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Role of non-*Helicobacter pylori* gastric Helicobacters in *H. pylori*-negative gastric mucosa-associated lymphoid tissue lymphoma

NHPHs in *H. pylori*-negative gastric MALT lymphoma

Fabian Felliipe Bueno Lemos, Marcel Silva Luz, Samuel Luca Rocha Pinheiro, Kádima Nayara Teixeira, Fabrício Freire de Melo

Abstract

Marginal zone lymphomas (MZLs) rank as the third most prevalent form of non-Hodgkin B-cell lymphoma, trailing behind diffuse large B-cell lymphoma and follicular lymphoma. Gastric MALT lymphoma (GML) is a low-grade B-cell neoplasia frequently correlated with *Helicobacter pylori* (*H. pylori*)-induced chronic gastritis. On the other hand, a specific subset of individuals diagnosed with GML does not exhibit *H. pylori* infection. In contrast to its *H. pylori*-positive counterpart, it was previously believed that *H. pylori*-negative GML was less likely to respond to antimicrobial therapy. Despite this, surprisingly, increasing evidence supports that a considerable proportion of patients with *H. pylori*-negative GML show complete histopathological remission after bacterial eradication therapy. Nonetheless, the precise mechanisms underlying this treatment responsiveness are not yet fully comprehended. In recent years, there has been growing interest in investigating the role of non-*H. pylori* gastric Helicobacters in the pathogenesis of *H. pylori*-negative gastric MALT lymphoma. However, additional research is needed to definitively establish the causal relationship between NHPHs and GML. In this minireview, we examined the current understanding and proposed future

prospects on the involvement of NHPHs in *H. pylori*-negative gastric MALT lymphoma, as well as their potential response to bacterial eradication therapy.

Key Words: Lymphoma; B cell; Marginal Zone; Gastric MALT lymphoma; *Helicobacter pylori*; non-*Helicobacter pylori* gastric *Helicobacters*; *Helicobacter heilmannii*; *Helicobacter suis*

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Core Tip: Gastric MALT lymphoma is a type of non-Hodgkin lymphoma that predominantly arises in the stomach. It has been well-established that *Helicobacter pylori* (*H. pylori*) infection plays a crucial role in the development of gastric MALT lymphoma. However, a subset of patients diagnosed with gastric MALT lymphoma are negative for *H. pylori*. In recent years, there has been growing interest in investigating the role of non-*H. pylori* gastric *Helicobacters* (NHPHs) in the pathogenesis of *H. pylori*-negative gastric MALT lymphoma. This article aims to explore the current understanding of the involvement of NHPHs in the development of gastric MALT lymphoma and its potential responsiveness to bacterial eradication therapy.

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INTRODUCTION

Marginal zone lymphomas (MZLs) rank as the third most prevalent form of non-Hodgkin B-cell lymphoma, trailing behind diffuse large B-cell lymphoma and follicular lymphoma^[1]. The 5th edition of the World Health Organization Classification of Hematolymphoid Tumors - Lymphoid Neoplasms further categorizes MZL into four subtypes: extranodal MZL of mucosa-associated lymphoid tissue (MALT), primary cutaneous MZL, nodal MZL, and pediatric MZL^[2].

Gastric MALT lymphoma (GML) is a low-grade B-cell neoplasia frequently correlated with *Helicobacter pylori* (*H. pylori*)-induced chronic gastritis^[3]. Although the normal gastric mucosa lacks lymphoid follicles, chronic inflammation can lead to the formation of MALT. Persistent antigenic stimulation promotes the clonal expansion of B cells within the MALT, facilitated by specific T helper cells, with the potential for malignant transformation^[4,5]. As GML progresses, genetic and epigenetic alterations occur in oncogenes and tumor suppressor genes, resulting in dysregulated cell growth and survival. Common genetic alterations observed in MALT lymphoma include chromosomal translocations involving the *API2-MALT1* gene fusion and mutations in genes such as *TP53* and *MYD88*^[5-7].

The current clinical guidelines advocate for the use of *H. pylori* eradication therapy as the primary treatment approach for localized gastric mucosa-associated lymphoid tissue lymphoma^[8-10]. In a recent systematic review conducted by our group, comprising meta-analyses, it was highlighted that bacterial eradication treatment resulted in the disappearance of lymphoma in over 75% of patients with low-grade, *H. pylori*-positive gastric MALT lymphoma^[11]. Hence, our results ratified that bacterial eradication is effective as the sole initial therapy for early-stage GML.

