

Pathology of extranodal marginal zone lymphoma at different anatomic sites

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Abstract: Extranodal marginal zone lymphomas arise within acquired lymphoid tissue at a variety of extranodal sites. They have characteristic architectural and morphological features that recapitulate those seen in constitutive lymphoid tissue in extranodal locations that is best exemplified by the mucosa (gut) associated lymphoid tissue (MALT) present as Peyer's patches in the terminal ileum. The morphology of these MALT lymphomas is constant across the various extranodal sites in which they are encountered although there is some variation between cases in the detailed cellular morphology with variable proportions of cells with centrocyte-like, monocytoid and plasmacytoid/plasmacytic appearances. Architecturally there is inter-case variation in the degree and type of follicular colonisation. The appearance of lymphoepithelial lesions varies between sites. There is variable association with light chain deposition disease and nodular amyloidosis which appear to be more frequently associated with a pulmonary origin. The immunophenotype is uniform across sites with a rather non-specific B-cell antigen expression with aberrant CD43 expression in a proportion of cases. There is infrequent expression of CD5 and this appears more frequent in lymphomas arising in the ocular/ocular adnexal region.

Keywords: Mucosa associated lymphoid tissue (MALT)

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Mucosa associated lymphoid tissue (MALT)

Within the body there are areas of organised lymphoid tissue within tissues that are not considered primary lymphoid organs. This lymphoid tissue is mostly found in the gastrointestinal tract (gut-associated lymphoid tissue, GALT) with a particular condensation in the terminal ileum in the form of Peyer's patches. In this location the lymphoid tissue has a specific relationship with the overlying epithelium. In the surface of the dome epithelium overlying the lymphoid tissue are specially adapted M-cells that facilitate the transfer of large molecules from the gut lumen for presentation to the immune system. Similar aggregates of lymphoid tissue are encountered in the lung (Bronchus-associated lymphoid tissue, BALT) and the skin (skin-associated lymphoid tissue, SALT).

This organised tissue, termed MALT, is exemplified by

the organised lymphoid tissue in the gut and is considered to include not only the organised lymphoid follicle but also the peri-follicular lymphocytes and plasma cells in the lamina propria, the intraepithelial B cells present in the dome epithelium and the mesenteric lymph nodes. The follicles in both the Peyer's patches and the mesenteric lymph nodes have a well developed marginal zone external to the mantle zone (*Figure 1*). This compartment is not well developed in other lymph node groups but is seen in the spleen. It is thought this is related to areas that are associated with exposure to significant amounts of external antigen.

Structurally the lymphoid tissue in the gut mucosa consists of a lymphoid follicle with a reactive germinal centre that has the dark zone at the base with the light zone closest to the mucosal surface (*Figure 2A*). The germinal centre is surrounded by a well formed mantle zone that

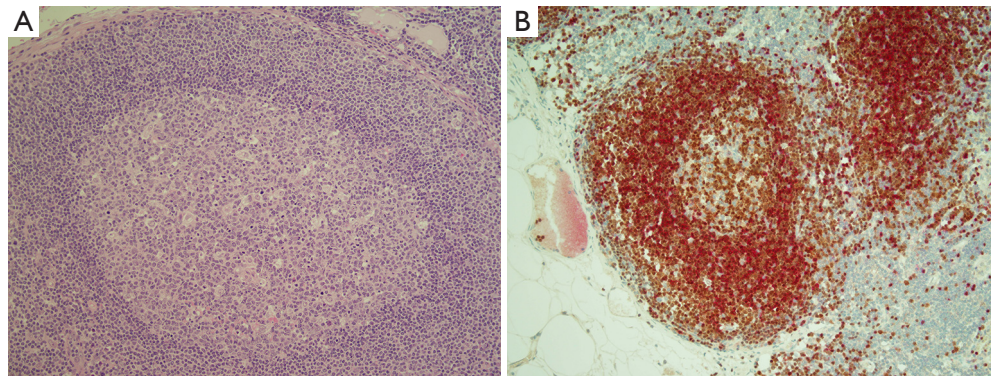


Figure 1 Marginal zone. (A) Follicle in mesenteric lymph node showing well developed marginal zone exterior to the mantle zone composed of cells with pale cytoplasm (Haematoxylin and eosin, $\times 10$). (B) Pax5 positive marginal zone B cells are seen outside the IgD expressing cells of the mantle zone (Pax5 brown, IgD red, $\times 20$).

