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Mucinous Ovarian Adenocarcinoma and CHD1 Germline Mutation: A Case Report

Christa Aubrey[1*]; Valerie Capstick[2]; Soufiane El Hallani[3]; Carol Ewanowich[4]

[1]Obstetrics and Gynecology, University of Alberta, Canada

[2]Division of Gynecological Oncology, Department of Obstetrics and Gynecology, University of Alberta, Canada

[3]Assistant Professor, Department of Laboratory Medicine and Pathology, University of Alberta, Canada

[4]Associate Clinical Professor, Department of Laboratory Medicine and Pathology, University of Alberta, Canada

***Corresponding Author(s): Christa Aubrey**

Department of Oncology, University of Calgary Tom Baker Cancer Centre, cc110D, 1331 29 Street NW Calgary AB, T2N 4N2, Canada

Email: Christa.Aubrey@albertahealthservices.ca

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Abstract

Background: CDH1 mutation is a rare autosomal dominant mutation in the gene encoding for E-cadherin, and a known familial cancer syndrome associated with hereditary diffuse gastric carcinoma and lobular breast carcinoma.

Case: A 21 year old with a known CDH1 mutation and history of diffuse hereditary gastric cancer with a prior total gastrectomy presented seven years later with a pelvic mass. Pathology was consistent with a FIGO stage IA1 mucinous adenocarcinoma, (intestinal type, expansile pattern) of the left ovary.

Conclusion: CDH1 germline mutation is not known to be associated with ovarian mucinous adenocarcinoma. Due to the rare incidence of CDH1 mutation, other tumors may be associated, but confirmatory evidence is still lacking.

Introduction

Cadherins are a superfamily of calcium-dependent transmembrane glycoproteins essential for cell-to-cell connections and tissue stabilization. Specific to epithelial tissue, the intercellular adhesion protein E-cadherin also functions as a cell invasion suppressor [1]. CDH1 is the gene responsible for encoding E-cadherin, and was first described as a familial cancer gene in 1998. linked to the incidence of Hereditary Diffuse Gastric Carcinoma (HDGC) in a large Maori kindred in New Zealand [2]. E-cadherin has subsequently been associated with Lobular Breast Cancer (LBC), and cleft lip/palate [1,3].

Epithelial ovarian cancer is the most common type of ovarian cancer, with several histologic sub-types. Although somatic mutations in E-cadherin have been associated with enhanced cell invasion and metastasis in ovarian cancer [4], an increased frequency of epithelial ovarian cancer has not been demonstrated in individuals with germline CHD1 mutations.

We describe a case of ovarian mucinous adenocarcinoma (intestinal type) in a 21 year old female with a history of diffuse hereditary gastric carcinoma and known CDH1 germline mutation.

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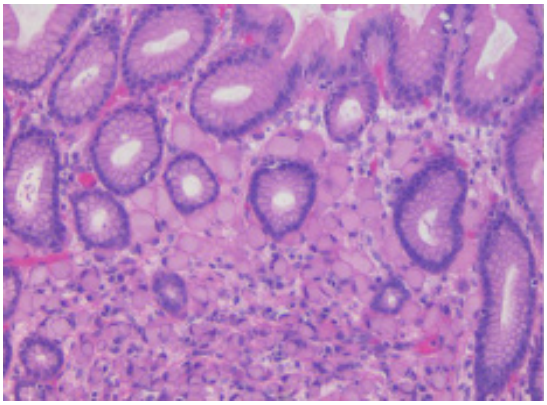
Case presentation

A 21 year old G0 woman was referred to gynecologic oncology with a new diagnosis of a large pelvic mass. She presented to the emergency department with acute abdominal pain in the context of a 2 month history of increasing abdominal girth. Ultrasound showed a large complex pelvic mass measuring 26.2 by 12.3 by 20.6 cm arising from the left ovary. CT abdomen and pelvis demonstrated no pelvic lymphadenopathy or evidence of metastatic disease. Tumor markers showed a slightly elevated CA125 (42 kU/L) and AFP (10 mcg/L), but were otherwise normal, including CEA (<1.0 ug/L).

