MALT GASTRIC LYMPHOMA: AN UPDATE OF PATHOGENETIC FEATURES

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Abstract – Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is a low-grade lymphoma comprising 7-8% of all B-cell non-Hodgkin lymphomas. Common sites of involvement include lung, head and neck, ocular adnexa, skin, thyroid and breast, but the gastrointestinal tract is by far the most common site and the stomach is involved in almost two-thirds of all cases. Infection and autoimmune diseases are commonly considered as etiopathogenetic factors, being related to chronic stimulation of B-cell proliferation. The association between Helicobacter pylori infection and gastric MALT lymphoma provides the best evidence of an etiopathogenetic link between lymphoma and infection. Indeed, successful eradication of this microorganism can be followed by lymphoma regression in most cases. In recent years the role of other pathogenetic factors including genetic predisposition, somatic genetic mutations and chemokines activity, has become more evident. Particularly specific genetic abnormalities have been observed in MALT lymphomas, with different distribution accordingly to the site of development.

This review, therefore, addresses the major findings obtained in the last few years about MALT lymphoma and summarizes recent advances in its molecular pathogenesis.

KEYWORDS: MALT, MALT lymphoma, Gastric lymphoma, Pathogenesis, H. pylori.

INTRODUCTION

Extra-nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue represents approximately 8% of all non-Hodgkin lymphomas¹.². Extranodal low-grade lymphomas were described at different sites including the gastrointestinal tract, salivary glands, lung and thyroid, showed similar clinical and histological features and are grouped into the MALT (Mucosa Associated Lymphoid Tissue) lymphoma.¹⁻⁶ The most common sites of involvement of MALT lymphomas include the stomach (70%), lung (14%), ocular adnexa (12%), thyroid (4%), and small intestine (including immunoproliferative small intestinal disease; 1%). Thus, the stomach is involved in almost two-thirds of all cases.¹ In some geographic areas, such as north-eastern Italy, the frequency of MALT gastric lymphoma is particularly high, with an incidence of 13.2 cases per 100,000 per year, significantly higher than in other European countries.³.⁴.⁵ Gastric MALT lymphoma is an indolent disease, remaining confined to the stomach for long periods, with ten-year survival rate approximately of 90%⁶,⁷. However, in some cases a diffuse large B-cell lymphoma (DLBCL) could develop in MALT lymphoma, reducing the ten-year survival rate drops to approximately 42%⁸,⁹.

HISTOPATHOLOGY AND IMMUNOHISTOCHEMISTRY

All tissues with native or acquired mucosa-associated lymphoid tissue can be involved by MALT lymphoma. Histologically MALT lymphoma is
characterized by marginal zone neoplastic cells diffusely infiltrating surrounding tissues, including reactive lymphoid tissue, a process known as follicular colonization\(^\text{12}\). In addition, in epithelized tissue, the neoplastic lymphoid cells often infiltrate the epithelial structures resulting in the formation of lymphoepithelial lesions (LELs). Neoplastic cells are constituted by centrocyte-like, monocytoid or plasmacytoid cells, with an admixture of scattered large cells. Finally, immunophenotypical profile (CD20\(^+\), CD21\(^+\), CD35\(^+\), IgM\(^+\), and IgD\(^−\)) is superimposable to normal marginal zone cells. DLBCL may be observed in MALT lymphoma, suggesting a derivation from MALT lymphoma. The demonstration of identically rearranged immunoglobulin (Ig) genes between the low- and high-grade components of the same cases seems to confirm this hypothesis\(^\text{13}\). Transformed MALT lymphomas are CD10\(^−\) and BCL2\(^−\) but, in contrast to MALT lymphoma, they usually express BCL6\(^\text{14}\). Rarely, DLBCL develops in extra-lymphoid tissues in the absence of a previous MALT lymphoma (de novo DLBCL), with no clinical difference with respect to ex MALT DLBCL\(^\text{10}\) (Figure 1).

**PATHOGENESIS**

The development of MALT gastric lymphoma has been related to certain *Helicobacter pylori* (*Hp*) strains affecting genetically predisposed patients, suggesting the need of a strain-host-organ specific process for the definitive neoplastic transformation of acquired MALT in gastric mucosa\(^\text{15-18}\) (Figure 2).

