

# Gastric MALT Lymphoma Treated With Primary Radiotherapy in the Setting of Autoimmune Disease

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## Abstract

Autoimmune and microbial-induced immune reactions are associated with lymphomagenesis, particularly of extranodal marginal zone B-cell lymphomas. This report presents a case of *Helicobacter pylori*-negative gastric extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in the setting of Sjögren syndrome and Hashimoto thyroiditis treated with primary involved-field radiotherapy. This report describes etiologic data, diagnostic and treatment considerations, and sophisticated radiation therapy techniques aimed at reducing long-term toxicity in this indolent disease. (*JNCCN* 2012;10:815–819)

**M**arginal zone lymphoma (MZL) describes 3 indolent B-cell non-Hodgkin's lymphomas (NHL): splenic MZL, nodal MZL, and extranodal MZL (of mucosa-associated lymphoid tissue [MALT]). Although all 3 share a common cell of origin, the marginal zone B cell, they are distinct diseases with unique clinicopathologic features. MALT lymphoma is the third most common NHL, representing roughly 8% of all cases.<sup>1</sup> It can arise in a variety of primary sites, including the stomach, ocular adnexa, salivary glands, thyroid, lung, breast, skin, and small intestine. The stomach is the most frequently involved site. Strong evidence suggests a causal role for chronic endogenous or exogenous antigenic stimulation in the development of MALT lymphomas. *Helicobacter pylori* (*H pylori*), *Chlamydia psittaci*, *Borrelia burgdorferi*,

and *Campylobacter jejuni* have been associated with gastric, orbital, cutaneous, and small intestinal MALT lymphomas, respectively.<sup>2–4</sup> Sjögren syndrome (SS) and Hashimoto thyroiditis (HT) dramatically increase the risk of developing lymphoma in the salivary glands and thyroid glands, respectively.<sup>5,6</sup>

The mainstay of therapy for stage I and II *H pylori*-negative gastric and nongastric MALT lymphoma is involved-field radiotherapy (IFRT). Because MALT lymphoma is an indolent disease in which long-term survival is the rule, limiting treatment-related morbidity is essential. Lymphoma in general is exquisitely radiosensitive; doses of 20 to 30 Gy can frequently be curative. This article describes an approach using 4-dimensional CT (4DCT) planning and intensity-modulated radiotherapy aimed at minimizing normal tissue toxicity.

## Case

A 46-year-old Caucasian woman with a longstanding history of HT and SS presented to her primary care physician complaining of bilateral upper quadrant pain. She was referred to her local gastroenterologist, who performed ultrasonography revealing cholelithiasis. Esophagogastroduodenoscopy (EGD) with biopsies of the gastric fundus and body and gastroesophageal junction was performed. Outside pathology review was consistent with a low-grade B-cell lymphoma. *H pylori* testing was not performed.

The patient presented to the authors' facility shortly thereafter for evaluation and treatment. Her upper abdominal pain resolved after recent administration of a proton pump inhibitor. She denied gastrointestinal symptoms. She denied melena, nausea, vomiting, anorexia, unintentional weight loss, fevers, and night sweats. Her medical history was notable for HT, SS,

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Submitted April 6, 2012; accepted for publication May 7, 2012.

The authors have disclosed that they have no financial interests, arrangements, or affiliations with the manufacturers of any products discussed in this article or their competitors.

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and secondary hypothyroidism. She had no history of radiation therapy or of lupus or scleroderma. She denied history of renal disease. She did report xerostomia and eye dryness requiring her to constantly carry a water bottle and use lubricating eye drops. Abdominal physical examination was benign, with no palpable masses. She had no clinically evident cervical, supraclavicular, axillary, or inguinal lymphadenopathy. Ophthalmologic and otorhinolaryngologic examinations were unremarkable.

