

Hereditary Diffuse Gastric Cancer Associated with E-cadherin Germline Mutation: A Case Report

Michael D. Black MD; Raynette Kaneshiro PA; Jennifer I. Lai; and David M. Shimizu MD

Abstract

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant cancer syndrome that leads to an increased risk of developing invasive diffuse type (signet ring cell) gastric carcinoma. Approximately 30% of HDGC cases are caused by a germline mutation involving the E-cadherin (CDH1) gene. Those with the CDH1 mutation have an 80% and 60% cumulative lifetime risk of developing diffuse type gastric carcinoma and lobular breast carcinoma respectively. Due to the focal nature of early diffuse type gastric carcinoma, identifying early lesions with surveillance endoscopy is limited. As a result, elective risk-reducing total gastrectomy is currently recommended. In this report, the clinical, intraoperative, and pathologic work-up is reviewed regarding a patient with known CDH1 germline mutation.

Introduction

Gastric cancer is the second leading cause of cancer death world-wide with nearly one million new diagnoses per year. More than three-fourths of those individuals die from their disease.¹ In Hawai'i, gastric cancer is the fifth leading cause of cancer-related death as reported by the Hawai'i Tumor Registry. The majority of gastric cancers are intestinal type adenocarcinomas that have been linked to *Helicobacter pylori* colonization and diet.² However, 1%-3% of all gastric cancers are attributed to hereditary diffuse gastric cancer (HDGC).³ HDGC is an uncommon autosomal dominant form of diffuse type gastric carcinoma that generally presents at an early age with advanced stage and poor prognosis.⁴

The first indication of a genetic link to certain diffuse-type gastric cancers was reported in 1998 when Guilford and colleagues discovered 3 germline truncating mutations in the E-cadherin (CDH-1) gene within a large New Zealand family of Maori ethnicity.⁴ Following this discovery, other germline CDH1 mutations have been identified in patients with HDGC from a wide range of ethnic backgrounds, including but not

limited to Filipino, African American, Korean, Japanese, and European.⁵⁻⁸ Mutations in the CDH1 gene result in its loss of expression that leads to defective intercellular adhesion (Figure 1). The Gastric Cancer Linkage Consortium currently specifies two criteria for the diagnosis of HDGC (Table 1).^{9,10,16} Of those individuals meeting either of these two criteria, approximately 25%-30% will demonstrate the CDH1 germline mutation.¹¹ The mechanism of disease in the remaining HDGC cases is largely unknown.

Once an individual meets the criteria for HDGC, it is recommended that the patient and at-risk family members be tested for the CDH1 germline mutation. Those with the mutation will carry an 80% risk of developing diffuse type gastric carcinoma by 80 years of age.¹¹ In addition, female patients carry an additional 60% lifetime risk of developing lobular breast carcinoma by 80 years of age.¹² Many of these individuals undergo annual endoscopic evaluation. However, the sensitivity of endoscopic biopsies has been called into question owing to the focal nature of early invasive/in-situ gastric carcinoma.³ In addition, there is conflicting data as to the predominant site of involvement, proximal versus distal, which may further limit the sensitivity of screening endoscopic biopsies.¹³

Pathologic handling of the total gastrectomy specimen consists of submitting the entire specimen for routine histologic examination. Traditionally only hematoxylin and eosin staining has been used. However, periodic acid-schiff (PAS) staining has demonstrated improved detection of invasive and in situ gastric carcinoma.^{11,12} Few studies have demonstrated the complete mapping of the total gastrectomy specimen using PAS staining. Therefore, this institution's experience using this technique is described.