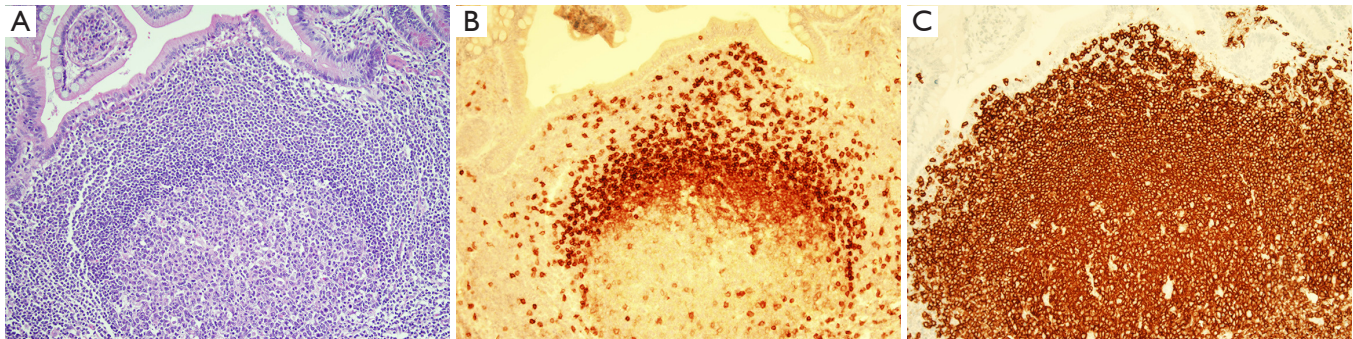


Figure 2 Peyer's patch. (A) Peyer's patch showing germinal centre with mantle and marginal zone covered on the luminal surface by dome epithelium (haematoxylin and eosin, $\times 10$). (B) Mantle zone is highlighted between the germinal centre and marginal zone (IgD, $\times 10$). (C) Occasional B cells are present within the dome epithelium (CD20, $\times 20$).

contains predominantly IgD positive naïve B cells and which is thickest below the surface epithelium and is rather thin where it abuts the muscularis mucosae (*Figure 2B*). External to this is the marginal zone that consists predominantly of slightly larger B cells with more abundant pale cytoplasm. There are other cell types in the marginal zone including plasma cells, T cells, macrophages and dendritic cells. This zone is also more developed below the surface where epithelial crypts are absent. The marginal zone abuts the overlying dome epithelium with infiltration of the epithelium by marginal zone B cells forming a lymphoepithelium (*Figure 2A,C*).

Extranodal marginal zone lymphoma of MALT (malt lymphoma)

Isaacson and Wright were the first to recognise a group

of lymphomas that arose in extranodal sites and which appeared to have characteristic clinico-pathological characteristics (1,2). In recognition that these occurred predominantly in the gastrointestinal tract, particularly in the stomach, and that the organisational features of the lymphoid infiltrate resembled that of the Peyer's patch these lymphomas became termed MALT lymphomas. Subsequent to this first description similar lymphomas have been recognised in almost every extranodal site in the body. The only site where MALT lymphoma is not encountered is in the area of highest quantity of constitutive GALT, the terminal ileum. It appears that acquisition of organised lymphoid tissue with the components similar to those of the mucosal compartment of GALT is the crucial first step in the development of MALT lymphoma. The stimulus to the acquisition of MALT varies between organs with some developing in response to a local prolonged low grade

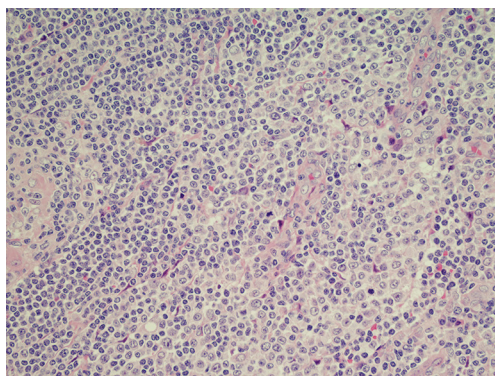


Figure 3 MALT lymphoma cells with a monocytoid appearance are present around a residual lymphoid follicle. Scattered larger activated cells are seen in the infiltrate and there is an occasional plasma cell (haematoxylin and eosin, $\times 20$). MALT, mucosa associated lymphoid tissue.

antigen stimulation associated with a generally indolent bacterial infection while others develop in the context autoimmune disease (3). At many sites the underlying prodromal event remains unclear. Notwithstanding the underlying pathogenetic pathway the resultant MALT lymphomas show remarkably similar histopathological features. Detailed morphological, immunohistochemical and molecular studies together with in-vitro experiments have indicated that the normal counterpart of the neoplastic cell of MALT lymphoma is the marginal zone B cell of the acquired MALT (4).

