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CASE REPORT | STOMACH

Management Considerations in a Patient With a Germline *CDH1* Pathogenic Variant and a History of Roux-en-Y Gastric Bypass Surgery

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ABSTRACT

Individuals with a germline pathogenic variant in the *CDH1* gene have a lifetime risk of advanced diffuse gastric cancer (DGC) of up to 10.3% and a 37%–52% risk of breast cancer, specifically the lobular subtype. Guidelines recommend prophylactic gastrectomy between ages 18-40 years for those with a family history of DGC. For patients declining surgery or lacking a family history of DGC, annual endoscopic surveillance according to recommended protocols is an alternative. This case reviews the management of a patient with a history of Roux-en-Y gastric bypass followed one year later by a diagnosis of lobular breast cancer due to a germline *CDH1* pathogenic variant.

KEYWORDS: Hereditary diffuse gastric cancer; *CDH1* pathogenic variant; Roux-en-Y gastric bypass; prophylactic gastrectomy; endoscopic surveillance

INTRODUCTION

Diffuse gastric cancer (DGC) constitutes 1%–3% of all gastric cancers. Germline pathogenic variants (PV) in the *CDH1* gene are the most prevalent hereditary causes of DGC.[1] *CDH1* gene encodes the glycoprotein E-cadherin, which is crucial for cell-to-cell adhesion.[1] E-cadherin functions as a tumor suppressor by maintaining intercellular adhesion and regulating cell proliferation. Consequently, individuals harboring a PV in the *CDH1* gene may exhibit a loss or dysfunction of E-cadherin, facilitating the formation of primary tumors, local tissue invasion, and eventual metastasis.[2,3]

The highest cancer risks in germline carriers of *CDH1* PV include signet ring cell DGC and lobular breast cancer.[4,5] In terms of DGC risk, guidelines recommend prophylactic gastrectomy for *CDH1* PV carriers with a family history of DGC.[1] Annual upper endoscopic surveillance to detect signet ring cell cancer (SRCC) according to recommended protocols is the alternative in patients refusing or delaying gastrectomy, or in those with no family history of DGC.[1]

Endoscopic surveillance for DGC of the stomach is a challenge in patients with altered gastrointestinal anatomy. We discuss our approach to manage a patient with a *CDH1* PV, who previously underwent Roux-en-Y gastric bypass (GIB) and interesting findings on resection of the excluded stomach.

CASE REPORT

A 60-year-old woman presented to our clinic with a history of obesity and laparoscopic Roux-en-Y GIB at the age of 52 years. One year later at the age of 53 years, she was diagnosed with a stage IA, grade 2, invasive right-sided lobular breast cancer, treated with

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partial mastectomy and radiation. The family cancer history included her mother diagnosed with intraductal breast cancer at the age of 58 years who died due to cholangiocarcinoma at the age of 82 years, her father with skin cancer who died from a hematologic malignancy at the age of 85 years, maternal grandfather who died of lung cancer at the age of 45 years, and paternal grandfather with a history of gastric surgery for unknown reasons who died at the age of 92 years. Germline genetic testing that included 55 high-risk genes identified a monoallelic *CDH1* PV (c.2165 – 1G>T). Her daughter was also found to carry a PV in *CDH1* (c.2165-1G>T), and SRCC was detected on baseline endoscopy, but a decision on gastrectomy vs ongoing endoscopic surveillance has not been determined.

A multidisciplinary team including surgeons and gastroenterologists discussed options with the patient including surgical resection of the excluded stomach and annual endoscopic surveillance of the gastric pouch, endoscopic surveillance using double-balloon enteroscopy, placement of a lumen-apposing metal stent, or a percutaneous endoscopic gastrostomy tube to access the remnant stomach. The patient opted for surgery.

Preoperative upper endoscopy revealed a 4 cm gastric pouch with a few 2–3 mm sessile polyps and a normal appearing gastrojejunal anastomosis, and pouch-to-jejunum limb. 26 random biopsies from the normal-appearing gastric pouch showed no evidence of SRCC, and the gastric polyps revealed foveolar hyperplasia, consistent with hyperplastic polyps. Immunohistochemical stains were negative for cytokeratin AE1/AE3 and *Helicobacter pylori*.