On the other hand, a specific subset of individuals diagnosed with GML does not exhibit *H. pylori* infection^[12-15]. Initially, it was assumed that these patients might not respond favorably to bacterial eradication therapy. However, another meta-analysis conducted by Jung *et al.*^[16] demonstrated that 29.3% (95%CI: 22.2%-37.4%, $I^2 = 41.5\%$) of *H. pylori*-negative GML patients experienced complete histopathological remission after eradication therapy. The underlying mechanisms for this responsiveness remain unclear^[16].

There has been a growing interest in exploring the involvement of species of non-*Helicobacter pylori* gastric Helicobacters (NHPHs) in the development of *Helicobacter pylori*-negative gastric MALT lymphoma and its responsiveness to bacterial eradication therapy^[17-20]. NHPHs represent a group of bacterial species that colonize the stomach but differ genetically and phenotypically from *H. pylori*^[21-24]. These differences include

variances in flagella, urease activity, and other virulence factors^[25,26]. While NHPHs have been detected in some patients with gastritis and peptic ulcers, their precise role and contribution to disease progression are not yet fully understood^[27].

Some studies have indeed suggested an association between specific NHPH species and the development of gastric MALT lymphoma, particularly in *H. pylori*-negative cases^[28]. However, further research is required to establish a definitive causal relationship between NHPHs and GML. This article aims to explore the current understanding and propose future prospects on the role of NHPHs in *H. pylori*-negative gastric MALT lymphoma and its potential responsiveness to bacterial eradication therapy.

H. PYLORI-NEGATIVE GASTRIC MALT LYMPHOMA

H. pylori-negative gastric MALT lymphoma accounts for around 10% of all GML cases^[29-31]. The cause of *H. pylori*-negative GML is not fully understood, and ongoing research aims to uncover the underlying factors contributing to its development. Symptoms of this type of lymphoma, such as abdominal pain, indigestion, bloating, nausea, vomiting, and weight loss, are similar to other gastric lymphomas but are nonspecific and can be caused by various conditions^[32]. Diagnosis is made based upon morphologic, immunophenotypic, and genetic analysis of biopsy material. Once the diagnosis is confirmed, a staging procedure to evaluate the extent of lymphoma dissemination is imperative^[33].

In contrast to its *H. pylori*-positive counterpart, it was previously believed that *H. pylori*-negative GML was less likely to respond to antimicrobial therapy. In this context, treatment options may involve watchful waiting, radiation therapy (RT), chemotherapy (ChT), and immunotherapy^[9]. Watchful waiting is suitable for slow-growing lymphomas without significant symptoms, with regular monitoring^[33]. However, RT is the preferred treatment for localized disease in the management of *H. pylori*-negative gastric MALT lymphoma. Several series have reported excellent disease control using RT alone, highlighting the efficacy of moderate-dose involved-field RT (IFRT). Typically, a dose of 24-30 Gy is delivered to the stomach and perigastric nodes over a period of 3-4 wk to achieve optimal outcomes in gastric extranodal marginal zone

lymphoma (EMZL)^[34,35]. Systemic treatment with ChT, immunotherapy⁴ or a combination of both (chemoimmunotherapy) is generally recommended for patients with symptomatic systemic disease, contraindications to RT, treatment failure following antibiotic therapy or local treatments (such as RT or surgery), and those with histological transformation^[36].

Despite this, surprisingly, increasing evidence supports that a considerable proportion of patients with *H. pylori*-negative gastric MALT lymphoma show complete histopathological remission after bacterial eradication therapy^[16,28,37]. Nonetheless, the precise mechanisms underlying this treatment responsiveness are not yet fully comprehended. Initially, it was attributed to false-negative tests for *H. pylori*^[8,37]. However, more recently, the infection with other *Helicobacter* species (NHPHs) is acknowledged as a potential explanation for this phenomenon.

NON-HELICOBACTER PYLORI GASTRIC HELICOBACTERS

The *Helicobacter* genus includes gram-negative, microaerophilic, spiral, helical, curved or fusiform rod-shaped bacteria that inhabits the gastrointestinal tract of several animals, such as humans, cats, dogs, pigs and mice^[38,39]. Currently, 53 species with validly published names comprise this genus^[40], with *Helicobacter pylori* being the most prevalent in humans and well-known to be related to the development of chronic gastritis, peptic ulcer and gastric cancer^[41–43]. However, emerging evidence has highlighted the potential role of non-*Helicobacter pylori* Helicobacters (NHPHs) in the progression of these diseases, including gastric MALT lymphoma^[24,44–46].

