Immunoproliferative Small Intestinal Disease and B-Cell MALT Lymphoma of the Digestive Tract

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Immunoproliferative small intestinal disease (originally called Mediterranean lymphoma and subsequently alpha chain disease) is a slowly progressive low grade primary small intestinal B-cell lymphoma characterized by the synthesis of a truncated alpha heavy chain without light chain by the neoplastic cells. The histological features of IPSID and low grade primary gastric B-cell lymphoma are closely similar and recapitulate the those of Peyer’s patches. This observation has led to the mucosa associated lymphoid tissue (MALT) lymphoma concept which encompasses a group of extranodal lymphomas including IPSID and primary gastric lymphoma. Unlike nodal low-grade B-cell lymphomas, IPSID and low grade gastric lymphoma remain localized to their sites of origin for prolonged periods. One possible explanation for this is that the growth of these lymphomas is influenced by a local antigen. This is supported by reports of clinical remissions induced in IPSID following sterilization of the small intestine using broad spectrum antibiotics. Similar findings have been reported in low grade gastric lymphoma following eradication of Helicobacter pylori which is almost invariably present in the patients’ stomachs. Laboratory experiments have shown that the growth of lymphomatous B-cells is stimulated via H. pylori specific T-cells. Further work is required to identify the antigen(s) operative in IPSID and, possibly, other low grade B-cell lymphomas.

IMMUNOPROLIFERATIVE SMALL INTESTINAL DISEASE

A high prevalence of small intestinal lymphoma in the middle east was first noted by Azar in 1962 [1]. This finding was subsequently confirmed by Frand and Ramot [2] and, later, Ramot [3] followed by Eidelman [4] identified a specific subset of these cases which were characterized by severe malabsorption. Reports of the association of this newly described disease, at first called “Mediterranean lymphoma” with an abnormal immunoglobulin alpha heavy chain in the serum [5] led to the term “alpha chain disease”. As more cases were reported from an increasing number of localities, including the Cape area of South Africa, where the first cases were reported in 1973, it became clear that the term Mediterranean lymphoma was inappropriate and also that alpha chain paraprotein was not always present in the serum [6]. At a specially convened World Health Organization conference the term Immunoproliferative Small Intestinal Disease (IPSID) was adopted as a more appropriate term [7].

Initially, IPSID was considered to represent a spectrum of disorders with similar clinical and histological features but the definition soon narrowed to indicate a disorder characterized by profound malabsorption and lymphoplasmacytic infiltration of the small intestinal mucosa together with the presence of alpha heavy chain in the serum, duodenal juice or, in the nonsecretory form, confined to the cytoplasm of the infiltrating plasma cells [8]. The perception was, and to a certain extent still is, that the lymphoplasmacytic

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Abbreviations: IPSID, immunoproliferative small intestinal disease; MALT, mucosa associated lymphoid tissue.
infiltrate is initially benign (stage A) but, with time, eventually becomes lymphomatous (stages B and C) [9]. Various studies purported to show that this transformation from benign hyperplasia to frank lymphoma was heralded both by increasing “dysplasia” and depth of invasion of plasma cells. Curiously, this view prevailed despite the fact that regional lymph node infiltration was well recognized in the early stages of IPSID [9].

Isaacson and co-workers challenged these concepts. With the help of immunohistochemistry [10, 11], they and subsequently others [12] showed that, even in stage A, IPSID is characterized by two cell populations. Apart from mature IgA-synthesizing plasma cells, which occupy most of the lamina propria, there are also variable numbers of B-lymphocytes sometimes forming follicles but also invading and destroying intestinal glandular epithelium to produce the so-called lymphoepithelial lesions. These B-cells are not always obvious in routinely stained sections but are clearly seen in preparations immunostained with antibodies specific for B-cells. The invasive nature of this B-cell infiltrate was regarded as evidence for the neoplastic nature of IPSID de novo. This circumstantial evidence that IPSID is a neoplasm de novo was soon further substantiated by identifying immunoglobulin light chain restriction in a small number of otherwise characteristic cases [13] and, later, by showing monoclonal immunoglobulin gene rearrangement by Southern blotting in 3 cases of IPSID, 2 of which were at stage A [14].

MUCOSA ASSOCIATED LYMPHOID TISSUE (MALT) LYMPHOMA

In 1983 Isaacson and Wright [15] described a case of primary low grade B-cell gastric lymphoma highlighting the similarity of the histological features to a case of IPSID described in parallel. They proposed that both lesions demonstrated the features of mucosa associated lymphoid tissue (MALT) (Figure 1) and coined the term MALT lymphoma. Subsequently, a number of other extranodal low grade B-cell lymphomas arising in mucosae were found to exhibit similar features and the MALT concept was expanded to include a wider variety of extranodal lymphomas [16]. Amongst the MALT lymphomas, IPSID is unique in that the neoplastic cells synthesize an abnormal alpha heavy chain without light chain [17].