Pathologic review of the outside specimens revealed a lymphoid infiltrate centered predominantly in the gastric fundus and multifocally involving the gastric body. The malignant lymphocytes were small cells that tested positive for CD20, CD43, and bcl-2. Lymphoepithelial lesions were present, and CD3-positive reactive/inflammatory T cells were present in the infiltrate. *H pylori* was not identified on periodic acid-Schiff or immunohistochemical staining. The final diagnosis was extranodal MZL of MALT. *H pylori* urea breath testing was negative.

Workup, which including CT imaging of the neck, chest, abdomen, and pelvis, revealed a 1.8-cm lymph node in the left axilla. Small nonspecific lymph nodes were present in the cervical, periportal, retroperitoneal, and pelvic lymph node distribution. Within the parotid gland, multiple cysts and calcifications were noted, consistent with SS. The thyroid gland was irregular, containing calcifications and hypodense nodules. Two thyroid nodules were targeted for biopsy, which showed only fragments of benign follicular cells in a background of normal lymphocytes and no lymphoma. Core needle biopsy of the left axillary lymph node showed fragments of benign lymphoid tissue. PET/CT imaging did not reveal any FDG-avid disease. Bilateral bone marrow biopsy and aspirate was negative with no morphologic evidence of lymphomatous involvement.

The patient was referred for IFRT. The authors performed 4DCT simulation with breath hold technique and treated the patient with 30 Gy of radiation administered in 20 fractions (Figure 1). The patient was treated with nil per os (NPO) 4 hours before radiotherapy. She tolerated radiation treatment well. She complained of increased flatulence, for which she was advised to adhere to a low-residue diet. She complained of intermittent grade I diarrhea that did not require pharmacologic intervention. She will be followed up posttherapy with repeat EGD and blind biopsies.

## Discussion

### Association of MALT Lymphoma and Autoimmune Disease

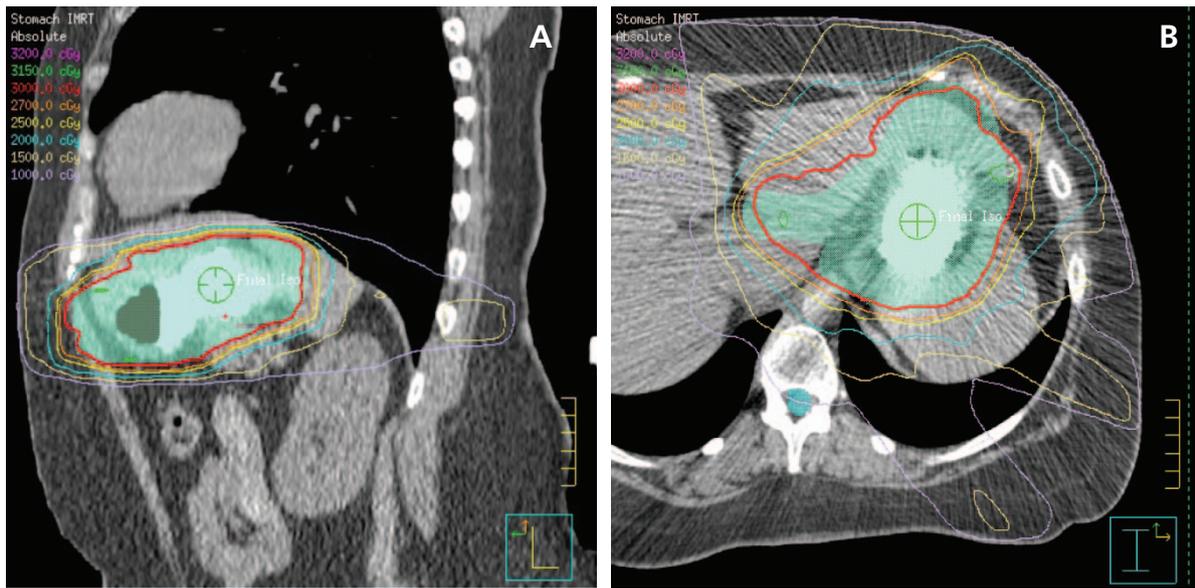
The association between autoimmune disease and lymphoma is well documented. Rheumatoid arthritis, SS, HT, and systemic lupus erythematosus have been linked to diffuse large B-cell lymphoma, MALT lymphoma, and Hodgkin lymphoma.<sup>7-9</sup> Several studies have shown that patients with lymphoma who have underlying autoimmune disease present with more advanced disease.<sup>10,11</sup> The link between autoimmune disease and lymphomagenesis is strongest for MALT lymphomas. Based on the highly established association between SS, HT, and *H pylori* with MALT lymphomas, the mechanism for disease pathogenesis is hypothesized to be predominantly immune mediated. Although those affected by HT have been shown to have a 70-fold increased risk of developing primary thyroid lymphoma,<sup>6</sup> a recent series reported an increased risk of extrathyroidal lymphomas in this patient population, including primary gastric, orbital, salivary gland, and small intestinal MALT lymphomas.<sup>12</sup>

