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CASE REPORT

Managing *CDH1* Cancer Risks in a Child: Complex Decision Making in a Family With Hereditary Diffuse Gastric Cancer

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ABSTRACT

Germline pathogenic variants (PVs) in *CDH1* cause hereditary diffuse gastric cancer. The management of *CDH1* cases with a positive family history includes total prophylactic gastrectomy or intensive surveillance. In this study, we report a 16-year-old boy with intramucosal gastric signet ring cells in the setting of a germline *CDH1* PV and a family history of early-onset gastric cancer. The approach to managing both the proband and their 9-year-old sister, who also had the *CDH1* PV, presented a challenge to both clinicians and the family. Herein, we present the complexities of managing gastric cancer risk when a *CDH1* PV is identified in childhood in the setting of a family history of early-onset gastric cancer.

CDH1 is a tumor suppressor gene encoding E-cadherin, a transmembrane protein that plays crucial roles in cell adhesion (Gall and Frampton 2013). Germline pathogenic variants (PV) of *CDH1* are one cause of autosomal dominant hereditary diffuse gastric cancer (HDGC) syndrome. HDGC is associated with diffuse gastric cancers (DGC) and lobular breast cancers (LBC) (Hansford et al. 2015; Huntsman et al. 2001). The cumulative risk of DGC by the age of 80 for individuals with a PV in *CDH1* is between 42%–70% for men and 33%–56% for women (Blair et al. 2020; Hansford et al. 2015; Roberts et al. 2019) while the risk of LBC in females is approximately 55% (Blair et al. 2020). Given the high penetrance and significant morbidity and mortality of DGC, together with the relatively limited surveillance methods for the early detection of signet ring cell carcinoma (SRCC), prophylactic gastrectomy in early adulthood has been the mainstay of management for individuals with PVs in *CDH1* (Blair et al. 2020; Hebbard et al. 2009; Tan and Ngeow 2015). Recent, more attenuated

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penetrance estimates (Katona, Clark, and Domchek 2020) coupled with improvements in surveillance (Curtin et al. 2021) have led to updated practice guidelines that shift to enhanced surveillance in lieu of risk reduction for some families (Blair et al. 2020). Management considerations are multidisciplinary, can be difficult, and may become especially complex when a *CDH1* PV is identified in the pediatric or adolescent setting. Herein, we present a case of a child found to have signet ring cells (SRC) in the setting of a germline *CDH1* PV and use this case to highlight the complexities of managing cancer risk in the proband's younger 9-year-old sibling.

1 | Case

The index patient (proband) presented to a pediatric gastroenterology department at an outside clinic, at age 16 with 2 months of epigastric pain. He underwent esophagogastroduodenoscopy (EGD), which revealed diffuse nodularity of the antral region. Pathology of the non-targeted biopsy samples demonstrated moderate *Helicobacter pylori* (*H. pylori*) infection without intestinal metaplasia. A small focus consisting of 6 pancytokeratin positive, CD68 negative SRC was identified within lamina propria of the corporal region. The biopsy specimen was sent for a second opinion pathology review that confirmed the presence of SRC in the corpus. In the interim, eradication therapy for *H. pylori* was initiated, and in accordance with the International Gastric Linkage Consortium (IGCLC) gastric cancer screening protocol (Blair et al. 2020), EGD per the Cambridge protocol was performed at intervals (Table 1). Time points were variable due to follow up performed at different centers. At the 14th month the *H. pylori* was negative but mild nodularity continued. Based on the paternal uncle's loss due to SRCC and the positive SRC findings in EGD, prophylactic total gastrectomy (PTG) was considered. After thorough discussion and obtaining consent from the proband, along with support from his family, the surgery was performed. Following PTG, the microscopic analysis of the entire stomach showed a single focus, 0.4 cm in diameter, encompassing SRC within the lamina propria of the corpus. Neither lymphovascular nor perineural invasion was observed in the surgical margins of the resection specimen. There was no tumor metastasis in 25 dissected lymph nodes.

