Gastric lymphoma: The histology report

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\section*{Abstract}

The diagnosis of gastric MALT lymphoma is frequently difficult for the general histopathologist. During recent years there have been relevant changes in the therapeutic approach to gastric MALT lymphoma and our knowledge about its pathogenesis has greatly improved. The management of this disease actually requires a close cooperation between the histopathologist and the clinicians. The histology report of biopsies of a newly diagnosed or of an already treated case implies information of clinical and therapeutical relevance. This paper aims at giving the histopathologist a general knowledge about the state of art of this disease and its management. The diagnostic process leading to a complete and competent report is then described step by step.

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\section*{1. Introduction}

The preferred site of primary GI lymphomas is the stomach where extranodal marginal zone (MALT) lymphoma is by far the most frequent histotype. Gastric MALT lymphoma represents the first lymphoma where an antigen-driven pathogenesis was documented together with the unexpectedly effective antibacterial treatment option, leading to the complete modification of its management [1,2]. However, the diagnosis of gastric lymphoma remains frequently a challenge and the evaluation of lymphoma regression after antibiotic therapy has opened new interpretative problems. This review focuses on the diagnostic criteria guiding gastric MALT lymphoma management at the initial diagnosis and during follow-up (Fig. 1), and on the relevant information that the histology report should convey to the Clinician for the best treatment of these patients.

\section*{2. Changing epidemiology of gastric lymphoma}

The etiopathogenesis of gastric extranodal marginal zone (MALT) lymphoma is linked to \textit{Helicobacter pylori} (\textit{H. pylori}) infection and its prevalence is similar in different geographical areas [3,4].

The diagnostic scenario of MALT lymphoma has changed...
as a consequence of the fact that remission is obtained in most cases by \textit{H. pylori} eradication only [2].

In addition, although epidemiologic data are still limited, there is some evidence that the declining rate of \textit{H. pylori} infection over the last 30 years in most industrialized countries has led to a significantly decreased incidence of gastric MALT lymphoma [5].

Whether the incidence and the clinico-pathological scenario of gastric Diffuse Large B Cell Lymphoma (DLBCL), with or without associated MALT lymphoma component, could also be influenced, is still unknown.

3. Clinical symptoms and endoscopic findings in gastric lymphomas

Gastric MALT lymphoma in most cases behaves as an indolent disease. However, its diagnosis involves important consequences for the patient.

In most cases a gastric MALT lymphoma is diagnosed following endoscopy performed for ordinary dyspeptic symptoms. Less frequently the presenting symptoms include vomiting or nausea, while more worrying symptoms, like pain, haematemesis, melaena or abdominal mass, are only rarely present.

The histologic diagnosis of lymphoma is often unexpected even by the endoscopist. In fact more than 50% of cases are associated with endoscopic features of gastritis, while 41% show single or multiple active or healing ulcers, and 5% show erosions. Irregular and serpiginous hypertrophic plicae, a feature classically described in association with gastric lymphoma, is detected in 3% of patients and a mass in 1% only (A.S. personal 94 case series – unpublished data). Altogether the endoscopic features may be suggestive of lymphoma in only one third of cases.

Consequently the initial diagnostic sample is usually represented by a limited number of biopsies (2 to 5), which can render the difficult diagnosis of gastric lymphoma a real challenge for the histopathologist.

Since gastric MALT lymphoma tends to be multifocal [6,7] and a DLBCL component may coexist in the stomach [8], a gastric biopsy mapping is advised after a first diagnosis, prior to therapy.

Should microbiology be available, biopsy samples for culture should also be taken during mapping endoscopy, with the aim of obtaining a resistance test.

No optimal standardized biopsy mapping procedure for histological assessment exists. However, adequate mapping should include multiple biopsies both from each endoscopic lesion and the macroscopically unremarkable mucosa of all main gastric regions (antrum, angulus, body and fundus). Biopsies from both walls and curvatures at different levels are suggested.

