ACG CASE REPORTS JOURNAL

CASE REPORT | STOMACH

Two Pediatric Cases Within a Familial Cluster and Hereditary Diffuse Gastric Carcinoma: A Tale of 2 Sisters

Lacey Falgout, MD[1], and Lawrence L. Gensler, MD[2]

[1]*Department of Medicine, Louisiana State University Health Sciences Center, New Orleans, LA*
[2]*Northlake Gastroenterology Associates, Covington, LA*

ABSTRACT

Hereditary diffuse gastric cancer is a familial form of poorly differentiated signet ring cell carcinoma (SRCC) caused by a mutation in the CDH1/E-cadherin gene-mediating cell adhesion. CDH1 mutations are inherited in an autosomal dominant fashion and exhibit a high level of penetrance. SRCC diagnosis is exceedingly rare in the pediatric population. We report a case of SRCC in 2 sisters (10 and 15 years) and their father (41 years).

KEYWORDS: stomach; gastric cancer; signet cell; pediatric; familial; genetic; gastrectomy

BACKGROUND

Hereditary diffuse gastric cancer (HDGC) is a familial form of poorly differentiated signet ring cell carcinoma (SRCC) caused by a mutation in the CDH1/E-cadherin gene-mediating cell adhesion.[1] Pathologic specimens exhibit cytoplasmic mucin with a crescent-shaped nucleus displaced to the periphery and poor cohesive properties with no gland formation. Early stages of HDGC can be exceptionally difficult to diagnose because there are characteristically widespread submucosal foci with no visible gross mucosal abnormalities or masses. This poses great difficulty in screening carriers of CDH1 mutations for HDGC. CDH1 mutations are inherited in an autosomal dominant fashion and exhibit a high level of penetrance.[2] Carriers are advised to undergo prophylactic total gastrectomy because of the high mortality associated with invasive HDGC.[3] Carriers also have an increased risk of lobular breast carcinoma and possibly colorectal adenocarcinoma.[4] Familial occurrence of HDGC is well-documented, but pediatric cases are rare. This report describes a familial cluster of the CDH1 mutation associated with gastric signet ring cell carcinoma. To our knowledge, this is the first reported case of SRCC in 2 pediatric siblings. This is also the first reported incidence of 3 first-degree family members being diagnosed with SRCC at the same time.

CASE REPORT

Our patient is a 15-year-old White adolescent girl who initially presented to our gastroenterology clinic with a 4-month history of right lower quadrant tenderness and generalized abdominal pain, which she characterized as "stabbing pain." She reported onset of menses as an aggravating factor and noted that nothing was effective in relieving the pain. Review of systems was significant for intermittent alteration in bowel habits, nausea, vomiting, and abdominal pain. She denied gastroesophageal reflux disease and irregular menstrual bleeding. Family history was significant for a paternal great-aunt who reportedly died of gastric cancer at 28 years. Physical examination revealed a pleasant, well-appearing girl who was not in acute distress. Abdominal examination revealed a soft, nondistended abdomen with tenderness in the right lower quadrant and periumbilical areas. Laboratory investigations showed C-reactive protein, erythrocyte sedimentation rate, and fecal calprotectin within normal limits. Outpatient abdominal ultrasound was ordered at this time, but the patient did not return to clinic immediately because of improvement in symptoms.

The patient presented to clinic to follow up abdominal ultrasound results, which showed no significant abdominal pathology and no appreciable stomach wall thickening. Esophagogastroduodenoscopy (EGD) revealed diffuse mild inflammation of the stomach with normal-appearing rugae without ulceration or masses and normal proximal duodenum (Figure 1). Biopsy

ACG Case Rep J 2023;10:e01100. doi:10.14309/crj.0000000000001100. Published online: July 19, 2023

Correspondence: Lawrence L. Gensler, MD (llgensler@gmail.com).