The patient underwent a laparoscopic gastrectomy preserving the previous Roux-en-Y reconstruction. On gross pathologic review of the resected remnant stomach, 4 sessile polyps (0.4 × 0.3 × 0.2 cm each) within a 2.2 × 1.8 cm area located 9 cm from the proximal margin, 9.2 cm from the distal margin, and 7 cm from the closest omental margin were observed. Postoperative histopathology revealed that the polyps were foveolar-type gastric adenomas (Figure 1). A single 0.5 mm focus of SRCC (pT1a, pN0) invading the lamina propria was found in the gastric body (Figure 2). There was no *H. pylori* or gastric intestinal metaplasia. Ten months postoperatively, surveillance upper endoscopy of the 4 cm gastric pouch revealed a healthy appearance of the gastric pouch, gastrojejunal anastomosis, jejunojejunal anastomosis, and jejunum. 25 random biopsies were taken from the gastric pouch. Pathology of the random biopsies identified a single focus of SRCC, measuring <0.1 cm, involving the epithelium (pTis), with no signs of dysplasia or *H. pylori*. The management plan includes repeat endoscopy every 6 months with consideration of completion gastrectomy with esophagojejunostomy.

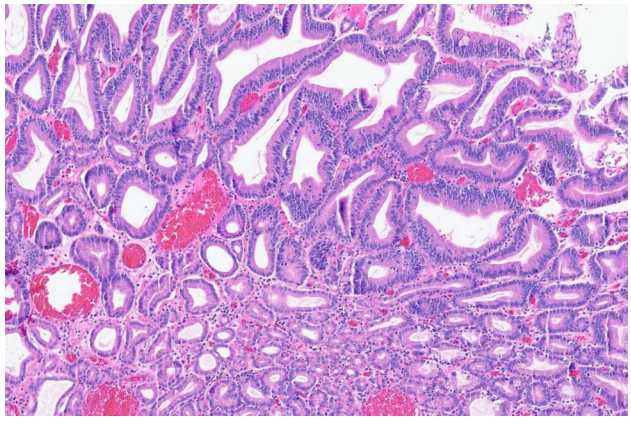

Figure 1. Gastrectomy specimen showing gastric adenoma (foveolar type) characterized by elongated, pseudostratified, hyperchromatic nuclei and low-grade dysplasia (hematoxylin and eosin, original magnification × 20).

DISCUSSION

This is the first known documented case of a patient with a germline *CDH1* PV and a prior Roux-en-Y GIB who had numerous gastric adenomas and SRCC in both the resected excluded stomach and in the gastric pouch on postoperative upper endoscopy. We review the cancer risks and recommended management of carriers of a *CDH1* PV, and our approach to overcoming challenges posed by standard endoscopic surveillance in the setting of a *CDH1* PV patient with modified anatomy secondary to Roux-en-Y GIB.

DGC has an estimated incidence of 5 to 10 cases per 100,000 births globally, with 40% of cases attributed to a germline mutation in the *CDH1* tumor suppressor gene.[1] The cumulative risk of breast cancer in female patients with *CDH1* PV carriers is 37%–52%.[6] Recent estimates suggest that *CDH1* PV carriers, regardless of family history, have a cumulative lifetime risk of developing any stage DGC ranging from 13.6%–42% and a 6.5%–10.3% risk of advanced DGC.[4–6] The risk of DGC increases with the number of affected first-degree relatives, reaching a lifetime risk of 38% when 3 first-degree relatives are affected. Among *CDH1* PV carriers with a family history of DGC, the cumulative lifetime risk of advanced DGC is reported to be 12.6%–19.1%.[6] Published recommendations for gastrectomy include individuals with a *CDH1* PV and a family history of DGC, or who have ≥ stage pT1b SRCC detected on

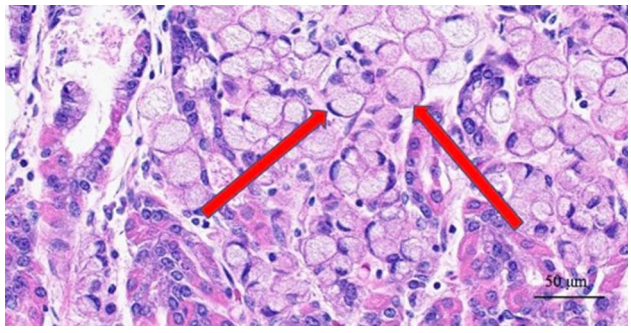

Figure 2. Gastrectomy specimen showing a single focus of signet ring adenocarcinoma invading lamina propria (red arrows, hematoxylin and eosin, original magnification × 40).

endoscopic biopsy.[1,7,8] Further details on the approach regarding endoscopic surveillance and gastrectomy are displayed in Figure 3.