Whatever the mapping procedure adopted at initial staging, it is important to keep the same protocol during the follow-up endoscopy, in order to allow a proper histological comparison.

4. The histopathological diagnostic process in gastric lymphoma (Fig. 2)

When examining a gastric biopsy with a dense lymphoid infiltrate mainly composed of small-sized lymphocytes, the first step for the histopathologist is distinguishing between reactive and neoplastic.

Once a neoplastic infiltrate is identified, it is necessary to define the lymphoma subtype (MALT versus non-MALT lymphoma and low grade versus high grade lymphoma) and to assess \textit{H. pylori} infection.

Differentiating an exuberant inflammatory infiltrate from a MALT lymphoma may be difficult and a degree of diagnostic uncertainty cannot be avoided in some cases. In 1993, Wotherspoon et al. [2] designed a morphological 5 grades score system aimed at better defining and differentiating the gastric lymphoid infiltrates. This score system clearly reflects these diagnostic difficulties in its grey zone, represented by grades 3 (suspect, probably reactive) and 4 (suspect, probably neoplastic).

However, the combination of morphology and immunophenotype make it possible to overcome these diagnostic difficulties in most cases. The molecular analysis of B-cell clonality...
allows for a confident confirmation of the histological diagnosis. Moreover, it can be used to differentiate between neoplastic and reactive lymphoid infiltrates in suspicious cases.

The diagnostic process is described step by step in the following paragraphs.

4.1. Reactive versus neoplastic lymphoid infiltrate

The most frequent diagnostic dilemma is differentiating between *H. pylori*-associated follicular gastritis and gastric MALT lymphoma. Morphologic criteria to be considered include: quantity and morphologic composition of the lymphoid infiltrate as well as the presence and characteristics of lymphoepithelial lesions and lymphoid follicles.

**Quantity:** The main criterion favouring the diagnosis of lymphoma is quantitative. The lymphoid infiltrate must be dense and occupy most of the lamina propria, destroying and replacing glandular structures; should lymphoid follicles be present, the interfollicular space should be completely filled by lymphocytes.

**Morphology:** The morphology of gastric lymphoid infiltrates, either reactive or neoplastic, is frequently heterogeneous, although it may be a little less diversified in lymphomas. Centrocyte-like cells, lymphocytes with monocytoid/marginal zone features, small round lymphocytes, cells with plasmacytic differentiation, plasma cells and scattered, single, large, centroblast or immunoblast-like cells, are the main cellular components of MALT-type lymphoma. Their proportion is variable in different cases and may be different through different areas of the same case. Plasma cells, when present, usually accumulate within the superficial lamina propria, just beneath the epithelium. The presence of PAS-positive intranuclear inclusions (Dutcher bodies), favours a neoplastic process.

**Lymphoepithelial lesions:** An important diagnostic clue of MALT lymphoma is the presence of lymphoepithelial lesions, represented by the infiltration and partial destruction of glandular structures by aggregates of at least four or five neoplastic cells. Their proportion is variable but is usually high. Follicles may be present, reactive germinal centres of reactive lymphoid follicles, although this feature is difficult to assess and very infrequently observed in biopsy specimens.

In case of diagnostic uncertainty, a second gastroscopy with extensive biopsy is advisable.

4.2. Immunophenotype of gastric MALT lymphoma

Immunophenotyping of relevant lymphoid infiltrates in gastric biopsies allows the assessment of their lineage distribution, the identification of an abnormal phenotype and of a monotypic immunoglobulin light chain restriction, and the differential diagnosis with other tumours of the lymphoid system. No specific markers of marginal zone lymphoid cells are available, the identification of which relies on the negativity of specific markers of different low grade B-cell lymphomas.

