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Difficulty swallowing solid foods; food 'getting stuck in the chest'

A 61-year-old woman presents to her primary care physician because for the last 4 weeks she has had difficulty swallowing solid food and a feeling of food "getting stuck in the chest." She also reports having nausea, mild epigastric pain, and heartburn. She denies having fevers, chills, night sweats, weight loss, vomiting, diarrhea, hematochezia, or melena.

She has had GERD for 20 years, intermittently treated with a proton pump inhibitor

Medical history

For the past 20 years, she has had gastroesophageal reflux disease (GERD), intermittently treated with a proton pump inhibitor. She also has arthritis, hyperlipidemia, hypertension, and asthma, and she has undergone right hip replacement for a hip fracture. She has no known allergies.

She lives in the Midwest region of the United States and is on disability due to her arthritis. She is divorced and has three children.

She quit smoking 3 years ago after smoking half a pack per day for 30 years. She drinks socially; she has never used recreational drugs.

She recalls that an uncle had cancer, but she does not know the specific type.

Physical examination

The patient's temperature is 96.7°F (35.9°C), heart rate 86 per minute, blood pressure 150/92 mm Hg, respiratory rate 16 per minute, and oxygen saturation 100% on room air.

She is alert and oriented to time, place, and person. Her sclera are white, her lymph nodes are not palpable, and her heart and lungs appear normal. Her abdomen is tender in the area of the stomach and in the left upper quadrant, there are no signs of peritonitis, the liver and spleen are not enlarged, and no masses can be palpated. She has no asterixis. Results of her complete neurologic examination are normal. Her extremities are normal with no edema. Her laboratory values are shown in **TABLE 1**.

Differential diagnosis

Although the differential diagnosis at this stage is broad, a few conditions that commonly present like this are:

- Esophageal cancer
- Esophageal stricture
- Esophageal webs
- Esophagitis (infectious, inflammatory)
- Peptic ulcer disease.

WHICH TEST SHOULD BE ORDERED?

1 Which test will you order now for this patient?

- ☐ Endoscopy (esophagogastroduodenoscopy)
- ☐ Serum *Helicobacter pylori* antibody testing
- ☐ Wireless pH monitoring
- ☐ Barium swallow

Endoscopy would be the best test to order. Esophageal cancer and esophageal stricture must be ruled out, in view of her long history of GERD, gastritis, and smoking and her alarming symptoms of difficulty swallowing and food sticking. In this situation, endoscopy is the first test recommended. In addition to its diagnostic value, it offers an opportunity to obtain tissue samples and to perform a therapeutic intervention, if necessary.[1,2]

***H pylori* antibody testing** is used in the "test-and-treat approach" for *H pylori* infection, an established management strategy for

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TABLE 1

The patient's laboratory values on presentation

TEST	RESULT	NORMAL RANGE
White blood cell count	4.5 x 10^9/L	4–11
Hemoglobin	11 g/dL	12–16
Platelet count	219 x 10^9/L	150–400
Aspartate aminotransferase	18 U/L	7–40
Alanine aminotransferase	25 U/L	0–45
Sodium	141 mmol/L	132–148
Potassium	4.5 mmol/L	3.5–5.0
Chloride	106 mmol/L	98–111
Bicarbonate	23 mmol/L	23–32
Blood urea nitrogen	16 mg/dL	8–25
Creatinine	1.0 mg/dL	0.7–1.4
Glucose	90 mg/dL	65–100
Albumin	4.1 g/dL	3.5–5.0
Total protein	9.9 g/dL	6–8.4
Total bilirubin	1.0 mg/dL	0–1.5

In view of her alarm symptoms, cancer and esophageal stricture need to be ruled out

patients who have uninvestigated dyspepsia and who are younger than 55 years and have no "alarm features," ie, red flags for cancer. The alarm features commonly described are anemia, early satiety, unexplained weight loss, bleeding, odynophagia, progressive dysphagia, unexplained vomiting, and a family history or prior history of gastrointestinal malignancy.[3]

Our patient's symptoms raise the possibility of cancer, so that *H pylori* testing would not be the best test to order at this point.

