

# Complete remission of late-stage *Helicobacter pylori*-associated gastric diffuse large B-cell lymphoma

## Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma and the gastrointestinal tract is the most common site of extranodal involvement. Studies have shown that *Helicobacter pylori* (*H. pylori*) may contribute to development of gastric DLBCL and *H. pylori* eradication is effective as the sole treatment in early stage gastric DLBCL. However, currently there is limited information on the relationship between *H. pylori* and late stage gastric DLBCL. We present a case report of a patient with stage IV gastric DLBCL and *H. pylori* who achieved complete remission after *H. pylori* eradication and chemotherapy.

**Keywords:** *helicobacter pylori*, gastric diffuse large b-cell lymphoma, late-stage

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**Abbreviations:** *H. Pylori*, *Helicobacter pylori*; DLBCL, diffuse large b-cell Lymphoma; MALT, mucosa-associated lymphoid tissue; GCB, germinal center b-cell; PET-CT, positron emission tomography-computed tomography; FDG, radiolabeled [<sup>18</sup>F]-2-fluoro-2-deoxy-d-glucose; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

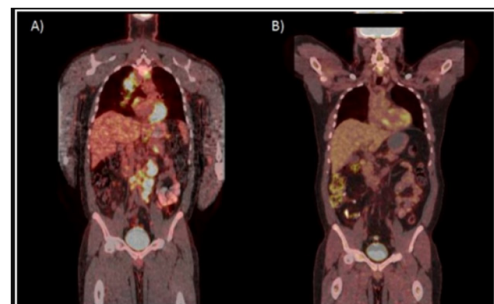
## Introduction

Gastric diffuse large B-cell lymphoma (DLBCL) is an aggressive disease that can have various manifestations. Some DLBCL tumors will have histologic features of mucosa-associated lymphoid tissue lymphoma (MALT) and those without evidence of MALT are “pure” gastric DLBCL.<sup>1</sup> The association between gastric MALT lymphoma and *Helicobacter pylori* (*H. pylori*) has been well-documented.<sup>2</sup> *H. pylori*, a gram-negative bacterium, was found to contribute to the pathogenesis of MALT lymphoma through stimulation of B cell proliferation. However, the eradication of *H. pylori* infection with antibiotics is very effective in patients with MALT lymphoma, leading to remission rates >75%.<sup>3</sup> MALT lymphoma confined to the submucosa or early stage (stage I/II) had especially good prognosis with *H. pylori* eradication alone and long term remission.<sup>4</sup> More recently, “pure” gastric DLBCL has also been shown to be epidemiologically associated with *H. pylori* infection.<sup>5</sup> Early stage gastric DLBCL patients with *H. pylori* were responsive to its eradication and had long term remission.<sup>6</sup> However, since *H. pylori*-associated DLBCL can progress rapidly if unresponsive to eradication, patients are often also started on chemotherapy. R-CHOP and triple therapy have been successful for patients with early-stage gastric DLBCL, but data is currently limited for late-stage gastric DLBCL.

## Case presentation

A 40 year old male presented with abdominal pain, fevers, lymphadenopathy, and recent hematemesis. The patient reported that he was in his usual state of health until one month ago, when he presented to an outside hospital with fevers, abdominal pain, and supraclavicular lymphadenopathy. At that time, the patient was without nausea, vomiting, hematochezia, or hematemesis. He underwent upper endoscopy with gastric biopsy which was reportedly consistent with MALT lymphoma but was discharged without

intervention after resolution of abdominal pain. One month later, the patient began to have coffee-ground hematemesis for two days and presented to our hospital for admission. There was no associated dizziness, constipation, diarrhea, hematochezia, melena, early satiety, or known weight loss. The patient had no previous medical history including history of peptic ulcer disease, bleeding diathesis, immunosuppression, or abdominal surgeries. There was no family history of colorectal cancer, smoking, or alcohol consumption.

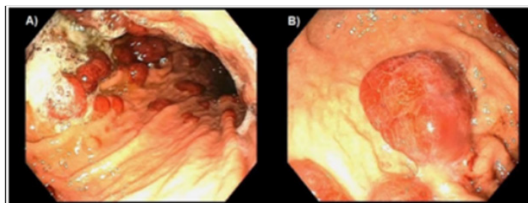


**Figure 1** Endoscopic view of gastric body showing multiple medium-sized nodules in gastric body (A) and fundus (B).

The patient was started on an esomeprazole drip but was hemodynamically stable with initial hemoglobin of 13.2g/dL and did not require blood product transfusion. He did not have further episodes of hematemesis or gastrointestinal bleeding during his hospitalization. The patient was made NPO and gastroenterology was consulted for upper endoscopy which revealed gastritis and medium-sized hemorrhagic nodules in the stomach (Figure 1). Final pathology report of the gastric nodule biopsy showed EBV negative, Germinal Center B-cell type DBCL that was positive for BCL2, BCL6 and CD10; negative for MUM1, CD5 and cyclin-D1; and with Ki67 of 80%. Per PET-CT (Figure 2A), the lymphoma was localized to the stomach (SUV Max 6.5) with FDG avid lymphadenopathy in the in the neck (SUV Max 10.7), chest (SUV Max 10.6), and pelvis (SUV Max 7.9) consistent with stage IV gastric DLBCL. Bone marrow biopsy was performed and returned negative. The patient was also found to have concurrent *H. pylori* infection.

