Clinicopathological Study of Extranodal Marginal Zone Lymphoma in a Tertiary Care Centre in North Kerala

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ABSTRACT

BACKGROUND

Extranodal marginal zone lymphomas are rare groups of B cell lymphomas that arise in mucosa associated lymphoid tissues of various sites. Strong association with autoimmunity and certain infections are its distinct features. Diagnosis is by histology with immunophenotyping alongside ruling out other low-grade lymphomas. In this study we wanted to analyse MALTomas with regard to their clinical features, relation to autoimmunity, histological and immunohistochemical profile.

METHODS

This is a descriptive study conducted from 2013 to 2018 at a tertiary care centre in North Kerala. Study sample included all cases of extranodal lymphomas obtained retrospectively from 2013 to 2017 and prospectively from 2017 to 2018. Blocks of all specimens were cut and stained with haematoxylin and eosin (H & E) and immunohistochemical markers.

RESULTS

Out of the 15 cases we analysed, the most common sites of involvement were gastrointestinal tract (40 %) followed by thyroid (27 %). Thyroid, which is a rarer site for MALT lymphoma, is detected as one of the frequent sites in this study. In our study, stomach was one of the less common site affected which is in contrast to other studies. Associated autoimmune disorder was detected in 20 % of cases. 46 % of cases show features of transformation to high grade lymphoma.

CONCLUSIONS

This study analysed the features of MALT lymphomas in different sites and found a strong association with autoimmune disorders. Rarer sites like thyroid were found to be more frequently involved and common sites like stomach was detected in only small percentage of cases. Although most cases are indolent low-grade lymphomas, possibility of transformation to a high-grade B cell lymphoma should always be considered when dealing with these cases. Utility of immunohistochemistry in ruling out other small cell lymphomas is also well demonstrated in this study.

KEYWORDS

Extranodal Marginal Zone Lymphoma, MALToma, Autoimmune Disorders, Immunohistochemistry

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BACKGROUND

Marginal zone lymphomas are a group of low-grade B-cell non-Hodgkin lymphomas in the World Health Organization (WHO) classification of lymphoid neoplasms. They are subdivided into 3 depending upon the sites of involvement as nodal, extranodal and splenic. Though there is no clinical overlap among these 3 categories, there are various morphological and immunohistochemical resemblances which indicates that they are related family of neoplasms showing morphologic evidence of differentiation into cells of marginal zonetype.[1,2]

Extranodal marginal zone B cell lymphoma, or low grade B cell lymphoma of mucosa associated with lymphoid tissue (MALT), is a rare type of extranodal lymphoma that arises in a number of tissues, including the stomach, salivary gland, lung, small bowel, colon, thyroid, orbit etc. They were previously known as pseudo lymphomas because of its indolent nature, but presently it is recognised as low grade clonal B cell lymphoproliferative disorders with chances for recurrence and even transformation to high grade B cell lymphomas.

MALTomas constitute 7 - 8 % of all B cell lymphomas. Majority of cases present in adults in their seventh decade with site dependent gender predilection. Females are affected more in thyroid and salivary gland MALTomas as they have a strong autoimmune association. In many cases, history of chronic inflammatory conditions which is stimulated by an infection or autoimmune disorder can be found. Examples include *Helicobacter pylori* in stomach,[3] *Chlamydia psittaci* in orbit,[4,5] Sjogren's syndrome in salivary glands[6] and Hashimoto thyroiditis in thyroid.[7] Stomach is the most common site of MALTomas followed by ocular adnexa, skin, lung, salivary glands, breast and thyroid.

Histologically, the characteristic marginal zone B cells resemble centrocytes with small to medium-sized, slightly irregular nuclei with moderately dispersed chromatin and inconspicuous nucleoli.

Monocytoid cells and cells with plasmacytic differentiation can be seen in variable numbers.[8] The lymphoma cells infiltrate around reactive B-cell follicles external to a preserved mantle in a marginal zone distribution. Characteristic lymphoepithelial lesions, defined as aggregates of ≥ 3 marginal zone cells with distortion or destruction of the epithelium, may be seen in glandular tissues. The neoplastic cells of MALT lymphoma are CD20 +, CD79a +, CD5 -, CD10 -, CD23 -, CD43 + / -, and CD11c + / -.[9]

Tumour cells express surface membrane immunoglobulin (IgM > IgG > IgA) and lack IgD. Chromosomal translocations associated with MALT lymphomas include t (11; 18) (q21; q21) in stomach and lung, t (14; 18) (q32; q21) in ocular adnexa, orbit, and salivary gland lesions; and t (3; 14) (p14.1; q32) in thyroid, ocular adnexa, orbit, and skin.[9]

MALT lymphomas have an indolent natural course and are slow to disseminate. Recurrences occur more often in patients with extra gastric MALT lymphomas than in patients with primary gastric disease.[10] They are sensitive to radiation therapy, and local treatment may be followed by prolonged disease-free intervals. In this study we wanted to analyse MALTomas with regard to their clinical features, relation to autoimmunity, histological and immunohistochemical profile.

