ACG CASE REPORTS JOURNAL

CASE REPORT | STOMACH

Gastric Non-Hodgkin Lymphoma in a *Helicobacter pylori*-Infected Patient

Maram Alenzi, MD[1], Iyiad Alabdul Razzak, MD[1], Darren Evanchuk, MD[2], Svetlana Kondratiev, MD[3], Syed Kashif Mahmood, MD[1], and Manish Tandon, MD[1]

[1]*Division of Gastroenterology, St. Elizabeth's Medical Center, Boston University School of Medicine, Boston, MA*
[2]*Division of Hematology and Oncology, St. Elizabeth's Medical Center, Boston University School of Medicine, Boston, MA*
[3]*Division of Histopathology, St. Elizabeth's Medical Center, Boston University School of Medicine, Boston, MA*

ABSTRACT

Primary gastric diffuse large B-cell lymphoma (PG-DLBCL) is a rare gastric malignant neoplasm. While the association between *Heliobacter pylori* infection and gastric mucosa-assisted lymphoid tissue lymphoma is well established, data supporting its association with DLBCL are less robust. Here we present a rare case of PG-DLBCL diagnosed with *H. pylori*. An 82-year-old man presented to clinic with complaints of worsening epigastric pain. He underwent an endoscopy which revealed 1 large nonbleeding gastric ulcer. Histopathological and immunohistochemical analysis confirmed PG-DLBCL. He was started on *H. pylori* eradication (HPE) and subsequently completed 6 cycles of R-mini-CHOP chemotherapy. Since then, the patient maintained clinical and radiological remission for more than a year without recurrence. PG-DLBCL is an aggressive Non-hodgkin lymphoma (NHL) that usually presents late. It has been shown that HPE without chemotherapy in DLBCL codiagnosed with *H. pylori* is not an effective strategy. Thus, the standard of care for patients would be HPE and chemotherapy as in our patient. More research is needed to better understand association between *H. pylori* and DLBCL.

KEYWORDS: gastric non-Hodgkin lymphoma; *H. pylori* associated lymphoma

INTRODUCTION

Primary gastric non-Hodgkin lymphoma is a malignant tumor of the stomach with or without lymph node involvement. It is a rare malignant neoplasm, but it is the most common extranodal non-Hodgkin lymphoma, accounting for 68%–75% of all primary gastrointestinal non-Hodgkin lymphomas.[1,2] Diffuse large B-cell lymphoma (DLBCL) is the most common subtype, accounting for 59.5% of primary gastric non-Hodgkin lymphoma, followed by mucosa-associated lymphoid tissue (MALT) lymphoma, which accounts for 37.9% of the cases.[3,4] Primary gastric DLBCL (PG-DLBCL) usually develop de novo; however, it can evolve from transformed high-grade MALT lymphoma, which is equivalent to DLBCL in the Revised European American Lymphoma classification.[5]

Multiple viral and bacterial infections have been linked to the development of primary gastric lymphomas, with *Helicobacter pylori* being a major predisposing factor. *H. pylori* can lead to both MALT and PG-DLBCL by causing chronic atrophic gastritis.[6,7] Studies have also shown that it is the bacterial carcinogenic effect in an underlying immunodeficient host that drives the pathogenesis of both disease entities.[8] About 35% of patients with PG-DLBCL are affected with *H. pylori*, but there is a higher proportion of *H. pylori* infection in PG-DLBCL with low-grade MALT components. This means that most PG-DLBCL may originate from low-grade MALT lymphoma associated with chronic *H. pylori* infection.[9]

PG-DLBCL occurs at a median age of 55 years and has a male predominance. The clinical presentation of PG-DLBCL is usually nonspecific, ranging from vague symptoms, including dyspepsia, epigastric pain or discomfort, to more serious symptoms, such as gastrointestinal bleeding. Some patients might also develop systemic B symptoms such as night sweats, weight loss, and fatigue.[1] Endoscopic biopsy and immunohistochemical examination, supplemented by cytogenetic and molecular tests, is the gold standard

ACG Case Rep J 2024;11:e01373. doi:10.14309/crj.0000000000001373. Published online: June 19, 2024

Correspondence: Maram Alenzi, MD (dr.maram.e@gmail.com).

