CLINICAL VIGNETTE

Hereditary Diffuse Gastric Cancer Syndrome

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Case Report

A 23-year-old woman with no significant past medical history was referred for newly diagnosed metastatic gastric adenocarcinoma. A few months before presentation, she developed abdominal bloating, early satiety, constipation and abdominal cramping. She was evaluated by Gastroenterology. Abdominal ultrasound revealed moderate abdominal ascites. Computed tomography of the abdomen and pelvis confirmed the ascites and showed diffuse thickening of the stomach wall, mesenteric/retroperitoneal lymph node enlargement, and evidence of peritoneal carcinomatosis. Paracentesis yielded over 3 liters of ascites with cytology positive for adenocarcinoma. Esophagogastroduodenoscopy found gastric body with ulceration and edematous appearance. Gastric body biopsy showed poorly-differentiated adenocarcinoma with signet ring features. Human epidermal growth factor receptor 2 (HER2) immunohistochemistry was negative with 1+ staining and HER2 fluorescence in situ hybridization was negative for amplification. Programmed death ligand 1 (PDL1) combined positive score was less than 1. Mismatch repair proteins were proficient. There was no evidence of Helicobacter pylori in the biopsy specimen. Colonoscopy showed scattered edematous mucosa, with benign biopsies. Medical Oncology consultation, identified a paternal uncle with gastric cancer in his late 40s. There was no other known history of gastric cancer in other family members or family history of breast cancer. Her maternal grandfather was diagnosed with pancreatic cancer at age 65. Invitae Multi-Cancer Panel sequence analysis and deletion/duplication testing of 84 genes confirmed a pathogenic mutation in CDH1 (c.60del, heterozygous), which codes for the cadherin 1 protein (E-cadherin). She was diagnosed with hereditary diffuse gastric cancer (HDGC) syndrome. She had formal genetic counseling and was advised to notify family members for cascade testing for HDGC. Based on positron emission tomography, she was also suspected to have malignant involvement of her colon, left ovary, and bones. Mammogram showed no evidence of malignancy and brain magnetic resonance imaging (MRI) was negative for metastases. She was enrolled on a clinical trial of capecitabine and oxaliplatin (XELOX) with novel agents. Unfortunately, her cancer progressed after 3 months of therapy. She was treated with two more lines of chemotherapy/targeted therapy, but died from progressive disease.

Discussion

Hereditary diffuse gastric cancer (HDGC) syndrome is characterized by an elevated risk for gastric cancer and lobular breast cancer with aggressive histology. It is driven by a pathogenic germline mutation in the CDH1 tumor suppressor gene. The loss of the CDH1 gene product, E-cadherin, leads to loss of cell-to-cell contact inhibition of proliferation and promotes oncogenesis. The incidence of HDGC is estimated to be between 5-10 cases per 100,000 births[1]. Genetic testing and early discovery of pathogenic CDH1 mutation carriers can prevent mortality from advanced gastric and lobular breast cancer with surveillance or prophylactic surgeries.

The genetic basis for HDGC was first reported in 1998 by Guilford et al.[2] Genetic linkage analysis revealed a strong association between germline inactivating mutations in the gene coding for E-cadherin and families with early-onset diffuse gastric cancer. The CDH1 mutation appears to be inherited in an autosomal dominant fashion with incomplete penetrance. Previously, low expression of E-cadherin was associated with poorly differentiated carcinomas and was considered a suppressor of tumor invasion. An updated germline mutation study of HDGC by Hansford et al.,[3] reported 155 distinct pathogenic CDH1 mutations spread across the entire gene. This study also discovered germline truncating mutations in CTNNA1 in a minority of CDH1 mutation-negative HDGC families. CTNNA1 is the gene that codes for a-catenin, which is a protein that associates with E-cadherin as described below.

E-cadherin is a transmembrane cell adhesion protein involved in cell polarity and cell to cell interactions that regulate proliferation and maintain tissue architecture homeostasis.[2,4] E-cadherin helps form the adherens junction and associates with the catenins (a-catenin, b-catenin, and p120) that attach to the actin cytoskeleton. When cells reach confluence, E-cadherin inhibits proliferation and maintains the epithelium. Loss of E-cadherin expression on cell surfaces leads to loss of contact inhibition of proliferation, one of the hallmarks of cancer, contributing to the process of tumorigenesis. E-cadherin loss can also contribute to epithelial mesenchymal transition (EMT) in which cells transition from a stationary epithelial state to a migratory mesenchymal state. EMT promotes cancer cells to break off from the primary tumor and metastasize to a distant site. E-cadherin is also involved in signal transduction and affects various downstream growth factor signaling pathways that regulate proliferation, including Hippo, Wnt, TGFb, and NF-kB.