**H. pylori strains**

*H. pylori* is the prerequisite for gastric MALT lymphoma development. Indeed chronic antigenic stimulation causes genetic instability and clonal growth of MALT lymphoma. Additional mutations of tumor suppressor genes such as p53 and p16, could induce progression to DLBCL\(^\text{15-18}\).

The role of antigen-driven clonal expansion of MALT lymphoma has been demonstrated by ongoing somatic hypermutation in the Ig V genes\(^\text{19}\). Also, the Ig V gene selection in MALT lymphoma development could suggest selective pressure of an antigen to increase the affinity of the immunoglobulin for antigens\(^\text{20}\). Thus, the early stages of gastric MALT lymphoma growth may be induced by antigen-driven T cells specific for the *H. pylori* and the cure rate after bacterial eradication is higher than 75\%\(^\text{21,22}\). However, the role of host immune response has been not well studied, but it could play a relevant function, being only a minority of infected patients affected by gastric MALT lymphoma\(^\text{23}\). Thus each *H. pylori*-related gastritis patients could develop gastric MALT lymphoma, but considering the very high prevalence of *H. pylori* infection in the general population and the low incidence of gastric lymphoma, it is arguable that some particular conditions

![Image](image.png)

**Figure 1.** Histology, Immunohistochemistry and FISH for t (11;18). A-B. Haematoxylin and eosin-stained section of a stomach biopsy with a dense infiltrate of small lymphocytes (objective 20x and 40x). C. Immunohistochemical stain for the B-cell antigen CD20, demonstrating a dominance of the B-lymphocytic population (objective 40x). D. FISH positive analysis of chromosomal translocations t(11;18) (q21;q21), the most common structural chromosomal abnormality in gastric MALT lymphomas (objective 60x).
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are needed for neoplasia development. Indeed, by co-culturing neoplastic lymphoid cells from gastric MALT-lymphoma patients and different inactivated H. pylori strains, a proliferation of B-cell expressing IL-2 receptors was observed, and IL-2 production by T cells in the supernatant was also detected. Only 1 of the 13 different H. pylori strains tested could induce B-cell proliferation. The virulent factor of H. pylori does not impact on the development of MALT lymphomas as in gastric cancer and peptic ulcer disease. However, CagA positive strains have been found significantly more present in DLBCL than in low-grade MALT lymphoma. In addition, H. pylori may localize CagA protein into B-cells where it stimulates Bcl-2 expression, with consequent apoptosis inhibition.

Host organ features

Genetic predisposition

Genetic predisposition or development of MALT gastric lymphoma has been postulated, being the prevalence of HLA-DQA1*0103 and HLA-DQB1*0601 alleles and of DQA1*0103-DQB1*0601 haplotypes higher in MALT-lymphoma patients as compared to controls. The allele frequencies of HLA-DQA1*0103 and HLA-DQB1*0601 in patients with gastric MALT lymphoma are about 41.6% and 36.1% respectively, resulting in the formation of the haplotype DQA1*0103-DQB1*0601 in approximately 55.5% of the patients. Also, the presence of TNF-857 T allele and the rare allele G of Toll-like receptor 4 (TLR4 Asp299Gly) were found approximately in 10% of MALT-lymphoma patients, suggesting their possible role in the genetic susceptibility to gastric lymphoma. Finally, homozygous haplotypes for the rare allele G of SNP3 (rs12969413) of the MALT1 gene was identified approximately in 30% of patients and seems to protect patients from high- but not from low-grade gastric lymphoma.

Chemokine receptors in MALT lymphomas

The large superfamily of chemokines includes peptides playing several biological functions. Indeed,
interaction between chemokines and chemokine receptors induces chemotaxis during inflammation. CCR6, CCR7, CXCR3, CXCR4, and CXCR5 play the main role in B-cell homing process. Integrated analysis of chemokine receptors in extra-gastric MALT lymphomas demonstrated the up-regulation of CXCR1 and CXCR2 with down-regulation of CCR8 and CX3CR1 and loss of XCR1 expression. Also, CXCL12-receptor CXCR4 loss was documented in gastric MALT lymphomas when comparing to gastric extranodal DLBCL, nodal MZL, and nodal DLBCL suggesting that CXCR4 expression is related to nodal lymphomas. Finally, another CXCL12 receptor, CXCR7, is overexpressed during the transformation of gastric MALT lymphomas into gastric DLBCL.