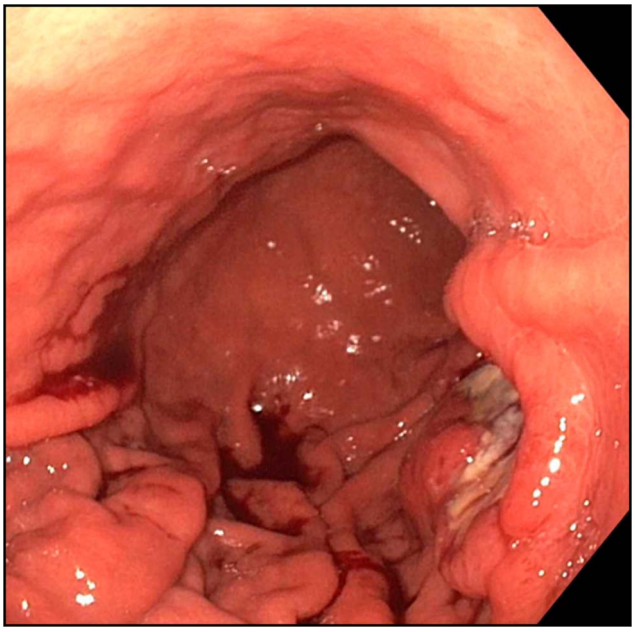

Figure 1. Esophagogastroduodenoscopy revealed 1 large nonbleeding gastric ulcer (>7 cm) in the posterior wall of the gastric body with heaped up margins.

for PG-DLBCL diagnosis.[10] Furthermore, imaging studies such as computed tomography (CT), magnetic resonance imaging, and fluorodeoxyglucose positron emission tomography play an important role in the diagnosis, staging, and treatment response evaluation.[11]

CASE REPORT

An 82-year-old man with a medical history significant for hypertension, gastroesophageal reflux disease, and chronic bronchitis presented to his primary care clinic with complaints of worsening epigastric pain and heartburn. His symptoms were worse with eating. He also reported an associated indigestion and burping. The patient denied any weight loss, nausea, vomiting, fever, or night sweats. His family history was significant for esophageal malignancy. Physical examination was unremarkable. His initial laboratory tests revealed normal white blood cell count $5.7 \times 10^3/\mu L$, normal Hgb 14.4 g/dL, and mild thrombocytopenia of $144 \times 10^9/L$. The liver function test was notable for hypoalbuminemia of 3.7 g/dL. Renal function test revealed no abnormalities. Lactate dehydrogenase was within normal range. He underwent an esophagogastroduodenoscopy (EGD) which revealed 1 large nonbleeding gastric ulcer (>7 cm) in the posterior wall of the gastric body with heaped up margins (Figure 1). Subsequent biopsy revealed high-grade DLBCL with signs of moderate chronic active gastritis (Figure 2). *H. pylori* stain was positive. Immunohistochemical staining revealed lymphoid infiltrates composed of CD20-positive B cells that coexpress BCL-6 and BCL-2 and were negative for CD5 (Figure 3). CD10 was positive in a subset of tumor cells (<30%). Ki-67 proliferation index was approaching 70%–80%. Small CD3/CD5-positive T cells were seen in the background. myelocytomatosis oncogene (MYC) expression was negative. The patient was placed on *H. pylori* eradication (HPE) therapy with a proton pump inhibitor, clarithromycin, and amoxicillin for 14 days, resulting in an improvement in his abdominal pain and food tolerance. Subsequently, the patient's urea breath test was negative. The patient underwent additional workup with a positron emission tomography-CT (PET/CT), which revealed multiple Fluorodeoxyglucose (FDG)-avid supra and infra-diaphragmatic lymph nodes with focal FDG uptake in the distal stomach consistent with the biopsy-proven site of lymphoma, establishing a diagnosis of stage III/IV DLBCL (GCB-type), with gastric involvement, international prognostic indices (IPL) 2-low intermediate risk, and 5-year estimated overall survival of 51%. After HPE therapy, the patient completed 6 cycles of R-mini-CHOP chemotherapy. Remission was confirmed by a follow-up EGD, which showed complete healing of the previously noted large ulcer and normal gastric mucosal endoscopic and narrow-band imaging appearance (Figures 4 and 5). Furthermore, multiple random biopsies from the stomach's antrum and body showed no abnormalities with negative immunohistochemical testing for *H. pylori*. Moreover, the patient had a follow-up PET scan, which revealed no foci of metabolic activity. An abdominal/pelvic CT with contrast conducted during a 1-year follow-up was normal with no supra or infra-diaphragmatic lymphadenopathy. Since then, the patient has maintained clinical and radiological remission for more than a year without recurrence.