Her past medical and family history were significant, as her mother died at age 32 from metastatic gastric cancer, and her maternal grandmother, aunt, and a second cousin had gastric cancer. As a result, starting from age seven she had annual screening upper endoscopies. At age 15, a random biopsy from a screening gastroscopy was consistent with signet ring cell adenocarcinoma confined to superficial lamina propria. She subsequently underwent a radical total gastrectomy with esophagojejunostomy and enteroenterostomy. Final pathology revealed a T1aN0 tumor, with no lymph vascular invasion, and negative margins. Genetic testing revealed a c.1779dupC pathogenic mutation in the CDH1 gene, autosomal dominant inheritance pattern. She was followed by pediatric oncology and did not require any further adjunct treatment.

Considering her imaging and laboratory investigations it was felt that this was a primary ovarian lesion, and a Krukenberg tumor metastatic from her gastric carcinoma was exceedingly unlikely given the seven year disease-free interval, and her gastric tumor pathology. She subsequently had a fertility-preserving staging laparotomy with left salpingo-oophorectomy. Intraoperatively the tumor was grossly suspicious for a mucinous borderline tumor. She had a previous appendectomy, and the omentum was not visible (given her previous gastrectomy). Cytology was negative, and the final pathology showed a grade 1 mucinous adenocarcinoma, expansile pattern of the left ovary, FIGO stage IA1. Pathology review by a gynecologic oncology pathologist confirmed an ovarian primary. E-cadherin staining showed mildly decreased expression, whereas in her prior gastric tumor the expression of E-cadherin was almost absent (Figures 1 & 2).

She was subsequently referred to reproductive endocrinology and underwent embryo cryopreservation, and genetic selection of embryos unaffected by CDH1 mutation. After this process was completed, 19 months later she underwent completion staging with laparoscopic right salpingoophorectomy and uterine preservation. The remaining ovary was not affected, and her final stage was unchanged: FIGO stage IA1 mucinous adenocarcinoma of the left ovary.



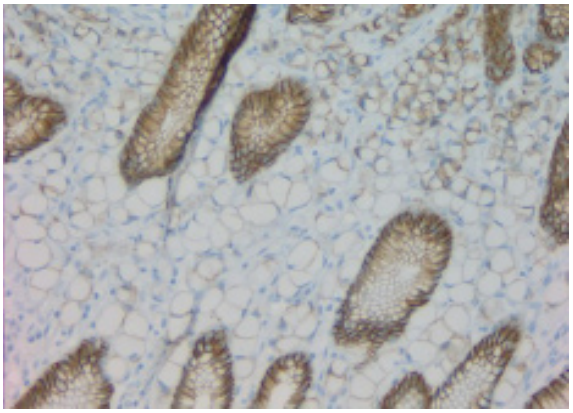


Figure 1: Gastric tumor; A: hematoxylin and eosin stain, high resolution (20x magnification); B: E-cadherin stain, high resolution (20x magnification)

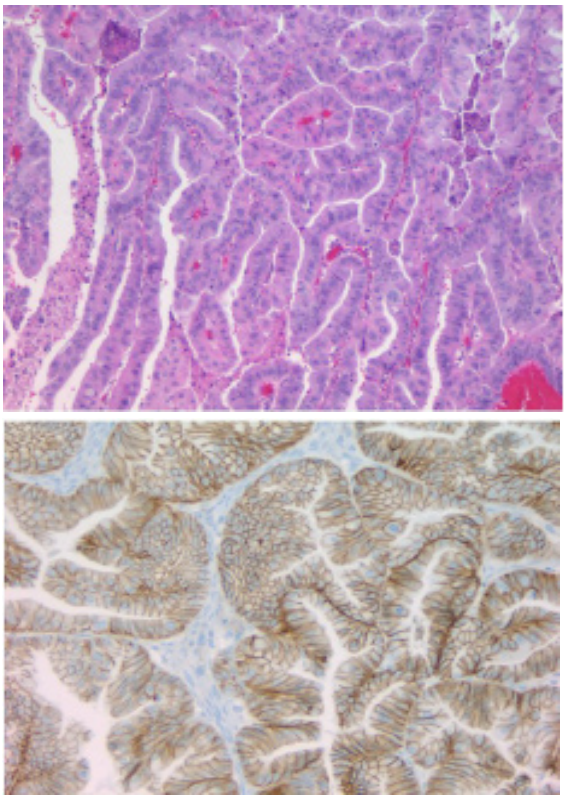


Figure 2: Ovarian mucinous tumor; A: Hematoxylin and eosin stain 10x magnification; B: E-cadherin staining 20x magnification