**SOMATIC HYPERMUTATION AND GENETIC ABNORMALITIES**

*H. pylori* infection increases activation-induced cytidine deaminase (AID) expression via NF-kB in gastric cells both *in vitro* and *in vivo*, with subsequent accumulation of p53 mutation *in vitro*. AID is a key enzyme somatic hypermutation (SHM) and class switch recombination (CSR), immunological events acting to generate antibody diversity and maturity. Thus AID activity seems to play a role in lymphomagenesis through aberrant SHM (ASHM) of the 5 sequences of several protooncogenes, including PIM1, PAX5, RhoH/TTF, and cMYC and/or distinct genetic lesions, including chromosomal translocations. ASHM has widely described in DLBCL, but it has also been found in 13 (76.5%) of 17 cases of MALT lymphomas and all 17 (100%) cases of extranodal DLBCL – still exhibiting a low-grade MALT lymphoma component (the so-called transformed MALT lymphoma) – were targeted by ASHM.

The main chromosomal and genetic abnormalities are reported in Table I.

Specific genetic abnormalities have been observed in MALT lymphomas, with different distribution accordingly to the site of MALT lymphomas development. Chromosome 3 and chromosome 18 trisomy have been described in up to 68% and 57% of patients, respectively. Particularly, trisomy of chromosome 3 has been mainly shown in orbital, than in lacrimal gland and conjunctival OAML. Trisomy of chromosome 18, instead, is more frequent in the conjunctival OAML and predominantly affects young women. A comparative genomic hybridization (CGH) carried out in 10 OAML cases showed recurrent chromosomal gains at 6p21 and 9q33-qter, in addition to trisomy 3, 12 and 18.

The mechanism through which these numerical aberrations are implicated in MALT lymphomagenesis has not been well studied, but some critical genes on chromosome 3 particularly have been proposed as related to lymphoma development, such as bcl6, FOXP1 and CCR4. t(11;18) (q21;q21) is the most common chromosomal aberration observed in MALT lymphomas, mainly of gastric and pulmonary districts. Particularly it occurs in 10-50% of gastric MALT lymphomas. The effect of translocation is the fusion of the N-terminal region of the BIRC2 (API2-apoptosis inhibitor 2) gene (located on chromosome 11) and the C-terminal region of the MALT1 gene (located on chromosome 18), with the formation of the API2-MALT1 chimeric fusion protein, able to activate the NF-kB pathway. Of note, it has been found that the prevalence of CagA-positive *H. pylori* strains was significantly higher in gastric MALT-lymphoma patients with the t(11;18) (q21;q21) compared to those without such a translocation.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Affected genes</th>
<th>Genetic alteration</th>
<th>Frequency</th>
<th>Main MALT lymphoma localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 3</td>
<td>FOXP1, BCL6, CCR4</td>
<td>Trisomy</td>
<td>68%</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>Unknown</td>
<td>Trisomy</td>
<td>57%</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>Unknown</td>
<td>Trisomy</td>
<td>20%</td>
<td>Gastrointestinal; mainly high grade</td>
</tr>
<tr>
<td>t(11;18)(q21;q21)</td>
<td>BIRC2(API2), MALT1</td>
<td>Translocation</td>
<td>10-50%</td>
<td>Stomach and lung</td>
</tr>
<tr>
<td>t(14;18)(q32;q21)</td>
<td>MALT1</td>
<td>Translocation</td>
<td>10-20%</td>
<td>Ocular adnexa, orbit, skin, and salivary glands</td>
</tr>
<tr>
<td>t(3;14)(p14;q32)</td>
<td>FOXP1, IGH</td>
<td>Translocation</td>
<td>1-2%</td>
<td>Stomach, lung, skin; mainly high grade</td>
</tr>
<tr>
<td>t(17p-;6q23)</td>
<td>TNFAIP3</td>
<td>Deletion</td>
<td>10%</td>
<td>Orbit, thyroid, skin</td>
</tr>
<tr>
<td>cMYC</td>
<td>cMYC</td>
<td>Mutation</td>
<td>10-15%</td>
<td>Gastrointestinal, lung, oculair adnexa</td>
</tr>
<tr>
<td>P16</td>
<td>P16/INK4A</td>
<td>Hypermethylation</td>
<td>40-60%</td>
<td>Lung; mainly high grade</td>
</tr>
<tr>
<td>P57</td>
<td>P57(KIP2)</td>
<td>Hypermethylation</td>
<td>20-30%</td>
<td>Stomach; mainly high grade</td>
</tr>
</tbody>
</table>
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The translocation t(11;18) (q21;q21) occurs in 15-20% of MALT lymphomas, mainly in non-gastrointestinal districts. This aberration leads MALT1 gene under the control of the IGH enhancer.