Ambulatory wireless pH monitoring with a wireless pH capsule is useful for confirming GERD in those with persistent symptoms (whether typical or atypical) who do not have evidence of mucosal damage on initial endoscopy, particularly if a trial of acid suppression has failed.[4–6]

Barium swallow is an x-ray examination of the esophagus with contrast. It can show both the anatomy and the function of the esophagus, and it would be the initial diagnostic procedure of choice for patients with dysphagia who have no alarm symptoms.[7] However, our patient does have alarm symptoms.

First highlight point

- Endoscopy is the first test in patients with dysphagia with alarm symptoms.

CASE CONTINUES: ENDOSCOPY

The patient undergoes endoscopy, which shows erosive esophagitis (grade B according to the Los Angeles classification[8]), gastritis, and multiple smooth nodules measuring 3 to 5 mm in the body of the stomach (FIGURE 1).

Multiple biopsies of the nodules show atypical lymphoid infiltrates with small cleaved lymphocytes that are mostly positive for CD5, CD20, and CD43 and negative for CD10 and CD23 by flow cytometry. In addition, a staining test for *H pylori* is positive.

Comment. Our patient has had GERD for the past 20 years, intermittently treated with a proton pump inhibitor. Acid suppressive therapy with a proton pump inhibitor is the standard of care of patients with erosive esophagitis. In standard doses, these drugs control symptoms in most cases and heal esophagitis in almost 90% of cases within 4 to 8 weeks.[9] Proton pump inhibitors are also effective for maintaining healing of esophagitis and controlling symptoms in patients who respond to an acute course of therapy for a period of 6 to 12 months.[10]

WHAT IS THE DIAGNOSIS?

2 Which is the most likely diagnosis for our patient?

- ☐ Fundic gland polyps
- ☐ Gastric hyperplastic polyps
- ☐ Gastric adenomas
- ☐ Mucosa-associated lymphoid tissue (MALT) lymphoma

Fundic gland polyps are small (0.1–0.8 cm), hyperemic, sessile, flat, nodular lesions that have a smooth surface. They occur exclusively in the gastric corpus and are composed of normal gastric corpus-type epithelium arranged in a disorderly or microcystic configuration.[11] This pattern does not match our patient's findings.

Gastric hyperplastic polyps are elongated, cystic, and distorted foveolar epithelium with marked regeneration. Other histologic find-

ings are stromal inflammation, edema, and smooth muscle hyperplasia.[12] This does not match our patient's findings.

Adenomas can be flat or polypoid and range in size from a few millimeters to several centimeters. Endoscopically, adenomatous polyps have a velvety, lobulated appearance. Most are solitary (82% of cases), located in the antrum, and less than 2 cm in diameter.[13] This does not match our patient's findings.

MALT lymphoma, the correct answer, is characterized by small cleaved lymphocytes positive for CD4, CD20, and CD43. Although CD5 positivity is not characteristic, rare cases of MALT lymphoma may be CD5-positive and may be more aggressive.[14]

Other common features of MALT lymphoma are erosions, small nodules, thickening of gastric folds—generally suggesting a benign condition—or hyperemic or even normal gastric mucosa.[15] Our patient's complaint of food sticking in her chest and difficulty swallowing was most likely related to the erosive esophagitis found on endoscopy.

A TYPE OF NON-HODGKIN LYMPHOMA

Normal gastric mucosa contains no lymphoid tissue.[16,17] Primary gastric lymphoma, of which MALT lymphoma is a subtype, accounts for around 5% of gastric malignancies, with an annual incidence rate of 0.5 per 100,000 people.[18–20] Although rare, it accounts for 60% to 70% of cases of non-Hodgkin lymphoma of the gastrointestinal tract and can involve the perigastric or abdominal lymph nodes or both.[21–23] Although earlier studies suggested that its incidence was increasing, recent data indicate the incidence may be decreasing, thanks to active *H pylori* treatment.[24–26]

Two subtypes of primary gastric non-Hodgkin lymphoma commonly described are MALT lymphoma and diffuse large B-cell (DLBC) lymphoma. In the Revised European-American Lymphoma Classification, high-grade MALT lymphoma is comparable to DLBC lymphoma and may have transformed from low-grade MALT lymphoma.[27,28] Another reported subtype, mantle cell lymphoma with MALT lymphoma features, should be considered in the differential diagnosis, although it is rare.[29]

