



Gastroesophageal Surgery Case Scenario

A 37-Year-Old Woman with Hereditary Diffuse Gastric Cancer (HDGC) Syndrome

JOHN T. MULLEN, MD

Massachusetts General Hospital

PRESENTATION OF CASE

A 37-year-old woman in otherwise excellent health and with no symptoms referable to the gastrointestinal tract was seen at our Gastrointestinal Cancer Genetics Clinic at Massachusetts General Hospital because of a significant family history of breast and gastric cancer. The patient had a normal physical examination. She was referred for genetic counseling and testing.

The patient had a family history of multiple malignant tumors. Her paternal grandmother was diagnosed with breast cancer at the age of 40 and with stomach cancer at the age of 60; she died at the age of 61. Two paternal great aunts were also diagnosed with stomach cancers, one at the age of 25 and the other at the age of 54. A paternal aunt was diagnosed with breast cancer at the age of 38 and died at the age of 48. A paternal cousin was diagnosed with diffuse-type gastric cancer at age 44, and she underwent genetic testing for mutations in the CDH1 gene and tested positive. Her father, age 67, also underwent genetic testing and was found to be a carrier of the familial CDH1 mutation, conferring a 50% risk that the mutation was passed along to her.

Hereditary Diffuse Gastric Cancer (HDGC) Syndrome

HDGC syndrome is caused by a germ-line mutation in the E-cadherin gene. Mutations in E-cadherin (the protein encoded by the gene

CDH1) cause a loss of normal adhesion, and an increase in cellular migration and invasion. The gastric cancers in HDGC syndrome are of the diffuse type, and the mean age at the time of diagnosis of gastric cancer is approximately 40 years. The lifetime risk of gastric cancer for those with the gene mutation is estimated to be 67% in men and 83% in women¹. Compared to other gastrointestinal cancer syndromes, there is also a significant risk of breast cancer (~40% in women), especially the lobular type. Hence, HDGC syndrome could explain the cancers seen in the family of this patient.

Genetic Testing

When the patient's father and cousin were found to be carriers of a mutation in the CDH1 gene, she was offered genetic testing. These tests indeed showed the same CDH1 mutation that had previously been identified in the family. Thus, in this patient with a family history of documented diffuse gastric cancer, a high prevalence of breast cancer and a mutation in the CDH1 gene, the diagnosis of HDGC syndrome was confirmed.

DISCUSSION OF MANAGEMENT

The care of patients with HDGC syndrome focuses largely on managing the risk of gastric cancer. The lifetime risks are high and increase with age. By age 30, the risk of gastric cancer for those with the E-cadherin gene mutation is approximately 4% for both men and women. By age 50, the risk



increases to 21% for men and 46% for women. Women appear to have a higher risk of developing gastric cancer at all ages, and the reason for this is unknown.

For this patient, there were two main options for screening for gastric cancer:

1. Surveillance upper endoscopy with random biopsies
2. Prophylactic total gastrectomy (PTG)

In gastrectomy specimens from patients in whom gastrectomy had been performed without a preoperative diagnosis of cancer, the pathological analysis of the entire stomach showed previously unrecognized cancer in more than 90% of the patients². The microscopic cancer foci are not visible with conventional white-light endoscopy, are often multifocal with up to 500 foci per stomach and can lie beneath a layer of normal epithelium. Hence, the only way to detect these cancers at an early stage is by performing a PTG.

Another important factor in this patient was the timing of the PTG. Gastric cancers have been reported in teenagers of affected families, and gastrectomy is often presented as a treatment option for patients before their early 20s. Although microscopic cancer foci are found in almost all gastrectomy specimens, including those from younger patients, the risk of a clinically significant cancer by age 50 is less than 50%. Therefore, not all of these microscopic cancers progress and the rates at which they do so vary. For now, the conservative approach is to treat each microscopic focus as if it is potentially an invasive cancer.

We recommended a PTG for this particular patient with a CDH1 mutation. If she declined the PTG, the recommended approach would have been an upper endoscopy every six months with random biopsies. After consultation with her Mass General surgeon, the patient elected to have a PTG.