In t(1;14) (p22;q32) the entire coding region of the BCL10 gene on chromosome 1 is under the control of the enhancer region of IGH gene on chromosome 14, leading to uncontrolled expression of the BCL10 gene. It is rarely observed, being described in 1-2% of MALT lymphomas, mainly stomach, lung, and skin. BCL10 is an intracellular protein that is essential for both the development and function of mature B-cells and T-cells. Recent studies show that BCL10 specifically links antigen receptor signaling in B and T cells to NF-κB activation. In MALT lymphomas with t(11;18) (q21;q21), t(14;18) (q32;q21) or t(1;14) (p22;q32) MALT1, with or without BCL10 cooperation, activates the phosphorylation cascade leading to IkB-α phosphorylation. IkB-α links NF-κB in the cytoplasm. IkB-α phosphorylation enables the release NF-κB, which shuttles into the nucleus, playing its transcriptional role with up-regulation of the cell cycle regulators expression anti-apoptotic proteins, growth factors, negative regulators of the NF-κB pathway and immunoregulatory cytokines.

The translocations could be demonstrated through Fluorescent In Situ Hybridization (FISH) on neoplastic cells. Alternatively, BCL10 immunohistochemical expression could be used as a good surrogate marker of translocations in MALT lymphomas. Thus, the nuclear BCL10 expression suggests NF-κB activation after t(11;18) (q21;q21) or t(1;14) (p22;q32), while strong cytoplasmic perinuclear expression is related to t(14;18) (q32;q21) [70, 76-79]. However, it has been noticed that MALT lymphomas lacking both t(11;18) or t(1;14) showed a moderate nuclear BCL10 expression, related to a poor prognosis. Moreover, an association between weak cytoplasmic BCL10 expression and translocation (14;18) has been found in only 3 cases.

Recently, FOXP1 (located at 3p14) was identified as a new translocation partner of IGH (q32) at low frequency in MALT lymphomas and DLBCL.
Overexpression of FOX1P in lymphoma cells demonstrates that FOX1P is a powerful transcriptional repressor of multiple pro-apoptotic genes.

The neoplastic growth-dependence from *H. pylori* has been associated to specific genetic status. Thus, *H. pylori*-dependent MALT lymphoma carrying trisomies 3, 12, or 18 could become *H. pylori*-independent and the transformation into high-grade tumors occurs through P53 inactivation, P16 gene deletion or chromosomal translocation of cMYC and BCL6. On the other hand MALT lymphomas with t(11;18)(q21;q21) are definitively *H. pylori*-independent but it rarely has the ability to transform into aggressive lymphomas.

Recently, another possible mechanism for uncontrolled NF-kB activation in MALT lymphoma, but not observed in gastric MALT lymphomas, is generated by homozygous deletion of the chromosomal band 6q23 with subsequent loss of the tumor necrosis factor alpha-induced protein 3 (TNFAIP3, A20)92, an essential global NF-kB inhibitor. In OAML, A20 inactivation is associated with poor lymphoma-free survival99-102 and with a range of chronic inflammatory disorders93-97. A20 is also inactivated frequently by somatic mutation90,98,99.

**CONCLUSIONS**

MALT lymphomas include a heterogeneous group of B-cell lymphomas, with different localizations and different genetic anomalies100-104. Infection and autoimmune disease are commonly considered as etiopathogenetic factors, being related to chronic stimulation of B-cell proliferation90,105-107. Thus eradication of bacterial pathogens, in the early stage of disease, could be the cause of MALT lymphoma regression, particularly in gastric and ocular adnexa B-cell lymphomas108,109. In more advanced stages some genetic alterations could occur in neoplastic B-cells. All the described genetic abnormalities concur to deregulate NF-kB signal pathways61,63,108-112. In this view, a complete remission in a large portion of MALT lymphoma patients has been obtained by the use of bortezomib113,114 – a proteasome inhibitor inhibiting the NF-kB signal pathway115. Also, the deregulation of NF-kB has also been found in MALT lymphoma patients without known genetic abnormalities.

In this view, the therapy targeting NF-kB may open new prospective in the treatment of this neoplasia.

**Conflict of Interests:**
The Authors declare that they have no conflict of interests.

**REFERENCES**

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