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Synchronous indolent primary gastrointestinal lymphomas managed successfully with conservative measures

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Abstract

We report the case of a 65 year-old man who presented with epigastric pain and guaiac-positive stool. Upper and lower endoscopy revealed abnormalities in the gastric antrum and terminal ileum. Biopsy of these sites revealed histologically and immunophenotypically distinct lymphomas: gastric extranodal marginal zone lymphoma in the background of *Helicobacter pylori* infection and follicular lymphoma of the terminal ileum. After treatment with an *H. pylori* eradication regimen, repeat endoscopy showed resolution of the gastric extranodal marginal zone lymphoma and persistence of the ileal follicular lymphoma. Interestingly, molecular studies performed on the biopsy specimens revealed a common IgH rearrangement, suggesting a common precursor cell responsible for these two malignant processes. We present this unique case with a review of the literature, highlighting treatment principles for these two subtypes of indolent gastrointestinal non-Hodgkin lymphoma.

Keywords

follicular lymphoma; extranodal marginal zone lymphoma; MALT; *Helicobacter pylori*

Introduction

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) is a B-cell neoplasm that constitutes about 7–8 percent of all non-Hodgkin lymphomas. MALT lymphomas can arise from almost any organ in the body, though roughly 50 percent arise from the GI tract, with one-third of these affecting the stomach. Chronic inflammation frequently precedes or accompanies MALT lymphoma and may be the result of a variety of stimuli. Typical of gastric MALT lymphoma is a well-documented association with *Helicobacter pylori* infection and a 50–80 percent complete regression rate after eradication of this infection [1–4]. Incidence of gastric MALT lymphoma may be decreasing as treatment aimed at eradication of *H. pylori* has become increasingly employed [5].

Primary gastrointestinal follicular lymphoma without peripheral lymphadenopathy is very uncommon, accounting for <7% of primary lymphomas of the GI tract. Small series characterize these tumors as having a predilection for the second part of the duodenum and the terminal ileum. Prognosis may be excellent, even without treatment [6–8].

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We present a case of a patient presenting with simultaneous gastric MALT lymphoma associated with *H. pylori* infection and follicular lymphoma of the terminal ileum. To our knowledge, there have been only two previously reported cases of coexisting primary gastrointestinal follicular lymphoma with gastrointestinal MALT lymphoma [9–10] and no previously reported cases of ileal follicular lymphoma simultaneously presenting with gastric MALT lymphoma. In our patient, after treatment of the *H. pylori* gastritis there was regression of the MALT lymphoma with persistence of the ileal follicular lymphoma. Interestingly, despite clear clinical and immunophenotypic differences in the two lymphomas, molecular analysis for IgH rearrangement showed a same-sized peak in both tumors. In light of this finding, this case may represent evolution of two distinct but clonally related lymphomas from a single precursor. A similar case has been reported in a patient who developed follicular lymphoma 2 years after being diagnosed with MALT lymphoma in the parotid gland [11].

Case Report

A 65 year-old male presented to his primary care doctor for symptoms of increasing reflux in the setting of long-term gastroesophageal reflux disease (GERD). He also at the time of evaluation began to experience mild dysphagia to solid foods. Initial evaluation was significant for positive fecal occult blood. He underwent evaluation with upper and lower endoscopy. Upper endoscopy showed an area of nodular, ulcerated tissue in the gastric antrum with a background of diffuse erythema in the stomach and duodenum. Biopsy was taken of the antral nodule. Colonoscopy showed an isolated patch of erythematous mucosa at the terminal ileum and biopsy of this area was taken. The pathological findings are reviewed below.

Staging was performed with CT and PET. Imaging showed a 1.4cm para-aortic lymph node that was mildly (SUV 3.16) PET-avid. There additionally were multiple sub-centimeter PET-negative mesenteric lymph nodes.