Although gastrectomy prevents advanced DGC, it carries risks of long-term complications, such as micronutrient deficiencies, metabolic bone disorders, weight loss, and fatigue, and significantly affects quality of life.[9] The risk of perioperative mortality is <1%.[10,11] Individuals with *CDH1* PV who refuse or delay gastrectomy, or those with no family history of hereditary diffuse gastric cancer (Figure 3), may alternatively have annual upper endoscopic surveillance.[1]

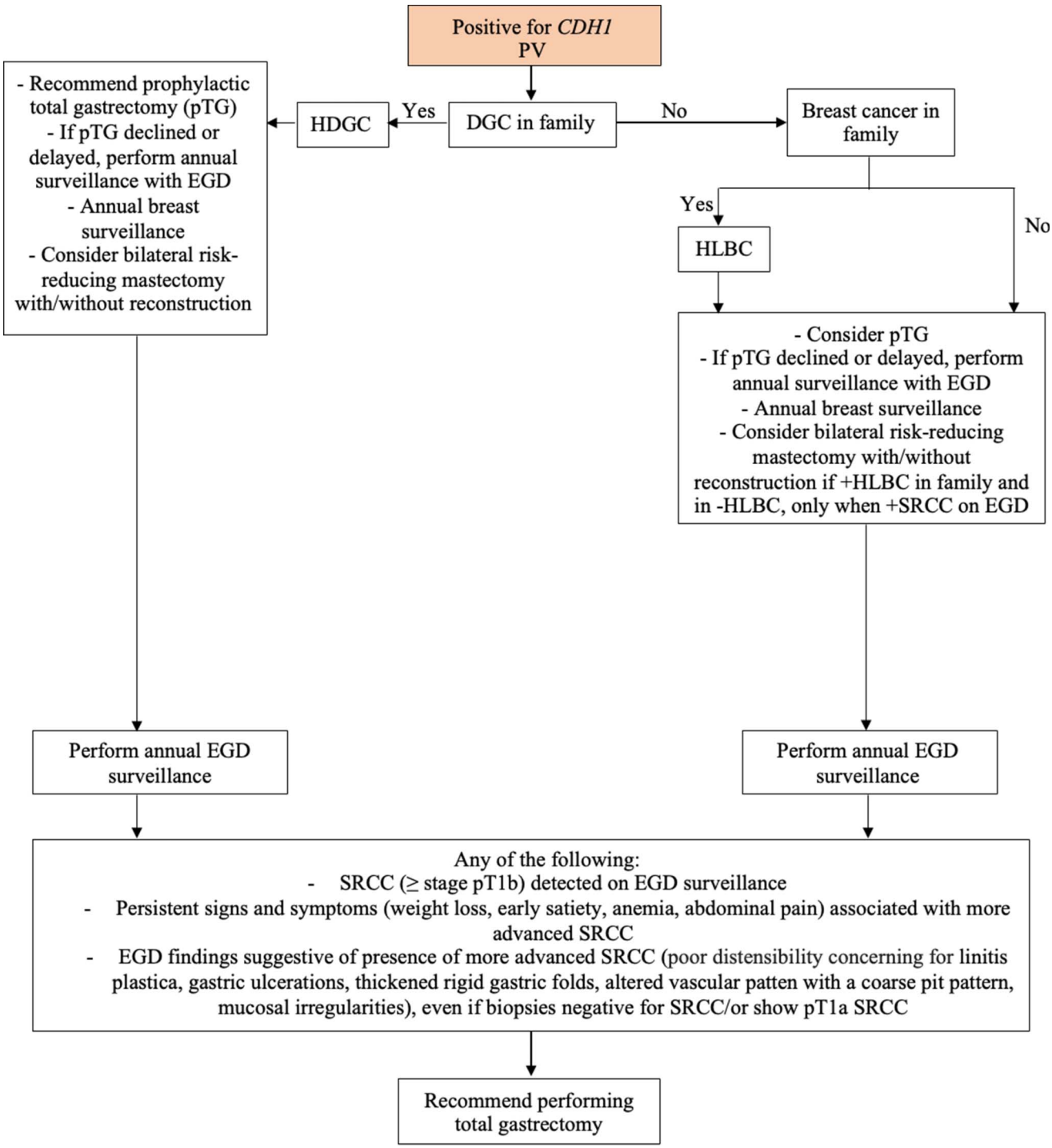

Figure 3. Flowchart for management of patients with *CDH1* pathogenic variant or who meet the revised hereditary diffuse gastric cancer genetic testing criteria. DGC, diffuse gastric cancer; EGD, endoscopy; HDGC, hereditary diffuse gastric cancer; HLBC, hereditary lobular breast cancer; pTG, prophylactic total gastrectomy; PV, pathogenic variant; SRCC, signet ring cell cancer. Figure 3 modified from Refs. 1 and 8.

Table 1. Endoscopic detection rates of signet ring cell cancer according to different endoscopic surveillance approaches

	International Gastric Linkage Consortium[1]	Bethesda[12]	Cleveland Clinic[13]
Endoscopy biopsy protocol	8–30 random biopsies from 5 areas of the stomach: 3-5 from cardia, 10 from body, 5 each from fundus, transition zone, and antrum	4 random biopsies from 22 separate anatomic sites of the stomach: antrum, lower body, incisura, middle upper body, cardia, and fundus	7 random, 4 quadrant biopsies from each of 11 areas of the stomach: cardia, prepylorus, distal and proximal antrum, transition zone, body (proximal, mid, distal), and fundus (proximal, mid, distal)
Targeted biopsies	Pale lesions, polyps, nodules, erosions, subtle changes in vascular pattern	Pale mucosal areas, nodularity, polyps, and ulceration	Pale patches, polyps, erosions, and ulceration
Preoperative detection rate of SRCC with targeted biopsies	26%[14]	NR	11%[13]
Preoperative detection rate of SRCC with random biopsies protocol	63%[19]	NR	81%[13]

NR, not reported; SRCC, signet ring cell cancer.