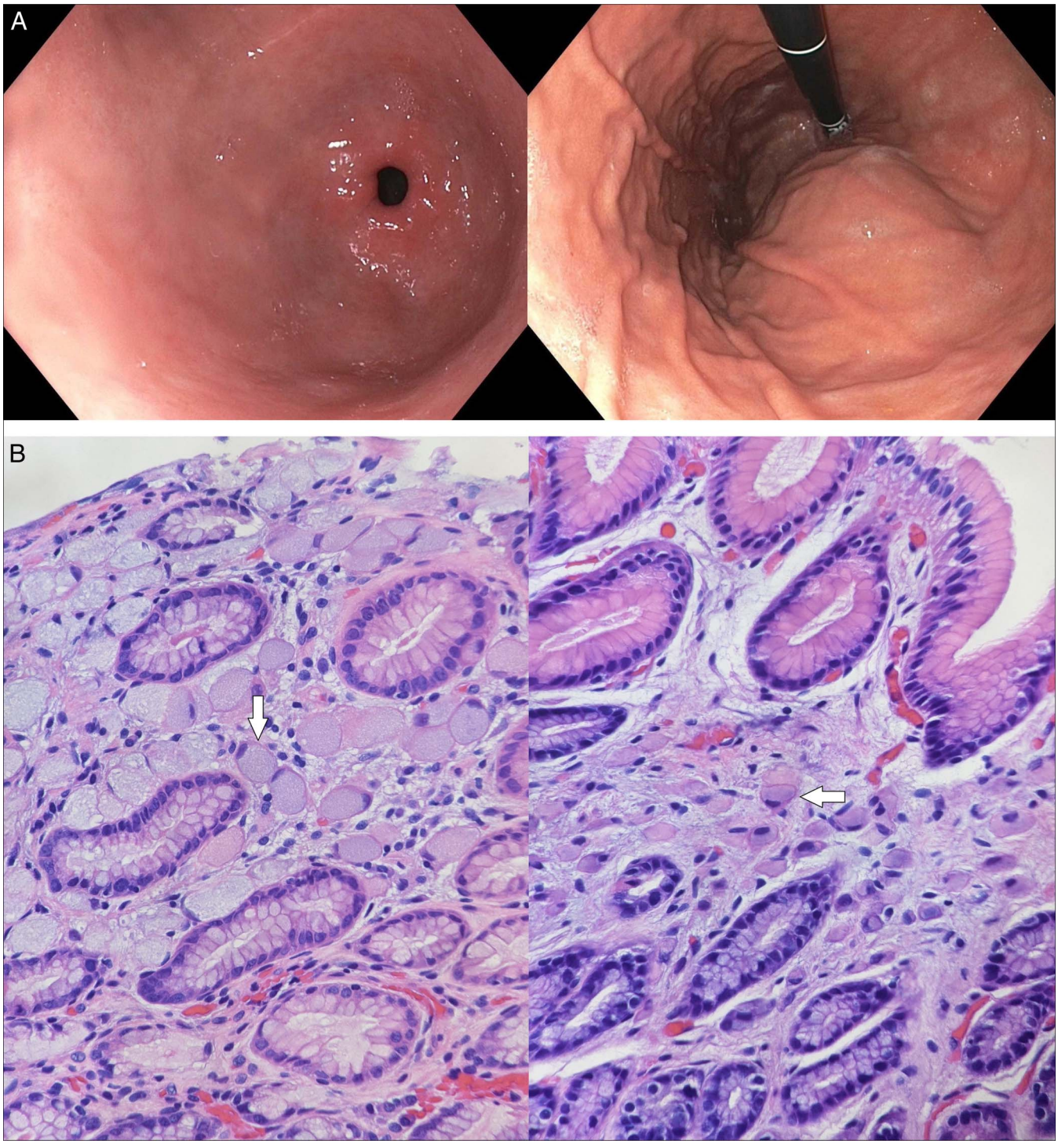

Figure 1. (A) Endoscopic view of the stomach revealing diffuse mild inflammation with normal-appearing rugae without ulceration or masses. (B) Biopsy from the gastric antrum demonstrating poorly differentiated signet ring cell carcinoma. The arrows indicate some of the signet cells for reference in the histopathologic specimen.

specimens were obtained from the gastroesophageal junction, antrum, stomach body, and duodenum. The antrum biopsy revealed poorly differentiated signet ring cell carcinoma (Figure 1). The cells of interest were negative for HER2 overexpression. All specimens were negative for Helicobacter pylori colonization.

A repeat EGD performed at an outside hospital confirmed the presence of SRCC. Abdominal computed tomography revealed normal appearance of the abdomen and pelvis with no evidence of mediastinal or hilar adenopathy. A positron emission tomography scan revealed increased uptake in the gastric antrum with no evidence of metabolically active distant disease. The

patient subsequently underwent a laparoscopic gastrectomy with Roux-en-Y esophagojejunostomy and jejunojejunostomy with exploratory laparoscopy. There was no evidence of carcinomatosis at surgery. Analysis of the stomach revealed 156 foci of SRCC confined to the lamina propria with the final proximal and distal surgical margins negative for the tumor by microscopy. Lymph nodes were negative.

