# Rapid resolution of a gastric lymphoma with Helicobacter eradication therapy

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## Abstract

As one of the most prevalent chronic bacterial infections, *Helicobacter pylori* (*H. pylori*) has had a uniquely sizeable impact on human pathology. Infection with H. pylori has been shown to be involved in a wide array of gastrointestinal diseases, from peptic ulcer disease to gastric malignancy. Here, we present an 82–year–old patient who was found to have a large ulcerated gastric mass along with a concomitant *H. pylori* infection. Gastric biopsies later revealed a gastric mucosa–associated lymphoid tissue (MALT) lymphoma, suspicious of transformation to a high–grade diffuse large B–cell lymphoma. Notably, primary treatment with Helicobacter eradication therapy resulted, remarkably, in complete endoscopic and histologic resolution of the lymphoma only three weeks after the completion of triple therapy. Through this illustrative case, we review the controversies in the management of high–grade gastric lymphoma as well as the clinical practice surrounding endoscopic surveillance for malignancy follow–up.

## Background

Ever since the paradigm–shifting discovery of the role of *Helicobacter pylori* (*H. pylori*) infection in peptic ulcer disease was made in 1982, this now notorious curved bacillus has become associated with an ever–broadening spectrum of human pathology. Colonizing an estimated 50% of the world's population, *H. pylori* is a prime example of the unique capacity of pathogens to adapt to the hostile conditions of their host environments.[1] These adaptations, from the pilus–based epithelial adhesion to the utilization of ureases and proteases to both neutralize and escape from gastric acid production, combined with the subsequent host inflammatory response, are responsible for the mucosal damage that precipitates symptomatic disease.[2] The consequent oxidative stresses result in rapid cellular damage and turnover, ultimately depleting the host's damage–repair resources and leading to the accumulation of significant DNA damage. This combination of direct epithelial toxicity and chronic gastric inflammation is thought to be a key element in the development of *H. pylori*–associated carcinogenesis.[3]

Here we review a case of a patient with a large ulcerated gastric mass, which was ultimately identified as a *Helicobacter*–driven extranodal marginal lymphoma (specifically, a mucosa–associated lymphoid tissue [MALT] lymphoma) with a region suspicious for transformation into high–grade diffuse large B–cell lymphoma (DLBCL). MALT lymphoma, a low–grade Non–Hodgkin's lymphoma comprising 50% of all gastric lymphomas, is associated in more than 90% of cases with *H. pylori* infection. As such, MALT lymphomas are traditionally treated with *Helicobacter* eradication as first–line therapy; this approach has been shown to achieve remission in 77.5% of patients without need for further therapy.[4] In contrast, gastric DLBCL is an example of a high–grade Non–Hodgkin's lymphoma, which can be subdivided into malignancies either with evidence of transformation from underlying MALT lymphoma or without (categorized as *de novo* DLBCL).[5] However, the role of *H. pylori* in the pathogenesis and treatment of gastric DLBCL, which has been traditionally managed with chemotherapy and radiation, is still controversial. Here we report the complete endoscopic and histologic resolution of a gastric MALT lymphoma a mere three weeks after *Helicobacter* eradication therapy, and we discuss the case's implications on our understanding of the management of high–grade gastric lymphoma.

## Case

An 82–year–old Caucasian woman initially presented to medical attention complaining of constant, long–standing atypical chest pain. The discomfort was neither related to exertion nor meals. There were no associated constitutional symptoms nor were there any associated gastrointestinal symptoms such as nausea, vomiting, or blood per rectum. Her past medical history included type 2 diabetes mellitus, hypercholesterolemia, hypertension, and hypothyroidism. She was a lifetime non–smoker and did not consume alcohol.

