UPDATE ON LYMPHOMA PATHOLOGY: IV EXTRANODAL LYMPHOMAS

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INTRODUCTION

(a) Extranodal lymphomas are different

Lymphomas are usually thought of as tumours of lymph nodes. About 30% of lymphomas⁽¹⁾, however, develop in extranodal sites where they display certain distinctive characteristics.

Extranodal lymphomas

- tend to remain localized
- have a better prognosis, on average, than nodal lymphomas
- include almost all cases of marginal zone lymphoma
- include most cases of lymphomas complicating immunodeficiency
- are hardly ever Hodgkin's disease.

(b) Definition of extranodal lymphoma⁽¹⁾

A lymphoma is regarded as extranodal when the main bulk of disease presents at an extranodal site. Extranodal lymphomas can spread to contiguous lymph nodes or even to bone marrow. Nodal lymphomas often spread to extranodal sites such as bone marrow, spleen and the gastro-intestinal tract.

(c) Sites of extranodal lymphoma⁽²⁾

Lymphomas can arise anywhere in the body. Over half of all extranodal lymphomas, however, occur in the gastro-intestinal tract (Figure 1) and tonsillar area (Waldeyer's ring). Skin is the next most favoured site, followed by salivary glands and lungs. About equally infrequent of the many remaining sites are thyroid, mediastinum, nose, orbit, brain, testis, spleen and bone.

Geographical factors affect the ratio of nodal to extranodal lymphomas and their sites of predilection⁽¹⁾:

- There is a very high incidence of gastro-intestinal lymphoma in the Middle East ('Mediterranean lymphoma')
- Burkitt's lymphoma, common in equatorial Africa, is usually extranodal, often affecting jaws, kidneys or ovaries.

(d) Marginal zone lymphoma

Most characteristic of extranodal disease is *marginal zone lymphoma*. As noted in Part III, this tumour is one of the low-grade B-cell lymphomas, and hardly ever occurs within lymph nodes. Marginal zone lymphoma consistently features in all extranodal sites, with the exception of Waldeyer's ring, thymus and brain where the tumour is rare.

Marginal zone lymphoma is synonymous with low-grade MALToma (tumour of Mucosa-Associated Lymphoid Tissue). The term "maltoma" has the advantage of brevity and a decade of usage; on the other hand, the stomach does

Figure 1 Sites of extranodal lymphoma

not normally possess mucosal lymphoid tissue and neither skin nor thyroid is mucosal. Marginal zone lymphoma is the term preferred in the REAL classification.

Marginal zone lymphoma can affect adults of any age, occasionally occurring in those under 40 years. The tumour is slow-growing and has a relatively good prognosis because it remains localised, often for prolonged periods, in the organ of origin. This is because small B-lymphocytes can recognise and home to their specific tissue. The lymphocytes bear homing receptors on their surface which bind to vascular addressins on endothelial cells of blood vessels in each type of lymphoid tissue⁽³⁾. Whereas small lymphocytic lymphoma cells will have access to all lymph nodes, via the recirculation pathway (see Part III), gastric marginal zone lymphoma cells, for example, will pass through local lymph nodes to blood, and then only back to the stomach.

The natural localisation of marginal zone lymphoma means that the tumour is potentially curable by surgery or local radiotherapy. *Marginal zone lymphoma is the only curable low-grade B-cell lymphoma.*

Marginal zone lymphoma often develops secondary to a long-standing inflammatory process in which a particular organ may acquire its own reactive lymphoid tissue. In some cases the nature of the inflammatory process is known; it can be either autoimmune or due to chronic infection (Figure 2).

ORGAN	PREDISPOSING CONDITION
Stomach	<i>Helicobacter</i> infection
Thyroid	Hashimoto's disease
Parotid	Sjogren's disease
Liver	Chronic hepatitis C
Skin	?Lyme disease
Lung	??

Figure 2 Inflammatory conditions predisposing to marginal zone lymphoma

Marginal zone lymphoma, like follicular lymphoma, is prone to undergo high-grade transformation.

Whatever the site, marginal zone lymphoma presents a consistent histological appearance, the main feature being a dense infiltrate of small B lymphocytes with a few scattered large lymphocytes. There are usually some residual benign lymphoid follicles within the tumour. Lymphoma cells occupy a 'marginal' position around and between the follicles, similar to that of the spleen (see Part III). Being post-germinal centre, the lymphocytes can be stained for IgG or IgA and usually have a moderate amount of pale cytoplasm unlike other types of low-grade B-cell lymphoma. Lympho-epithelial lesions are a further useful diagnostic feature (Figure 3) in which residual epithelial glands are infiltrated by small lymphocytes.