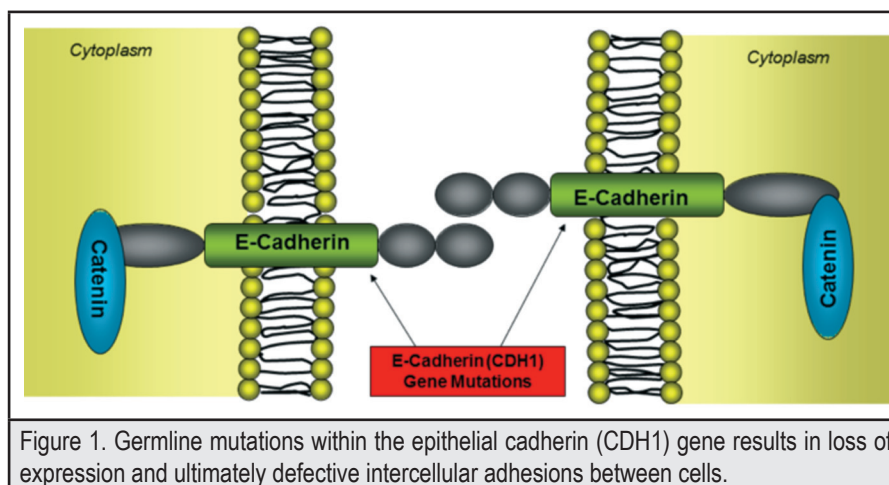


Table 1. The Gastric Linkage Consortium Criteria for Hereditary Diffuse Gastric Cancer requires Criteria 1 or Criteria 2 to be met before the diagnosis of HDGC.	
Gastric Cancer Linkage Consortium Criteria for Hereditary Diffuse Gastric Cancer ^{9,10,16}	
Criteria 1	Two or more documented cases of diffuse gastric cancer in first or second degree relatives, with at least one diagnosed before the age of 50
Criteria 2	Three or more cases of documented diffuse gastric cancer in first/second degree relatives, independent of age of onset

Case Report

A 22-year-old woman presented for genetic work-up due to strong family history of early onset diffuse gastric carcinoma. The patient's mother was diagnosed with stage IV diffuse type gastric cancer at the age of 41 despite having negative endoscopic gastric biopsies the year prior (Figure 2). In addition, the patient's aunt died of gastric cancer in her early 40's and maternal grandfather died of gastric cancer in his 50's (Figure 2). As a result of her strong family history, the patient underwent CDH1 germline testing that demonstrated a deleterious trp20stop CDH1 germline mutation. She subsequently underwent three screening endoscopic gastric biopsy evaluations that were negative for malignancy or dysplasia. It was the patient's decision then to undergo a prophylactic total gastrectomy.

Pathology

Intraoperative consult was obtained to ensure that margins were free of gastric mucosa. This was done by taking sections of the entire proximal and distal margins and embedding en face. Once negative margins for gastric mucosa were obtained, the

specimen was opened along the greater curvature, pinned to a cork board, and allowed to fix in formalin overnight. No lesions were identified grossly (Figure 3). The entire specimen was mapped using a photograph with superimposed graph (Figure 4) and submitted for histologic examination in 225 cassettes. Each section was stained with PAS as recommended by current guidelines.^{11,12}

Histologic examination revealed 109 foci of invasive diffuse type (signet ring cell) gastric carcinoma and 6 foci of in situ (including pagetoid spread) diffuse type gastric carcinoma. The size of invasive foci ranged from single cells to 1.5 mm in greatest dimension (Figure 5). They were predominantly seen within the proximal two-thirds of the stomach with a single focus in the distal one-third (Figure 4). The invasive component was limited to the superficial lamina propria and no perineural or lymph-vascular invasion was identified. Fifteen regional lymph nodes were also examined that were negative for metastasis.

Discussion

The world-wide incidence of sporadic gastric cancers has been decreasing over recent years.¹ One hypothesis for the decrease in sporadic carcinoma is increased recognition and treatment of *Helicobacter pylori* infection. While the incidence of sporadic gastric carcinoma appears to be decreasing there has been increased awareness of non-sporadic gastric carcinomas such as hereditary diffuse gastric carcinoma.

This institution received the risk-reducing total gastrectomy specimen from a patient known to harbor the CDH1 germline mutation. As has been reported by Rogers and colleagues, when dealing with prophylactic total gastrectomy specimens there is