Prophylactic Total Gastrectomy (PTG)

The patient was well informed about the benefits and risks of surgery through discussions with her doctors, nutritionist and support groups. We performed a PTG, Roux-en-Y reconstruction and a stapled end-to-side esophagojejunostomy (Figure 1). A swallowing study on the fourth postoperative day showed no evidence of anastomotic leak, and the patient started a clear liquid diet. She was discharged on the seventh postoperative day, tolerating a soft solid diet. Three years post-surgery, her weight had stabilized at 134 pounds (decreased from 148 pounds), and she was eating six to eight meals per day.

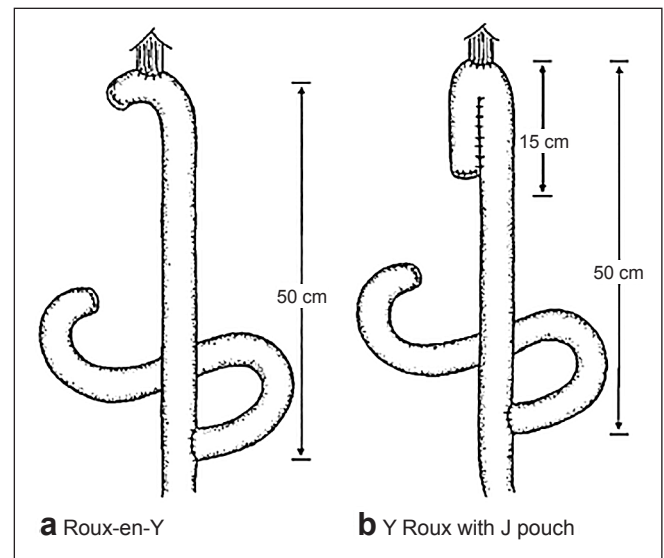


FIGURE 1. Prophylactic total gastrectomy and reconstruction with Roux-en-Y, end-to-side esophagojejunostomy, without (a) or with (b) a jejunal J pouch³.

We published our initial experience from 2006-2009 on 10 patients on whom we performed PTGs⁴. We have now performed more than 20 PTGs at Mass General, and all patients have enjoyed excellent short- and long-term outcomes. Patients are managed by a multidisciplinary



team, including a gastroenterologist, surgeon, genetic counselor and nutritionists. The risks of complications and death are lower in this group of patients compared to patients with sporadic cancer, likely because of their relatively young age, healthier status and the fact that a regional lymph node dissection is not necessary. Microscopic foci of pT1a gastric cancer have not been shown to metastasize to lymph nodes in this population. Therefore, most surgeons recommend a D1 lymphadenectomy at the time of the PTG. If a patient undergoing a gastrectomy for this syndrome is found to have a more advanced invasive cancer on preoperative upper endoscopy, a formal D2 lymphadenectomy should be performed⁵.

The pathologic features specific to the disease dictate the removal of the entire stomach to ensure that no at-risk gastric mucosa is left behind. Accordingly, the surgeon must ensure by frozen section pathologic analysis that the proximal margin contains 100% esophageal squamous mucosa and that the distal margin contains 100% duodenal mucosa. Gastrointestinal continuity is re-established with an end-to-side Roux-en-Y esophagojejunostomy with a 50- to 60-cm Roux limb to limit the risk for bile reflux. Some surgeons favor the creation of an intestinal pouch because some reports show that patients who are reconstructed with a pouch have fewer symptoms of dumping and heartburn, resulting in some improvement in quality-of-life scores⁶.

Nutritional consequences after a PTG are important to note. It is critical for the surgeon and the nutritionist to set reasonable expectations for patients regarding long-term quality of life. Following a PTG, eating habits are significantly altered, including a reduced meal size, a slower

rate of eating and an increased frequency of meals. Virtually all patients lose weight, averaging approximately 15-25% of the baseline preoperative weight. Early dumping syndrome and diarrhea develop in up to 30% of patients, with lactose intolerance and bacterial overgrowth reported. Vitamin deficiencies of B12, A, D, E and K are common, as well as malabsorption of iron and calcium⁷. However, with time, most patients adapt remarkably well to these changes and report satisfaction with the procedure.

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