In keeping with the normal behaviour of marginal zone B cells the neoplastic cells retain the ability to recirculate through the body relocating to the mucosa through interaction with appropriate cell adhesion molecules (5,6). In the stomach it has been clearly shown that this results in multifocal disease with neoplastic cells from the main bulk of the tumour found in the marginal zone/peri-follicular zones of lymphoid tissue elsewhere in the gastric mucosa, sometimes forming micro-lymphomas around a single follicle (7,8). This recirculation to other areas of MALT may explain multifocality in other organs, the tendency for ipsilateral involvement in paired organs such as salivary glands and the risk of spread to other extranodal sites rather than peripheral lymph nodes.

Histology of malt lymphomas

MALT lymphoma cells are initially located in the region

of the peri-follicular marginal zone. This infiltrate expands to occupy the surrounding tissue to efface the surrounding stroma. While residual remnants of the acquired lymphoid tissue are usually present in the form of all or parts of reactive germinal centres in established MALT lymphoma these are frequently overrun.

The neoplastic cells of MALT lymphoma have a variable morphological appearance both between cases in different cases but also within any individual lymphoma deposit. The original descriptions recognised a cell with rather scanty cytoplasm and irregular nuclei with dense chromatin and no nucleolus (1,2) (*Figure 3*). The resemblance of this cell type to the small cells in the germinal centre led to the use of the term centrocyte-like (CCL) cell. In addition to CCL cells the cells may resemble monocytoid B cells with more abundant pale cytoplasm, well demarcated cytoplasmic borders and round nuclei that lack nucleoli while other cells show plasmacytoid features. A degree of plasmacytic differentiation is seen in many cases but is more pronounced in approximately a third of cases although this may rise to 40% in MALT lymphomas of the ocular region (9,10). In some cases the plasma cell component may be sufficiently extreme to almost completely eclipse the small B cell component raising a differential diagnosis with plasmacytoma. Cells with Dutcher bodies may be seen and in some instances the presence of periodic acid schiff (PAS) positive IgM-type Dutcher bodies may be useful in the distinction between MALT lymphoma and plasmacytoma in aspiration cytology preparation (11). Deposition of amyloid and light chain disease has been associated with MALT lymphoma with this a more frequent occurrence in lymphomas involving the lung (12-17). Amyloid associated with MALT lymphoma is more frequently of nodular rather than systemic type and may be in a peritumoural location (14-16). Up to 80% of pulmonary light chain deposition disease has been associated with MALT lymphoma with 50% of these patients having associated Sjogren's syndrome (17). Rare cases of MALT lymphoma have also been associated with crystal storing histiocytosis (18,19).

Scattered large transformed/activated B cells are a constant feature but are not seen in clusters or groups. These cells have abundant cytoplasm and large nuclei that have open chromatin with eosinophilic nucleoli. Significant clusters of large cells are not seen and if present should raise the possibility of progression to diffuse large B cell lymphoma.

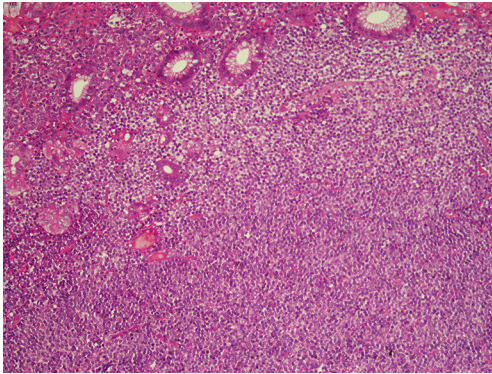


Figure 4 Two lymphoepithelial lesions in a case of gastric MALT lymphoma. One shows early infiltration by a cluster of neoplastic lymphocytes. The other shows a more advanced lesion with eosinophilic change to the epithelial cells (haematoxylin and eosin, $\times 10$). MALT, mucosa associated lymphoid tissue.