One year following PTG, the patient (age 19) was referred for genetic evaluation. In the paternal lineage, his uncle (II-3) died from SRCC at age 42, one of his aunt (II-5) had invasive ductal carcinoma (IDC) at age 38, and his grandmother (I-2) had colorectal adenocarcinoma at age 69 (Figure 1).

Given the cancer family history and biopsy results, he underwent germline genetic testing (gGT) with a multigene panel (Sophia hereditary cancer solution panel). The proband was found to have a pathogenic *CDH1* variant NM_004360 c.1137G > A, p.Thr379 (Landrum et al. 2018). At the last base of exon 8, this synonymous variant affects a donor splice site, resulting in an abnormal, out-of-frame transcript (Frebourg et al. 2006). The variant has been reported in families with HDGC and is not found in gnomAD (Frebourg et al. 2006; Hüneburg et al. 2016; Kaurah et al. 2007; Lynch, Aldoss, and Lynch 2011; More et al. 2007).

Cascade testing confirmed that the PV was paternally inherited (41, II.6). The uncle (II.3) who died of gastric cancer was an obligate carrier as his daughter (21, III.4) and mother (70, I.2) were found to have the *CDH1* PV (Figure 1). Based on the family history and at the request of the parents, the proband's siblings were tested, and his youngest sister (age 9, III.7) was also found to have the *CDH1* PV (Figure 1).

After discussion and consent, family members with the *CDH1* PV underwent EGD with the Cambridge protocol. The proband's father underwent a PTG at 41; pathology did not reveal any evidence of neoplasia, and no SRC was identified. Given her brother's presentation, the 9-year-old sister (III.7) underwent EGDs performed with the Cambridge protocol that revealed complete intestinal metaplasia in both the antrum and corpus after diagnosis and one year later. No atypical cells were detected in any of the biopsies. Her management was discussed

TABLE 1 | The pathology analysis of the index case by time points.

Time of the procedure	Chronic active gastritis	Intestinal metaplasia	H pylori	Signet ring cell (localization)	Procedure (center)
0	Yes	Negative	Positive	Positive (LP, corpus, single focus)	EGD and biopsy (UTRH)
	Yes	Negative	Positive	Positive (LP, corpus, single focus)	Consultation of first biopsy (OIIU)
2 months	Yes	Negative	Positive	Negative	EGD and biopsy (UTRH)
5 months	Yes	Negative	Positive	Negative	EGD and biopsy (UTRH)
14 months	Yes	Positive	Negative	Negative	EGD and biopsy (UTRH)
27 months	Yes	Positive	Negative	Positive (LP, antrum, single focus)	EGD and biopsy (OIIU)
34 months	Yes (and foveolar hyperplasia)	Positive	Negative	Positive (in LP, corpus, single 0.4 cm microscopic focus)	Total gastrectomy (OIIU)

Abbreviations: LP, lamina propria; OIIU, oncology institute of istanbul university; UTRH, umraniye training and research hospital.