The structure of low grade MALT lymphomas closely recapitulates that of Peyer’s patches [18, 19]. Reactive B-cell follicles are a constant feature and these are surrounded by an infiltrate of cells which are cytologically and immunophenotypically similar to B-cells of the marginal zone which is a prominent feature of Peyer’s patches [20]. The characteristic lymphoepithelial lesions are the neoplastic counterpart of the normal Peyer’s patch dome lymphoepithelium. Low grade MALT lymphomas, including both gastric lymphoma and IPSID, commonly involve the local draining lymph nodes but peripheral spread, if it occurs, is a late event; this results in a very favorable prognosis quite unlike that of the indolent yet inexorably progressive and widely disseminated low grade B-cell lymphomas of lymph nodes [21]. This pattern of clinical behavior is well illustrated by both low grade gastric lymphoma and IPSID although in the latter this is somewhat countered by the effects of the accompanying malabsorption which is often severe and may on its own prove fatal relatively early in the course of the disease.

The tendency for low grade MALT lymphomas to remain localized to their site of origin for prolonged periods is well illustrated by both gastric lymphoma and IPSID. In seeking an explanation for this tendency, a number of factors need to be considered. The possibility that this group of lesions are, after all, not malignant lymphomas but, as has been previously suggested, hyperplasias or at best “pseudolymphomas” needs to be critically addressed. The possibility that lymphocyte-homing phenomena, which have been shown to operate in mucosal immunity, might underlie the curious behavior of MALT lymphomas should also be examined and, finally, consideration should be given to the possibility that, although lymphomatous, their behavior might be affected by the presence of a local antigen.
Figure 1.

**Upper Left:** Peyer’s patch showing a B cell follicle (F) with surrounding marginal zone (M) and lymphoepithelium (arrow).

**Lower Left:** Low grade gastric MALT lymphoma showing reactive B cell follicle (F) with tumor infiltrate in marginal zone (M) forming lymphoepithelial lesions (arrows).

**Upper Right:** Immunoproliferative small intestinal disease showing reactive B cell follicle (F) with tumor infiltrate in marginal zone (M) and lymphoepithelial lesions (arrows).

Note structural similarity between all three.
PATHOGENESIS OF IPSID AND MALT LYMPHOMA

The constellation of properties which define a lesion as a malignant tumor include monoclonality, the presence of a clonal genetic abnormality, invasiveness and the ability to disseminate. Both low grade gastric MALT lymphoma and IPSID are monoclonal. Various clonal cytogenetic abnormalities have been identified in both disorders. In gastric lymphoma trisomy 3 is the most common abnormality being present in 60 percent of cases but translocations involving chromosome 14q32 at the putative immunoglobulin heavy chain gene locus have also been reported [22, 23]. Relatively few cytogenetic studies have been carried out in cases of IPSID but here too, among other abnormalities, translocations involving chromosome 14q32 have been reported, importantly, in early cases which were not thought to be "overtly" lymphomatous [24]. Both low grade gastric lymphoma and IPSID are invasive but this property in the context of a lymphoproliferative lesion is not necessarily indicative of malignancy. Dissemination to local lymph nodes is common in both gastric lymphoma and IPSID but more peripheral dissemination is uncommon in both conditions, especially the latter. Taking all these factors into consideration the weight of the evidence is that it is, indeed, appropriate to designate both low grade gastric MALT lymphoma and IPSID as malignant lymphomas.

Lymphocyte homing refers to a receptor ligand system whereby circulating lymphocytes express homing receptors which recognize organ or tissue specific vascular addressing on high endothelial venules and through this mechanism migrate into specific organs or tissues. Lymphocyte homing phenomena were first described in the context of MALT [25] and initially were suggested a possible explanation for the favorable behavior of MALT lymphomas. There is some evidence for this in that MALT lymphomas, when they do spread, tend to involve other mucosae, but there is no receptor ligand system sufficiently finely tuned as to cause a lymphoma to home back to itself. Thus although lymphocyte homing may influence the behavior of low grade MALT lymphomas it does not, on its own, provide an explanation for the clinical behavior of these lymphomas.