Initial cardiac investigations, including exercise stress test, were all negative. Ultimately, a gastroscopy demonstrated a large, 2-3 cm ulcerated mass on her gastric incisura. Multiple biopsies were taken, and the histopathology revealed an atypical lymphoid infiltrate composed mainly of small lymphocytes, but which also included large, poorly differentiated malignant cells with hyperchromatic nuclei and scanty cytoplasm (Figure 1A,B). There was no glandular formation, and immunohistochemical staining was CD20 positive, indicating B cell lineage (Figure 1C). *H. pylori* organisms were present, further supporting a diagnosis of MALT lymphoma (Figure 1D). However, the final characterization of the lymphoma was challenging. Although there was clearly evidence of low–grade MALT lymphoma, there were also regions of large cells that were concerning for transformation into high–grade DLBCL. Ki–67 analysis demonstrated that areas with a higher concentration of large cells had an increased proliferative rate relative to the smaller neoplastic cells, but the higher degree of gastric epithelial inflammation in these areas made the results difficult to interpret. Further detailed B–cell marker analysis demonstrated CD43 positivity and CD23 negativity, and cytogenetic analysis established consistent MUM1 and patchy Bcl–2 positivity. All of these findings supported the diagnosis of a MALT lymphoma but could not definitively rule out the presence of high–grade transformation. Notably, c–myc was negative, which can confer a poor prognosis in DLBCL.[6]

Given the substantial difference in the accepted first–line treatment

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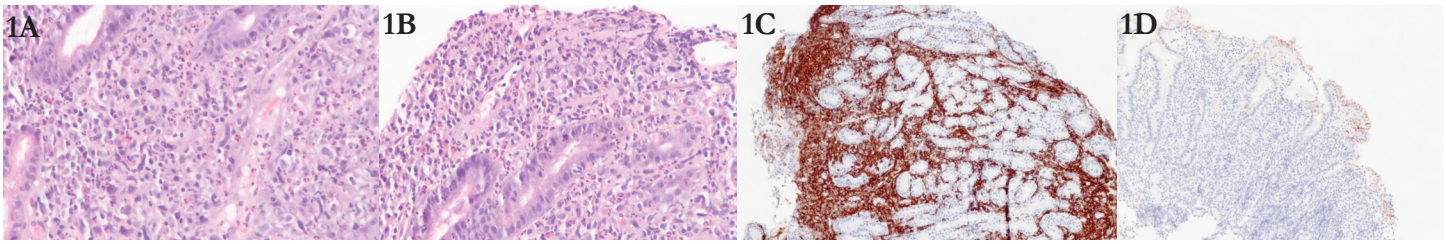


**Figure 1 |** Histological findings from pre–treatment biopsies stained with hematoxylin and eosin (A: 200x; B: 400x) include gastric mucosa with florid active gastritis and dense atypical lymphoid infiltrate. The lymphoid infiltrate is composed mainly of small lymphocytes, but some large atypical cells are also present. Immunohistochemical staining for (C) CD20, a B–cell marker, shows strong positivity in the neoplastic cells and (D) *Helicobacter pylori* antibody reveals numerous *H. pylori* organisms. (C: 10x; D: 10x)

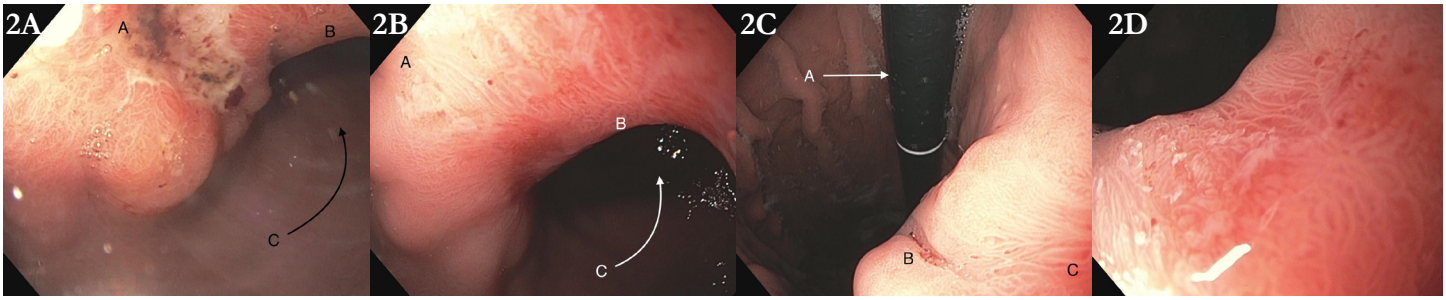


**Figure 2 |** (A) Pre–treatment endoscopy in forward view. A: Gastric ulcer at the incisura. B: Incisura angularis. C: Pyloric Channel. (B) Post–treatment anterograde view. A: Site of previous gastric ulcer. B: Incisura angularis. C: Pyloric channel. (C) Post–treatment retrograde view, with endoscope retroflexed. A: Proximal portion of endoscope in retroflexed position. B: Small erosion at the site of the previous ulcer. C: Incisura angularis. (D) En fasse view of the site of the previous ulcer.