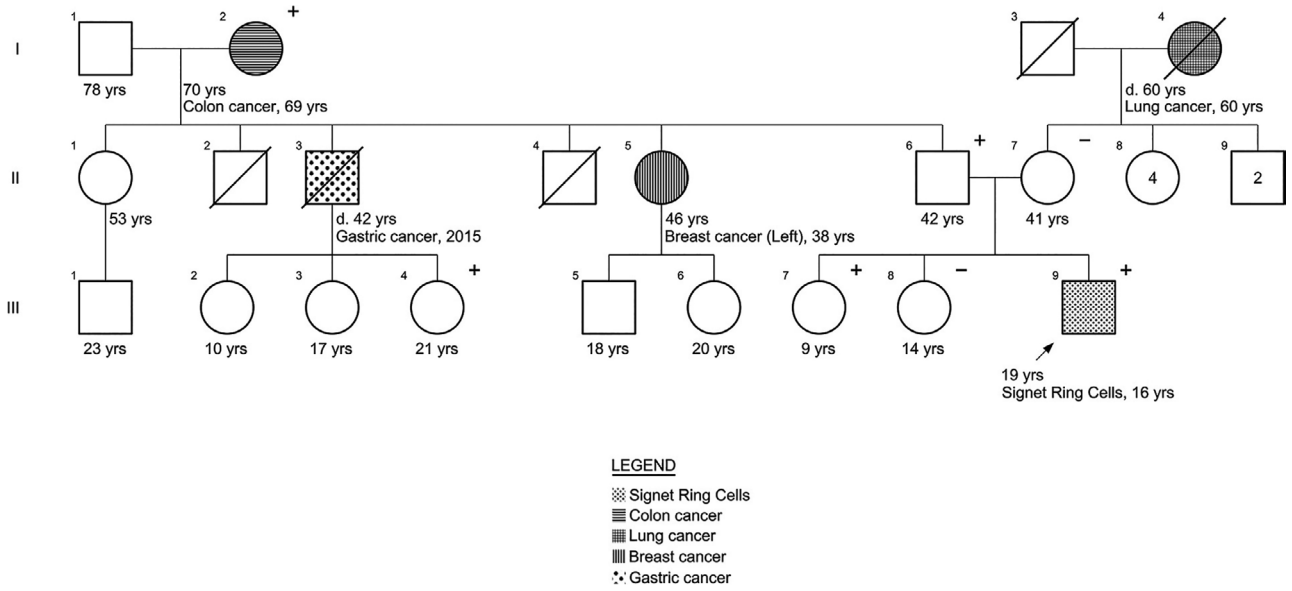

FIGURE 1 | The pedigree for the *CDH1* family. Cases marked with (+) are *CDH1* variation positive, and (–) are noncarriers. Individuals with no marking declined genetic testing, including the aunt (II.5) with a history of invasive ductal breast cancer.

in a multidisciplinary setting consisting of pediatric and general surgeons, pediatric and adult oncologists, pediatric and adult gastroenterologists, pediatric psychiatrists, pathologists, and pediatric and adult geneticists and genetic counselors, and the decision was made to defer PTG and continue close surveillance given her young age. Additionally, the family member underwent a dental consultation and had no evidence of a high-arched palate and/or cleft lift/palate.

2 | Discussion

HDGC accounts for 1%–3% of all malignant gastric tumors (Oliveira, Seruca, and Carneiro 2009). Germline *CDH1* PVs are currently the most common inherited cause of HDGC (Guilford et al. 1998). Here, we present a family with HDGC due to a germline *CDH1* variant (Frebourg et al. 2006; Hansford et al. 2015; Hüneburg et al. 2016; Kaurah et al. 2007; Lynch, Aldoss, and Lynch 2011; More et al. 2007). This family illustrates the complexity of management, especially for pediatric patients with PVs in *CDH1*.

The IGCLC has well-delineated criteria for HDGC gGT (Blair et al. 2020). This family meets a clinical diagnosis of HDGC as the paternal uncle had gastric cancer under age 50, and the proband had early-stage gastric SRC carcinoma at 16. Notably, the paternal aunt of the index case was diagnosed with IDC rather than LBC. *CDH1* has been associated with HDGC and LBC, and reports on ductal breast carcinoma are increasing (Lei et al. 2002).

PTG is recommended for individuals with *CDH1* PVs and a family history of DGC, and remains the gold standard for definitive management in this setting (Blair et al. 2020; Caldas et al. 1999; Pandalai et al. 2011; van der Post, Vogelaar, Manders, et al. 2015; Vos et al. 2020). The proband's father underwent a PTG, and notably, there were no neoplastic or malignant cells identified, as well as no evidence of metaplasia, dysplasia or atrophy. Lee et al. has shown that the role of specialized surveillance with random biopsies enhances the early detection of signet ring cell carcinoma. Moreover, together with the Cambridge and Bethesda protocols, some groups recommending EGD in patients who are considered to be unsuitable for PTG or do not have a family history of gastric cancer (Blair et al. 2020; Fitzgerald et al. 2010; van der Post, Vogelaar, Carneiro, et al. 2015). In a recent study by Asif et al. endoscopic cancer surveillance was shown to be an effective alternative to surgery for cases with *CDH1* variants who declined total gastrectomy (Asif et al. 2023).

