Ocular Extranodal Marginal Zone Lymphoma - A Study of Twenty-Two Cases Presented at Bangalore, Karnataka

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ABSTRACT

BACKGROUND

Ocular adnexa lympho-proliferative disorders are a divergent diverse category of ocular malignancies, comprising roughly about 1 % to 2 % of Non-Hodgkin's lymphomas (NHLs) and 8 % of extranodal lympho-proliferative disorders. The most frequent type, approximating for up to 80 % of cases that constitutes the primary is marginal zone lymphoma of mucosa associated lymphoid tissue (MALT) type. Marginal zone lymphomas which usually have an extranodal presentation are routinely diagnosed by histomorphology by the diffuse infiltration of atypical lymphoid cells with plasmacytoid appearance and presence of pathognomonic lymphoepithelial lesions. Lymphoepithelial lesions are the existence of lymphocytes in the cytoplasm of epithelial cells. Immunohistochemistry shows a consistent absence of CD5 and CD23 staining, hence considered as diagnosis of exclusion on histo-immunomorphology.

METHODS

This is a case-series study. Twenty-two cases of ocular extranodal marginal zone lymphoma were obtained from the archives of pathology from 2013 to 2015. The histopathology and immunohistochemistry slides were reviewed by three expert histopathologists for confirmation of diagnosis. Immunohistochemical markers mainly used were CD45, CD3, CD5, CD20, cyclin D1, CD10, Ki - 67, BCL - 2, PAX 5 and CD23. The immunohistochemical markers such as CD10, BCL - 2 and cyclin D1 IHC expression were studied in cases of ocular extranodal marginal zone lymphoma (OENMZL). Relevant clinical details were collected from the patients such age, sex and history of autoimmune condition if any.

RESULTS

Eighteen cases (81 %) of OENMZL belonged to the age group of more than 40 years. There was a definite male preponderance (77 %) and it was associated with autoimmune conditions such as Hashimoto's thyroiditis (18 %) and Sjogren's syndrome (22 %). 22 cases of OENMZL were analysed and all showed consistent immunoexpression for CD20, CD45 while were immunonegative for CD5, CD23 and cyclin D1. 6 cases (27 %) showed CD10 positivity while 20 cases showed Bcl-2 positivity (90 %).

CONCLUSIONS

OENMZL shows positivity for CD20 and CD45 while immunonegative for CD5, CD23 and cyclin D1**,** and a fraction of cases can show IHC positivity for CD10 and Bcl-2.

KEYWORDS

OENMZL: Ocular Extranodal Marginal Zone Lymphoma, MZL: Marginal Zone Lymphoma, CD: Cluster Differentiation. NHL: Non-Hodgkin Lymphoma. OL: Ocular Lymphoma. PCR: Polymerase Chain Reaction, FISH: Fluorescent In Situ Hybridization

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BACKGROUND

Lymphomas of the eye are a heterogeneous group of malignancies, accounting for approximately 1 % to 2 % of non-Hodgkin lymphomas (NHLs) and 8 % of extranodal lymphomas.[1] The majority of ocular lymphomas (OL) are primary extranodal neoplasms; however, 10 % to 32 % are secondary tumours in patients with disseminated lymphoma.[2–5] 95 % and more are of B-cell origin, 80 % of which are low-grade lymphomas. The most common subtype of primary OL, accounting for 35 % to 80 % of cases, is extra nodular marginal zone lymphoma of mucosa associated lymphoid tissue type, followed by follicular lymphoma (~ 20 %), diffuse large B - cell lymphoma (~ 8 %), and less commonly mantle cell lymphoma, small lymphocytic lymphoma, and lymphoplasmacytic lymphoma.[2,4,6–12] Few cases of primary T-cell lymphoma and Hodgkin lymphoma of the ocular adnexa have been reported.[8] In Japan and Korea, the proportion of MALT lymphoma among primary ocular extranodal marginal zone lymphoma appears to be higher (80 % - 90 %) than in Western countries.[9,13-15] Marginal zone lymphoma is composed of lymphocytes and plasmacytoid lymphocytes with formation of lymphoepithelial lesions. The atypical lymphoid cells are positive for CD20 while are negative for CD5, CD23 and bcl - 2. KI - 67 proliferation index is usually low. Lymph nodal tissue displays partial or diffuse obliteration of nodal architecture by presence of parafollicular infiltration of monocytoid appearing B cells that are 3 times larger than small lymphoid cells. Tumour cells envelope and permeate the follicles. The neoplastic cells exhibit modest to ample clear cytoplasm, round to irregular cleaved nuclei with coarse nuclear chromatin. Benign follicular centres are seen in around 30 % cases displaying neoplastic plasma cells. Follicular dendritic meshwork shreds are noted reminiscent of colonized follicles. Ocular adnexal affection occurs secondarily in 2.4 % to 5.3 % of cases with multi-systemic marginal zone lymphoma.