Discussion

Classically, CDH1 germline mutation is an autosomal dominant mutation with high penetrance and associated with HDGC, LBC, possibly colorectal cancer, and some cases of cleft lip/palate [3]. Other cancers that have been observed in individuals with CDH1 mutations have included lung, salivary gland and prostate; with an incidence not greater than that of sporadic frequency and therefore cannot be associated with the CDH1 mutation [1]. We describe a case of a young nulliparous woman with a history of HDGC and a second primary cancer: ovarian mucinous adenocarcinoma (intestinal type).

Somatic mutation of CDH1 is common in many different sporadic epithelial tumors, and has been demonstrated specifically in epithelial ovarian tumors. In general, E-cadherin loss has been a late finding, its loss a critical step in tumor progression, and therefore associated with increased tumor aggressiveness and

metastasis [4]. In an assessment of the molecular expression of cadherin and catenins in ovarian cancer, Sarrio *et al.* demonstrated E-cadherin levels differentially expressed in varying histologic subtypes of epithelial ovarian cancer [5]. Specifically they demonstrated a strong expression of E-cadherin in the 13 mucinous tumors that were analyzed, and postulated that this was a positive prognostic sign, in line with the excellent prognosis of early mucinous ovarian tumors [5]. CDH1 mutation in the context of an ovarian mucinous carcinoma has to our knowledge only been described by Ardakani *et al.*, where a somatic CDH1 mutation was identified in a mucinous ovarian tumor and associated mural carcinomatous nodule, which was advanced stage (Stage IV) [6].

In contrast to somatic CDH1 loss related to tumor progression, germline CDH1 mutation in HDGC and LBC has shown E-cadherin loss associated with tumor initiation. The mechanism by which this occurs specifically in HDGC is unclear, and why the mutation predisposes predominately to gastric cancer is unknown [1]. CDH1 mutation is a classic tumor suppressor gene, and requires two hits for the initiation of disease. In the majority of cases this is due to CDH1 promoter hypermethylation, which is a mechanism of epigenetic variation in gene expression [7], but can also be due to mutation and loss of heterozygosity mediated hits, or histone modifications [1].

Since CDH1 mutation has not been classically demonstrated in mucinous ovarian adenocarcinoma, the question remains if our case is related to the mutation, or rather represents a sporadic second primary. Ottenhof *et al.* described a case of a pancreatic ductal adenocarcinoma in the context of an individual with a history of HDGC and CDH1 mutation. They concluded that this case was a sporadic tumor since E-cadherin was strongly expressed in the pancreatic ductal adenocarcinoma, and no E-cadherin promoter hypermethylation was found, suggesting intact E-cadherin signalling [8]. In our case, the ovarian mucinous adenocarcinoma showed weak E-cadherin signalling (Figure 1). This does contrast the findings of Sarrio *et al.*, which showed strong E-cadherin expression in mucinous ovarian adenocarcinomas. A recent paper by Choi *et al.* evaluated various germline mutations in patients with peritoneal and fallopian tube carcinoma, and found the same 3 variants of unknown significance in the CDH1 gene in 3 individuals with peritoneal carcinoma, the significance of which is currently unknown [9].

However, contrasting the E-cadherin expression in the ovarian tumor to that of her gastric tumor, the E-cadherin signalling was almost entirely absent, which is more classic for a double-hit event (Figure 2). Promoter hypermethylation could explain why the E-cadherin expression is variably downregulated in the ovarian tumor; however, the gold standard for this would be sequencing the CDH1 gene in the tumor tissue, which was not available in our center.

CDH1 germline mutation is a rare familial cancer gene associated with HDGC, LBC, possibly colorectal carcinoma, and cleft lip/palate. Our case of an ovarian mucinous adenocarcinoma in a patient with a known CDH1 germline mutation postulates whether they are related. Immunohistochemistry described here suggests they are likely unrelated, but if the second hit of the CDH1 germline mutation was due to promoter hypermethylation it may explain the differential CDH1 expression patterns between the ovarian and gastric tumors. Particularly with rare familial cancer syndromes such as CDH1, as identification and understanding of tumor biology and genetics evolves, more associated tumors and conditions are likely to be identified.

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