The neoplastic cells in MALT lymphoma express B-cell markers, CD20, CD79a, IgM and less frequently IgG or IgA; clonality of light chain restriction may be demonstrated by immunohistochemistry in a minority of cases, mostly with plasma cell differentiation. IgD, CD5, CD10, Bcl6 and cyclin D1 immunostains are usually negative in MALT lymphoma and allow for the exclusion of other small B-cell lymphomas (see below) (Table 1). CD5 expression has been reported in occasional extra-gastric marginal zone lymphomas but never in primary gastric MALT lymphoma. CD43 immunoreactivity is present in B cells in about 40 to 50% of gastric MALT lymphoma cases and is strongly suggestive for lymphoma. A dense CD20+ B-cell infiltrate, substituting and infiltrating glandular structures is the expected pattern of MALT lymphoma in gastric biopsies. The number of scattered accompanying CD3+ non-neoplastic small T lymphocytes is variable but is usually high. Follicles may be present, reactive or with follicular colonisation, and can be highlighted by CD21, CD35 or CD10 immunostains. Cytokeratin immunostaining makes more evident the presence of lymphoepithelial lesions and of scattered single residual signet-ring like epithelial cells, especially when the lymphoma infiltrates the oxyntic mucosa.

4.3. Molecular biology techniques useful in MALT lymphoma diagnosis

Molecular biology techniques can be helpful in confirming the diagnosis of lymphoma and allow for the identification of specific genetic alterations, relevant for therapeutic and prognostic purposes.

**Table 1**

<table>
<thead>
<tr>
<th>Immunophenotype</th>
<th>CD20</th>
<th>CD5</th>
<th>CD3</th>
<th>CicD1</th>
<th>CD43</th>
<th>CD10</th>
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<tr>
<td>B-MALT</td>
<td>+</td>
<td>−</td>
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<td>−</td>
<td>+/−</td>
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<td>MCL</td>
<td>+</td>
<td>+</td>
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<tr>
<td>B-CLL</td>
<td>+</td>
<td>+</td>
<td>−</td>
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<td>FL</td>
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B-MALT: Extramedullary Marginal Zone Lymphoma MALT Type; MCL: Mantle Cell Lymphoma; B-CLL: B-Cell Chronic Lymphocytic Leukemia; FL: Follicular Lymphoma.
In selected cases, when morphology and immunophenotyping are not sufficient for a conclusive diagnosis of MALT lymphoma (mainly Womersley score ≥4), the application of PCR-based methods for the determination of B-cell clonality can be of help in the diagnostic process. This analysis must be performed utilizing the PCR primers and protocols for the analysis of IGH, IGK and IGL gene rearrangement, developed by the European BIOMED-2 Concerted Action Program [9]. Using these protocols, monoclonal B-cell populations are detected in approximately 80–90% of overt gastric MALT lymphomas and detection of B-cell monoclonality in suspicious cases strongly favours a diagnosis of lymphoma [10].

Previous reports of detection of B-cell clonality in a high percentage of *H. pylori* gastritis were flawed by technical and interpretative biases. On the contrary a PCR negative result does not exclude a diagnosis of lymphoma.

PCR for IGH gene rearrangement should be performed only when there is a lymphoid infiltrate morphologically suspicious for lymphoma; MALT lymphoma should not be diagnosed by clonal analysis alone in the absence of, at least suspect, morphological evidence: the presence of only a limited number of reactive B lymphocytes could result in a misleading result of pseudo-clonality. It must be stressed that the interpretation of PCR results of B-cell clonality should always be evaluated in conjunction with histopathologic and immunophenotypic data. B-cell clonality evaluation is not considered useful in follow-up management of patients with gastric MALT lymphoma.