Lymphoproliferative lesions in the eye environs a broad rainbow of diseases, including benign reactive lymphoid hyperplasia (RLH) to neoplastic ocular lymphomas. The introduction of immunohistochemical staining and molecular diagnostics, the MALT lymphomas were increasingly misinterpreted as RLH because of their poly morphosis and subsistence of benign follicular germinal centers. Reports of ocular RLH with consequent evolution of disseminated lymphoma were seen, favouring unfolding of malignant lymphoid disease. However, the preponderance of the cases was illustrated before realization of marginal zone lymphoma as a distinct neoplastic lymphoid disease. Therefore, further systematic study of the natural history of orbital RLH in the current era of clinicopathologic diagnosis is needed before final conclusions can be drawn.

Histopathologically, RLH displays a marked permeation of mature lymphoid cells with sprinkling of macrophages and plasma cells. Distinctively, OAMLs are outlined by an extension of a heterogeneous populace of cells, comprising of centrocyte - looking, monocytoid neoplastic cells and plasmacytoid cells, with diminutive immunoblasts percolating the marginal zones enveloping and blanketing the reactive lymphoid follicles. Classical histologic findings portray "the characteristic follicular migration" - insinuation of follicular light zoned germinal centres by neoplastic lymphoid cells and the development of pathognomonic "lymphoepithelial lesions" through infringement of epithelial cell clusters by lobules of marginal zone monocytoid, plasmacytoid lymphoid cells. The well-established "Dutcher bodies," which are eosinophilic pseudo-inclusions found in the nucleus, stain pathognomonically by PAS stain and is seen in low-grade lymphomas, particularly the OAMLs displaying plasmacytoid differentiation. Disparate chromosomal and genetic alterations are depicted in MZL. Cytogenetic aberrations encompass trisomy 3 and trisomy 18 in 67 % and 56 % of MZL lymphomas, respectively 18 - 21. Gain of 3 have been consistently seen in orbital (80 %), in contrast to conjunctival and lacrimal gland OAML.[16] A corroboration between plasmacytic maturation and the evidence of gain in chromosome 3 and/or gain 18 q gains was seen. Trisomy 18 is found chiefly in adolescent females, lymphomas of conjunctival origin, linked with marked lymphoepithelial lesions and disease recurrence.[17]

The commonest translocation in OAML, recognised in 16 % to 41 % of cases is t (11; 18) (q21; q21), fusing the API2 (apoptosis inhibitor 2) present on 11th chromosome and the MALT1 gene present on 18th chromosome, creating the API2 - MALT1 gene fusion protein. The t (14; 18) fusion, seen in 37 % of cases, pairs the MALT1 gene and the IgH gene on chromosome 14. The t (1; 14) (p22; q34) fusion, observed in less than 5 % of patients, activates fusion of the BCL - 10 gene on chromosome 1 and the IgH gene. The t (3; 14) (p14; q32) translocation, found in 20 % of patients, causes fusion of the FOXP1 gene on chromosome 3 and the IgH gene. This translocation is generally associated with karyotypic aberrations such as trisomy 3. All of these karyotypic abnormalities influence a frequent downstream pathway – NF - KB complex activation, leading to synthesis of multitude of proteins devoting to malignant conversion, cell division, and survival.