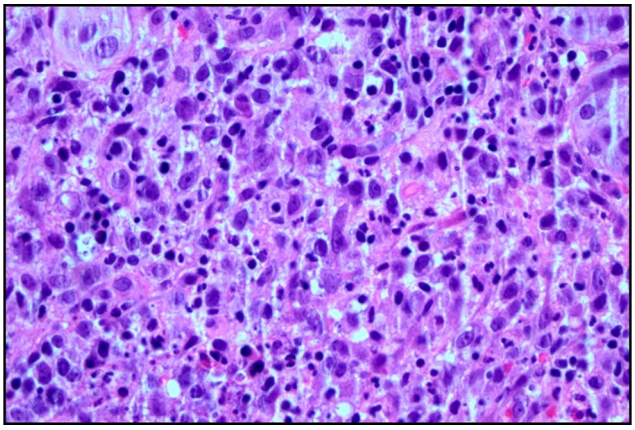

Figure 2. Gastric mucosa with diffuse infiltration by intermediate-to-large lymphoid cells (H&E, original magnification 200×).

DISCUSSION

The link between gastric MALT lymphoma and *H. pylori* infection is well documented, with HPE therapy being the primary treatment, particularly for early stage MALT lymphoma, obviating the need for oncological interventions.[12] Recently, an association between *H. pylori* infection and de novo DLBCL was validated in a large cohort.[13] Certain PG-DLBCL types evolve from transformation of high-grade MALT lymphoma, and studies have shown that HPE therapy by itself can lead to

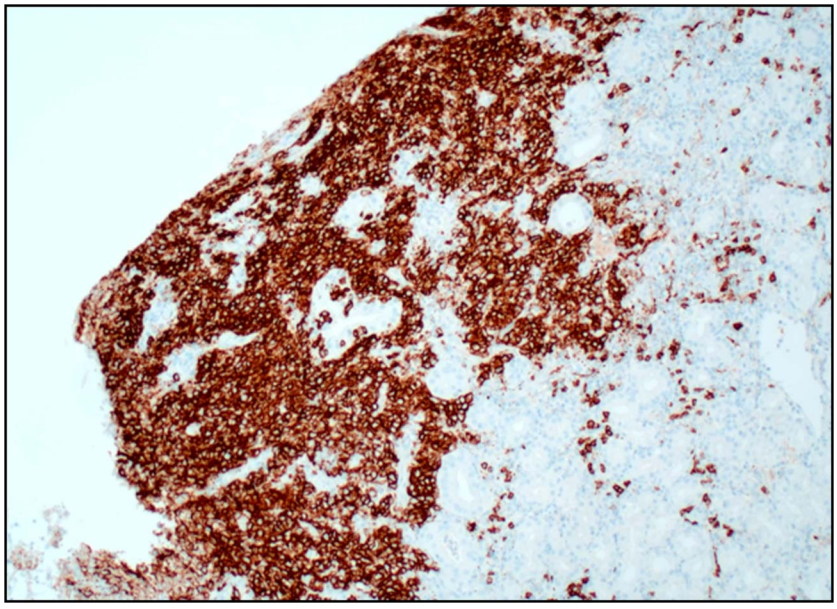

Figure 3. Neoplastic cells show immunoreactivity for CD20.

complete remission in a small proportion of patients with early stage transformation.[14] Some cases of de novo DLBCL with concomitant *H. pylori* infection also achieved complete remission after HPE alone.[15] Nevertheless, there have been recent reports of advanced PG-DLBCL cases that progressed within a year despite successful HPE therapy.[16]

H. pylori-induced lymphomagenesis is a multistep process involving *H. pylori* virulence factors (such as CagA and VacA), host factors, and environmental conditions. Cytotoxin-associated gene A protein, which is present on the surface of *H. pylori* cells, is the most extensively studied *H. pylori* virulence factor. It can directly pass through the host membrane through an interaction with phosphatidylserine, after which it perturbs cell signaling in a way that can lead to oncogenesis.[17] Despite these carcinogenic factors, *H. pylori* infection was associated with less aggressive forms of DLBCL and better overall prognoses. Further subgroup analyses suggested that *H. pylori* infection was significantly associated with better survival outcomes in patients with early stage gastric DLBCL.[18]

