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CASE REPORT | STOMACH

Prophylactic Total Gastrectomy for Hereditary Diffuse Gastric Cancer

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ABSTRACT

Germline mutations in the *CDH1* gene that produces E-cadherin have been implicated in the development of early-onset diffuse gastric cancer, termed hereditary diffuse gastric cancer. The mean age of gastric cancer diagnosis in affected individuals is 37 years. By age 80, *CDH1* mutation carriers who fulfill the clinical criteria for hereditary diffuse gastric cancer have an estimated lifetime risk of gastric cancer development of 67% for men and 83% for women. Data suggest that endoscopic surveillance for mutation carriers is largely ineffective. Prophylactic total gastrectomy between the ages of 18 and 40 years is recommended in carriers of germline-truncating E-cadherin mutations.

INTRODUCTION

Gastric cancer is the fifth most common type of cancer diagnosed worldwide and represents the third most common cause of cancer death.[1] The vast majority of gastric cancers are considered to be sporadic and are associated with various environmental factors, but 1–3% are associated with genetically inherited syndromes.[2,3] Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant syndrome characterized by the development of diffuse type gastric cancer. It is defined clinically by 2 or more familial cases of diffuse gastric cancer, with at least one diagnosed at <50 years; 3 or more cases of documented diffuse gastric cancer in first- or second-degree relatives independent of age of onset; diffuse gastric cancer diagnosed at <40 years; and a personal or family history of diffuse gastric cancer and lobular breast cancer with one diagnosed at <50 years.[4] Germline mutations in the *CDH1* gene that produces E-cadherin gene account for 25–50% of cases of HDGC.[3,5,6] While endoscopic surveillance is proven beneficial in many types of cancer, upper endoscopy with mucosal biopsies in *CDH1* mutation carriers frequently renders false negative results.[7-9] This is largely due to the highly focal nature of HDGC and may lead to a false sense of security in affected patients. Due to the difficulty of diagnosing early disease and the lack of sensitive surveillance methods, prophylactic total gastrectomy is advised before age 40 in *CDH1*-positive patients fulfilling criteria for HDGC.[10,11] Published data from >100 prophylactic gastrectomies reveal that nearly all pathologic specimens exhibit tiny foci of signet ring cell carcinoma or in situ signet ring cells, starkly contrasting the usually normal appearance of the gross specimens.[2]

CASE REPORT

A 37-year-old female presented for a third opinion regarding a recently diagnosed *CDH1* germline mutation. She was previously seen by two local gastroenterologists near her hometown, one of whom recommended upper endoscopy with biopsies every 3 months while the other recommended undergoing a total gastrectomy. The patient reported a significant family history of both gastric and breast cancer, which prompted genetic testing and led to subsequent diagnosis of a positive *CDH1* germline mutation. Two first cousins were diagnosed with gastric cancer,

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the earliest of which was identified at 22 years of age. Upper endoscopy was performed 2 months prior to presentation at our facility, revealing normal-appearing gastric mucosa with no evidence of malignancy on multiple biopsy specimens. Additionally, the patient complained of a 4-month history of epigastric abdominal pain, 5-kg weight loss, and anorexia. After the patient was seen for genetic counseling, repeat upper endoscopy and upper endoscopic ultrasound were performed to screen and evaluate for pathologic lymphadenopathy or gastric wall thickening, respectively.

The gastric mucosa appeared grossly normal on upper endoscopy, and biopsies showed normal gastric mucosa, without evidence of malignancy. Upper endoscopic ultrasound demonstrated a normal appearance to the gastric wall, with no pathologic thickening or identifiable lymphadenopathy. The patient's case was presented before a multidisciplinary panel, and the recommendation for a total prophylactic gastrectomy was made. Open total gastrectomy was performed, with proximal and distal margins verified by pathology. Grossly, the specimen was unremarkable, with no nodules or focal lesions identified. The gastric mucosa was blocked and mapped, and representative sections were submitted for microscopic evaluation. A single focus of intraepithelial signet ring change was found in the deep gastric pits, demonstrating pagetoid migration along the basement membrane beneath benign overlying glandular epithelium, representing in situ carcinoma (Figure 1). This focus of in situ carcinoma measured 0.3 mm in its greatest dimension by slide measurement. No lamina propria invasion was identified in this focus, and no in situ or invasive carcinoma was otherwise identified in the entirety of sections examined. Six lymph nodes were submitted in the surgical specimen, all of which were negative for carcinoma. The patient tolerated the operation well, but did complain of intermittent nausea at 60-day follow-up.

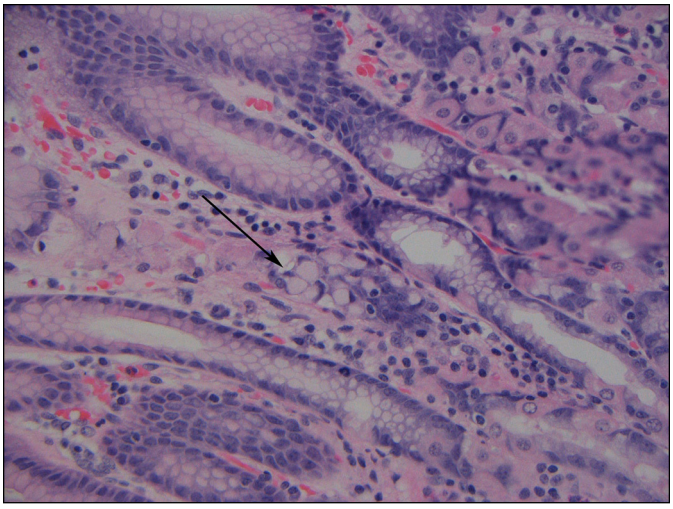

Figure 1. Carcinoma in situ involving the epithelial lining of the gastric mucosa. Arrow designates a cluster of signet ring malignant cells confined to the crypt epithelium.