between MALT lymphoma and DLBCL, multiple pathologists and a multidisciplinary lymphoma conference reviewed the case. Ultimately, the conference concluded that the presence of high–grade transformation to DLBCL could not be diagnosed with certainty, especially given the extensive concurrent gastritis complicating the diagnosis. Therefore, the consensus was to manage the mass as a low–grade MALT lymphoma. Importantly, as part of the staging process, full–body CT scans, a PET scan, and a bone marrow aspirate and analysis were conducted, all of which were negative for disease spread.

As a trial, the patient was treated with *H. Pylori* eradication triple therapy (including amoxicillin, clarithromycin, and pantoprazole) twice daily for 14 days, the standard therapy for low–grade MALT lymphoma. Three weeks after completion of triple therapy, our patient returned for follow–up, her symptoms having completely resolved. Her gastroscopy was repeated and, remarkably, no further evidence of the mass was found. At the incisura where the previous ulcerated mass had been, there was only subtle residual scarring (Figure 2). Pathologic review of the gastric biopsies demonstrated complete resolution of the lymphoproliferative disease with no remaining evidence of *H. pylori* infection (Figure 3A,B).

## Discussion

In this case, the ambiguity of the pathologic diagnosis became a critical factor in the determination of definitive treatment, making it an exceptional illustration of the many controversies in our understanding of the management of *Helicobacter*–associated high–grade lymphoma. Whereas the role of first–line triple therapy in the treatment of low–grade MALT lymphoma has been widely accepted since the early 1990s, for years, the understanding in the medical community was that high–grade transformation eliminated the dependence of the tumour on the original inciting infection. As a result, gastric DLBCL has traditionally been treated with first–line chemotherapy and radiation, although concomitant bacterial eradication was advised in order to avoid further oncogenic stimulus.[5]

However, in the past decade, there have been emerging data to suggest that *Helicobacter* eradication could have an important role in the initial management of DLBCL as well. A multicentre prospective trial in Taiwan assessed the effect of first–line antibiotic therapy on low–stage (stage IE/IIE1) MALT–transformed DLCBL, comparing

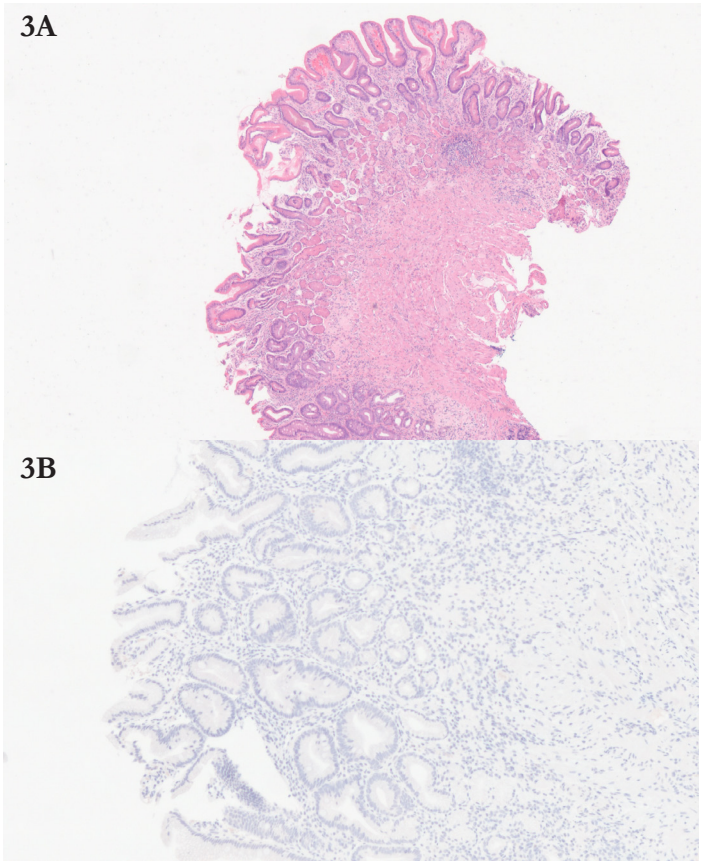


**Figure 3 |** Post–treatment gastric biopsies stained with (A: 4x) hematoxylin and eosin demonstrate complete resolution of active gastritis and regression of the atypical lymphoid infiltrate. Focal chronic nonspecific gastritis is present. Immunohistochemical staining with (B: 4x) *Helicobacter pylori* antibody is negative.