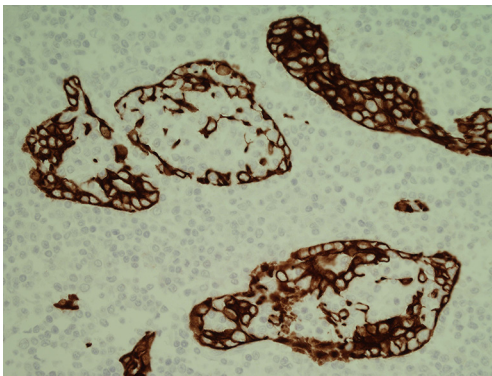


Figure 5 Cytokeratin stain highlights lymphoepithelial lesions in a case of thyroid MALT lymphoma showing expansion of the thyroid follicle by neoplastic lymphocytes. (AE1/AE3, $\times 40$). MALT, mucosa associated lymphoid tissue.

Lymphoepithelial lesions

Although termed MALT lymphomas due to the overall resemblance to the organised lymphoid tissue found at extranodal sites, predominantly mucosal, not all MALT lymphomas arise in true mucosae and many arise at sites devoid of epithelial structures such as soft tissue. However, when epithelial structures are present the neoplastic interact with them in a way that partly recapitulates the lymphoepithelium of the Peyer's patch. In contrast to the single B cells seen in the dome epithelium the neoplastic marginal zone B cells infiltrate in clusters and exert a destructive/toxic effect on the epithelial cell and these

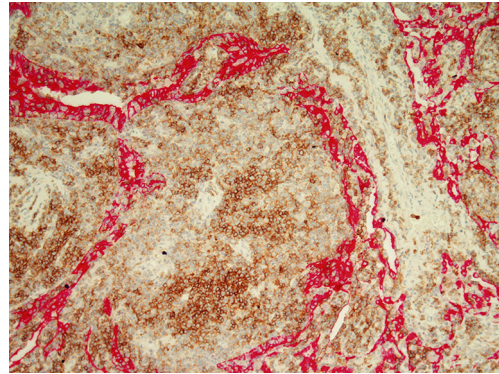


Figure 6 A case of follicular lymphoma in the lung showing well formed lymphoepithelial lesions with CD10 positive follicular lymphoma cells within the epithelium stained for cytokeratin (CD10 -brown, AE1/AE3 - red, $\times 20$).

structures are termed lymphoepithelial lesions (LELs) (20). The interaction between the neoplastic lymphocytes and the epithelial structures varies between sites. LELs in the stomach show infiltration of the epithelium by groups of three or more neoplastic cells (21). With time the epithelial cells become enlarged with cytoplasm that becomes more eosinophilic (*Figure 4*). This is due to initial swell of intracellular organelles which subsequently are destroyed. Eventually the epithelial structure is lost although in some instances isolated endocrine cells may remain (22). In salivary glands the LELs resemble the epi-myoe epithelial lesions of myoe epithelial sialadenitis (23) while in the thyroid the neoplastic marginal zone cells frequently fill and expand the thyroid follicles (24) (*Figure 5*). Cyst formation in the lungs has been described in association with MALT lymphoma of the thymus (25,26).

While initially thought to be pathognomonic for MALT lymphoma it is now recognised that the LELs are not essential for a diagnosis even in mucosal locations nor are they specific. Identical structures can be encountered in reactive infiltrates such as rheumatoid lung disease and in association with other histologically low grade B cell lymphoma (*Figure 6*), particularly in follicular lymphoma of the thyroid but also with follicular lymphomas at other sites and in mantle cell lymphoma involving the gastrointestinal tract.

Follicular colonisation

Lymphoid follicles are a ubiquitous feature in MALT lymphoma, being a constant component of the organised

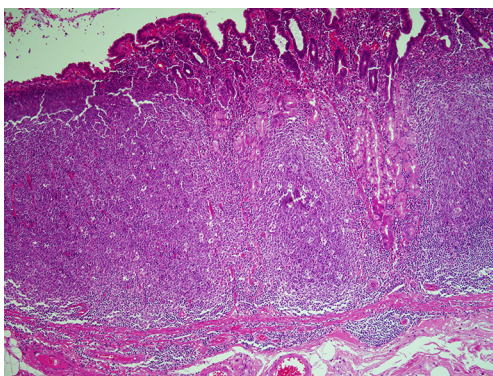


Figure 7 Lymphoepithelial lesion in a case of thyroid lymphoma showing expansion of the thyroid follicles stained for cytokeratin by the neoplastic MALT lymphoma cells (AE1/AE3, $\times 4$). MALT, mucosa associated lymphoid tissue.

lymphoid tissue that is a pre-requisite for the development of the lymphoma. While in many cases the follicles are largely or completely effaced by the neoplastic infiltrate there are some instances where the neoplastic cells specifically colonised by the neoplastic cells leaving the underlying follicular structure intact (27). This is a recapitulation of the normal response of reactive marginal zone B cells under the influence of antigen exposure (28).

