CLINICAL VIGNETTE

A Colorectal Cancer Patient with CDH1 Mutation: Is This a Case of Hereditary Diffuse Gastric Cancer (HDGC) Syndrome?

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Case

A 45-year-old female presented with one-year of gradual changes in bowel movements. She reported great difficulty having bowl movements in the morning, but reported multiple movements, up to 10 in the late day and night. She denied weight loss, fatigue, nausea, or vomiting.

She has no significant past medical history and does not drink alcohol or smoke. She reported no family history of colon cancer.

Physical examination revealed a well-appearing female. BP 101/63 mmHg, Pulse 88 bpm, Ht 5' 7.5", Wt 141 lbs, BMI 21.82 kg/m². Abdomen: soft, nontender with normal bowl sounds. Labs included Hemoglobin: 13.7 g/dL Hematocrit 42.4% WBC 6.07 x10E3/uL; AST 16 UL, ALT 12 UL, Total bilirubin 0.4 mg/dL, and Alkaline phosphatase 60 UL.

She was referred to gastroenterology and colonoscopy was ordered but as not immediately scheduled for a few months, after her symptoms worsened. Colonoscopy revealed an obstructing circumferential mass 30 cm from the anal verge. The mass prevented visualization proximal to the mass, which was biopsied. The area was tattooed and CT abdomen and pelvis obtained, revealing concentric wall thickening and hyperenhancement at the rectosigmoid junction, corresponding to the observed colon mass. There was no infiltration of pericolonic fat and no evidence of pulmonary or abdominopelvic metastatic disease.

Biopsies showed at least high-grade dysplasia, and could not exclude adenocarcinoma.

She also developed hematuria was referred to colorectal surgery, urology and radiation oncology. MRI of pelvis showed a T3N+ tumor in the upper rectum. She was scheduled for laparoscopic surgery after five days of neoadjuvant radiation therapy to the rectum and pelvis. Laparoscopic low anterior resection was completed with diverting loop ileostomy as well as cystoscopy with excisional resection of a 3 mm papillary bladder mass near the left ureteral orifice and bladder fulgeration.

Final surgical pathology was moderately differentiated T3N1a high rectal cancer, stage IIIB, as well as low grade papillary urothelial carcinoma.

After surgery she completed adjuvant FOLFOX chemotherapy. She was also evaluated by a genetic counselor and underwent cancer susceptibility genetic testing for BRCA1/2, Lynch syndrome and other hereditary cancer. Testing revealed CDH1 heterozygous mutation, consistent with Hereditary Diffuse Gastric Cancer. Additional family history was obtained and identified early breast cancer in her maternal grandmother in her 40s and gastric cancer in her great aunt also in her 40s.

Because CDH1 mutation is associated with high risk of Lobular Breast Cancer. She was seen by a breast specialist who obtained Breast MRI and Mammogram which were normal. A general surgeon consulted for possible prophylactic total gastrectomy because of high risk of Gastric Cancer and she was scheduled for close follow up with early cancer surveillance.

Upper endoscopy (EGD) was negative for gastric cancer and surveillance cystoscopy after a year was unremarkable. She awaits Ileostomy reversal and complete colonoscopy.

Discussion

Hereditary Diffuse Gastric Cancer (HDGC) is a rare, autosomal dominant, highly invasive diffuse-type of gastric cancer characterized by late presentation and poor prognosis. It is associated with increased risk of lobular breast cancer. Diffuse Gastric Cancer accounts for approximately 5% of all invasive gastric tumors.[1]

Colorectal cancers have also been reported in carriers of the genetic mutation. Currently, there is limited clinical evidence linking increased risk of colorectal cancer to HDGC. Current guidelines strongly recommend enhanced colonoscopy surveillance starting at 40 years or 10 years younger that the earliest incident diagnosis of colon cancer with repeat colonoscopy at 3-5-year intervals.[2]