In the literature, the frequency of autoimmune disease in patients diagnosed with MALT lymphoma is variable, ranging from 12% to 39%.<sup>13,14</sup> The incidence of extragastric MALT seems to be higher, however, in those afflicted with autoimmune disease, with one series reporting 64% of MALT parotid cases that were diagnosed in the setting of autoimmune disease.<sup>9,15</sup> In patients with gastric MALT lymphoma with underlying autoimmune disease, lower rates of lymphoma regression are noted after *H pylori* eradication, suggesting a distinct mechanism of pathogenesis.<sup>9</sup>

### Diagnostic Considerations

The most common presenting symptom in cases of gastric MALT lymphoma is abdominal pain, followed by nausea, vomiting, dyspepsia, and anorexia. Gastrointestinal bleeding can occur but is less common, occurring as the initial symptom in roughly 20% to 30% of cases.<sup>16</sup> B symptoms are rare. Although once considered largely to be an extranodal disease limited to the site of origin (i.e., Ann Arbor stage IE), peripheral lymph node and bone marrow involvement is actually not infrequent. In a review of 211 patients treated for extranodal MZL at MD Anderson Cancer Center, 42% of overall patients had stage III or

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**Figure 1** Intensity-modulated radiation treatment (IMRT) plan for gastric mucosa-associated lymphoid tissue lymphoma. Sagittal (A) and axial (B) representative slices from the 4-dimensional CT-based IMRT plan. The patient was simulated with small volume oral contrast to assist with target delineation. The planning target volume (PTV) encompassed the entire stomach and perigastric nodes with margins. The PTV was treated with 30 Gy of radiation administered in 20 fractions (red isodose line) with nil per os 4 hours before daily radiotherapy. IMRT permits excellent cardiac and renal sparing.

IV disease and 25% of patients with gastric MALT had disseminated disease.<sup>13</sup> A published series from France reported disseminated disease in one-third of patients with MALT lymphoma.<sup>17</sup> Although the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NHL suggest bone marrow evaluation in selected cases,<sup>18</sup> the authors routinely stage all patients with newly diagnosed MALT using bilateral bone marrow biopsy and aspirate (to view the most recent version of the NCCN Guidelines, visit NCCN.org). CT images of the neck, chest, abdomen, and pelvis with contrast are performed to evaluate for lymph node involvement.

Immunophenotypic and histopathologic analysis is performed to establish the diagnosis of gastric MALT. The neoplastic cells are small B lymphocytes that are CD20-positive and CD3-negative, indicating their B-cell origin. They can be seen invading reactive germinal centers (i.e., follicular colonization). Lymphoepithelial lesions are often identified. Within the neoplastic infiltrate, moderate to high concentrations of CD3-positive and CD5-positive T cells may be appreciated but the MALT lymphoma cells themselves are CD5-negative. *H pylori* testing should be performed.