The cell morphology in the colonised follicles varies between cases. In some cases there is a mixture of cells similar to that seen in follicular lymphoma (27). Other cases have intrafollicular cells with a more activated cellular appearance that are larger than the extra-follicular component, while some cases appear to have an intra-follicular component that is mainly composed of plasma cells (27). In some cases the colonisation may be sufficient to make the distinction between follicular lymphoma and MALT lymphoma challenging (27) (*Figure 7*). This is particularly true in small or distorted biopsies that frequently are derived from delicate sites such as the peri-ocular region. This problematic differential can be further compounded by the fact that the neoplastic marginal zone B cells have the potential to up-regulate germinal centre associated markers such as CD10 and bcl-6 protein.

Immunophenotype

The immunophenotype of MALT lymphoma is not specific. There is expression of pan B cell markers CD19, CD20, CD22 and CD79a. The neoplastic cells also express CD27, a marker of activated and memory B cells. The plasma

cell component can be highlighted with an antibody to CD138. There is expression of immunoglobulin which may be easier to demonstrate in cases showing plasmacytoid or plasmacytic differentiation. Expression of IgM heavy chain is most frequent with some expressing IgA while IgG expression is rare (21). There is light chain restriction. Approximately 30–50% of cases express CD43 (29) and this may be helpful in distinguishing MALT lymphoma from reactive infiltrates. Expression of CD5 is seen in 5–10% of cases (30) but these lack expression of CD23 and cyclinD1 distinguishing the infiltrate from other CD5 positive B cell lymphomas. Cases with expression of CD5 appear to have a more aggressive course with higher potential for dissemination, including bone marrow infiltration, and for early relapse (30). Many CD5 positive cases arise in the orbital/peri-orbital area (30). While the neoplastic cells of MALT lymphoma may upregulate CD10 and bcl-6 protein in the germinal centre the extra-follicular component is negative for these markers. There is expression of bcl-2 protein.

Proliferation is low consistent with an indolent B cell lymphoma. Staining for cytokeratin may be useful in highlighting lymphoepithelial lesions. Staining for follicular dendritic cells (CD21 and/or CD23) highlights residual meshworks in cases where the follicular structures have been entirely effaced. Staining for IgD can be used to highlight the mantle zone B cells and is particularly useful in identifying subtle expansion of the marginal zone in the early MALT lymphoma particularly those arising in the salivary gland and thyroid.

Immunoproliferative small intestinal disease

Immunoproliferative small intestinal disease (IPSID) is a particular type of MALT lymphoma first described by Ramot in 1965 (31). The disease has a distinctive geographic distribution being found most commonly around the Mediterranean area, the Middle East and the Cape area of South Africa (32). Histologically the disease is characterised by extreme plasmacytic differentiation. The villi are broad but not shortened. Three stages are recognised (33). In stage A the infiltrate is confined to the mucosa and mesenteric lymph nodes. In stage B the infiltrate extends beyond the muscularis mucosae and in stage C there is progression to lymphoid masses with or without transformation. In stage A the B cell component is usually very scanty and may only be present around the crypts forming lymphoepithelial lesions which

can be difficult to identify without the use of an anti-cytokeratin antibody. With progression to stage B and C the B cell component becomes more prominent. The immunohistochemical characteristic of this disorder is the production of IgA without light chain. The heavy chain is IgA1 although a minority of cases show both IgA1 and IgA2 (34).