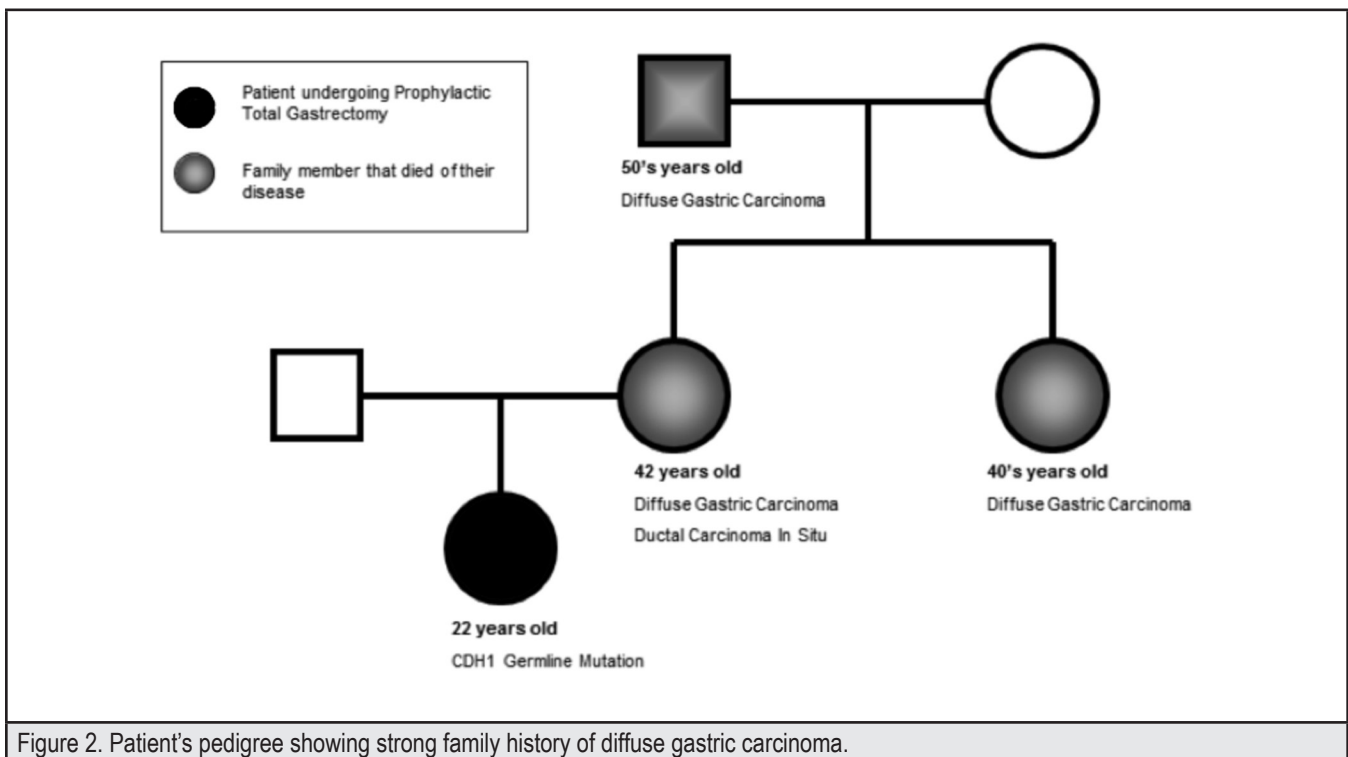


Figure 2. Patient's pedigree showing strong family history of diffuse gastric carcinoma.