MZL characteristically emanates in organs that are habitually bereft of any organised lymphoid tissue, such as the ocular region, but amass reactive lymphoid tissue in retort to continuous antigenic stimulation. Study and scrutiny of alterations in the variable (V) region and heavy chain of the immunoglobulin gene segment have demonstrated an aspect of continuous antigenic protein stimulation in the aetiology and pathology of OAML.[18] Chronic antigenic stimulation may stride towards chromosomal instabilities leading to malignant conversion of a cluster of lymphoid tissue to MZL. Subsequent genetic and chromosomal alterations, such as p53 or p16 mutations, may in conclusion result in advancement to a more rigorous lymphoma such diffuse large B-cell lymphoma in fewer than 11 % of cases.

METHODS

This is a case-series study. Twenty-two cases of ocular extranodal marginal zone lymphoma were obtained from the archives of pathology from 2013 to 2015.

	AGE	SEX	CD45	CD3	CD5	CD20	CYCLIN D1	CD10	KI 67	BCL2	PAX5	CD23	CD45
1	55	F	P	R	N	P	N	P	15	P	P	N	P
2	26	F	P	R	N	P	N	P	15	P	P	N	P
3	60	F	P	R	N	P	N	P	15	P	P	N	P
4	30	F	P	R	N	P	N	N	ND	P	P	N	N
5	32	F	P	R	N	P	N	N	10	P	P	N	P
6	45	M	P	R	N	P	N	N	40	N	P	N	P
7	60	M	P	R	N	P	N	P	20	P	P	N	P
8	65	M	P	R	N	P	N	N	5	P	P	N	N
9	45	M	P	R	N	P	N	P	10	P	P	N	N
10	47	M	P	R	N	P	N	P	5	P	P	N	N
11	41	M	P	R	N	P	N	N	20	P	P	N	N
12	61	M	P	R	N	P	N	N	10	P	P	N	P
13	47	M	P	R	N	P	N	N	15	P	P	N	P
14	62	M	P	R	N	P	N	N	20	N	P	N	P
15	66	M	P	R	N	P	N	N	20	P	P	N	N
16	6	M	P	R	N	P	N	N	5	P	P	N	N
17	43	M	P	R	N	P	N	N	10	P	P	N	P
18	55	M	P	R	P	P	N	N	10	P	P	N	P
19	51	M	P	R	N	P	N	N	5	P	P	N	N
20	37	M	P	R	N	P	N	N	25	P	P	N	N
21	37	M	P	R	N	P	N	N	15	P	P	N	N
22	53	M	P	R	N	P	N	N	12	P	P	N	N

Table 1. Immunohistochemical Markers and Clinical Parameters in Cases of OENMZL

The histopathology and immunohistochemistry slides were reviewed by three expert histopathologists for confirmation of diagnosis. Immunohistochemical markers mainly used were CD45, CD3, CD5, CD20, cyclin D1, CD10, Ki - 67, BCL - 2, PAX 5 and CD23. The immunohistochemical markers such as CD10, BCL - 2 and cyclin D1 IHC expression were studied in cases of ocular extranodal marginal zone lymphoma (OENMZL). Relevant clinical details were collected from the patients such age, sex and history of autoimmune condition if any.

RESULTS

Eighteen cases (81 %) of OENMZL were more than 40 years of age, with maximum age limit of 66 years. A rare case of OENMZL was seen in a child of 6 years age. Five cases (22 %) had a history of Sjogren's syndrome and four cases (18 %) had a history of Hashimoto's thyroiditis. There was a male preponderance (77 %) in our cohort. All cases of OENMZL displayed immunopositivity for CD20 (100 %) and CD45 (100 %) in the B cells while were immuno negative for CD23 (0 %). Cyclin D1 was consistently negative (0 %) in all cases. CD10 was immuno positive in 6 (27 %) cases while Bcl - 2 was immuno positive in 20 (90 %) cases. 11 (50 %) cases of OENMZL showed CD43 immunopositivity. CD5 immunopositivity was seen in 1 (4 %) case.