Precursor lesions

The background tissue in most cases will show evidence of the predisposing disorder such as Hashimoto's thyroiditis in the thyroid or Sjogren's syndrome in salivary glands. Where an infective organism is implicated then this can either be demonstrated by a direct method in the tissue such as histochemical or immunohistochemical staining of *Helicobacter pylori* on gastric mucosa. In ocular adnexal lymphoma *Chlamydia* (also sometimes referred to as chlamydophilia) psittaci can be detected by immunohistochemical or PCR based techniques from formalin fixed paraffin embedded material (35). In other cases appropriate serological studies are recommended such as for *Borrelia burgdorferi* in cutaneous MALT lymphoma. In gastric MALT lymphoma cases the organism is sometimes so scanty to demonstrate histologically or has been eradicated prior to biopsy and in these cases serological assessment is necessary to detect low organism numbers or prior infection, as antibodies may remain detectable for up to 2 years following eradication therapy (36). *Helicobacter* associated gastric MALT lymphoma is most frequently located in the antrum or distal stomach as this is where the acquired lymphoid tissue is most pronounced. In recent years the level of association between gastric MALT lymphoma and *Helicobacter pylori* has dropped significantly. In the United Kingdom this association has dropped from an initial reported rate of 92% (37) to a level in the region of 30% (38). This may have implications for the location of the lymphoma in the stomach with more tumours presenting more proximally in the gastric wall.

Recently an association between MALT lymphoma and IgG4 related disease (IgG4-RD) has been proposed (39-41). Any association remains uncertain but it has been suggested that there may be an increased risk of developing lymphoma in patients with IgG4-RD while it has also been suggested that MALT lymphoma may predispose to the development of IgG4-RD (39,42,43). Most of these cases arise in the ocular region (39) and have been described in patients in

the East Asia (40,41,44). One report suggested that there is a group of primary cutaneous MALT lymphomas that show plasmacytic differentiation are frequently associated with IgG4 expression (45).

Differential diagnosis

The principle differential diagnoses lie on the one hand with the pre-existing/underlying reactive proliferation from within which the lymphoma might develop and on the other hand with other histologically low grade B-cell lymphomas. More recently it has been recognised that MALT lymphoma may be associated with a striking infiltrate of T cells with a T follicular helper phenotype which may be sufficient to raise the possibility on angioimmunoblastic T cell lymphoma (46).

Reactive vs. neoplastic MALT

This distinction may be problematic in small biopsies from any extranodal site and repeated biopsies may be necessary to achieve a confident diagnosis. In the stomach the Wotherspoon score was developed to indicate the degree of certainty for a diagnosis of lymphoma (47) with the higher scores (scores 4 & 5) being associated with the presence of clonal populations detected by molecular techniques while lower scores were not associated with clonal populations (48).

The earliest morphological indication for the development of a neoplastic population is an expansion of the marginal zone component of the acquired MALT. In the stomach this is characterised by infiltration of small B cells into the more superficial parts of the mucosa, surrounding the glands with an irregular periphery. In the thyroid and the salivary gland the earliest change is expansion of the marginal zone between the follicle mantles and the epithelial structures resulting in a zone of cells with monocytoid appearance that appears pale at low power external to the mantle (23,24).

Immunohistochemical staining for light chain expression may be helpful but interpretation can be problematic in small or distorted biopsies. Aberrant expression of CD43, if present, is helpful in identifying a neoplastic population. Staining for IgD, while not identifying the lymphoma cells, can be helpful in defining the mantle zone and distinguishing these cells from any neoplastic component exterior to the mantle.

Clonality studies, when applied with the BIOMED

2 primer set, give a high rate of detection of a clonal population. False positive results are rare but there is potential for false negative results due to the ongoing somatic mutation in the immunoglobulin genes that are seen in MALT lymphoma (49). This should be reduced if all the primer sets are included in the study.

Atypical marginal zone hyperplasia mimics MALT lymphoma (50). This condition is encountered mainly in children at ages when MALT lymphoma is rare. In addition to the morphological similarities the atypical marginal zone cells aberrantly express CD43 and show light chain restriction (always lambda-type) (50). Distinct from MALT lymphoma the atypical marginal zone cells do not express CD27 (50). Cases of atypical marginal zone hyperplasia, while showing monotypic light chain restriction, are always polyclonal at the genetic level (50) and appropriate clonality studies can confidently distinguish between this condition and MALT lymphoma.

MALT vs. other indolent B cell lymphoma.