the results with a retrospective review on the role of antibiotic therapy in *de novo* (non–MALT) DLBCL. In this seminal study, 58% of patients experienced complete remission with anti–bacterial therapy alone, with no signs of recurrence after five years. When split into histological subtypes, there was a 68% remission rate in *de novo* DLBCL, with 56.3% complete pathological remission for those with underlying MALT lymphoma. The median time to complete pathologic remission was 2.1 months in the former group, and 5.1 months in the latter.[7] A follow–up multicentre trial (the HGL–1 study) corroborated these results, reporting that a full two–thirds of patients underwent long–term remission on triple therapy alone.[8]

However, while these studies have challenged the paradigm of the management of gastric DLBCL, the use of triple therapy as a sole first–line treatment in these cases has not been as widely accepted as it has been for low–grade MALT lymphoma. To begin with, the standard chemotherapeutic regimens (typically R–CHOP therapy) for stage IE/IIE disease undoubtedly have a significantly higher remission rate, quoted as 95% in recent studies.[9] Understandably, there is concern that for the considerable proportion of patients who do not respond to antibiotics, the delay to accessing chemotherapy may worsen prognosis. To address this concern, in the initial studies investigating the efficacy of triple therapy, endoscopic evaluations were performed every six weeks and any patients with stable or progressive disease were immediately initiated on standard chemotherapy regimens. Fortunately, the safety of this approach was ultimately supported; of these patients, 100% of the *de novo* DLBCL group and 93.8% of the MALT–transformed group achieved complete remission with chemotherapy. In this latter group, one of the sixteen patients did, however, die of disease progression.[7]

Although these preliminary results have been encouraging, in order to consider *Helicobacter* eradication as a legitimate first–line therapy for gastric DLBCL, it is imperative to understand the patient–specific factors that could influence response to antibiotic therapy. Despite extensive study on these factors in low–grade MALT lymphoma, identifying genetic abnormalities such as the translocation t(11;18) and aberrant nuclear BCL10 as high–risk features, research on similar genetic factors in DLBCL has not been pursued.[5] Additionally, gross pathologic features may play an important role, as the original 2012 Taiwanese trial demonstrated that depth of tumour invasion was significantly correlated with response to antibiotics in MALT–associated DLBCL; 87% of patients with tumours confined to the submucosa achieved complete remission, as opposed to only 39% in those with tumour infiltration into the muscularis propria.[7]

All in all, the use of *Helicobacter* triple therapy as a first–line treatment for gastric lymphoma, both low and high–grade, has exceptional potential, as demonstrated by the rapid endoscopic remission achieved by our patient. Apart from lending insight into the interdependence of *Helicobacter* infection and tumour survival, this concept could represent a new direction in patient care, enabling patients who may otherwise have been very vulnerable to the effects of chemotherapy (such as the elderly, as in our case) to achieve a cure with a short course of generally well–tolerated antibiotic therapy. However, further research is necessary to identify pathologic and epidemiological factors that could predict those with the highest likelihood of response, as well as those at risk for requiring subsequent salvage chemotherapy. Furthermore, the case highlights the potential for a new paradigm for the timing of endoscopic surveillance. Although there are no set guidelines for the timeframe for endoscopic re–evaluation, low–grade MALT lymphomas are typically reassessed from six weeks to three months after completing antibiotic therapy, though some cases may take up to twelve months to demonstrate histologic regression.[10] Given the potential for such rapid remission as demonstrated in this case, moving towards an earlier surveillance system would enable more timely identification of responders; in similar cases of diagnostic uncertainty, early assessment could be crucial for identifying those in need of further therapy.

Further research into the intimate connection between *Helicobacter* infection and gastric lymphoma could have far–reaching implications in the broader field of oncology. There are numerous associations between chronic infections and neoplasia, from Epstein–Barr virus and lymphoma to schistosomiasis and bladder cancer. As we continue to learn more about the interdependence between malignancies and their underlying infectious etiologies, it will be fascinating to see if our burgeoning understanding of *Helicobacter*–associated lymphoma will lend insight, on a larger scale, to our approach to cancer therapeutics.

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