DISCUSSION

Ocular adnexal lymphoma is a distinctive group of lymphomas, comprising of 1 % to 2 % of non-Hodgkin lymphomas and 8 % of extranodal Non Hodgkin lymphomas. The most frequent type, amounting up to 80 % of cases of primary ocular adnexal lymphoma, is MZL MALT type, abbreviated as Maltomas.[19,20] In the past, there has been sizeable advancements in our reasoning of the clinical particulars, histopathology and immune - phenotype, causation, pathogenesis, treatment, and prognosis of this disease entity. New immunophenotypical and molecular diagnostics have helped in the differentiation between MALT lymphoma and other lymphoproliferative disorders leading to the demonstration of tissue markers of predictive and prognostic importance. Modern radiological tests contribute beneficial appliances for precise staging and curative treatment planning of the disease. Likewise, radiation oncology treatments and chemotherapeutic agents, a myriad of novel remedial options have materialized in the treatment of cases with OENMZL, principally monoclonal antibody therapy and antibiotic therapy against Chlamydia psittaci, which has been corroborated with the pathology of OENMZL in some countries. [21-23] MZLs are a class of inert non-Hodgkin's lymphomas of B cell phenotype that develop from the extrafollicular marginal zones of lymphoid tissues which may rarely transform into a high-grade lymphoma such as DLBCL. The world health organization subclassifies MZL into 3 typical entities: splenic MZL, nodal MZL, and MALT lymphoma.

MALT lymphoma separates from its splenic and nodal types, as it forms in organs in the absence of lymphoid tissue (like stomach, lung etc). The entity which was first chronicled to involve the stomach, MALT lymphoma has now been outlined to present in bountiful number of organs such as the major and minor salivary glands, thyroidal tissue, small intestine, ocular lacrimal exocrine gland, ocular conjunctiva and skin. MALT lymphomas are usually precursored by continuous and chronic antigenic stimulation which includes activation of the NF - κB pathway. A bacterium named *Chlamydia psittaci* is apparently a pertinent etiologic factor in the pathogenesis of orbital MALT lymphoma.[24]

MALT lymphomas display the classic infiltration of neoplastic monocytoid and plasmacytoid lymphoid cells between remnant lymphoid follicles infiltrating germinal centres. The histomorphology of these tumour lymphoid cells may alter within the same lymphoid neoplasm. The neoplastic cells are of small to intermediate sized, exhibiting scant to moderate clear cytoplasm with irregular cleaved nuclei. Plasmacytic differentiation is identified and may occasionally be obvious. The bona fide finding, characterised by pathognomonic "lymphoepithelial lesions", displaying tumour cells which are permeating and dismantling the glandular epithelium, diagnoses MZL lymphoma.[25]

There is no specific marker for MZL, however MNDA and IRTA are novel markers. By immunohistochemistry, the neoplastic cells express CD79a, CD45, CD20, MUM - 1 and surface light-chain kappa/lambda restriction but are immuno negative for Bcl - 2, ALK, CD30, CD10 and CD5. Infrequently, CD5 IHC has been depicted in MALT lymphomas.[25,26] The role of CD5 IHC immune-expression in the prognosis and prediction of MALT - lymphomas is disputable.[27] The CD5 aberrant immune-expression is associated with aggressive behaviour and disease progression. Nevertheless, studies of indolent CD5-positive MZL is seen in literature 33.