Among the NHPHs, *H. suis*, *H. heilmannii*, *H. felis*, *H. salomonis* and *H. bizzozeronii* are the most common species associated with human infection^[47,48]. According to Yakoob *et al.*^[49], the prevalence of *H. heilmannii* and *H. felis* among patients with dyspepsia was 6% and 4%, respectively. On the other hand, Øverby *et al.*^[48] revealed a prevalence of gastric NHPH in Japanese patients of 6.1% and within this group, *H. suis* was the most prevalent, followed by *H. heilmannii*. This latter finding agrees with Nakamura *et al.*^[50], who found a prevalence of NHPHs of 20.8% in gastric mucosal samples of *H. pylori*-negative gastric disease patients, with *H. suis* and *H. heilmannii* also as the most

prevalent species. However, it is important to note that the current diagnostic methods available, such as polymerase chain reaction (PCR) and immunohistochemistry, have limited accuracy in detecting NHPHs infections^[26]. In a specific study, researchers faced difficulties in identifying the species associated with the infection in approximately 50% of the cases^[50]. This challenge can be attributed to several factors, including the high genetic similarity between different NHPH species, significant genetic variation within a single species, limitations imposed by identification methods, and the concurrent presence of multiple NHPH species^[51–53]. As a result, there is a concern that the actual prevalence of NHPHs infections among patients with dyspepsia may be underestimated.

Regarding the association of NHPHs with gastric MALT lymphoma, some studies have evaluated the prevalence of infections by these species and its correlation with the complete remission of *H. pylori*-negative gastric MALT lymphoma through eradication therapy. In this regard, Takigawa *et al*^[54] reports that the rate of complete remission in NHPH positive group of patients was significantly higher (75%) when compared to the negative cases (23%) of *H. pylori*-negative gastric MALT lymphoma, which suggests a potential role for NHPHs in the pathogenesis of gastric MALT lymphoma and in the treatment effectiveness of *H. pylori*-negative GML. Such data are corroborated by Morgner *et al.*^[17], which advocate that *H. heilmannii* infection might be a causative factor in GML and that the current eradication therapy employed for *H. pylori* [standard antibiotics combined with proton pump inhibitors (PPIs)] is effective and results in complete remission of the lymphoma^[17]. Nevertheless, upon confirming the presence of NHPH infection, it is strongly advised to implement a therapeutic approach that is tailored to the susceptibility profile of the individual bacterium.

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PATHOGENESIS OF GASTRIC MALT LYMPHOMA

The pathogenesis of gastric MALT lymphoma is a complex event that involves the antigen-induced transformation of normal marginal-zone B-cells into malignant cells^[55]. In contrast to MALT lymphomas observed in various locations, GML is distinguished by its association with specific microbial species: primarily, *H. pylori*, and to a lesser

extent, *Helicobacter heilmannii*^[17,54,56]. Under normal physiological conditions, the stomach does not possess MALT. However, in the presence of chronic antigenic stimulation,² gastric mucosal cells produce proinflammatory cytokines [such as lymphotoxin beta (LT- β)] and B-cell homing factors (e.g., BCA-1), leading to the infiltration of lymphoid cells into the gastric tissue. This cascade of events ultimately leads to the development of MALT^[32,57,58](Figure 1A).

In the case of *H. pylori* infection, it is well-established that certain T helper cells target specific epitopes of the bacterium and aid polyclonal B cells^[59,60]. These B cells possess receptors that can recognize autoantigens found in the gastric mucosa due to cross-reactivity. Consequently, the polyclonal B cell population expands and undergoes a selection process, resulting in the emergence of an antigen-dependent marginal zone lymphoma (MZL) clone^[61,62].

Sustained antigenic exposure not only stimulates the proliferation of a diverse array of B cells but also attracts neutrophils to the site of inflammation. The inflammatory process initiates the release of reactive oxygen species (ROS), leading to the occurrence of various genetic abnormalities^[55,63,64]. Furthermore, the persistent proliferation of B cells during chronic inflammation increases the risk of double-stranded DNA breaks and translocations^[5] (Figure 1B).

Likewise, the involvement of NHPHs in *H. pylori*-negative GML could also be attributed to the induction of chronic inflammation, resulting in the local aggregation and proliferation of antigen-dependent B cells and T cells. Indeed, the infection of mice with NHPHs species, including *H. felis*, *H. suis*⁶ and *H. heilmannii*, also leads to a similar process of chronic gastritis and GML development with similarities to the human disease^[65–69]. Possibly, the inflammatory microenvironment associated with NHPH-induced gastritis also facilitates the acquisition of genetic abnormalities by B cell clones. Nevertheless, further studies are required to construct a more comprehensive pathogenesis model.