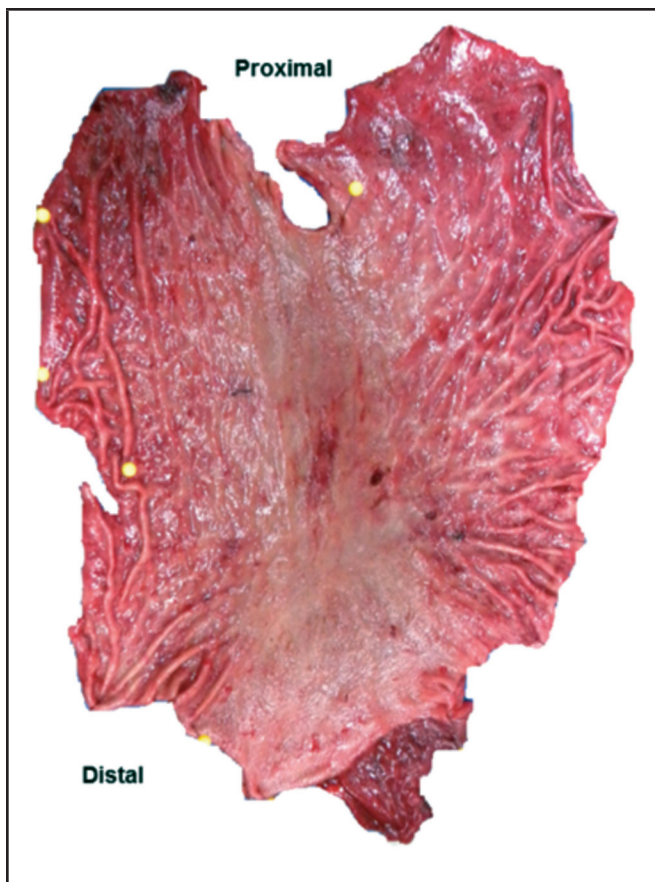


Figure 3. Gross total gastrectomy specimen opened along the greater curvature with no identifiable lesions.

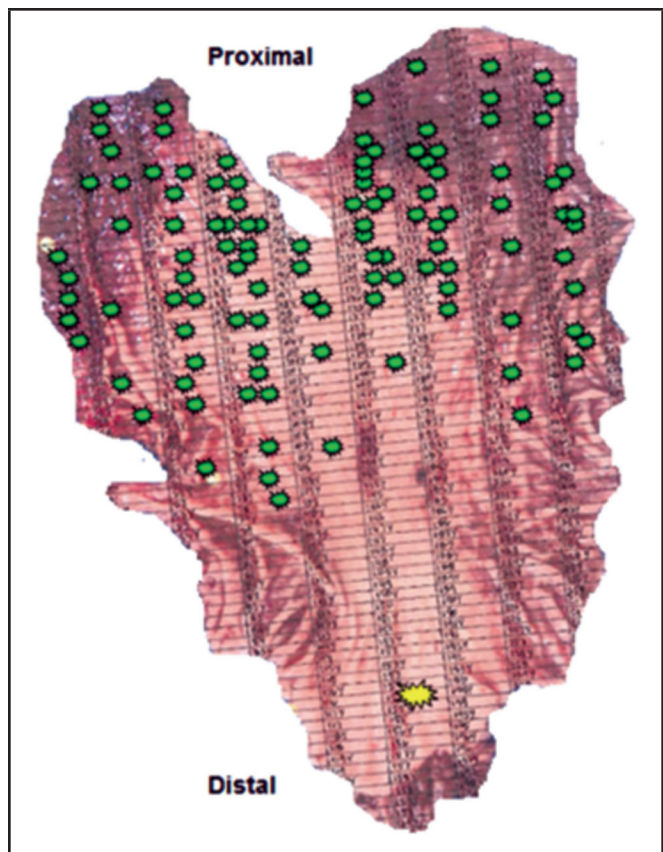


Figure 4. Total gastrectomy specimen with grid used for mapping. Green indicates foci of invasive or in-situ diffuse-type gastric carcinoma. Yellow indicates a single focus of invasive diffuse-type gastric carcinoma in the distal half of the stomach.

commonly no gross evidence of disease.¹³ It is therefore necessary to sample the entire specimen in order to detect microscopic foci of invasive and/or *in situ* tumor.

It was found that carefully graphing a photograph of the pinned out gastrectomy was the most efficient means of correlating the gross with microscopic findings. Two hundred and twenty-five slides were examined that revealed 109 and 6 foci of invasive and in situ diffuse-type gastric (signet ring cell) carcinoma, respectively. The 6 small foci of in-situ diffuse-type carcinoma (Figure 5) are characteristic of HDGC as described by Oliveira and colleagues.¹⁴ Moreover, it is this institution's experience that the use of PAS staining was helpful in identifying these small tumor foci. This technique as outlined by Lee and colleagues allows for the detection of invasive and in situ components with increased sensitivity as compared to routine hematoxylin and eosin sections.¹² The average number of foci identified in gastrectomy specimens as seen in prior reports was 10.9 using H&E alone, compared to the 115 foci found in this case using PAS.¹³

In addition, this case showed tumor burden was concentrated within the proximal stomach. A review of the literature shows

this is in concordance with Rogers and colleagues.¹³ However, Charlton and colleagues reported two out of six cases with a distal stomach predominance.¹⁵ This suggests variability may exist in regards to the predominant location of early CDH1 diffuse gastric carcinoma. In addition to this variability, multiple foci of tumor may be identified throughout the entire specimen as highlighted in this case by a single focus of invasive diffuse gastric carcinoma within the distal stomach (Figure 4). Such variability reiterates the importance of submitting the entire gastrectomy specimen for histologic examination.