MALT lymphomas are characterized by a series of recurrent genetic alterations. The translocation t(11;18)(q21;q21), resulting in the fusion of the genes for the inhibitor of apoptosis API2 and MALT1, with the expression of the API2-MALT1 chimeric protein, is present in about 25% of gastric MALT lymphomas and is particularly frequent in *H. pylori*-negative cases [11]. This translocation has a pathogenetic role and represents an unfavourable prognostic marker, being associated with advanced stage and poor or no response to antibacterial therapy [12,13]. It is only rarely detected in high grade gastric lymphomas and is absent in other lymphomas [14]. t(11;18)(q21;q21) can be detected in formalin-fixed specimens, by interphase fluorescence in situ hybridisation (FISH) or RT-PCR assays. Presently t(11;18)(q21;q21) evaluation at diagnosis is advised, but not considered mandatory, while it is recommended when considering further therapeutical options, particularly in cases of presumed failure of the antibacterial therapy, before opting for an oncologic treatment. In fact the translocation t(11;18) is considered associated with the acquisition, by the lymphoma, of autonomous proliferation and its detection predicts likelihood of achieving a remission in further follow-up, unless alternative oncologic therapy is given.

4.4. Helicobacter pylori detection

Careful evaluation of *Helicobacter pylori* infection is very important for therapy and the histology report of a gastric MALT lymphoma must include *H. pylori* status. The gold standard diagnostic test is histology, which should be preferentially matched by serology at the initial diagnostic phase. *H. pylori* infection is usually easily demonstrated in biopptic specimens; when bacteria are rare, their identification may require special stains such as Giemsa, immunohistochemistry or fluorescence in situ hybridization (FISH). Should the patient be under PPI treatment, this medication has to be withdrawn at least two weeks before endoscopy, to avoid false negative results. If *H. pylori* is not demonstrated in histologic specimens, it is advisable to perform other diagnostic tests like serum specific IgG antibody detection or stool antigen test. For a reliable *H. pylori* assessment, at least two diagnostic tests are required. The detection of serum antibodies can specifically confirm the actual infection or demonstrate a previous infection in negative cases.

However, even combining more tests, the negative predictive value of *H. pylori* assessment remains below 100%. In addition, there is evidence that antibacterial treatment could be effective in some of *H. pylori* negative cases too [15,16].

4.5. MALT vs non-MALT lymphoma

Some B-cell lymphomas, including mantle cell, follicular, and lymphocytic lymphoma, may mimic gastric MALT lymphoma in gastric biopsies. In most of these cases the involvement of gastric mucosa represents a secondary localization of an already known disseminated disease. More rarely a non-MALT B-cell lymphoma composed of small lymphocytes is firstly diagnosed in gastric biopsies. A complete immunophenotypical evaluation, including cyclin D1, CD10, CD5, Bcl6 and Bcl2, is necessary in these cases for a correct differential diagnosis. Mantle cell lymphoma is the most frequent and clinically relevant non-MALT lymphoma with gastric involvement.

Rarely, T-cell lymphomas may primarily affect gastric mucosa; most of these cases have been reported in Asian patients [17].

4.6. Low grade vs high grade lymphoma

MALT lymphomas usually host scattered large transformed blasts; their number varies from case to case, but it does not exceed 10% of lymphoid population. MALT-type lymphomas may progress to high grade, large B-cell lymphoma (DLBCL); MALT lymphoma and high grade large cell lymphoma may therefore coexist. Gastric Diffuse Large B Cell Lymphoma (DLBCL) may also arise de novo, without an accompanying low grade component. The distinction between transformed MALT-type lymphoma and DLBCL arising de novo, is at present, impossible. The current World Health Organization classification recommends that cases showing transformation to large-cell lymphoma should be called DLBCL instead of high grade MALT lymphoma; in this context the occurrence of lymphoepithelial lesions composed of large lymphoid cells does not modify the diagnosis of DLBCL [18]; however, the presence of an accompanying MALT lymphoma component...
should always be reported. As a practical point, the recognition of the high grade component and the distinction between a low and high grade lymphoma could be a diagnostic challenge. Morphologic criteria for distinction between low and high grade are not well established and are difficult to apply to small biopsies [19]. In high grade lymphoma large blasts are present in clusters – containing at minimum 20 large cells – or as sheet-like proliferations. A proliferation marker, like Ki67, could be helpful in delineating the large cell component, but attention must be paid to avoid the misinterpretation of fragments of reactive germinal centres as areas of high grade transformation.