METHODS

A descriptive study was conducted in a tertiary care centre of north Kerala. Study sample included all cases of extranodal marginal zone lymphomas diagnosed during the period, 2013 to 2018. All other lymphomas were excluded from the study. After ethical clearance, informed consent was obtained from patients under prospective study group. The clinical history was collected from the case sheets and operation notes as well as pathology requisition forms for the retrospective cases. Significant clinical history like site and duration of the swelling, symptoms, history of site-specific infections and autoimmune disorders were collected. The blocks of all specimens were cut at 5 mm and stained with H & E. After making a morphological diagnosis of extranodal lymphoma, immunohistochemistry was done with a panel of markers including CD3, CD20, CD10, CD5, Ki67 and pan CK.

Statistical Analysis

Because of the rarity of MALT lymphomas, the sample size obtained was too small to apply any tests of significance in this study, which would also lead to false interpretation if used. Hence, no tests of significance or statistical software support were used for analysis.

RESULTS

Histopathological examination of 15 cases were done. Majority of the patients belonged to the age group of 60 - 70 yrs. Females were more affected in this study group. The most common site involved by the tumour was found to be the gastrointestinal tract (40 %) of which 20 % (3) cases were in the small intestine, 13 % (2) in the colon and 7 % (1) in the stomach. Another frequent site was thyroid with 27 % (4) of the total MALToma cases. Other less frequent sites were orbit, nasopharynx and urinary bladder with one case each. [Table 1].

Site	Parotid	Orbit	Thyroid	Stomach	Small intestine	Colon	Urinary bladder	Nasopharynx
No. of cases	2 (13 %)	1 (6 %)	4 (27 %)	1 (6 %)	3 (20 %)	2 (13 %)	1 (6 %)	1 (6 %)

Table 1. Frequency Distribution of MALTomas

Almost all cases had a long indolent course with average duration more than 2.5 years with recent increase in size and symptoms. Of the 15 cases, 3 had history of

autoimmune disease. All these 3 cases involved the thyroid gland in a background of Hashimoto thyroiditis.

No significant history of autoimmune disorder was obtained from any other sites except for florid lymphoplasmacytic infiltrate in the background of a parotid MALToma; possibly immune mediated. No preceding history of infection was noted in any cases. Regional lymph nodes were enlarged and involved by the same tumour in 5 cases.

Prominent lymphoepithelial lesions were noted in all sites with destruction of the glands. This was demonstrated better using immunohistochemical stains especially CD20 which was takenup by the tumor cells. These cells were seen infiltrating the glands / thyroid follicles, which was negative for CD20 [Figure 1].

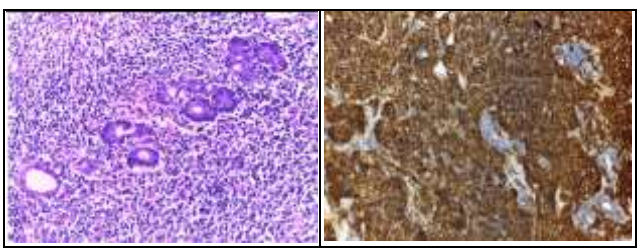

Figure 1. Lymphoepithelial Lesions from Stomach Seen in H & E Staining and Immunohistochemical Staining with CD20

7 out of the 15 cases showed areas with high grade nuclear features which includes vesicular nucleus, prominent nucleoli and moderate pleomorphism (Figure 2). The Ki67 score was high (> 10 %) in the areas coresponding to these high grade features. All the other areas showed a low proliferative index as evidenced by a proliferation index of < 3 %.

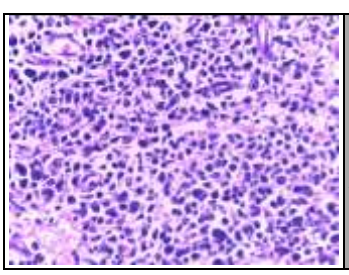

Figure 2. Areas with High Grade Nuclear Features

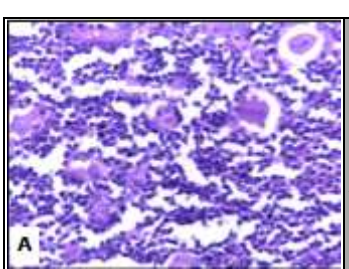

Figure 3A. Atypical Lymphoid Cells Infiltrating Thyroid Follicles

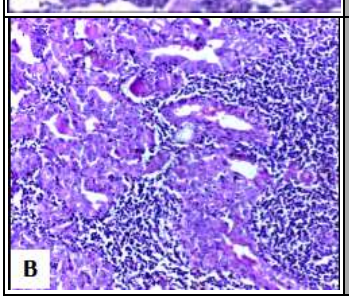

Figure 3B. Hashimoto Thyroiditis in the Adjacent Area

The surrounding tissue showed features of autoimmune diseases in 3 cases. All these cases were seen in thyroid as Hashimoto thyroiditis (Figure 3a & 3b). Other 6 cases (2 each from parotid, small intestine and colon) showed diffuse lymphoplasmacytic infiltrate in the background.

