Helicobacter Pylori Negative Extra-nodal Marginal Zone B Cell Lymphoma of Mucosa Associated Lymphoid Tissue (MALT) Type Following Roux-en-Y Gastric Bypass (RYGB)

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Abstract

Gastric MALT lymphoma is a common type of non-Hodgkin's lymphoma that has the potential for cure in patients found to have concomitant Helicobacter pylori infection.1,2 This case report explores the evaluation, diagnosis, and treatment of H. pylori negative MALT lymphoma in a patient with a history of a RYGB.

Title: ***Helicobacter Pylori Negative Extranodal Marginal Zone B Cell Lymphoma of Mucosa Associated Lymphoid Tissue (MALT) Type Following Roux-en-Y Gastric Bypass (RYGB)***

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Abstract:

Gastric MALT lymphoma is a common type of non-Hodgkin's lymphoma that has the potential for cure in patients found to have concomitant *Helicobacter pylori* infection.[1,2] This case report explores the evaluation, diagnosis, and treatment of *H. pylori* negative MALT lymphoma in a patient with a history of a RYGB.

Key clinical message:

In patients with gastric MALT lymphoma and a RYGB, surveillance of both the gastric pouch and remnant should be performed as it can occur in both locations despite anatomical separation.

Introduction

Extra-nodal marginal zone lymphoma (MZL) of MALT type compose 7% of all non-Hodgkin's lymphomas.[1] Approximately one-third present as a primary gastric lymphoma; 90% are associated with *Helicobacter pylori* (*H. pylori*).[1,2] The etiology of *H. pylori* negative lymphoma of MALT type remain controversial. Differentiating *H. pylori* negative from *H. pylori* lymphoma of MALT type is important in regards to treatment and prognosis. The incidence of primary MALT lymphoma of the gastric remnant or gastric pouch is not well defined but appears to be quite rare with less than 35 cases reported worldwide. In this case report, we discuss the suspected etiologies, diagnosis, treatment, and outcome of a 36-year-old female found to have *H. pylori* negative gastric lymphoma of MALT type. The case is further complicated by history of Roux-en-Y gastric bypass (RYGB) for treatment of refractory gastroesophageal reflux disease (GERD).

Case Description

A 36-year-old African American female with history of systemic sclerosis and refractory GERD status post RYGB presented to her primary care provider with complaints of daily nausea, non-bloody emesis, dysphagia, and abdominal pain refractory to all medical therapy. Patient had undergone endoscopic evaluation multiple times for this complaint initially limited to the gastric pouch secondary to surgical anatomy with no abnormalities noted. Laboratory analysis was notable for normal CBC, CMP, negative serologic and stool Helicobacter pylori antigen testing. The patient was referred back to gastroenterology for repeat upper endoscopic evaluation. The gastric pouch was notable for diffuse edema, punctate erythema, and friability (**Figure 1)** . Biopsies demonstrating chronic gastritis with extra-nodal marginal zone lymphoma of MALT type **(Figure 2, 3)** . A single balloon enteroscopy was then performed for evaluation with biopsies obtained of the gastric remnant. Similar gross findings were seen in the gastric remnant, however, biopsies showed dense lymphoid infiltrate consistent with MALT lymphoma. All biopsies were negative for *H. pylori* by immunohistochemical stains. Previous biopsies prior to RYGB surgery were reviewed and confirmed to be negative for H pylori infection as were serologic and stool antigen tests.

The patient was diagnosed with H pylori negative gastric MALT lymphoma, Lugano stage I, Ann Arbor IE. The case was discussed with a multi-disciplinary team including medical and radiation oncology. After discussion with the patient, the decision was made to treat with rituximab given the risk of large field radiation and her underlying systemic sclerosis. Repeat endoscopy with biopsy after 4 weeks of treatment showed no appreciable gross or histologic changes. Having failed immunosuppressant therapy, patient was initiated on radiation therapy for a total dose of 30 Gy. On follow up symptoms had improved; repeat single balloon enteroscopy showed mucosal improvement. Biopsies were notable for focal atypical lymphoid infiltrate with monocytoid cytomorphology and focal lymphoepithelial lesion formation, compatible with focal, residual marginal zone lymphoma (partial histologic regression). The amount of atypical lymphoid infiltrate was too small for further assessment by immunohistochemistry. Repeat endoscopy was planned within the next three months but unfortunately with the advent of COVID patient was lost to follow up.