DISCUSSION

E-cadherin is a transmembrane glycoprotein encoded by the *CDH1* gene that functions as a tumor suppressor, and is intricately involved in modulation of cellular proliferation, survival, invasion, and migration. Downregulation leads to aberrant function of gastric epithelial cells, contributing to gastric cancer development.[12] In addition to gastric cancer, *CHD1* mutation positivity confers an increased risk of breast and colon cancer development. An estimated 60% of *CDH1* mutation-positive women will develop lobular breast cancer.[3] Annual mammography, breast magnetic resonance imaging, and clinical breast examination should be conducted beginning at age 35.[13] Evidence of increased risk of signet ring cell colon cancer exists, but exact risk estimates are not well defined.[14] Colon cancer screening beginning at age 40 should be considered in families with individuals affected by colon cancer.[13]

Early HDGC detection in *CDH1* mutation carriers is severely limited, given its lack of symptomatology, microscopic foci of signet ring cells, and endoscopically undetectable disease.[3] While our patient presented with symptoms that can be seen in diffuse gastric cancer, in situ carcinoma is unlikely to produce symptomatic disease. Her gastrointestinal symptoms are more plausibly attributed to the psychological burden of her mutation status, in concert with a significant family history of early disease onset. Those who develop symptomatic invasive diffuse carcinoma have an exceedingly poor prognosis, with only 10% expected to have curable disease.[15] A comprehensive endoscopic surveillance protocol for individuals with HDGC was devised by a multidisciplinary, multinational workshop in 2010, but this is recommended only for those refusing gastrectomy or with a prohibitive physical or psychological comorbidity.[2] As in the case presented here, microscopic analysis of gastrectomy specimens indicates that tiny foci of signet ring cells are nearly always present in *CDH1* mutation carriers. Therefore, total prophylactic gastrectomy, performed between the ages of 18 and 40 at a high-volume cancer center with low perioperative mortality rates, is advised in *CDH1* mutation carriers fulfilling the clinical criteria for HDGC.[2,11,16]

DISCLOSURES

Author contributions: All authors contributed equally to manuscript creation. B. Shepard is the article guarantor.

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Informed consent was obtained for this case report.

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REFERENCES

1. Pharoah PD, Guilford P, Caldas C. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. *Gastroenterology*. 2001;121:1348–53.
2. Van der Post RS, Vogelaar IP, Carneiro F, et al. Hereditary diffuse gastric cancer: Updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. *J Med Genet*. 2015;52:361–74.
3. Fitzgerald RC, Hardwick R, Huntsman D, et al. Hereditary diffuse gastric cancer: Updated consensus guidelines for clinical management and directions for future research. *J Med Genet*. 2010;47:436–44.
4. Seevaratnam R, Coburn N, Cardoso R, et al. A systematic review of the indications for genetic testing and prophylactic gastrectomy among patients with hereditary diffuse gastric cancer. *Gastric Cancer*. 2012;15:10.
5. Gayther SA, Gorringe KL, Ramus SJ, et al. Identification of germ-line E-cadherin mutations in gastric cancer families of European origin. *Cancer Res*. 1998;58:4086–9.
6. Fitzgerald RC, Caldas C. Clinical implications of E-cadherin associated hereditary diffuse gastric cancer. *Gut*. 2004;53:775–8.
7. Chen Y, Kingham K, Ford JM, et al. A prospective study of total gastrectomy for CDH1-positive hereditary diffuse gastric cancer. *Ann Surg Oncol*. 2011;18:2594–8.
8. Pandalai PK, Lauwers GY, Chung DC, et al. Prophylactic total gastrectomy for individuals with germline CDH1 mutation. *Surgery*. 2011;149:347–55.
9. Lim YC, di Pietro M, O'Donovan M, et al. Prospective cohort study assessing outcomes of patients from families fulfilling criteria for hereditary diffuse gastric cancer undergoing endoscopic surveillance. *Gastrointest Endosc*. 2014;80:78–87.
10. Tan RYC, Ngeow J. Hereditary diffuse gastric cancer: What the clinician should know. *World J Gastrointest Oncol*. 2015;7(9):153–60.
11. Hebbard PC, Macmillan A, Huntsman D, et al. Prophylactic total gastrectomy (PTG) for hereditary diffuse gastric cancer (HDGC): The Newfoundland experience with 23 patients. *Ann Surg Oncol*. 2009;16:1890–5.
12. Liu X, Chu KM. E-Cadherin and gastric cancer: Cause, consequence, and applications. *Biomed Res Int*. 2014;2014:637308.
13. Syngal S, Brand R, Church J, Giardiello F, Hampel H, Burt R. ACG Clinical Guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol*. 2015;110:223–62.
14. Brooks-Wilson AR, Kaurah P, Suriano G, et al. Germline E-cadherin mutations in hereditary diffuse gastric cancer: Assessment of 42 new families and review of genetic screening criteria. *J Med Genet*. 2004;41:508–17.
15. Koea JB, Karpeh MS, Brennan MF. Gastric cancer in young patients: Demographic, clinicopathological, and prognostic factors in 92 patients. *Ann Surg Oncol*. 2000;7:346–51.
16. Yamada H, Shinmura K, Ito H, et al. Germline alterations in the CDH1 gene in familial gastric cancer in the Japanese population. *Cancer Sci*. 2011;102:1782–8.