Immunostains for germinal centre cells or follicular dendritic cells could be of help in these cases.

*H. pylori* status must be determined also in high grade cases, irrespective of the presence of low grade MALT component; there is evidence that some cases of gastric DLBCL may also regress after *H. pylori* eradication [20].

**5. Staging procedures (Fig. 3)**

Gastric MALT lymphoma tends to remain localized for a long time [21] and to deepen progressively into the gastric wall. Perigastric lymph nodes are the first affected. A spread to distant organs harbouring the MALT (colon, salivary glands, thyroid, lacrimal glands, lungs) is common in more advanced cases while distant lymph node and bone marrow involvement are late and rare events. Its pattern of dissemination is therefore different from that of nodal lymphomas.

The recently updated ESMO guidelines for gastric MALT Lymphoma indicate, as staging procedures, the ordinary evaluation performed for lymphomas (complete blood counts, basic biochemical studies, including lactate dehydrogenase and β2-microglobulin, computed tomography of the chest, abdomen, and pelvis, bone marrow aspirate and biopsy) and in addition Endoscopic Ultrasound to evaluate the regional lymph nodes and the gastric wall infiltration [22]. Some studies have demonstrated that the response to the antibacterial treatment is dependent on the depth of infiltration into the gastric wall [23,24] and to the involvement of perigastric lymph nodes [25]. Endoscopic ultrasound (EUS) provides the best assessment of these parameters. Its sensitivity in assessing depth of wall involvement and status of perigastric lymph nodes is in fact superior to CT scan [26].

Besides these systemic staging procedures for gastric MALT lymphoma, some authors suggest also the assessment of the organs possibly harbouring the MALT [27]. The EGILS consensus report [28] suggests not performing a bone marrow biopsy as a part of the initial staging of patients with gastric MALT lymphoma. In fact the bone marrow involvement represents a rare and late event of this disease. A bone marrow biopsy is instead suggested as part of the stage reassessment prior to oncologic treatment for patients non respondents to eradication of *Helicobacter pylori*.

The peculiar pattern of dissemination of gastric MALT lymphoma is the reason why the Ann Arbor Staging for lymphomas is not entirely appropriate to address therapy and follow-up choices.

A better stage assessment is provided by the Paris Staging System proposed by the European Gastro Intestinal Lymphoma Study Group, a modified TNM staging that takes into account: (a) depth of tumour infiltration into the intestinal wall; (b) extent of lymph nodal involvement; (c) specific pattern of dissemination [29].

**6. Antibacterial therapy**

There is general agreement that antibacterial treatment is the first choice therapy in gastric MALT lymphoma, regardless of its stage.

*Helicobacter* negative cases and cases with *H. pylori*-positive diffuse B-cell gastric lymphoma are also suitable for a first attempt with antibiotics. There is, in fact, evidence that some patients with *Helicobacter* negative gastric MALT lymphoma or gastric diffuse B-cell high grade lymphoma, do undergo complete remission after eradication of *H. pylori* only [15,16,20].

In case of diffuse B-cell gastric lymphoma treated with
antibiotics as a first line therapy, it is advisable to enrol the patients in ongoing clinical trials or to perform a very strict follow-up. Should a MALT lymphoma be associated with a gastric Diffuse Large B cell Lymphoma (DLBCL), even if a traditional oncologic treatment is chosen as the first line therapy, eradication of *H. pylori* is mandatory in order to control the low grade lymphoma, which is frequently resistant to the chemotherapy combinations effective on DLBCL. Clinical stage and depth of tumour invasion are the most important factors predictive of responsiveness to antibiotic therapy. However, locally advanced cases may also regress. Regression after anti-*H. pylori* antibiotic therapy has also been reported in a single case of gastric Burkitt’s lymphoma [30].

7. *Helicobacter pylori* eradication assessment

To assess *H. pylori* eradication, a first endoscopy should be done 6–8 weeks after antibacterial treatment completion. Urea breath test (UBT) should be matched to histology at this stage as it is a very specific and sensitive test.

