Somatic Mutation of CDH1 Leading to Diffuse Gastric Cancer

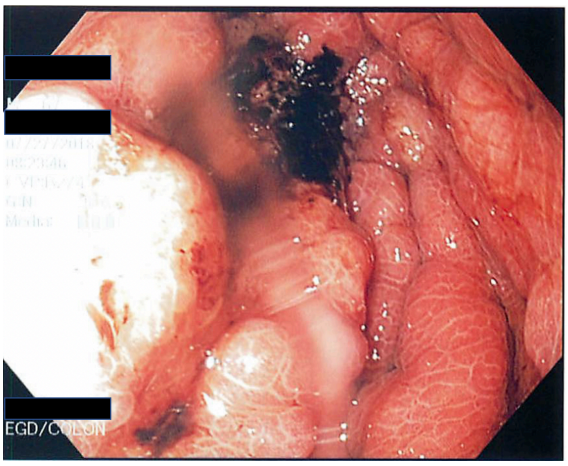
Introduction

Signet Ring Cell Carcinoma (SRCC) is associated with Hereditary Diffuse Gastric Carcinoma (HDGC) and has known etiology resulting from the loss of e-cadherin and cell-to-cell adhesion[1]. It is well known to be related to a germline mutation leading to hypermethylation of CDH1 with an autosomal dominant inheritance pattern[2] with an 80% penetrance at 80 years[3]. E-cadherin mutations are also associated with an increased risk for lobular breast carcinoma (LBC), warranting genetic testing for germline mutations in CDH1 if a family history of LBC or DGC is positive before age 50[4-6]. Given the poor prognosis of HDGC[7], familial inheritance pattern, and treatment being surgical resection and prophylactic gastrectomy in known carriers[2-6,8], it is a cancer requiring an exhaustive work-up for both patient and family members.

Case Summary

This is a case of a 68-year-old man who presented to the clinic with complaints of early satiety, postprandial fullness, loss of appetite and an unintentional 10-pound weight loss over two months. He denied nausea, vomiting, diarrhea, constipation, and abdominal pain. Past history was significant for successfully treated H. pylori infection and secondary peptic ulcer disease, gastritis, and colonic polyposis (CP). No hospitalizations. Six colonoscopies for monitoring of CP. He had a 50 pack-year smoking history, drank 3-4 alcoholic drinks per day, had no drug use history, and was the owner of an energy company – with no identified exposure. He worked in a building with known disturbed asbestos and had an identical twin brother who had together served with him in Vietnam with possible exposure to Agent Orange. His brother remains unaffected.

Multiple biopsies established a diagnosis of SRCC and laparoscopy with peritoneal biopsies confirmed presence of metastases to the peritoneum, omentum, and falciform ligament. Initial CT/PET did not reveal distant metastasis but did show gastric thickening of the antrum. Repeat imaging including an MRI and two CT scans found no areas of metastasis. The patient was started on Palliative Chemotherapy with poor tolerance of FOLFOX therapy. He ultimately received 5-Fluorouracil only. Molecular diagnostics confirmed a somatic variant alone of CDH1, p.P625_A62Bdel – excluding the need for surgical treatment of his family members. Follow-up CT of the abdomen 12 months after initial biopsy confirmed carcinomatosis including: large volume ascites, peritoneal carcinomatosis, and gastric thickening. The patient passed away on hospice approximately 12 months after diagnosis.



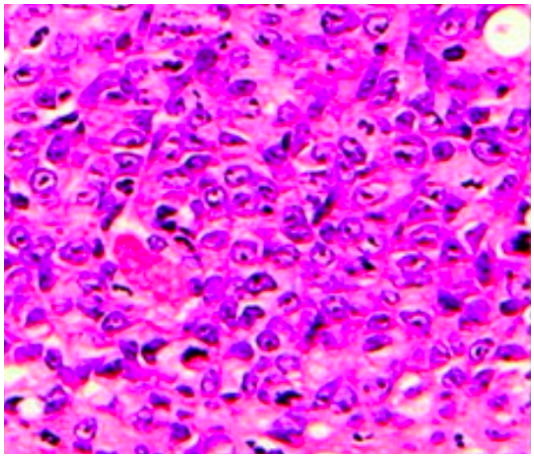


Figure 1: Picture taken during EGD and biopsy demonstrating thickened folds, inflammation, and appearance of diffuse wall infiltration.
Figure 2: Histopathology of SRCC on biopsy. (Photo taken from https://cancerres.aacrjournals.org/content/69/5/2050 on 4/3/2021[1]).

Discussion

Increasingly, the literature is identifying cases of CDH1 somatic mutations[9]. It is known to be related to hypermethylation of the gene and may be secondary to Ebstein-Barr virus (EBV) infection[6,10,11]. We share this case report in a hope to raise awareness of the reality of gastric cancers in those who do not have a family history. We also wish to provide hope to 1st and 2nd generation family members of those with DGC with somatic mutations alone. Identifying somatic vs germline mutations of DGC is of paramount importance to the nutritional status and recommendations of family members of those with CDH1 mutations.

Works Cited

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