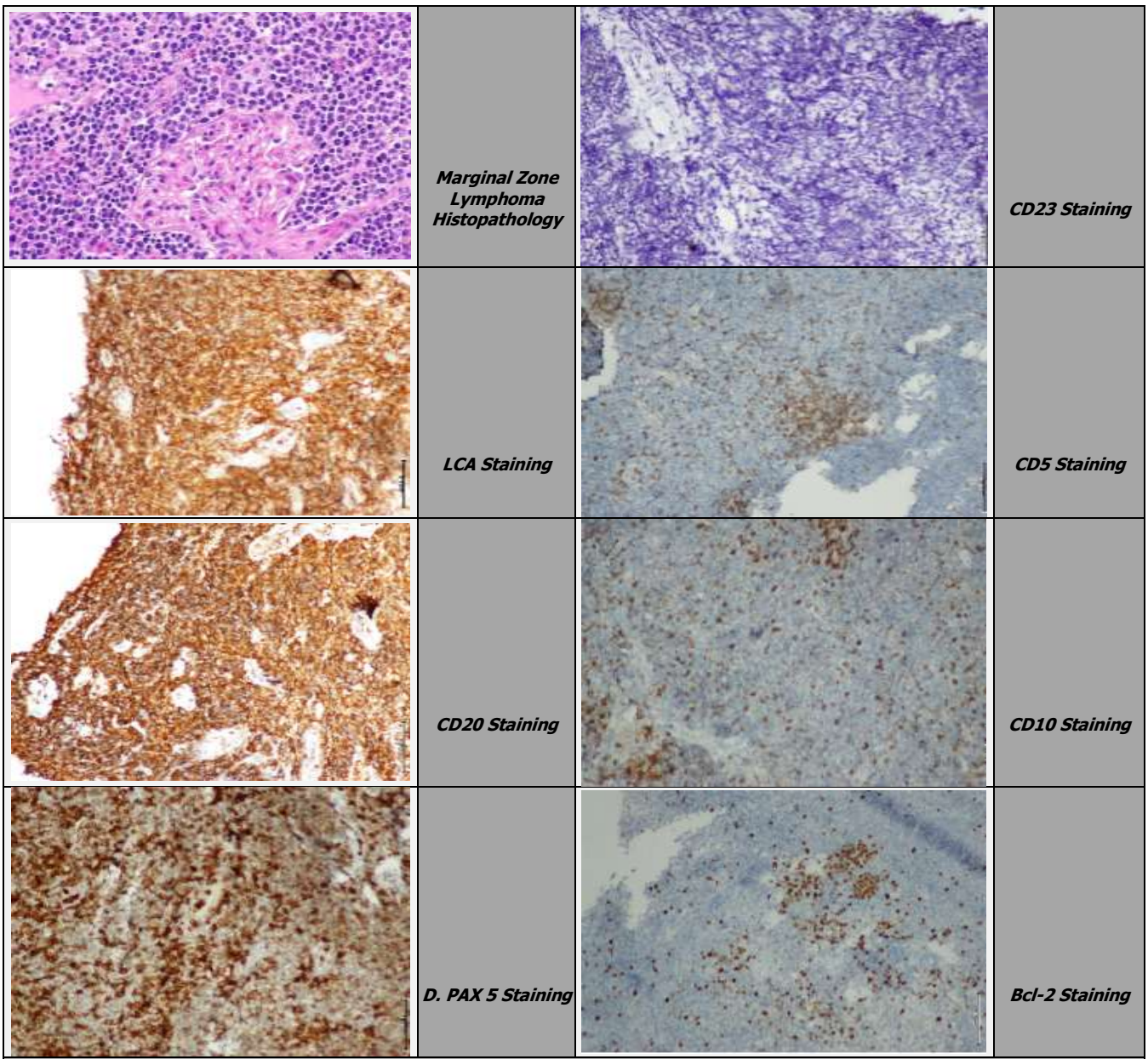

Figure 1. IHC Marker Expression in Cases of OENMZL

Lymphoplasmacytic lymphoma and small cell lymphoma/chronic lymphocytic leukemia (SLL CLL) are other CD5 positive, B-cell lymphoma that contribute to morphology and immunohistochemistry similar to MALT lymphomas. Lack of immune-expression for CD23, as seen in our case, would exclude possibility of SLL which is almost always CD23-positive. LPL may have a CD23-negative immunophenotype similar to MALT lymphoma. LPL and SLL/CLL are systemic diseases while MALT lymphoma is localized to extranodal regions.

MALT lymphoma is a B-cell neoplasm that is mostly CD5 immuno negative but may occasionally exhibit a CD5 immunoreactivity. It is frequently a localized disease of the extranodal sites, but may in few cases show systemic involvement. OENMZLs are frequently observed in the 5th to 7th decade of life with female preponderance (male/female = 1 : 1.5/2) unlike our study which exhibited a male predominance.