He was treated with anti-*H. pylori* therapy consisting of amoxicillin, clarithromycin and a proton pump inhibitor. Presenting symptoms of worsening reflux and dysphagia resolved with this treatment. Repeat upper and lower endoscopy was performed approximately 6 weeks after completion of therapy. Upper endoscopy showed successful *H. pylori* eradication and complete resolution of the antral lesion; multiple biopsies near the site showed no residual disease. Colonoscopy showed residual terminal ileum lesion and repeat biopsy showed persistent follicular lymphoma involvement. No further treatment was undertaken for the follicular lymphoma as it was felt to be an asymptomatic incidental finding. Surveillance CT imaging was performed 6 months and 1 year after diagnosis and showed stable sub-centimeter mesenteric lymphadenopathy unchanged from previous evaluation.

Materials and Methods

Tissue samples and Immunohistochemistry

Biopsies were fixed in 10% neutral buffered formalin, embedded in paraffin, and stained with hematoxylin-eosin (H&E).

A panel of immunohistochemical stains (CD20, CD5, CD10, CD23, CD43, Bcl-2, Bcl-6, and cyclin D1) were performed using commercially available antibodies, on formalin-fixed paraffin embedded (FFPE) sections according to previously published techniques [12, 13].

Immunoglobulin Polymerase Chain Reaction (PCR)

DNA extraction was performed on FFPE with QiaCUBE extraction platform using their proprietary buffer and proteinase K digestion. PCR was performed using consensus primers directed to V_H framework (FR) III and joining region (J_H) of the immunoglobulin heavy chain gene (FRIII-IGH PCR) and to V_H FR region II and the joining region (FRII-IGH PCR), according to the method of Ramasamy *et al.* [14]. Testing for the IGκ locus was additionally performed using the Biomed II primer set described by van Dongen *et al.* and supplied by *InVivoScribe* Technologies (IGK@ Gene Clonality Assay-ABI Fluorescence Detection, Cat#: 1-102-0031)[15]. These reactions interrogate rearrangements involving the Vκ loci and Jκ (tube A), the Vκ locus and the κDE locus (tube B), and the κ-intron RSS locus and the κDE locus (tube B). The products from all reactions were separated by capillary electrophoresis on an ABI 3130xl Genetic Analyzer and the electropherograms analyzed using GeneMapper software version 3.7 (ABI).

Fluorescence in situ hybridization (FISH)

FFPE sections were pretreated (deparaffinization, protein digestion, and DNA neutralization) and hybridized using the Vysis *IGH/BCL2* t(14;18)(q32;21) dual color, dual fusion translocation probe set from Abbott Molecular, Inc. (Downers Grove, IL). Quantitative analysis of the images were performed manually on selected tissue areas with the Bioview image system (Billerica, MA). Positive cases for detection were defined when fusion signals were greater than 11.55%.

Results

The antral biopsy showed a dense atypical proliferation of B-cells (CD20 positive) in the lamina propria and focal lymphoepithelial lesions in a background of active chronic gastritis (Figure 1). These cells were negative for CD5, CD10, CD23, CD43, Bcl-2, Bcl-6, or cyclin D1. Microorganisms consistent with *H. pylori* were present on special stain. A diagnosis of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) was rendered.

Terminal ileum biopsy showed a vaguely nodular monotonous atypical lymphoid infiltrate in the lamina propria (Figure 2). Immunohistochemical analysis showed the atypical cells were positive for CD20, Bcl-2, CD10, and Bcl-6 and negative for CD5, CD23, CD43, and cyclin D1. A diagnosis of follicular lymphoma, grade 1–2, was rendered.

Molecular studies were performed on samples from both sites. FISH for t(14;18) *BCL/IGH* was performed and was positive in the terminal ileum biopsy and suggestive but indeterminate in the antral gastric sample. Further PCR for IgH and IgK rearrangements revealed an identically sized fragment (258–259 base-pair size) in both biopsy sites at the FRII-IgH locus, suggesting a clonal relationship (Figure 3A, B).