Gastric cancer accounts for about 1.5% of all new cancers diagnosed in the US. The American Cancer Society estimates about 26,560 new cases and 11,180 deaths from gastric cancer in the United States in 2021.[3] Globally, Gastric Cancer is the 4th most prevalent type of cancer and mortality is predicted to increase in the future from 15th to the 10th leading cause of mortality by 2030.[4] Although the majority of gastric cancers are sporadic in etiology, it is now known that 1-3% of gastric

cancers arise from inherited gastric cancer predisposition syndromes.[5]

Most confirmed HDGC cases are caused by an inactivating germ line mutation in the E- cadherin (CDH1) tumor suppressor gene with likely pathogenic variants of the CDH1 gene in chromosome 16q22.1. Pathogenic and likely pathogenic germ line CDH1 variants have been identified in 15-50% of affected siblings of patients that fulfill clinical criteria for HDGC.[2] Affected patients develop gastric cancer at an average age of 38 years, with age range from 14 to 82 years. Prophylactic total gastrectomy may be recommended in families with the HDGC genes since the lifetime time risk of gastric cancer is very high, estimated at 70% for men and 56% for women.[6]

The 2015 International Gastric Cancer Linkage Consortium Diagnostic Criteria for HDGC include:

1. Family history with at least two gastric cancer cases regardless of age, with at least one confirmed diffuse gastric cancer (DGC)
2. One case of DGC < 40 years of age
3. Personal or family history of DGC and Lobular Breast Cancer, with one case diagnosed < 50 years old

In most cases, the frequency of acquiring the pathogenic and likely pathogenic variants of HDGC is inversely associated with the baseline incidence of gastric cancer. This results in higher detection rates for the CDH1 pathogenic gene in families in countries with a lower incidence of gastric cancer like the United States, United Kingdom and Canada.[7]

Gastric cancers that develop are multifocal and located beneath an intact mucosal surface. The gastric cancer often has "signet ring" cells throughout the stomach wall. The signet ring cell results from intracellular mucin formation that pushes aside the nucleus of individual cells.[8]

There is no current data about the degree of penetrance or incidence of developing HDGC in patients with positive CDH1 pathogenic gene who do not completely fulfill the diagnostic criteria for HDGC, such as those without personal of family history of HDGC.[9] There are no well-defined, concrete recommendations for such patients. They advise referral to specialty centers for consultation about screening and preventive surgical procedures. Current consensus is regular endoscopic screening and deferring total prophylactic gastrectomy.[10]

Women with HDGC or family members with known genetic mutation carriers also have an elevated risk of developing lobular breast cancer, with 42% estimated lifetime risk. Current guidelines recommend annual breast magnetic resonance imaging which can be combined with a mammogram starting at age 30 years in women carriers of the pathogenic gene.[11]

Genetic counselling and testing are an integral component of the evaluation and management of HDGC. Comprehensive genetic evaluation incorporates family pedigree, histopathological confirmation of diffuse gastric cancer diagnosis or precursor lesions with a discussion of lifetime risk of HDGC.[12] Testing should be initiated in patients with the pathologic germ line mutation.

Genetic testing currently begins at age 16 to 18 but testing family members younger than 18 years can be considered based on the earliest age of cancer onset in HDGC families.[8] Blood samples is the best method for genetic testing, although DNA can be extracted from saliva.

Prophylactic total gastrectomy is recommended for asymptomatic patients positive for the pathogenic germ line CDH1 mutation with a positive family history of HDGC.[13] The optimal timing of prophylactic total gastrectomy is between 20 and 30 years.[14]

Annual surveillance endoscopy with random biopsies is recommended for patients who are diagnosed as carriers before age 20. Screening endoscopy is also recommended for patients over 20 years' old who elect to defer or postpone gastrectomy.[15]

Conclusion

Our 45-year-old female was diagnosed with Colorectal and Urothelial cancers. She completed age-appropriate screening including breast and cervical cancer screening. After multidisciplinary evaluations she and her family will follow current recommendations for cancer surveillance and screening family members.

She has completed initial chemotherapy and deferred prophylactic gastrectomy. She is scheduled for surveillance EGD every 6-12 months and annual breast MRI screening.

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