Traditionally gGT has been limited to adults at increased risk for DGC. The median age of gastric cancers among individuals with a PV in *CDH1* is 49.3 (Roberts et al. 2019). This family was unique in that the index case presented at an early age. Prioritizing the best interest of the child both medically and psychologically has been endorsed by the American College of Medical Genetics (ACMG, Bioethics Comittees et al. 2013). The proband's younger siblings underwent gGT after detailed discussion and parental consent and assent from the 14-year-old sister were obtained. Given her age, the 9-year-old was not required to assent, but she was present for pretest genetic counseling.

PTG has been performed in a 14-year-old individual with a *CDH1* PV because of an 18-year-old sibling with metastatic DGC (Gullo et al. 2018). In our case, for the 9-year-old child, multiple clinical perspectives were considered. At the Umraniye Training and Research Hospital (UTRH), the medical oncologists considered the aggressive nature of SRCC and favored PTG. The pediatric psychiatrists were concerned that adverse psychological effects would be heightened during pubertal development and recommended avoiding this complex developmental time period by pursuing surgery during childhood or after adolescence. A pediatric surgeon and gastroenterologists ensured the procedure would be well tolerated

and that nutritional support was given post-operatively to help mitigate the adverse effects of early gastrectomy. Given the poor sensitivity of EGD with biopsy for early diagnosis of SRCC, the UTRH council strongly considered PTG for the 9-year-old sister with *CDH1* PV.

At a subsequent multidisciplinary review at the Dana-Farber Cancer Institute/Boston Children Hospital (DFCI/BCH), the consequences of gastrectomy in early childhood, the limited data regarding management of *CDH1* PVs in pediatrics as well as age-specific penetrance of phenotypes among family members were considered. While an uncle died of gastric cancer at age 42 and the index case had isolated SRC at age 16, the father had no pathologic evidence of disease, and the grandmother had no known cancer at ages 41 and 70, respectively. Weighing the impact of nutritional deficiencies on growth, bone density (Gamble et al. 2023), potential effects on quality of life (Gallanis et al. 2024), and morbidity of the gastrectomy, as well as future patient autonomy and choice, the recommendation was made to defer PTG and continue with EGD at least annually with the Cambridge protocol. This would allow the 9-year-old to achieve further growth and development, participate in shared decision-making, and potentially benefit from improved surveillance for DGC.

Managing gastric cancer risk in pediatric patients with *CDH1* PVs involves weighing multiple factors, including age, family history, potential medical and psychological impact, autonomy, and family preferences. Evidence shows that individuals with *CDH1* PV may have quiescent SRC for years before developing invasive gastric cancer (Fitzgerald et al. 2010). Our study emphasizes the importance of genetic counseling in cancer management. Cancer genetic counseling differs across countries and even within the same country. For our study, the index went under PTG prior genetic testing due lack of cancer predisposition awareness in the centers. Detection of *CDH1* variation is a direct indication for PTG planning, hence cases should be analyzed with cancer MGPT before surgery (Blair et al. 2020). Here, we present family members from three different generations with a *CDH1* PV and how each was managed differently based on their phase of life. Moreover, multidisciplinary discussions at different institutions broadened the perspectives of the family and involved medical specialists. Multiple considerations contributed to the counseling discussions with the family and their decision-making processes. These complex considerations are likely to become more prevalent, especially among children found to carry PVs in *CDH1* at young ages.

Author Contributions

Conceptualization: N.B.A., O.H.N., H.Q.R. Methodology: B.U., I.E.Z., N.G., I.K., H.Y. Analysis: N.B.A., O.H.N., B.U., H.Y., J.K., H.Q.R. Investigation: I.E.Z., N.G., I.K., H.Y., U.O. Writing – Review & Editing: O.H.N., N.B.A., J.K. and H.Q.R.

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Conflicts of Interest

H.Q.R. reports research collaboration with Ambry Genetics (no compensation). The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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