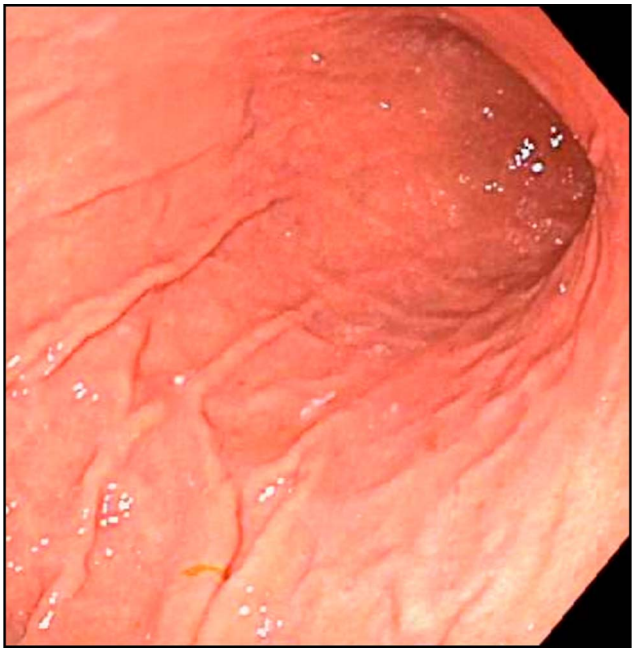

Figure 4. Esophagogastroduodenoscopy revealed complete healing of the previously noted large ulcer.

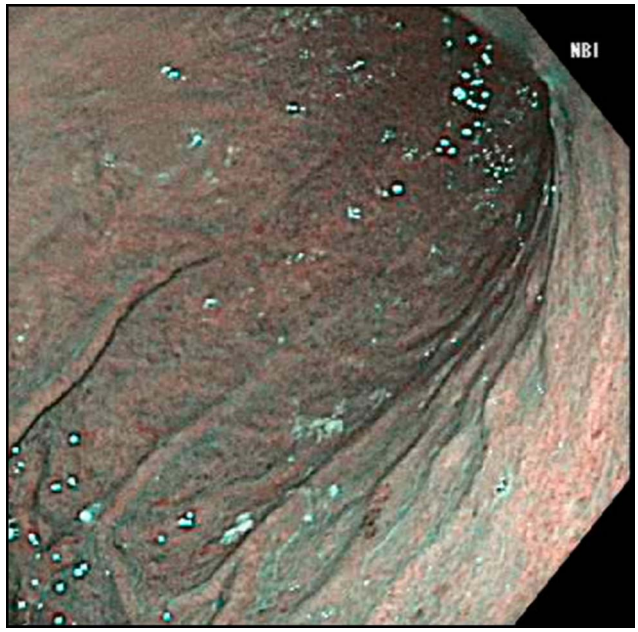

Figure 5. Narrow-band imaging revealed normal gastric mucosa.

One possible explanation for the critical role of *H. pylori* infection in improving the outlook of gastric DLBCL is the antigenic mimicry between *H. pylori* and the gastric mucosa, resulting in immune cross-reactions that affect tumor cells and suppress tumor progression.[19,20] Immune cross-reactions with malignant cells are characterized by the presence of mimic or absorbed *H. pylori* antigens, which results in improved survival outcomes in *H. pylori*-positive gastric DLBCL.[21]

Our case further supports the favorable outcome of PG-DLBCL associated with *H. pylori* infection. Perhaps, *H. pylori* infection status should be considered as a prognostic factor in patients diagnosed with PG-DLBCL. This consideration could also have therapeutic implications, potentially leading to the use of less cytotoxic therapies in this subgroup of patients.

PG-DLBCL is an aggressive NHL that usually presents late and has an estimated survival of months without treatment. *H. pylori* infection leading to DLBCL without MALT lymphoma features has not been well established. In our case, nonetheless, it appears that HPE without chemotherapy is an inadequate treatment approach, as opposed to cases of *H. pylori*-driven MALT lymphoma. Thus, the standard of care for patients with concomitant advanced PG-DLBCL and *H. pylori* infection would be combination of HPE and chemotherapy as in our patient. More research is needed to better understand the association between *H. pylori* and DLBCL in terms of causation, prognosis, and therapeutic implications.

DISCLOSURES

Author contributions: M. Alenzi: conceptualization, data curation, methodology, writing – original draft, writing – review & editing. I. Alabdul Razzak: writing – review & editing. D. Evanchuk: critical review of manuscript. S. Kondratiev: critical review of manuscript. SK Mahmood: conceptualization, supervision, critical review of manuscript. M. Tandon: conceptualization, methodology, supervision, critical review of manuscript. M. Alenzi is the article guarantor. All authors approved the final manuscript before submission.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received December 5, 2023; Accepted April 22, 2024