Conclusion

Recognition of a strong family history of diffuse type gastric carcinoma and/or lobular breast carcinoma is critical for identifying those patients at risk for HDGC. Individuals at risk can be tested for the germline mutation of the epithelial cadherin (CDH1) gene and those with a positive test should be offered prophylactic/risk-reducing total gastrectomy.¹¹ Lastly, it is this institution's experience that surveillance endoscopy has limited sensitivity in identifying occult diffuse gastric carcinoma in patients with CDH1 germline mutations.

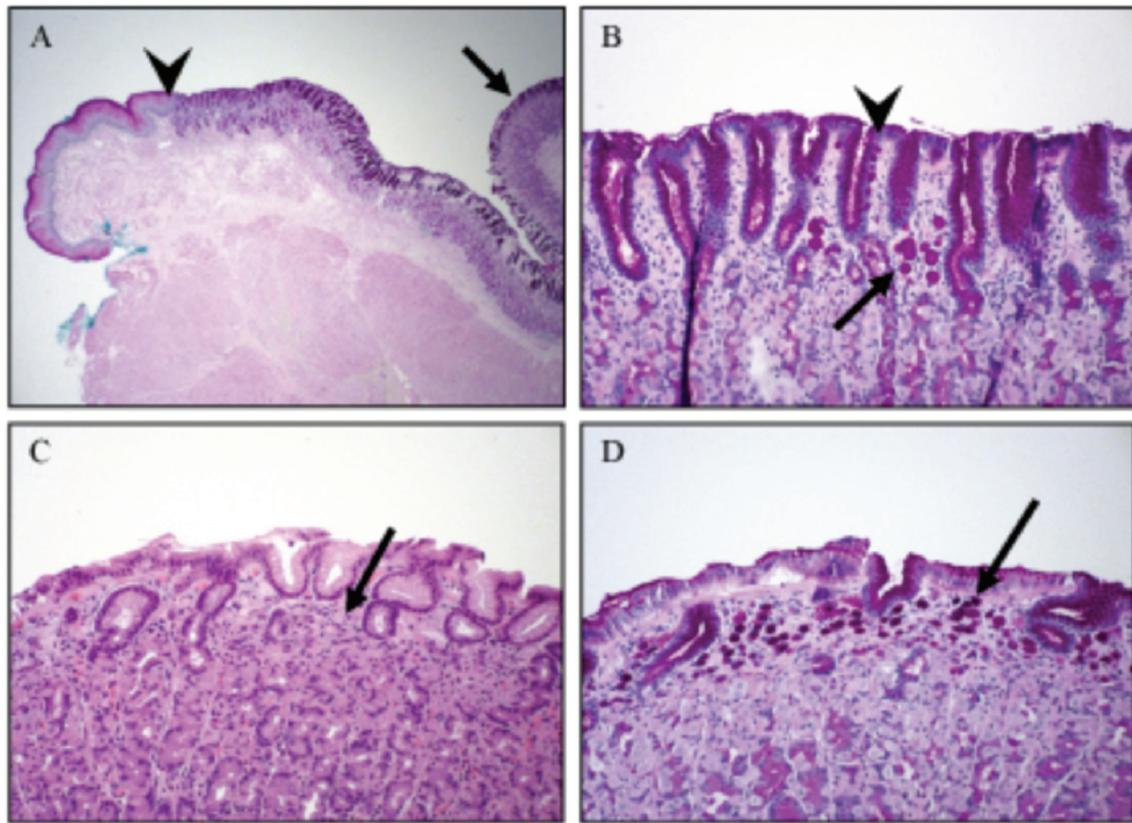


Figure 5.

Disclaimer

The findings and conclusions of this study do not necessarily represent the views of the Queen's Medical Center.

Conflict of Interest

None of the authors identify a conflict of interest.

Authors' Affiliations:

- University of Hawai'i, John A. Burns School of Medicine, Honolulu, HI (MDB, DMS)
- The Queen's Medical Center, Honolulu, HI (RK, DMS)
- Massachusetts Institute of Technology, Cambridge, MA (JIL)

Correspondence to:

Michael D. Black MD; Ph: (727) 415-0720; E-mail: blackm@hawaii.edu

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