Immunohistochemical stains used were CD3, CD20, CD10, CD5, Ki67 and panCK. CD20 shows consistent diffuse membranous positivity in the tumour cells irrespective of low grade and high grade features. CD3, which highlighted the background reactive T cells, were clearly demonstrated in all sections. Ki67 index was found to be low (≈ 5 %) in most cases which showed low grade cytological features. 7 out of 15 cases had high grade areas which also corresponds to the high Ki67 scores. CD10, CD5 and pan CK were negative in all cases.

DISCUSSION

Extranodal marginal zone lymphomas are indolent lymphomas that can arise in muosa associated lymphoid tissue of varoius organs. Clinical features vary depending on the tissue involved. Majority of the patients present with localised symptoms, generalised systemic symptoms are not common.

MALTomas of certain sites are as a result of chronic inflammatory conditions specific to those sites which includes infections and autoimmune disorder. This includes *Helicobacter pylori* in stomach, *Chlamydia psittaci* in orbit, *Campylobacter jejuni* in small intestine etc. Most common autoimmune disorders associated are Hashimoto thyroiditis in thyroid, Sjogren syndrome in parotid and systemic lupus erythematosus.

Diagnosis is based upon histological, immunohistochemical and genetic studies. Though classical histomorphology consist of small to medium size lymphocytes which are centrocyte like and with monocytoid features, areas with high grade features can also be seen. Immunophenotyping shows positivity for B cell markers including CD19, CD20 and CD22, and negative for CD5, CD10 and CD23. Chromosomal abnormalities like trisomy 3 or t (11; 18), are found in most cases.

We analysed 15 cases of extranodal marginal zone lymphoma which affected various tissues including stomach, small intestine, colon, parotid, thyroid, orbit, nasopharynx and urinary bladder. In our study, the most common site of involvement was the gastrointestinal tract (40 %) with more cases affecting the small bowel and the least being the stomach. This finding is in contrast with other studies which states the most common site of extranodal marginal zone lymphoma as stomach.[11] Another common site found in our study group was thyroid which constitute 27 % of the total cases that is comparatively a higher incidence when analysing previous study reports.[12,13]

Regarding head and neck extranodal marginal zone lymphomas, the most frequent site found in our study was the thyroid (27 %) followed by parotid (13 %). This finding is different from the previous reports[14] which states orbit as a common site than salivary glands. The differences in incidence can be attributed to the small sample size. Other

rare sites we found in this study were urinary bladder and nasopharynx.

Associated autoimmune disorders were found in 20 % of cases, all in the form of Hashimoto thyroiditis which further enforces the etiopathogenesis of MALToma in thyroid. Other organs like parotid, small intestine and colon showed dense background lymphoplasmacytic infiltrate which indicates a possible immune aetiology, though there were no clinical features suggestive of autoimmune disorder in those patients. No organisms could be demonstrated from any of the sites including stomach, intestines and orbit.

Histopathological examination revealed diffuse infiltrate of lymphoid cells of low grade morphology, prominent lymphoepithelial lesions, adjacent lymphoplasmacytic infiltrate and features of Hashimoto thyroiditis (in thyroid). 7 cases showed a transition from low grade to high grade morphology which correlated with high MIB index (> 10 %) in those areas. This indicates a progression to diffuse large lymphomas and are associated with a worse prognosis. Diffuse CD20 positivity with absence of CD3, CD5, CD10 and panCK, ruled out other small cell lymphomas like mantle cell lymphoma, follicular lymphoma and CLL / SLL and poorly differentiated carcinomas. Genetic studies were not done in any of the cases due to financial constraints.

CONCLUSIONS

To summarise, extranodal marginal zone lymphomas are rare low grade B cell lymphomas which behave in a very indolent manner except for those showing features of transformation to higher grade histologically. History of infections and autoimmunity should be sought for, in all suspected cases. Systemic involvement with generalised lymphadenopathy is usually absent in MALTomas, and in such situations other lymphoid malignancies should be ruled out. Diagnosis is based on a combination of clinical features, histopathological and immunohistochemical features and genetic studies whenever possible.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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