Culture and sensitivity testing is indicated to guide further treatment in case of a resistant strain.

Serology is not advised at this point, as a significant change in antibody levels would be detectable only 6 months after eradication.

In case of failure of the first antibacterial treatment, further anti-*Helicobacter pylori* alternative treatments are chosen based on the internationally approved “salvage” protocols (Maastricht Consensus) [31] and, possibly, on antibiotic sensitivity testing.

8. Follow-up strategies (Fig. 4)

Once eradication is documented, the follow-up of gastric MALT lymphoma is usually represented by endoscopy with biopsy mapping every 6 months, until complete remission is observed in two subsequent checks.

Thereafter a yearly interval is considered adequate.

Data concerning the use of endoscopic ultrasound for response evaluation are controversial and EUS is not generally recommended in this context [32].

8.1. Histologic assessment of response (Table 2)

At a variance with most extranodal and nodal lymphomas, gastric MALT-type lymphoma carries the unique opportunity to be monitored with histopathological examination.

Assessment of MALT lymphoma response to *H. pylori* eradication is based on the comparison of histology of original biopsies with that of biopsies obtained after therapy. A specific post-treatment grading system has been proposed under the auspices of GELA (Groupe d’Etude des Lymphomes de l’Adulte) group [33], with the aim of using a common language among pathologists and clinicians, thus allowing the comparison of data among clinical trials.

The GELA grading system takes into consideration three parameters evaluable exclusively on H&E stained sec-

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**Fig. 4.** Follow-up flow chart for gastric MALT lymphoma management after *H. pylori* eradication.
Table 2
The GELA system

- Complete histological response (CR): Both neoplastic lymphoid infiltrate and lymphoepithelial lesions have completely disappeared. Areas of “empty lamina propria” devoid of glands.

- Probable minimal residual disease (pMRD): Small aggregates or nodules of lymphoid cells are present, usually adjacent to the muscularis mucosae, and associated with regressive stromal changes. The biological significance of this minimal lymphoid population is uncertain, but probably it is of no clinical significance. No molecular biology assessment is indicated in this context.

- Responding residual disease (rRD): Residual diffuse or nodular lymphoma is present associated with evident regressive stromal changes. A comparison with the original histology is particularly helpful in this context. These features are considered as expression of a partial ongoing response and allow the postponement of the decision for a second line oncologic treatment.

- No change (NC): Persistent lymphoma is present, consistent with that originally diagnosed, in the absence of stromal changes suggestive of response.

Adapted from Copie-Bergman et al. [33].

... to a complete remission and no adverse prognostic significance associated with this pattern has been demonstrated so far. Therefore, this category has to be considered most probably associated with a clinical complete remission and no further therapy is needed. As a practical consequence, no molecular biology assessment is indicated in this context.

Responding residual disease (rRD): residual diffuse or nodular lymphoma is present associated with evident regressive stromal changes. A comparison with the original histology is particularly helpful in this context. These features are considered as expression of a partial ongoing response and allow the postponement of the decision for a second line oncologic treatment.

No change (NC): persistent lymphoma is present, consistent with that originally diagnosed, in the absence of stromal changes suggestive of response.

The appearance of signs of regression can be delayed in some cases up to several months after eradication. However, the absence of regression in multiple sequential biopsies is an indication for considering a second line oncological treatment.

Based on the clinical and histological data, four clinical categories identify the possible response to treatment.

8.2. Management options

- Complete remission: no endoscopic and histologic evidence of lymphoma (GELA: CR or pmRD) documented in two subsequent follow-ups.

- Partial remission: disappeared or reduced macroscopic lesions associated with signs of histological response (GELA: rRD) in the absence of progressive disease. The clinical management in these cases should be individually evaluated in each case.