Discussion

The gastrointestinal tract is the most common extranodal primary site for non-Hodgkin lymphoma, accounting for 40% of cases. The stomach is the most commonly involved site; this is particularly true for gastrointestinal MALT lymphomas where 85% arise in the stomach [16-17].

MALT lymphoma is mainly a tumor of adults with a slight female predominance. The incidence of gastric MALT lymphoma declined in the late 1990s, possibly associated with the increased treatment for *H. pylori* infection, but has since leveled [5,18]. MALT lymphomas appear to arise from post-germinal center marginal zone B cells and have a

typical immunophenotype: positive for B cell markers CD19, CD20, and CD22 and negative for CD5, CD10, and usually CD23 [19]. Cytogenetic abnormalities are common in MALT lymphoma. Most common are trisomy 3 and four translocations, t(11;18)(q21;q21), t(1;14)(p22;q32), t(14;18)(q32;q21) and t(3;14)(p13;q32) [20–22]. Interestingly, the genes affected by these translocations seem to involve a similar pathway, leading to the activation of nuclear factor-kappaB [23]. MALT lymphomas tend to be indolent lesions, though around 30% can present with dissemination to other MALT sites, lymph nodes, or bone marrow. However, even patients with disseminated disease at presentation tend to have long periods (>5years) of progression-free survival [24].

The majority of gastric MALT lymphomas are associated with *H. pylori* infection. Despite lack of prospective randomized trials, *H. pylori* eradication has emerged as the preferred treatment in this situation because of its low toxicity and high efficacy. With this treatment, 50–80% of cases achieve complete remission on repeat endoscopy and biopsy [1–4]. Of note, patients whose tumors demonstrate t(11;18) tend to behave more aggressively and are much less likely to respond to *H. pylori* eradication [3,25–26]. Therefore this subset of patients may be considered for alternate, more aggressive treatment strategies.

Follicular lymphoma is the most common indolent non-Hodgkin lymphoma; however primary gastrointestinal follicular lymphoma is uncommon [6–7]. The immunology, immunophenotype, and molecular genetics of gastrointestinal follicular lymphoma are similar to the nodal counterpart [6–7, 27]. Typical follicular lymphomas express pan-B cell antigens (CD19, CD20, CD79a), CD10 (majority), Bcl-2, and Bcl-6 and lack CD5, CD43 (most cases), and CD11c. Both nodal and gastrointestinal follicular lymphoma frequently have the t(14;18)(q32;q21) translocation [27–28]; other cytogenetic abnormalities are less common.

Optimal treatment of primary gastrointestinal follicular lymphoma is not well established due to the relative rarity of this disease. Retrospective analysis, however, suggests an indolent disease course and excellent prognosis, including in cases where therapy was not initiated at the time of diagnosis [6–7, 27]. These findings suggest watchful waiting as a reasonable approach in this patient population.

To our knowledge, this is the first reported case of primary ileal follicular lymphoma coexisting with gastric MALT lymphoma. This case highlights the indolent nature of these two diseases and the role for a conservative treatment approach. Interestingly, despite clear clinical and immunophenotypic differences between the two tumors in this patient, both lymphomas were found to have clonally identical IgH rearrangement suggesting a common precursor cell. These findings suggest that an important interplay exists between local microenvironment, such as *H. pylori* infection, and genetics in the development of gastrointestinal low grade B-cell lymphomas.

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Figure 1. Antral biopsy showing small atypical cells with round nuclear contours, coarse chromatin, and moderate cytoplasm, invading glandular cells resulting in lymphoepithelial lesions characteristic of MALT lymphoma (H&E).

Figure 2. Ileal biopsy showing a dense vaguely nodular lymphoid infiltrate (inset) composed of mostly small atypical cells characteristic of follicular lymphoma, grade 1–2 (H&E).

Figure 3. Immunoglobulin gene rearrangement studies for IGH-FR2 showing same sized peaks in the (A) antral biopsy and (B) ileal biopsy.