Pathogenic germline CDH1 mutations dramatically increase the risk of diffuse gastric cancer and lobular breast cancer in carriers, making early detection of carrier status and surveillance/preventative measures imperative. Diffuse gastric cancer and lobular breast cancer infiltrate surrounding tissue without forming well-defined masses, which can be explained by the decreased expression of E-cadherin. These specific cancer types are distinguished from intestinal-type gastric cancer and ductal breast cancer, which are not associated with CDH1 mutations. According to Hansford et al.,[3] the cumulative incidence of diffuse gastric cancer was 70% in male and 56% in female CDH1 mutation carriers by age 80 years. The cumulative incidence of lobular breast cancer was reported to be 42% in female CDH1 mutation carriers by age 80 years. More recent penetrance estimates for diffuse gastric cancer in CDH1 mutation carriers are 37-42% in men and 25-33% in women.[5] According to updated International Gastric Cancer Linkage Consortium (IGCLC) guidelines published in 2020,[1] HDGC is diagnosed by the presence of a pathogenic germline variant in CDH1 or CTNNA1 in an individual with diffuse gastric cancer or in a family with one or more diffuse gastric cancer cases in first- or second-degree relatives. Hereditary lobular breast cancer (HLBC) is defined in a similar way by the presence of a germline pathogenic variant in CDH1 in an individual with lobular breast cancer or in a family with one or more lobular breast cancer cases in first- or second-degree relatives but redefined as HDGC if diffuse gastric cancer or its precursor is subsequently found in a family member.

Genetic testing for HDGC is now recommended for individuals meeting the following criteria: 1) Diffuse gastric cancer diagnosed before age 50 years. 2) Diffuse gastric cancer at any age and Maori ethnicity (given the high prevalence). 3) Diffuse gastric cancer at any age and a personal or family history (first degree) of cleft lip/palate (known association). 4) Diffuse gastric cancer and lobular breast cancer both diagnosed before age 70 years. 5) Bilateral lobular breast cancer diagnosed before age 70 years. 6) Diffuse gastric cancer precursor lesions (gastric in situ signet ring cells) before age 50 years. Family criteria for genetic testing of first or second degree relatives include: 1) Two or more cases of gastric cancer in the family regardless of age with at least one diffuse gastric cancer. 2) One or more cases of diffuse gastric cancer at any age and one or more cases of lobular breast cancer before age 70 years in different family members. 3) Two or more cases of lobular breast cancer in family members before age 50 years.[1] Referral for formal genetic counseling is recommended, where psychological needs, reproductive matters, and cascade testing can be considered.

Management of HDGC germline mutation carriers should be done with a multidisciplinary approach. CDH1 mutation carriers from confirmed HDGC families are recommended to undergo prophylactic total gastrectomy starting as young as age 20 years given the substantial risk of developing gastric cancer and uncertainties of endoscopic surveillance.[1,5] Prophylactic total gastrectomy can eliminate the risk for gastric cancer-related death[6] and should preferably be performed at centers with expertise in gastric cancer surgery and HDGC longitudinal management. Although prophylactic total gastrectomy can lead to complications and side effects that may impair quality of life, patient satisfaction following decision to undergo surgery has been reported at about 90%. Carriers that decline initial surgery should undergo cancer surveillance with annual upper gastrointestinal endoscopies at centers experienced in HDGC. Upper GI endoscopies and gastric mucosal biopsies can detect precursor signet ring cell foci or superficial signet ring cell carcinoma. Unfortunately, endoscopic surveillance may miss diffuse gastric cancer as the malignant cells are not associated with a visible mucosal abnormality under direct visualization. This may delay timely diagnosis and appropriate treatment.[1] Currently management of advanced gastric cancer in HDGC is the same as sporadic gastric cancer. However, targeting E-cadherin with activating or inhibiting agents is an area of active research and which may lead to future therapies.[7] Surveillance for lobular breast cancer in female CDH1 carriers involves annual breast MRIs starting at age 30 years. Surveillance with mammography alone is considered unreliable given the low sensitivity at detecting lobular breast cancer but can be used to supplement breast MRIs. Bilateral risk reduction mastectomy is also a consideration for these carriers but is not considered routine, given less robust data guiding management.[1]