In distinction, reports in Korean and south-eastern population demonstrates an undoubtedly younger age (median, ~ 46 years) at the time of diagnosis, with male preponderance.[28,29] Most incessant site of origin is the orbit (~ 40 %), pursued by conjunctiva (30 % - 40 %), lacrimal gland (10 % - 20 %), and eyelid (~ 15 %). 2 Bilaterality is seen in 11 % to 20 % of cases. Immunohistochemistry staining for CD43 and BCL2 can be useful in the immunodiagnosis of MZL, but may show divergence among cases and in rates of immune positivity recorded in formerly pronounced studies. Immunostaining for CD43 is said to range from 25 - 70 % while the staining for BCL2 has been recorded to range from 60 - 95 %.[30,31,17,32,16,33,34]

Lai et al. reported CD43 immunostaining was positive in 20 - 40 % of nodal and extranodal MZL and staining for CD43 in our study was in the similar proportion. However, BCL2 immunopositivity was also increasingly higher in our cohort. Nonetheless, it is significant to identify that immunohistochemical stains for CD43 and BCL2 are useful when seen and help in characterising the pathognomonic B-cell infiltrates on which they are co-expressed, their staining is not important for the characterisation of NMZL.

Consequently, other B-cell lymphoma such as mantle cell lymphoma (frequently positive for both CD5, CD43 and BCL2) and follicular lymphoma (particularly, diffuse follicle center lymphoma) should also be carefully waived from the differential diagnosis.

Hernandez et al.[35] elucidated that MZL most commonly are CD20 positive B-cell lymphomas that lose immune-expression of CD5, CD10, CD43, and cyclin D1. Sprinkled medium to large lymphoid cells are exemplary, seen within the marginal zone of involved follicles. OAMLs are almost always immuno negative for CD5, differentiating them from mantle cell lymphoma and small lymphocytic lymphoma/chronic lymphocytic leukemia. Cases of OAMLs with CD5 immunoreactivity have been seen, strutting riveting differential diagnostic dilemma. In this context, mindful histomorphological interpretation, mingled with immunohistochemistry appraisal of cyclin D1 immunoexpression and FISH study for translocation t (11; 14) (q13; q32), is useful in concluding the exact diagnosis. B-cell monoclonality can be established by molecular diagnostic tests for heavy chain gene rearrangements in immunoglobulin, using PCR, and can help in the differentiating RLH from MZL, which exhibits polyclonal lymphoid proliferation.

There has been worldwide rise in the incidence of OENMZL over the several decades mostly because of increase in autoimmune disorders. We are applying an interdisciplinary approach in the diagnosis and treatment of these cases, including medical oncology and radiotherapy. Clinical and pathological staging is paramount for treatment and prediction because in around 15 % of cases present with systemic disease. Standards of care at our hospital include radiation oncology (30 Gy) for localized disease with excellent loco-regional control and combined chemotherapy/immunotherapy for systemic MZL.

CD5 was immuno positive only in one case of OENMZL. Ballesteros et al.[36] mentioned that CD5 - positive MALT lymphoma tended to show widespread disease in the literature, and presented three cases of CD5 - positive MALT lymphoma and stated that CD5 - positive MALT lymphomas were localized tumours. The sites of the lymphoma were uterus, lymph nodes, lung, and conjunctiva.[36] Tasaki et al. [37] reported two cases of CD5 - positive MALT lymphoma of ocular adnexa. They stressed the differential diagnosis between CD5 - positive MALT lymphoma and mantle cell lymphoma.[37] Hisabe et al.[38] reported a case of CD5 - positive MALT lymphoma of the rectum which regressed after administration of antibiotics. Sundeen et al.[39] mentioned 11 cases of CD5 - positive B - cell small lymphocytic malignancies of various organs. Mikolaenko and Listinsky[40] reported a case of CD5 - positive MALT lymphoma with systemic involvement and Waldenstrom syndrome. Ferry et al.[41] reported 3 cases of CD5 - positive MALT lymphoma of orbit and tongue with recurrence. Kubota et al.[42] reported 3 case of CD5 - positive MALT lymphoma of orbit with autoantibodies. Tsukamoto et al.[43] reported a case of cutaneous CD5 - positive MALT lymphoma resembling the plasma cell variant of Castleman's disease. Wenzel et al.[44] reported a case of CD5 - positive MALT lymphoma of the conjunctiva with early dissemination and aggressive clinical behaviour. Batstone et al.[45] reported a case of CD5 - positive MALT lymphoma of the breast and lymph nodes with genetic analyses. Heuring et al.[46] reported a case of conjunctival CD5 - positive MALT lymphoma. Because the number of cases of CD5 - positive MALT lymphoma is very small, its biological characteristics are unknown.