- Stable disease: no endoscopic and/or histologic changes (GELA: NC) in comparison with initial diagnosis. If macroscopic changes persist, an oncologic treatment should be proposed. In case only microscopic disease is documented, oncologic treatments could be postponed up to 24 months after H. pylori eradication.

- Progressive disease: is defined either by worsening of the endoscopic lesion, or dissemination, or evolution to Diffuse Large B Cell Lymphoma. When progressive disease is documented, oncologic treatment is mandatory.

8.3. Management of patients not achieving complete remission with eradication of Helicobacter pylori

A number of second-line treatments for patients not responding to eradication therapy have been developed, including chemotherapy, radiotherapy, immunotherapy, and radioimmunotherapy. The decision on a second line oncologic treatment in case of failure of the antibacterial therapy is influenced by the assessment in lymphoma cells of the translocation t(11;18). Besides being associated with a very
low possibility of obtaining remission with antibacterial treatment only (20% of cases) [35], the presence of t(11;18) in gastric MALT lymphoma is also predictive of resistance to oral alkylating agents, with less than 10% durable remission at long term follow-up [36].

In case of stable disease or partial remission the patient can also be re-evaluated with systemic staging 12–24 months after eradication. Whether to continue a “watch-and-wait” follow up or to begin a second line treatment should be an individually tailored multidisciplinary decision, based on clinical, histological and molecular data, patient’s preferences and data emerging from ongoing trials.

In case complete remission is not obtained, a “watch-and-wait” follow-up duration of 24 months after eradication of H. pylori is generally considered adequate, before considering alternative treatments in early stage H. pylori positive cases. This interval might be shorter in patients with involved perigastric lymph nodes or more advanced disease.

8.4. Management of relapsing lymphoma

After histological complete remission a relapsing lymphoma can occasionally be documented in follow up biopsies. If H. pylori is also present, a failed eradication is more probable than a true relapse. In fact, the occurrence of a reinfection with H. pylori is exceptional if compared to its regrowth after incomplete clearance. The possibility of a sampling error of a persistent disease after eradication should also be taken into account, especially if NC is documented [37].

However, all the trials demonstrate a tendency of these histologically relapsing cases to undergo further remission without additional therapy, so justifying the continuation of a “watch-and-wait” strategy, in the absence of documented progressive disease [37–40].

8.5. Follow-up of patients in continuous complete remission

Whether to stop the endoscopic follow-up of patients in remission after antibiotic therapy at a certain point is still an open issue. The duration of the small number of trials published so far is still too short to draw any conclusion. However, at present, an indefinite continuation of yearly endoscopic follow up after complete remission is suggested. In fact, besides the possibility of a lymphoma recurrence or of its transformation into DLBCL [35], a 6 times higher risk of developing gastric adenocarcinoma has been demonstrated in patients with MALT lymphoma compared to the general population [41].

9. The histology report

The histopathology report dealing with a lymphoid infiltrate diagnostic for lymphoma at first diagnosis, must contain the lymphoma istotype according WHO classification [18], site of mucosal involvement, H. pylori status and immuno-phenotypic profile. Molecular biology results, such as IgH gene rearrangement and FISH for t(11;18), must be included when performed. In dubious cases as Wotherspoon scores 3 and 4 [2] a descriptive report must be issued, including anatomical site where the lymphoid infiltrate has been observed, immunohistochemical and molecular biology results and a suggestion for a new endoscopic procedure with extensive biopsy sampling.

In post-treatment follow-up biopsies, the use of GELA diagnostic categories [33] is suggested; H. pylori status and immunophenotype results must be reported; a comment on the comparison of the histology of original biopsies with that of biopsies obtained after therapy should also be included.

Since the discovery of the etiopathogenetic role of H. pylori, deep changes in the diagnostic and therapeutic approaches to patients affected by gastric lymphomas, have occurred. Integration of endoscopy, histology and clinical data is crucial throughout the minimally invasive, but continuous follow-up at present recommended for these patients.

Conflict of interest

The authors declare no conflict of interest.

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