Figure 3 Lympho-epithelial lesion, typical of marginal zone lymphoma. The epithelial cells are highlighted by an immunostain for cytokeratin (CAM 5.2); lymphocytes are unstained.

(e) Other types of extranodal lymphoma⁽¹⁾

Wherever marginal zone lymphomas occur, there will also be *diffuse large B-cell lymphomas* due to high-grade transformation of marginal zone lymphomas. Probably the majority of extranodal diffuse large B-cell lymphomas arise in this way. In fact *high grade B-cell lymphomas* heavily outnumber their low-grade counterparts at all extranodal sites.

In addition to this pattern of B-cell lymphomas the small intestine is subject to *enteropathy-associated T-cell lymphoma*. Skin is unique in having a preponderance of T-cell lymphomas, mostly *mycosis fungoides*. Thymus is the only extranodal site where primary *Hodgkin's disease* occurs.

GASTRIC LYMPHOMA

(a) Classification and pathogenesis

Extranodal lymphoma affects the stomach more than any other organ in the body⁽²⁾, and we shall therefore pay particular attention to gastric lymphoma.

TYPE	GRADE	FREQUENCY
Marginal zone lymphoma	low	25%
Diffuse large B-cell lymphoma	high	75%

Figure 4 Classification of primary gastric lymphoma

Primary gastric lymphomas are virtually all of B-cell type (Figure 4), derived from mucosa-associated lymphoid tissue (MALT). Unlike the intestine, however, normal stomach does not possess lymphoid tissue; this is acquired as a result of chronic infection by *Helicobacter pylori*. Figure 5 outlines the sequence of steps by which high-grade B-cell lymphoma is believed to develop in the stomach⁽⁴⁾.

Figure 5 Stages in the development of gastric lymphoma

About 50% of high-grade gastric lymphomas contain some residual low-grade tumour⁽⁵⁾. Rare high-grade lymphomas occurring in immunodeficiency states (see Part 1) arise *de novo* in the stomach.

(b) Secondary gastric lymphoma

Occasionally the stomach is involved in spread from nodal lymphoma⁽⁶⁾, such as mantle cell lymphoma or follicular lymphoma; distinguishing these from primary low-grade gastric lymphoma is both clinically important and diagnostically exacting.

(c) Clinical features

Gastric lymphoma is considerably less common than carcinoma (ratio about 1:40) and has a much better prognosis. Clinical presentation and macroscopical features of gastric lymphoma are not significantly different from carcinoma (Figure 6) but lymphoma tends to affect a slightly younger age-group and lesions can be multifocal in the stomach. Low-grade lymphomas usually form granular mucosal plaques containing one or more ulcers. High-grade lymphomas tend to form bulky tumours.

(d) Diagnosis

Diagnosis of gastric lymphomas is usually made by endoscopic mucosal biopsy and is often clinically

Figure 6 Gastric lymphoma. This ulcerated tumour could equally be carcinoma to the naked eye

unexpected. Mucosal biopsies can, however, present diagnostic difficulty to the pathologist. A dense infiltrate of small lymphocytes in the biopsy raises the suspicion of low-grade lymphoma and should prompt a search for lympho-epithelial lesions (see above). Mucosal lymphocytes can be numerous in chronic *Helicobacter* gastritis and a diagnosis of low-grade lymphoma may require careful clinico-pathological correlation and repeated biopsies. In high-grade lymphomas the malignant cells are usually more obvious, but immunostains are essential to distinguish them from undifferentiated carcinoma.

(e) Prognosis (Figure 7)

Marginal zone lymphomas remain localised for prolonged periods in the stomach and contiguous lymph nodes. Following gastrectomy, with or without radiotherapy or chemotherapy, the prognosis is excellent. This is in marked contrast to nodal low-grade B-cell lymphomas, most of which are disseminated at presentation (see Part III).

Almost all cases of low-grade gastric lymphoma have co-existing infection with *Helicobacter pylori*⁽⁷⁾. Eradication of infection has in some cases led to regression of the lymphoma⁽⁸⁾. In its early stages, therefore, gastric marginal zone lymphoma may be dependent on the presence of *H. pylori* (see Figure 5); further mutational change may then lead to autonomous tumour growth⁽⁴⁾.