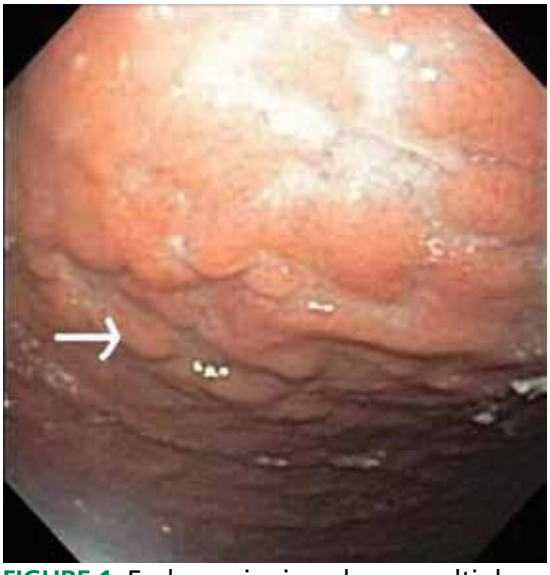

FIGURE 1. Endoscopic view shows multiple nodules in the body of the stomach (arrow).

MALT lymphoma is linked to *H pylori*

H pylori infection is a factor in the development of MALT lymphoma,[30] as multiple lines of evidence show:

- *H pylori* infection has been reported in more than 90% of patients with MALT lymphoma.[31–35]
- *H pylori* antibodies have been found in stored serum drawn from patients who subsequently developed MALT lymphoma.[35]
- In response to *H pylori* antigens, T cells from MALT lymphoma proliferate and cause an increase in tumor immunoglobulin production.[36]
- In animals experimentally infected with *H pylori*, around one-third develop lymphoid follicles and lymphoepithelial lesions including B cells, which are similar to human MALT lymphoma.[37]

However, only a minority of patients with *H pylori* develop lymphoma, owing to a host immune response that is not well defined.

***H pylori* has been reported in more than 90% of patients with MALT lymphoma**

Second highlight point

- Gastric MALT lymphoma is associated with *H pylori*.

Associated genetic translocations

Three translocations, t(11;18), t(1;14), and t(14;18), are specifically associated with MALT lymphoma, and the genes involved have been characterized.

The t(11;18) translocation, seen in gastric and nongastric MALT lymphoma, is not seen in *H pylori* gastritis.[38] This translocation is usually associated with extension of the disease outside the stomach (ie, to regional lymph nodes or distal sites).[27] Most cases that do not respond to *H pylori* eradication involve the t(11;18) and t(1;14) translocations.[28]

Clinical presentation of gastric MALT lymphoma

The average age at presentation with gastric MALT lymphoma is 54 to 58 years.

The most common complaint is nonspecific abdominal pain in the epigastric region, sometimes accompanied by weight loss, nausea, vomiting, and, in a quarter of cases, acute or chronic bleeding.[39–41] Weight loss is common, and its extent is associated with the location and the grade of the disease.

Most cases of MALT lymphoma are found serendipitously during endoscopy, on which the appearance of the lesions ranges from small ulcerations to polypoid masses with infiltrated, thickened folds involving predominantly the antrum or prepyloric region.[15,41]

H pylori eradication is the treatment of choice for stage I low-grade gastric MALT lymphoma

MANAGING MALT LYMPHOMA

Our patient undergoes endoscopic ultrasonography, which reveals she has stage I disease, ie, it is limited to the stomach without involving the lymph nodes (stage II), adjacent organs (stage III), or distant organs (stage IV).