There is a considerable body of evidence that suggests that the growth of low grade MALT lymphomas, more specifically gastric lymphoma and IPSID, is under some sort of immunological control and may be influenced by local antigen. If this were the case it could explain the tendency of the lymphomas to remain localized since lymphoma cells disseminating to peripheral locations would fail to proliferate in the absence of the specific antigen. Many of the histological features of low grade MALT lymphomas [19] are consistent with this hypothesis. Both low grade gastric lymphoma and IPSID contain variable numbers of transformed tumor cells and show plasma cell differentiation which tend to be maximal beneath the surface epithelium. These characteristics would be consistent with a luminal or epithelial antigen causing these effects. The phenomenon of "follicular colonization," [11, 26] whereby lymphoma cell migrate into the centers of reactive B-cell follicles, is also seen in both disorders and this, too, is very likely a manifestation of an antigen effect.

In keeping with the likelihood that the growth of low grade MALT lymphoma is influenced by antigen are the numerous reports of significant, sometimes complete, regression of the lymphoplasmacytic infiltrate in cases of IPSID treated with broad spectrum antibiotics alone. The effect of the antibiotics is, presumably, to sterilize the small intestinal lumen which removes the (bacterial) antigen(s) responsible for driving the proliferation of the lymphoma cells. The evaluation of the effects of treating IPSID with antibiotics alone is fraught with difficulty because of insufficient information regarding the diagnostic criteria, the frequent use of other forms of therapy and the large proportion of cases lost to follow up. However, analysis of two recent papers including one from Cape Town [27, 28], has shown convincing long-standing remissions in at least 5 of 13 stage A IPSID patients treated with antibiotics alone.
The link between *Helicobacter pylori* infection and gastric MALT lymphoma is similar to that between the putative small intestinal infection and IPSID only much more fully characterized. In the normal stomach there is no MALT which begs the question as to the origin of gastric lymphoma. As a consequence of infection with *H. pylori*, MALT, comprising lymphoid follicles and a lymphoepithelium, accumulates in the gastric mucosa. Several groups have shown that this acquisition of MALT by the stomach is highly specific for *H. pylori* infection [29-31]. Following up on these observations, Wotherspoon et al. examined 110 cases of gastric lymphoma for the presence of *H. pylori* and were able to identify the organism in 101 (92 percent) of these [32]. Further evidence for a link between this infection and gastric lymphoma came from an epidemiological study which showed a high incidence of gastric lymphoma in northeastern Italy [33], where there is a high prevalence of *H. pylori* infection and a case control study which showed that patients with gastric lymphoma are much more likely to have been infected with *H. pylori* than those with other types of lymphoma.

In the context of this circumstantial evidence, Hussell et al [35] investigated the in vitro responses of cells teased from gastric lymphomas when co-cultured with heat-killed *H. pylori*. Hussell et al. were able to show that cells from individual cases of low grade gastric MALT lymphoma were stimulated to divide and secrete tumor specific immunoglobulin by specific strains of *H. pylori*. These and subsequent experiments [36] showed that this reaction on the part of the lymphomatous B-cells was mediated via contact with *H. pylori* specific T-cells and that the B-cells themselves did not produce *H. pylori* specific immunoglobulin [37].

In a parallel clinical study, Wotherspoon et al. [38] treated 6 patients with low grade gastric MALT lymphoma, all of whom were infected with *H. pylori*, with antibiotics to eradicate the organism. This therapy resulted in complete regression of the lymphoma in 5 cases. These clinical responses have been confirmed in at least two subsequent studies [39, 40]. Most of the successfully treated cases have been early superficial lesions and further work is needed to study the effects of antibiotic therapy on more deeply invasive tumors. Another interesting aspect will be to investigate whether there are any specific genetic changes in those gastric lymphomas that have disseminated beyond the stomach and local lymph nodes whose growth, presumably, would be independent of *H. pylori* stimulated T-cells.

The discovery that the growth of gastric MALT lymphomas is under antigen specific T-cell control has direct bearing on the nature of the clinical response of IPSID to antibiotics. Given that the B-cells in IPSID synthesize an incomplete immunoglobulin molecule which specifically lacks the variable region and, therefore, would not express any antigen receptors, it was unclear how the growth of this tumor could be influenced by removal of antigen(s). As in gastric lymphoma these B-cells would, however, still be open to stimulation by antigen specific T-cells via the CD40/CD40 ligand system [36].

The early suggestions that low grade primary gastric lymphoma and IPSID exemplified a distinctive new type of lymphoma have been substantiated by further studies. Clinical experience with IPSID hinted, for the first time, that bacterial infection might play an important role in the pathogenesis of lymphoma and this has been borne out by studies firmly linking *H. pylori* to the development and progression of gastric MALT lymphoma. These studies have also drawn attention to the role of tumor-infiltrating T-cells in supporting the growth of low grade MALT lymphomas. Future work will develop these themes further in identifying the nature of the antigens operative in IPSID and other MALT lymphomas, and clarifying the mechanisms of T-cell help for the growth of low grade MALT and, possibly nodal lymphomas.
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