REFERENCES

1. **Blair VR, McLeod M, Carneiro F, Coit DG, D'Addario JL, van Dieren JM, Harris KL, Hoogerbrugge N, Oliveira C, van der Post RS, Arnold J, Benusiglio PR, Bisseling TM, Boussioutas A, Cats A, Charlton A, Schreiber KEC, Davis JL, Pietro MD, Fitzgerald RC, Ford JM, Gamet K, Gullo I, Hardwick RH, Huntsman DG, Kaurah P, Kupfer SS, Latchford A, Mansfield PF, Nakajima T, Parry S, Rossaak J, Sugimura H, Svrcek M, Tischkowitz M, Ushijima T, Yamada H, Yang HK, Claydon A, Figueiredo J, Paringatai K, Seruca R, Bougen-Zhukov N, Brew T, Busija S, Carneiro P, DeGregorio L, Fisher H, Gardner E, Godwin TD, Holm KN, Humar B, Lintott CJ, Monroe EC, Muller MD, Norero E, Nouri Y, Paredes J, Sanches JM, Schulpen E, Ribeiro AS, Sporle A, Whitworth J, Zhang L, Reeve AE, Guilford P**. Hereditary diffuse gastric cancer: updated clinical practice guidelines. *Lancet Oncol*. 2020 Aug; 21(8):e386-e397. doi: 10.1016/S1470-2045(20)30219-9. PMID: 32758476; PMCID: PMC7116190.
2. **Guilford P, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, Taite H, Scoular R, Miller A, Reeve AE**. E-cadherin germline mutations in familial gastric cancer. *Nature*. 1998 Mar 26;392(6674):402-5. doi: 10.1038/32918. PMID: 9537325.
3. **Hansford S, Kaurah P, Li-Chang H, Woo M, Senz J, Pinheiro H, Schrader KA, Schaeffer DF, Shumansky K, Zogopoulos G, Santos TA, Claro I, Carvalho J, Nielsen C, Padilla S, Lum A, Talhouk A, Baker-Lange K, Richardson S, Lewis I, Lindor NM, Pennell E, MacMillan A, Fernandez B, Keller G, Lynch H, Shah SP, Guilford P, Gallinger S, Corso G, Roviello F, Caldas C, Oliveira C, Pharoah PD, Huntsman DG**.

Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. *JAMA Oncol*. 2015 Apr;1(1):23-32. doi: 10.1001/jamaoncol.2014.168. Erratum in: *JAMA Oncol*. 2015 Apr;1(1):110. PMID: 26182300.

4. **Mendonsa AM, Na TY, Gumbiner BM**. E-cadherin in contact inhibition and cancer. *Oncogene*. 2018 Aug;37(35):4769-4780. doi: 10.1038/s41388-018-0304-2. Epub 2018 May 21. PMID: 29780167; PMCID: PMC6119098.
5. **Gamble LA, Heller T, Davis JL**. Hereditary Diffuse Gastric Cancer Syndrome and the Role of CDH1: A Review. *JAMA Surg*. 2021 Apr 1;156(4):387-392. doi: 10.1001/jamasurg.2020.6155. PMID: 33404644.
6. **van der Post RS, Vogelaar IP, Carneiro F, Guilford P, Huntsman D, Hoogerbrugge N, Caldas C, Schreiber KE, Hardwick RH, Ausems MG, Bardram L, Benusiglio PR, Bisseling TM, Blair V, Bleiker E, Boussioutas A, Cats A, Coit D, DeGregorio L, Figueiredo J, Ford JM, Heijkoop E, Hermens R, Humar B, Kaurah P, Keller G, Lai J, Ligtenberg MJ, O'Donovan M, Oliveira C, Pinheiro H, Ragunath K, Rasenberg E, Richardson S, Roviello F, Schackert H, Seruca R, Taylor A, Ter Huurne A, Tischkowitz M, Joe ST, van Dijck B, van Grieken NC, van Hillegersberg R, van Sandick JW, Vehof R, van Krieken JH, Fitzgerald RC**. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. *J Med Genet*. 2015 Jun;52(6):361-74. doi: 10.1136/jmedgenet-2015-103094. Epub 2015 May 15. PMID: 25979631; PMCID: PMC4453626.
7. **O'Driscoll L**. When E-Cadherin Becomes Unstuck in Cancer. *N Engl J Med*. 2020 Aug 27;383(9):871-873. doi: 10.1056/NEJMcibr2018713. PMID: 32846069.