Usually this distinction is not a significant problem if appropriate immunohistochemical studies are undertaken. Mantle cell lymphoma can be distinguished from MALT lymphoma by the application of antibodies to cyclinD1 and SOX11, particularly in cases with expression of CD43 or CD5. The distinction with follicular lymphoma may be more problematic, particularly in small or crushed biopsies. MALT lymphomas with follicular colonisation can resemble true follicular lymphoma. While application of antibodies to CD10 and bcl-6 protein may help distinguish the two the possibility of upregulation of these germinal centre related proteins by neoplastic marginal zone cells when they relocate to the follicle centres can make the distinction difficult. In these instances careful assessment of the extra-follicular component may be helpful as, while neoplastic follicle centre cells down-regulate expression of CD10 and bcl-6 in the interfollicular compartment MALT lymphoma cells in this area do not express germinal centre related proteins. Fluorescent in-situ hybridisation (FISH) studies for the translocations t(14;18)(q32;q21) and/or t(11;18)(q21;q21) may help in the distinction between follicular and MALT lymphoma but neither is found in all cases of the respective lymphoma. In addition the t(14;18)(q32;q21) [IGH-BCL2 fusion] found in follicular lymphoma must be distinguished from the t(14;18)(q32;q21) [IGH-MALT1] found in some MALT lymphomas, particularly in the ocular and gastric context.

Assessment of gastric biopsies following helicobacter eradication for MALT lymphoma

Following Helicobacter eradication in the context gastric MALT lymphoma regular follow up endoscopy is advised (36). An initial biopsy is recommended to assess for successful eradication. This and subsequent endoscopies are also essential as the only way to assess for response. Time to remission is very variable and may take up to 5 years (unpublished data). Reporting of sequential biopsies should not only be used to assess for the presence or absence of complete response but can also inform as to whether the lymphoma is responding in a more gradual way. This can prevent the application of unnecessary and more aggressive intervention such as chemotherapy or radiotherapy. In order to give a temporal comparison in sequential biopsies The GELA group devised a reporting system to describe the appearances in post-eradication biopsies (51). This assessed the presence of cellular density and the presence of stromal changes to give a spectrum of appearances from “no change” to “complete remission”. Between these extremes two other groups were identified. Cases with “responding disease” showed reduction of the cellular infiltrate with fibrosis of the lamina propria indicating some regression of disease and suggesting no further intervention was necessary as the regressive changes could continue. A group of cases in which there were residual nodular lymphoid aggregates were labelled “minimal residual disease”. These are innocuous infiltrates with low risk of progression to significant recurrent disease, but sensitive molecular studies have shown that these may harbour residual clonal lymphoma cells. This GELA scheme has been shown to be clinically useful and reproducible between pathologists (52,53).

Over time follow up biopsies may identify relapses that may be detected either on routine histology or by molecular studies (54,55). Some of these will be associated with Helicobacter reinfection and may respond to further eradication therapy. Others may be persistent and require additional intervention but a proportion will transiently regress spontaneously (54,55).

Transformation

Transformation of MALT lymphoma to diffuse large B cell lymphoma is less frequent than is seen in follicular lymphoma, occurring in 3–12% of cases (56,57). While many are of non-germinal centre/activated B cell type a

significant number have a germinal centre phenotype while being clonally related to the underlying MALT lymphoma at the genetic level (58,59).

The criteria for the diagnosis of transformation are vague and controversial (60,61). While the presence of sheets of neoplastic large cells is not a significant diagnostic issue, the lower cut off for the diagnosis of a sheet of cells in early transformation is vague. A large cell component of up to 10% of total tumour cells or clusters of to 20 large cells has been suggested as significant finding with an outcome that is worse than for standard pure low grade cases and large cell infiltrates greater than this have been considered to be a diffuse large B cell component (61). Crucial to the assessment of transformation is the exclusion of the possibility that the large cell clusters are not residual reactive germinal cells in partially colonised or partly overrun follicles. This can be achieved by application of antibodies against germinal centre cell related antigens (CD10, bcl-6 protein), lack of expression of bcl-2 protein and the presence of follicular dendritic cells associated with the large cells.

Conclusions

Extranodal marginal zone lymphomas of MALT have been described in almost all locations in the body with possible exception of the terminal ileum. They arise in acquired lymphoid tissue that has usually undergone prolonged antigen stimulation. The cause of the development of MALT varies from site to site but where this has been ascertained is usually the result of chronic infection or an autoimmune disorder.

Morphologically and immunophenotypically MALT lymphomas are very similar at all sites with minor variation in the degree of plasmacytic/cytoid differentiation, the appearance of lymphoepithelial lesions and expression of CD5.

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