Gastric *high-grade lymphoma* has a worse prognosis than low-grade disease⁽⁹⁾, although the relative importance of tumour grade and stage are not yet clear⁽⁵⁾. Treatment will usually entail gastrectomy and intensive chemotherapy. High-grade gastric lymphoma does not respond to *H. pylori* eradication.

DISEASE	5-year survival	10-year survival	reference
Gastric marginal zone lymphoma	91%	75%	9
Gastric high-grade lymphoma	75%		9
Follicular lymphoma of lymph node	65%	45%	13, 14
Gastric carcinoma	5-25%		15, 16

Figure 7 Prognosis of gastric lymphomas compared with carcinoma and follicular lymphoma

INTESTINAL LYMPHOMA

Intestinal lymphomas are only half as common as gastric lymphomas and predominantly affect the small intestine. As in the stomach, marginal zone lymphoma and its high-grade counterpart (diffuse large B-cell lymphoma) are the

commonest intestinal lymphomas. In addition, the small intestine is subject to mantle cell lymphoma and a T-cell lymphoma associated with coeliac disease. Intestinal lymphomas often present with obstruction.

(a) Intestinal marginal zone lymphoma

This is rarely encountered in western individuals but a variant of the disease is common in the Middle East, and causes severe malabsorption in young adults⁽¹⁰⁾. Termed 'Mediterranean lymphoma' or 'immunoproliferative small intestinal disease' (IPSID) the lymphoma cells synthesize part of the immunoglobulin molecule, alpha heavy chain, which can be detected in blood. The disease is suspected to be a complication of chronic infection of the bowel by an as yet unrecognised agent (analogous to *H. pylori* and gastric lymphoma). High-grade transformation can occur.

(b) Diffuse large B-cell lymphoma

High-grade B-cell lymphoma (Figure 8) is much commoner than low-grade, just as in the stomach. Prognosis is believed to be inferior to that of the stomach. Some cases arise *de novo* in the intestine, rather than from a low-grade precursor.

Figure 8 Intestinal lymphoma often appears as an annular ulcerated lesion, in this case in two separate foci

(c) Mantle cell lymphoma

Described in Part III, mantle cell lymphoma commonly affects the intestine, producing lymphomatous polyposis (Figure 9). The tumour is usually disseminated at diagnosis, as in nodal lymphoma, and the primary site of the tumour may therefore be difficult to establish.

Figure 9 Mantle cell lymphoma causing lymphomatous polyposis in the small intestine

(d) Enteropathy-associated T-cell lymphoma

This unique tumour complicates coeliac disease⁽¹¹⁾ (Figure 10) and develops on average about 20 years after diagnosis of coeliac disease. Quite a number, however, arise in a setting of undiagnosed (subclinical) coeliac disease. Strict adherence to a gluten-free diet is believed to protect coeliac patients from

malignancy, not only lymphoma, but also carcinoma of the small intestine.

Enteropathy-associated T-cell lymphoma usually develops after the age of 50 years and typically presents with the reappearance of malabsorption and abdominal pain in a patient with previously controlled coeliac disease. The tumour may also present as a surgical emergency due to intestinal obstruction or perforation. Proximal jejunum is the most frequently affected site and the tumour is often multifocal, producing circumferential mucosal ulcers and strictures.

The tumour is histologically high-grade, composed of large cells. Adjacent mucosa will usually show the villous atrophy and intra-epithelial lymphocytes of coeliac disease.

Enteropathy-associated T-cell lymphoma is an aggressive tumour, usually disseminated at diagnosis. Prognosis is poor.

Figure 10 Small intestinal mucosa showing villous atrophy of coeliac disease. Lymphoma is a rare complication of this condition

LYMPHOMA OF WALDEYER'S RING⁽¹²⁾

Waldeyer's ring comprises the pharyngeal tonsils, adenoids and lingual tonsil which form a ring of lymphoid tissue, guarding the upper end of the gastrointestinal tract.

The great majority of primary lymphomas of Waldeyer's ring are diffuse high-grade B-cell lymphomas. Low-grade B-cell lymphoma of Waldeyer's ring, however, is mostly follicular lymphoma, not marginal zone lymphoma. In terms of lymphoma, therefore, Waldeyer's ring behaves more like lymph nodes than gastro-intestinal tract.

CONCLUSION

We shall conclude the Update on Lymphoma Pathology in Part V with a review of skin lymphomas.

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