Discussion

Development of gastric MALT lymphoma appears to arise from two distinct pathways both involving dysregulation of nuclear factor kappa light chain enhancer of activated B-cells (NF-kB) activity.[7]There is a B-Cell receptor (BCR) dependent NF-kB activation pathway and BCR-independent NF-kB activation pathway.[7,8] BCR dependent NF-kB activation relies on persistent antigen stimulation which elicits inflammation and

accelerated lymphoid proliferation through a polyclonal B-cell response.[7,9,10] This pathway is also recognized as an anti-microbial responsive lymphoid proliferation as when the stimulating antigen is removed, the inflammation and lymphoid proliferation resolves.[11]The above mechanism is further supported by the effectiveness of eradication therapy in the treatment of *H. pylori* associated MALT lymphoma. Current literature suggests regression in up to 83% of*H. pylori* associated MALT lymphoma cases when given triple or quadruple therapy.[12,13]

Though uncommon, there are reports showing *H. pylori* negative MALT lymphoma similar to our case presented above. The predominating theory suggests a BCR-independent NF-kB activation pathway. Though there is a clear theory describing the pathway for lymphoid proliferation in*H. pylori* negative patients, the exact mechanism is yet to be determined and is likely multifactorial. One known etiology is a pseudo-negative *H. pylori* associated MALT lymphoma. In these patients, *H. pylori* testing is negative due to previous use of antibiotics, bismuth, proton pump inhibitors (PPIs), or a combination of the three despite active infection with *H. pylori* .[14] Some studies indicate t certain chromosomal translocations or tumor suppression gene mutations can cause constitutive lymphoid proliferation independent of a stimulating antigen.[15] Multiple publications demonstrate a high incidence of translocation (11;18)(Q21;Q21) in *H. pylori* negative MALT lymphomas.[7,16-18] These translocations cause a fusion of the N-terminus of the API2 gene to the C-terminus of the MALT1 gene and generates a functional API2–MALT1 fusion product which can constitutively activate the NF-kB pathway.[19]

Presence of the t(11;18)(q21:q21) is seen in up to 30% of all gastric MALT lymphomas and are demonstrated in up to 68% that are at stage IIE or above.[20] Unfortunately, the current available data has not closely evaluated the incidence of these translocations in patients with *H. pylori* negative gastric MALT lymphoma, though there are multiple studies that show expression of these translocations in up to 88% of these patients.[7,16-20] Regardless, the presence of t(11;18)(q21:q21) can help guide therapy as they are only seen in approximately 3% of gastric MALT lymphomas that do respond to traditional *H. pylori* eradication therapy.[20]Further studies noted that the presence of t(11;18)(q21:q21) predicted poor response to alkylating agents (chlorambucil or cyclophosphamide) but was unable to predict the response to rituximab.[21,22]

Treatment of patients with *H. pylori* negative MALT lymphoma is complicated and differs depending upon the patient's comorbidities, staging, and the presence or absence of translocations. Current literature suggests using radiation therapy for patients with early stage (Lugano I/II) gastric MALT lymphoma without evidence of *H. pylori* infection and reported clinical remission rates in up to 100% of patients.[23,24] If radiation therapy fails or the patient is found to be at an advanced stage, treatment with immunotherapy (Rituxumab) can be trialed and has shown complete response in up to 46% of patients.[22,25] Prior to discovery the of *H. pylori* , targeted gastric resection was used to great therapeutic effect and long term survival.[22,26]However, more recent studies suggest that organ conserving therapy presents no long-term disadvantages but spares the patient from permanent nutritional and metabolic derangements.[27]For these reasons, surgical treatment of gastric MALT lymphoma is rarely pursued.

In the case above, testing for t(11;18)(q21:q21) was negative. Rituximab was preferred over radiation therapy in our patient with history of systemic sclerosis but was ineffective.. She has shown endoscopic and histologic improvement with radiation therapy with 3 month repeat follow up endoscopy pending.

In conclusion, *H. pylori* negative gastric lymphoma of MALT type is an uncommon presentation of non-Hodgkin lymphoma. Though the mechanism appears well researched, the specific etiology remains controversial. In patients with gastric lymphoma of MALT type, it is important to rule out *H. pylori* infection. If negative, further evaluation of the t(11;18)(q21:q21) can help further guide therapy and predict patient outcomes. Lastly, MALT lymphoma in patients that have undergone Roux-en-Y gastric bypass is uncommon with less than 40 cases in the reported literature. Thus diagnosis can be delayed due to mimicking symptoms typically attributed to the bypass. Evaluation, not only of the gastric pouch, but also the gastric remnant should be performed in all at risk patients as gastric MALT lymphoma can occur in both locations despite post-operative anatomical separation.

The authors confirm contribution to the paper as follows:

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All authors discussed the results and contributed to the final manuscript.

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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