REFERENCES

1. Koch P, del Valle F, Berdel WE, et al, German Multicenter Study Group. Primary gastrointestinal non-Hodgkin's lymphoma: I. Anatomic and histologic distribution, clinical features, and survival data of 371 patients registered in the German multicenter study GIT NHL 01/92. *J Clin Oncol.* 2001;19(18):3861–73.
2. Papaxoinis G, Papageorgiou S, Rontogianni D, et al. Primary gastrointestinal non-hodgkin's lymphoma: A clinicopathologic study of 128 cases in Greece. A Hellenic cooperative oncology group study (HeCOG). *Leuk Lymphoma.* 2006;47(10):2140–6.
3. Koch P, Probst A, Berdel WE, et al. Treatment results in localized primary gastric lymphoma: Data of patients registered within the German multicenter study (GIT NHL 02/96). *J Clin Oncol.* 2005;23(28):7050–9.
4. D'amore F, Christensen BE, Thorling K, et al. Incidence, presenting features and prognosis of low-grade B-cell non-hodgkin's lymphomas population-based data from a Danish lymphoma registry. *Leuk Lymphoma.* 1993; 12(1-2):69–77.
5. Sander CA, Kind P, Kaudewitz P, Raffeld M, Jaffe ES. The revised European-American classification of lymphoid neoplasms (REAL): A new perspective for the classification of cutaneous lymphomas. *J Cutan Pathol.* 1997;24(6):329–41.
6. Cheng Y, Xiao Y, Zhou R, Liao Y, Zhou J, Ma X. Prognostic significance of helicobacter pylori-infection in gastric diffuse large B-cell lymphoma. *BMC Cancer.* 2019;19(1):842.
7. Olszewska-Szopa M, Wrobel T. Gastrointestinal non-Hodgkin lymphomas. *Adv Clin Exp Med.* 2019;28(8):1119–24.
8. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. *Cancer.* 1972;29(1):252–60.
9. Ferreri AJ, Freschi M, Dell'Oro S, Viale E, Villa E, Ponzoni M. Prognostic significance of the histopathologic recognition of low-and high-grade components in stage I-ii B-cell gastric lymphomas. *Am J Surg Pathol.* 2001; 25(1):95–102.
10. Rotaru I, Găman GD, Stănescu C, Găman AM. Evaluation of parameters with potential prognosis impact in patients with primary gastric diffuse large B-cell lymphoma (PG-DLBCL). *Rom J Morphol Embryol.* 2014;55(1):15–21.
11. Perry C, Herishanu Y, Metzer U, et al. Diagnostic accuracy of PET/CT in patients with extranodal marginal zone MALT lymphoma. *Eur J Haematol.* 2007;79(3):205–9.
12. Yoon SS, Coit DG, Portlock CS, Karpeh MS. The diminishing role of surgery in the treatment of gastric lymphoma. *Ann Surg.* 2004;240(1):28–37.
13. Kuo SH, Yeh KH, Wu MS, et al. Helicobacter pylori eradication therapy is effective in the treatment of early-stage H pylori-positive gastric diffuse large B-cell lymphomas. *Blood.* 2012;119(21):4838–5057.
14. Chen LT, Lin JT, Tai JJ, et al. Long-term results of anti-helicobacter pylori therapy in early-stage gastric high-grade transformed MALT lymphoma. *J Natl Cancer Inst.* 2005;97(18):1345–53.
15. Sugimoto M, Kajimura M, Sato Y, Hanai H, Kaneko E, Kobayashi H. Regression of primary gastric diffuse large B-cell lymphoma after eradication of Helicobacter pylori. *Gastrointest Endosc.* 2001;54:643–5.
16. Saito M, Mori A, Ogasawara R, et al. Progression of primary gastric diffuse large B-cell lymphoma after Helicobacter pylori eradication. *Case Rep Gastroenterol.* 2020;14(3):534–9.
17. Murata-Kamiya N, Kikuchi K, Hayashi T, Higashi H, Hatakeyama M. Helicobacter pylori exploits host membrane phosphatidylserine for delivery, localization, and pathophysiological action of the CagA oncoprotein. *Cell Host Microbe.* 2010;7(5):399–411.
18. Kuo SH, Yeh KH, Chen LT, et al. Helicobacter pylori-related diffuse large B-cell lymphoma of the stomach: A distinct entity with lower aggressiveness and higher chemosensitivity. *Blood Cancer J.* 2014;4(6):e220.
19. Negrini R, Savio A, Poiesi C, et al. Antigenic mimicry between Helicobacter pylori and gastric mucosa in the pathogenesis of body atrophic gastritis. *Gastroenterology.* 1996;111(3):655–65.
20. Xue LJ, Su QS, Yang JH, Lin Y. Autoimmune responses induced by Helicobacter pylori improve the prognosis of gastric carcinoma. *Med Hypotheses.* 2008;70(2):273–6.
21. Kuo SH, Chen LT, Lin CW, et al. Detection of the Helicobacter pylori CagA protein in gastric mucosa-associated lymphoid tissue lymphoma cells: Clinical and biological significance. *Blood Cancer J.* 2013; 3(7):e125.