Table 1).

**Table 1.** Orbital and ocular adnexal lymphoid lesions frequency

Type	No	%
Reactive lymphoid hyperplasia	8	20
Lymphoma	26	65
Indeterminate	6	15
total	40	100

### Clinical features

Fifty-five percent of patients were male and the others females, ages at diagnosis varied between 3 to 75 years with median age 62 years. Fifty-seven percent of

patients had right sides, 7.5% both side and the others had left side involvement. The most common symptoms and signs at presentation were swelling and mass respectively (Table 2 and 3).

**Table 2.** Patient's symptom at presentation

Symptom *	No	%
Swelling	26	85
Mass	12	30
Proptosis	3	7.5
Lacrimation	3	7.5
Pain & redness	1	2.5

\* Some patients had several symptoms

**Table 3.** Signs of orbital and ocular adnexal lymphoid lesion at presentation

Sign	No	%
Mass	27	87.5
Proptosis	12	10
Periorbital edema	1	2.5

Table 4 Shows frequency of anatomic site of involvement.

**Table 4.** Frequency of anatomic site involved by lymphoid lesions in descending order

Site *	No	%
Orbit	23	57.5
Upper eyelid	13	32.5
Conjunctiva	8	20
Lacrimal gland	3	7.5
Eyebrow	1	

\* Some of patients had several sites involvement at presentation

Three patients (7.5%) showed extraocular involvement, but none of them had past lymphoma history.

**Table 5.** Lymphoma type based on working

Histologic type	No	%
Small lymphocytic	17	65.8
Diffuse large cell	2	7.6
Follicular small cleaved cell	2	7.6
Mycosis fungoides	1	3.8
Plasmacytoma	1	3.8
Diffuse small noncleaved cell	1	3.8
Diffuse mixed small and large cell	1	3.8
Unclassifiable	1	3.8
Total	26	100

### Pathologic features

Frequency of lymphoma subtypes are shown (Table 5). Eighty-one percent of lymphomas were well differentiated, 15% low and the remaining were moderately differentiated. Some lymphomas were classified according to real classification.

The others which we could not reclassify based on this system, were generally defined as low grade lymphoma groups (Table 6).

**Table 6.** Lymphoma types based on real classification.

Histologic type	No	%	note
Maltoma	8	33.6	
S.L.L*	4	14.2	
Low grade lymphoma	4	14.2	
Follicular center lymphoma	3	11.4	
Diffuse large cell	2	7.6	B-cell type CD <sub>20</sub> <sup>+</sup>
Burkitt like	1	3.8	B-cell type CD <sub>20</sub> <sup>+</sup>
Mycosis fungoides	1	3.8	B-cell type CD <sub>3</sub> <sup>+</sup>
Plasma cell myeloma	1	3.8	
Immunocytoma	1	3.8	B-cell type CD <sub>20</sub> <sup>+</sup> LCA <sup>+</sup>
Unclassifiable	1	3.8	
total	26	100	

\* Small lymphocytic lymphoma

## DISCUSSION

In our study 55% of forty diagnosed patients with orbital and ocular adnexal lymphoid tumors were male and the others as females. The youngest patient was a 3 years old child with burkitt like lymphoma.

It is necessary to note that there was not meaningful statistical correlation between gender, age and anatomic site with histologic subtypes of orbital lymphoid lesions.

The median age at diagnosis was 62 years (range: 3-75 years). The most common site of involvement was orbit. We found sporadic involvement of conjunctiva, lacrimal glands and eyelids, these findings generally correlated with other studies (2,5-7). Bilaterality was seen only in orbital lymphomas as other studies have shown (3).

Three patients had extraocular manifestation of lymphoid diseases, others showed only orbital involvement but none of them had a past history of lymphoma. The other investigators showed somewhat similar extraocular manifestations (3,4).

The most common type of orbital lymphoid lesions were lymphoma with 65% frequency, reactive lymphoid hyperplasia (20%) as the second one and indeterminate (15%) was third one. This study which had been done to reduce indeterminate cases correlated with other studies which showed 3-13% (6) or some 50% (3) indeterminate cases. Also one study showed frequency of lymphoma as 88.3%, reactive lesions 10.7% and indeterminate cases with molecular methods decreased to under 1% (4). The discrepancy between our study and

the one mentioned later may be due to loss of two paraffin block for immunohistochemical staining and nonavailability of molecular methods for determining neoplastic population.

This article showed small lymphocytic lymphoma with 65.8% frequency, as shown in table 5, as the most common subtype of ocular lymphoma like other literatures (3,5,7). Also based on real classification, maltoma with 33.6% frequency was the most common type of orbital and ocular adnexal lymphoma. Recent studies showed that maltoma with 47-63.6% frequency was the most common lymphoma of this region (1). Also we determined orbital plasmacytoma immunocytoma, mycosis fungoides and burkitt like lymphoma, as shown in table 6.

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