3 How will you treat this patient, given the present information?

- ☐ Chemotherapy
- ☐ Radiation therapy
- ☐ Surgery
- ☐ Antibiotics with a proton pump inhibitor

Antibiotics with a proton pump inhibitor would be best. According to the Maastricht III Consensus Report,[42] *H pylori* eradication is the treatment of first choice for *H pylori* infection in patients with stage I low-grade gastric MALT lymphoma. This therapy can induce complete histologic remission in 80% to 100% of patients with MALT lymphoma.[43] Several studies have shown regression[44] or complete remission of low-grade gastric MALT lymphoma after eradication of *H pylori* with antibiotics, making it a reasonable initial treatment.[45–49]

Several regimens are used. The first choice in populations in which the prevalence of resistance to clarithromycin (Biaxin) is less than 15% to 20% is a proton pump inhibitor, clarithromycin, and either amoxicillin or metronidazole (Flagyl). (Metronidazole is preferable to amoxicillin if the prevalence of resistance to metronidazole is less than 40%.)

Sequential treatment—ie, 5 days of a proton pump inhibitor plus amoxicillin followed by 5 additional days of a proton pump inhibitor plus clarithromycin plus tinidazole (Tindamax)—may be better than a 7-day course of the combination of a proton pump inhibitor, amoxicillin, and clarithromycin.[50,51]

Treatment with a proton pump inhibitor, clarithromycin (500 mg twice a day), and either amoxicillin (1,000 mg twice a day) or metronidazole (400 or 500 mg twice a day) for 14 days is more effective than treatment for 7 days.[52]

H pylori reinfection in the general population is quite rare, with an estimated yearly rate as low as 2%.[53] Recurrence of the infection is a risk factor for lymphoma relapse.[17,54]

Several predictors of the response of MALT lymphoma to eradication therapy have been recognized: *H pylori* positivity, stage I, lymphoma confined to the stomach; gastric wall invasion confined to mucosa and submucosa, and the absence of the t(11;18) translocation.

The time between *H pylori* eradication and complete remission of primary gastric lymphoma varies and can be longer than 12 months.[55]

Chemotherapy. In a single study,[56] complete remission was achieved with oral cyclophosphamide (Cytoxan) in cases of antibiotic-refractory gastric MALT lymphoma. Comparable results were achieved after radiation therapy (see below); hence, oral monotherapy with cyclophosphamide might also be a suitable second-line therapy.[57]

The regimen of cyclophosphamide, hydroxydaunomycin, vincristine, and prednisone (CHOP) has been recommended for patients with stage III and IV disease.[41,58]

Rituximab (Rituxan) has been proven effective in treating t(11;18)-positive MALT lymphoma.[59]

Radiation therapy. Two studies have shown a 100% complete response rate after radiation therapy with a median dose of 30 Gy.[57,60] Tsang et al[61] reported complete remission in up to 90% of patients receiving radiation therapy alone, with excellent 5-year progression-free and overall survival rates of 98% and 77%, respectively.

Although surgery, radiotherapy, and chemotherapy have been used in cases in which eradication therapy failed and in more advanced stages of MALT lymphoma, there is no consensus about their use, so therapy must be individualized.

Fourth highlight point

- Antibiotic treatment for eradication of *H pylori* infection is the recommended treatment only for stage I low-grade MALT lymphoma.

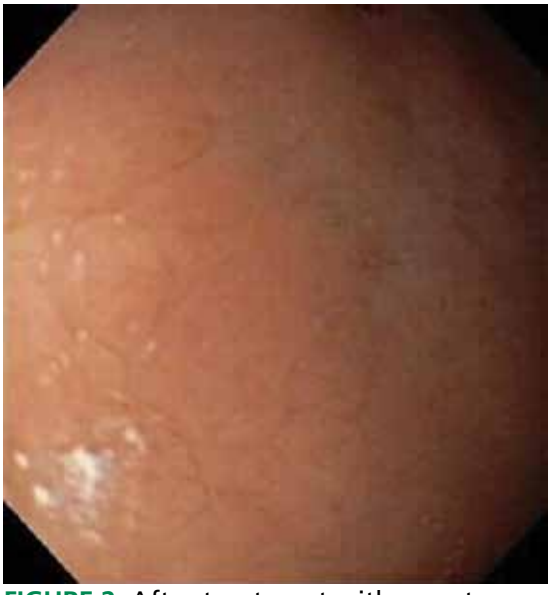

FIGURE 2. After treatment with a proton pump inhibitor, clarithromycin, and amoxicillin for 14 days, no nodules are visible.