R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) therapy was initiated for 6 cycles. For *H.*

*pylori* infection, the patient was started on a 14-day course of azithromycin, clarithromycin, and esomeprazole. After six cycles of R-CHOP, endoscopy showed resolution of the previous nodules. Endoscopic biopsies showed no evidence of DLBCL and rapid urease test was negative for *H. pylori* infection. Six months after the final R-CHOP cycle, PET-CT showed complete resolution of FDG avid lymphadenopathy (Figure 2B). The patient remains in remission one year after completion of R-CHOP.



**Figure 2** PET-CT before chemotherapy. (A) showing pulmonary, mediastinal, hilar, and para-aortic lymphadenopathy and after 6 cycles of chemo and *H. pylori* triple therapy showing resolution (B).

## Discussion

DLBCL is the most common subtype of non-Hodgkin lymphoma and the gastrointestinal tract is the most common site of extranodal involvement. Primary gastric DLBCL can present with various, nonspecific symptoms but is generally more aggressive than MALT lymphomas. The diagnosis is made by endoscopy with biopsy usually showing large B-cells with pronounced nucleoli, basophilic cytoplasm, and a high proliferation fraction.

Treatment with a combination of chemotherapy, radiation, and surgery have all been used in gastric DLBCL. For early stage disease, surgical resection/gastrectomy was used in the past but recently chemotherapy has become the standard therapy since a large randomized controlled trial found that surgery was associated with more acute and long-term complications.<sup>7</sup> Gastric DLBCL is generally diagnosed at an early stage and treatment with conventional regimens for DLBCL, such as R-CHOP, has led to complete remission rates greater than 90%.<sup>8</sup> While radiotherapy is sometimes used in conjunction with chemotherapy, a randomized trial comparing chemotherapy to chemotherapy/radiotherapy found that radiotherapy did not improve survival in patients with early-stage gastric DLBCL.<sup>9</sup>

After finding that early-stage gastric MALT lymphomas could be treated solely with *H. pylori* eradication, there has been more exploration of treating gastric DLBCL for *H. pylori*. This distinction is of particular importance since *H. pylori*-associated gastric DLBCL may have different biology, leading to a distinct tumor entity and response to chemotherapy.<sup>3</sup> A recent trial assessed the efficacy of *H. pylori* eradication as exclusive treatment of early-stage gastric DLBCL with remission rate greater than 60% and a 5-year overall survival of 94%.<sup>10</sup> The study also found that patients who first failed a trial of *H. pylori* eradication were subsequently treated with chemotherapy and all were able to achieve remission of DLBCL. Another study found that over two-thirds of patients with “pure” gastric DLBCL (without MALT features) achieved complete pathologic remission with *H. pylori* eradication alone.<sup>4</sup>

Compared to early stage gastric DLBCL, late stage DLBCL (stage III/IV) has been poorly characterized and studied. Treatment algorithms have suggested that all patients greater than Stage II should be treated with chemotherapy.<sup>11</sup> While this is a rational treatment plan for disseminated disease, little consideration has been given to the benefit of *H. pylori* eradication in this population. Our case gives support for eradication of *H. pylori* in late stage DLBCL. Given *H.*

*pylori*'s contribution to development of lymphoma, patients that have not been treated for *H. pylori* may still be at high risk of relapse. Testing and treatment for *H. pylori* is especially important given the high rate of DLBCL patients with concomitant MALT features.

We reported a case of a patient who achieved remission of Stage IV gastric DLBCL after therapy for *H. pylori* eradication and R-CHOP. This suggests that diagnosing and treating *H. pylori* in late-stage gastric DLBCL may have benefit eliminating B cell stimulation from *H. pylori*. Given the response of early-stage gastric DLBCL to *H. pylori* treatment, this case also raises questions of whether effective antibiotic treatment should precede the risks of aggressive chemotherapy. Further studies are necessary to understand the prognostic factors and treatment options for late-stage gastric DLBCL and its relationship with *H. pylori*.

## Conflicts of Interest

The authors do not have any personal or financial interests.

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