Irrespective of the etiology, progression toward antigen-independent marginal zone lymphoma (MZL) is associated with genetic events, while the role of direct antigenic

stimulation gradually decreases in the development of GML^[5,70](Figure 1B). Four recurrent chromosomal translocations have been found in MZL: t(1;14)(p22;q32), t(11;18)(q21;q21), t(14;18)(q32;q21), and t(3;14)(p14.1;q32)^[71-73]. In GML, the translocation t(11;18)(q21;q21) is the prominent structural chromosomal abnormality, occurring in approximately 10%-50% of cases^[74-76]. This translocation leads to the activation of NF-κB, the downstream target of B-cell receptor (BCR) signaling, independent of BCR signaling itself. The activation is mediated by the disruption of a signalosome complex involving CARD11, BCL10, and MALT1. In this context, the occurrence of the MALT1 fusion protein is particularly associated with more advanced cases of MALT lymphoma^[77-80].

Indeed, numerous studies have demonstrated that gastric MALT lymphomas harboring the t(11;18)(q21;q21) translocation are frequently resistant to *H. pylori* eradication treatment compared to tumors that do not possess this specific translocation^[11,81,82]. The decrease in the rate of complete histopathological remission following eradication therapy was also observed in *H. pylori*-negative GML cases; however, its influence on the treatment of NHPHs-positive GML is still unclear^[16].

CLINICAL IMPLICATIONS AND RESEARCH PROSPECTS

Given the limited regression observed in *H. pylori*-negative gastric MALT lymphoma after antibiotic treatment, clinical guidelines previously advised the prompt initiation of targeted anti-lymphoma treatments^[8,83]. Currently, the European Society for Medical Oncology (ESMO) Guidelines Committee suggests that a trial of anti-*Helicobacter* therapy may be worthwhile in *H. pylori*-negative early-stage GML (stages I and II₁)^[9]. This recommendation presents new opportunities for research in the field. Specifically, future studies could focus on investigating the mechanisms underlying the response to this therapy and further exploring the involvement of other *Helicobacter* species (NHPHs) in the development of *H. pylori*-negative GML. Additionally, it is crucial to investigate the long-term outcomes and assess the effects of early intervention with targeted anti-lymphoma treatments on patient prognosis.

In this context, accurate detection of NHPHs is vital for precise clinical diagnosis and targeted treatment strategies. However, current diagnostic methods primarily focus on *H. pylori*, leaving a gap in the diagnosis of infections caused by other *Helicobacter* species. Goji *et al*^[26] conducted a review of 26 articles and determined that the sensitivities of diagnostic methods for *H. pylori* infection, such as the rapid urease test, urea breath test, blood antibody analysis, immunohistochemical analysis, and stool antigen analysis, were low for NHPHs. The calculated sensitivities were only 40.0%, 14.8%, 23.1%, 40.0%, and 0%, respectively^[26]. Therefore, at present, the most effective diagnostic tools for identifying NHPH infections are histological techniques and genetic diagnosis based on polymerase chain reaction (PCR), which hinders the clinical diagnosis of NHPHs infection, both due to the high cost and to the dependence on laboratory apparatus. In order to address this, the development of tests that possess sensitivity, specificity, and the ability to detect different strains of NHPHs is crucial. The availability of reliable diagnostic methods for NHPHs will not only enable timely diagnosis and treatment for *H. pylori*-negative GML, but also contribute to a better understanding of their epidemiology and impact on human health.

When it comes to comprehending the pathogenesis of NHPH-positive gastric MALT lymphoma, the significance of molecular and immunological studies cannot be overstated. These investigations should encompass the analysis of gene expression profiles in affected tissues, identification of pertinent genetic mutations, and study of cellular signaling pathways involved in the development and progression of the lymphoma. Additionally, it would also be interesting to analyze cytokine profiles, characterize immune cells infiltrating the affected gastric tissue, and conduct studies on the interaction between NHPHs and the host immune system. This deeper understanding might open doors to the development of targeted therapeutic strategies and hold promise for improved clinical outcomes in patients with NHPH-positive GML.

CONCLUSION

While *H. pylori* remains the primary pathogenic factor in the development of gastric MALT lymphoma, the role of non-*H. pylori* gastric Helicobacters in *H. pylori*-negative cases is an emerging area of research. It is crucial to identify these alternative pathogens and understand their mechanisms of pathogenesis to improve diagnostic accuracy and guide appropriate treatment strategies for patients with *H. pylori*-negative gastric MALT lymphoma. Further research is warranted to elucidate the complex interplay between these bacteria, the host immune system, and the gastric microenvironment, which may ultimately lead to the development of novel therapeutic interventions and personalized approaches for this subset of patients.

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