FOLLOW-UP

4 How should you follow patients with MALT lymphoma?

- ☐ Endoscopy
- ☐ *H pylori* testing
- ☐ Computed tomography and magnetic resonance imaging
- ☐ No surveillance required after treatment

Endoscopy is the correct answer. As initial diagnostic biopsies do not exclude aggressive lymphoma, careful endoscopic follow-up is recommended. A recommended schedule is a breath test for *H pylori* every 2 months in conjunction with repeat endoscopy with biopsies every 3 to 6 months for the first 2 years, and then annually.[62]

Although *H pylori* may be eradicated within 1 month of drug therapy, lymphoma may take several months to disappear histologically. In patients with stage I disease with residual lymphoma after *H pylori* eradication therapy, a simple wait-and-watch strategy is a suitable alternative to oncologic therapy.[63,64]

Local relapse may occur after many years of complete remission; thus, patients should be followed closely long-term with endoscopy and possibly endoscopic ultrasonography.[47–49,63]

Patients who fail to attain a complete remission within 12 months should undergo radiation therapy, with or without chemotherapy. The same therapy should be started as soon as possible in patients with progressive disease after antibiotic therapy. Patients negative for *H pylori*, patients with stage II disease, and patients with t(11;18) translocation should receive antibiotic treatment with endoscopic surveillance every 3 months.

Long-term follow-up is essential after treatment for MALT lymphoma

Fifth highlight point

- Surveillance endoscopy is recommended for follow-up of MALT lymphoma.

CASE CONTINUES: HER CONDITION IMPROVES, THEN WORSENS

The patient receives a proton pump inhibitor, clarithromycin, and amoxicillin for 14 days. Her dysphagia improves, and endoscopy with biopsies 3 months later is negative for MALT lymphoma and *H pylori* (FIGURE 2).

However, when she undergoes endoscopy with endoscopic ultrasonography again 6 months after her second endoscopy, it shows multiple 3-to-5-mm smooth nodules in the body of the stomach (FIGURE 3). Multiple biopsies are then performed; the findings in the gastric body are consistent with extranodal marginal zone B-cell lymphoma of MALT

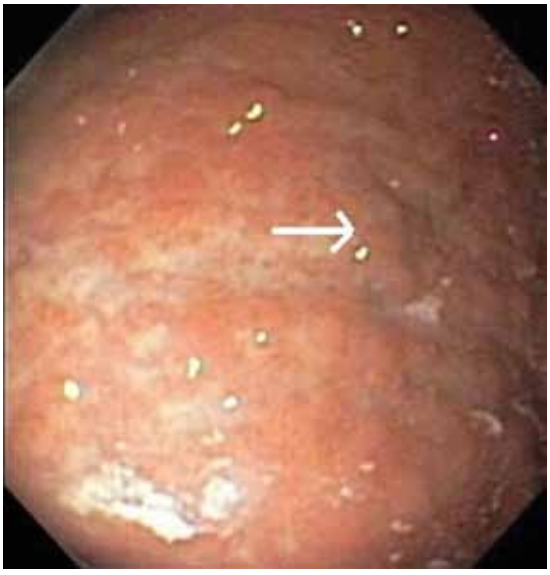

FIGURE 3. Follow-up endoscopy demonstrates stomach mucosa with multiple nodules (arrow) due to recurrence of mucosa-associated lymphoid tissue (MALT) lymphoma after treatment for *Helicobacter pylori* and remission.

type, t(11;18)-negative. Giemsa stain is negative for *H pylori*.

Computed tomography of the chest, abdomen, and pelvis reveals no evidence of additional sites of tumor. Positron emission tomography reveals increased uptake in the left tonsillar region, for which she has undergoes an ear, nose, and throat evaluation, and no pathology is found.

Due to recurrence of her marginal zone B-cell lymphoma of MALT type of the stomach, the patient is referred to an oncology service. She is treated with radiation, receiving 15 sessions of 30 Gy localized to the stomach. Three months after radiation therapy, she undergoes endoscopy again, which shows no evidence of the previously described nodules. Repeat biopsies are negative for *H pylori* and MALT lymphoma.

Annual surveillance endoscopy and computed tomography for the past 3 years have been negative for any tumor recurrence. ■

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