In patients with nongastric MALT lymphoma, the authors have reported an incidence of simultaneous gastric MALT involvement in 18% to 33% of pa-

tients.<sup>19,20</sup> Therefore, in cases of nongastric MALT the authors routinely include endoscopy of the upper gastrointestinal tract, with directed biopsies as part of the workup. In this case, however, gastric MALT was diagnosed, but in the setting of 2 autoimmune diseases, predisposing her to an increased risk of lymphoma in the thyroid and salivary glands. It is plausible that her gastric involvement was disseminated disease related to a thyroid or salivary primary site of disease. Imaging of the head and neck did not uncover any suspicious lesions in the thyroid or salivary glands. Ophthalmologic and otorhinolaryngologic examinations did not reveal any suspicious lesions. Biopsy of 2 radiographically detected thyroid nodules was negative.

### Treatment

In stages IE and IIE (gastrointestinal tract confined or with locoregional lymph node involvement, respectively) *H pylori*-negative gastric MALT lymphoma, IFRT is the preferred primary treatment. Patients with persistent lymphomatous disease after *H pylori*-directed antibiotic therapy are also treated with radiotherapy. Patients with the t(11;18) translocation (regardless of *H pylori* status) and those with disease extending into the muscularis exhibit low rates of lymphoma regression after *H pylori* eradication and are better suited for radiation.<sup>21,22</sup>

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Radiation is extremely effective and is often curative in early-stage gastric MALT. When peritoneal spread was thought to be a mechanism of disease dissemination, patients were treated with total abdominal irradiation, often to a dose of 20 to 30 Gy followed by a 10-Gy boost to the stomach, para-aortic lymph nodes, and spleen.<sup>23</sup> The current standard of care is 30 Gy of IFRT administered in 20 fractions to the stomach and perigastric lymph nodes. Several institutions have reported excellent outcomes with this approach. In the Memorial Sloan-Kettering Cancer Center series of 51 patients with predominantly stage I and II *H pylori*-negative gastric MALT lymphoma, biopsy results showed a complete response in 96% of patients. The 4-year freedom from failure rate was 89% (+/- 5%) and cause-specific survival was 100%.<sup>24</sup> Princess Margaret reported similar outcomes, with 10-year recurrence-free rates of 92%.<sup>25</sup> In the setting of excellent outcomes, limiting toxicity is of utmost importance. Because side effects from radiotherapy are largely related to normal tissue toxicity, which is heavily influenced by field size and dose, IFRT given at lower doses of 30 Gy yields favorable long-term morbidity profiles.<sup>26</sup>

Advances in image-based radiotherapy have allowed highly conformal treatment to be delivered with minimal fear of missing the target. This is key in gastric radiotherapy because of the proximity of vital organs, including the heart, lungs, liver, and kidneys.<sup>27</sup> Radiation treatments are administered in a fasting state (typically 4–6 hours NPO) to reduce gastric motion. Often the authors use 4DCT planning to account for motion that occurs secondary to respiration. Radiation treatments can be delivered during the inspiratory phase of the respiratory cycle (breath hold technique) to further reduce target expansions in an effort to minimize surrounding normal tissue dose. Image-guided administration of radiotherapy is essential when highly conformal techniques are used to assure the target is irradiated as planned. This is imperative in gastric irradiation because of the highly variable gastric position caused by gastric motion. Daily cone beam CT imaging can be used for this purpose. Overall, late toxicity is uncommon. The gastric mucosa can tolerate 30 Gy, often without long-term consequence. Appropriate dose constraints should be used for the liver and kidneys. The dose to the heart should be as low as reasonably possible.

## Conclusions

MALT lymphoma is an indolent B-cell lymphoma with endogenous and exogenous pathogens implicated in its development. Patients with an autoimmune disease have an increased risk of developing MALT lymphoma, although further investigations are warranted to elucidate the mechanisms of pathogenesis. In *H pylori*-negative gastric MALT lymphoma, primary radiotherapy is the mainstay of treatment, with excellent control and disease-free survival rates. Treatment morbidity is low, especially in this era of more sophisticated radiotherapy techniques.

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