CONCLUSIONS

OENMZL is an uncommon lymphoma accounting for 1 - 2 % of NHL and 8 % of all ENHL with an incidence of about 0.28 person per year. This lymphoproliferative disorder is usually seen in the adults, with a mean age of about 65 years, and a slight female preponderance. OENMZL is the most frequent orbital non Hodgkin lymphoma, (80 % of primary cases), followed by follicular lymphoma, diffuse large B-cell lymphoma and mantle cell lymphoma.

Clinical details depend upon the involved anatomical sites: the most frequent sites are the superior orbit (45 %) and conjunctiva (30 - 40 %), followed by the lacrimal gland (10 - 20 %) and the eyelids (15 %). Bilateral OENMZLs account for about 10 - 15 % of cases. OENMZL is usually asymptomatic in the early stages of the disease. When emblematic, it frequently presents as mass in the intraorbital region or less commonly as a conjunctival patch ("salmon red patch"). Usual signs and symptoms incorporate pain, irritation, and conjunctival redness. Since these signs are nonspecific, ocular biopsy is imperative for an unambiguous diagnosis.

Pre-treatment tests such as bone marrow biopsy are indispensable for staging of the disease. In annexation to conventional procedures, peripheral blood smear, complete blood count, biochemical serum tests as well as tests for infections such as *Chlamydia psittaci*, *Helicobacter pylori* are fundamental. Urease breath test along with gastric biopsy to know *Helicobacter pylori* status is also pertinent. Chlamydia infestation can be determined in peripheral blood smear and conjunctival swab by polymerase chain reaction. Radiological diagnostic tests such as magnetic resonance imaging with enhancement of the orbit and adjacent soft tissue, total body contrast CT scan or PET/CT OENMZL accords the histomorphological findings of other MZL, showcased by small to medium sized lymphoid cells with monocytoid characteristics and with occasional plasmacytic differentiation; a small element of scattered centroblasts or immunoblasts are seen. Sprinkled T-cells and secondary follicles with reactive germinal centres infiltrated by neoplastic B–cells; and/or destroyed by malignant lymphocytes. These neoplastic cells can colonize adjoining epithelia and acini to model lymphoepithelial lesions, represented as collection of ≥ 3 MZL cells. In MZL, lymphoepithelial lesions are demonstrated commonly in the lacrimal gland.

The pathognomonic IHC of OAMZL incorporates exhibition of B cell immunophenotypic markers such as CD79a, CD19, CD22 CD79a and PAX5, variable expression of CD43, CD11c and IRTA - 1. Contrarily CD5, cyclin D1, bcl - 6 and MUM1 are negative. IHC for CD23, CD21, CD35, clusterin and fascin features residual processes of follicular

dendritic cells. Tumour B cells commonly types IgM and may display immunoglobulin light-chain restriction. Cyto *Chlamydia psittaci* - specific lipopolysaccharide may be stained in the tumour - associated macrophage by IHC. Plasma cell maturation may be seen and sometimes can be jutting; rarely, plasma cells may be highlighted by IgG4 IHC. Differentials includes benign lymphoproliferations, in singular, reactive lymphoid hyperplasia and IgG4 - related autoimmune diseases. Differentiation from reactive hyperplasia in borderline cases, reckons on the interpretations of monoclonal immunoglobulin and finally on molecular diagnostic studies for clonal rearrangement of the heavy chain region (IgH), detectable by PCR in 55 % of MZL. IgG4 - related disease is a multisystemic disease portrayed by increased IgG4 levels and permeation of polytypic IgG4 positive plasma cells linked with reactive lymphoid follicles, phlebitis and fibrosis. OENMZL are consistently positive for CD20 and PAX5 emphasizing their B cell origin of the tumour while are consistently negative for CD5 and CD23. CD43 and Bcl - 2 are showed significant IHC staining, while were negative for cyclin D1 and CD10.

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