Endoscopic surveillance has been recommended according to specific protocols, whereby targeted biopsies of suspicious abnormal areas (pale mucosa, polyps, and ulcerations) along with random biopsies to detect SRCC are obtained.[1,12,13] A transition to targeting biopsies to endoscopic features, which may be associated with higher risk lesions rather than random biopsy, may be preferred as the sensitivity of endoscopic biopsy to detect SRCC varies from 12%–81% (Table 1), and up to 97% of asymptomatic patients with a *CDH1* PV have early-stage DGC (stage pT1a) on gastrectomy specimen, regardless of preoperative detection of SRCC.[13–17] The indolent nature of early-stage SRCC and time to progression to advanced DGC is not fully understood, but accumulating evidence suggests endoscopic surveillance is a reasonable alternative to prophylactic gastrectomy, and progression to advanced DGC is rare.[14,18]

Although the detection of SRCC foci in our patient's gastrectomy specimen was not surprising, the presence of multiple gastric adenomas was not anticipated. The reported prevalence of gastric adenomas among individuals undergoing diagnostic upper endoscopy for epigastric pain, gastroesophageal reflux, and anemia is 0.09%–0.69% in the United States.[20] Gastric adenomas are not reported to be associated with *CDH1* PV and confers a second pathway to gastric cancer in our patient.[7] The detection of SRCC on postoperative random biopsy of the gastric remnant was not anticipated.

Although endoscopic gastric surveillance in *CDH1* PV carriers is an alternative to gastrectomy, it becomes much more complex, higher risk and costly in patients with altered gastrointestinal anatomy, such as those with a Roux-en-Y GIB, and presents additional challenges.[1] Access with advanced endoscopic techniques such as endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiopancreatography, single/double-balloon enteroscopy, percutaneous endoscopic gastrostomy tube, and enteroscopy would need to be used and their success not necessarily guaranteed.

DISCLOSURES

Author contributions: Manuscript writing: Z. Naseem. Critical review of the manuscript and editing: LK Mejia-Perez, L. LaGuardia, RM Walsh, CA Burke. Studied and provided the pathology slides with description of the specimens: K. Friedman, LK Mejia-Perez, L. LaGuardia, RM Walsh, CA Burke. Financial support and conflict of interest: None. CA Burke is the article guarantor.

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