Based on the unusual occurrence of SRCC in an adolescent girl, the patient and her family underwent genetic testing. Family screening was performed because the patient was found to be positive for a CDH1/E-cadherin mutation. It was found that the patient's father and her 10-year-old sister also carry this mutation. The mother tested negative for the mutation. The 10-year-old sister and the father underwent screening EGD with more than 40 biopsies obtained throughout the stomach, esophagus, and duodenum in representative areas. Surprisingly, both patients were also found to have gastric SRCC. The father subsequently underwent a laparoscopic gastrectomy with Roux-en-Y esophagojejunostomy with no recurrence at 1 year. The 10-year-old sister is being managed conservatively with yearly endoscopies and plans to undergo a laparoscopic Roux-en-Y esophagojejunostomy in a few years.

DISCUSSION

Worldwide, approximately 990,000 people are diagnosed with gastric cancer, of which approximately 738,000 die of this condition yearly.[5] Gastric carcinoma primarily affects patients between 50 and 70 years and is uncommon before the fifth decade of life.[6] Early-onset gastric cancer is defined as gastric cancer occurring at 45 years or younger. Among those with early-onset gastric cancer, the most common lesion is the diffuse-type SRCC.[7] Gastric carcinoma is exceedingly rare in the pediatric population and is associated with a worse prognosis than adults.

HDGC should be considered when a patient presents with gastrointestinal symptoms and has a positive family history of gastric cancer among first and second-degree relatives, particularly if a relative was diagnosed before 50 years. HDGC may exhibit indolence for decades within the lamina propria. The molecular mechanisms that initiate the transition from indolent to invasive behavior are unknown and require more research.

For carriers of the CDH1 mutation, prophylactic total gastrectomy is recommended with intraoperative confirmation of squamous epithelium in the esophagus at the proximal margin and duodenal mucosa at the distal margin. Total gastrectomy has significant morbidity because of weight loss, dumping syndrome, and change of eating habits. Gastrectomy should be considered at an age younger than that of the youngest affected family member of CDH1 carriers. If gastrectomy is contraindicated, yearly endoscopic surveillance with random biopsies is recommended.[3]

Gastric carcinoma in the pediatric population is exceedingly rare. This case report highlights the importance of considering gastric carcinoma in children presenting with nonspecific gastrointestinal symptoms with a positive family history of gastric cancer. Early identification and treatment of gastric signet ring cell carcinoma is imperative for a more favorable prognosis. In this case, the family history of stomach cancer was found out retrospectively, and this highlights the importance of a well-taken history. Finally, we also highlight the importance of performing biopsies during endoscopy even with normal or minor findings.

DISCLOSURES

Author contributions: Both authors listed contributed to the design, drafting, and final approval of the manuscript. LL Gensler is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Previous Presentation: Presented as a poster at ACG National Conference 2022 in Charlotte, North Carolina, and at the ACG Regional Conference in 2022 in New Orleans, Louisiana.

Received March 14, 2023; Accepted June 12, 2023

REFERENCES

1. Waldum HL, Fossmark R. Types of gastric carcinomas. *Int J Mol Sci*. 2018;19(12):4109.
2. Huntsman DG, Carneiro F, Lewis FR, et al. Early gastric cancer in young, asymptomatic carriers of germ-line E-cadherin mutations. *N Engl J Med*. 2001;344(25):1904–9.
3. Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer: Updated clinical practice guidelines. *Lancet Oncol*. 2020;21(8):e386–97.
4. Luo W, Fedda F, Lynch P, Tan D. CDH1 gene and hereditary diffuse gastric cancer syndrome: Molecular and histological alterations and implications for diagnosis and treatment. *Front Pharmacol*. 2018;9:1421.
5. 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(6):361–74.
6. Hallinan JT, Venkatesh SK. Gastric carcinoma: Imaging diagnosis, staging and assessment of treatment response. *Cancer Imaging*. 2013;13(2):212–27.
7. Milne AN, Sitarz R, Carvalho R, Carneiro F, Offerhaus GJ. Early onset gastric cancer: On the road to unraveling gastric carcinogenesis. *Curr Mol Med*. 2007;7(1):15–28.