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CASE REPORT

Gallbladder Adenocarcinoma as the First Manifestation of Germline BRCA1 Mutation

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Introduction

Gallbladder adenocarcinoma (GBAC) is an uncommon, but highly fatal malignancy that follows an aggressive course and complete remission is rare. Germline mutations in BRCA1 genes have been associated with a significantly increased risk of breast and ovarian cancers as well as other malignancies. Here, we describe the first case of gallbladder adenocarcinoma as the initial presentation of BRCA1 mutation.

Case Presentation

A 47-year-old Caucasian female presented to the clinic with a 2-month history of right upper quadrant abdominal pain and skin discoloration. Past medical history was remarkable for gastroesophageal reflux disease and aneurysmal bone cysts. She had a 20-pack year history of tobacco smoking but quit 15 years ago. Famotidine was the only home medication. Family history was unknown as the patient did not have contact with her parents.

Vital signs were unremarkable, and exam was notable for a thin female patient with a weight of 105 lb (48 kg), scleral icterus, and right upper quadrant tenderness to palpation. Labs were remarkable for conjugated hyperbilirubinemia but with a normal WBC count. Abdominal ultrasonography showed a hyperechoic gallbladder mass with biliary dilation. Computed tomography of the abdomen revealed a 6 × 5-cm heterogeneous mixed solid and cystic mass in the porta hepatis with invasion of the left hepatic lobe (Fig. 1). It also demonstrated intra and extrahepatic biliary dilation as well as periportal and peripancreatic lymphadenopathies. CA 19–9 was elevated at 214 units/mL (reference range 0–35 units/mL). Magnetic resonance cholangiopancreatography showed an intraluminal gallbladder mass with common bile duct obstruction but without evidence of hepatic metastasis. Due to concern for biliary obstruction, endoscopic retrograde cholangiopancreatography with papillotomy and common bile duct stenting was performed. Aspiration biopsy of the peripancreatic lymph nodes as well as common bile duct brushing cytology revealed adenocarcinoma.

Patient underwent exploratory laparotomy followed by Whipple's procedure. Biopsy of the lesion revealed primary gallbladder adenocarcinoma with papillary features (Fig. 2). Adjuvant chemotherapy with gemcitabine and cisplatin was started, but the patient completed four cycles only due to side effects. About 3 years later, she was diagnosed with stage IA invasive ductal carcinoma of the right breast after a suspicious lesion was noted on screening mammography. Biomarker testing revealed positive estrogen and progesterone receptors and negative HER2. She underwent right mastectomy and was started on Letrozole. Two years later, surveillance imaging did not show evidence of recurrence of either malignancy.

The patient was referred for genetic evaluation and counseling. She thought she was of Western European ancestry with no known Ashkenazi ancestry. Unfortunately, she had limited contact with her family and could not provide further

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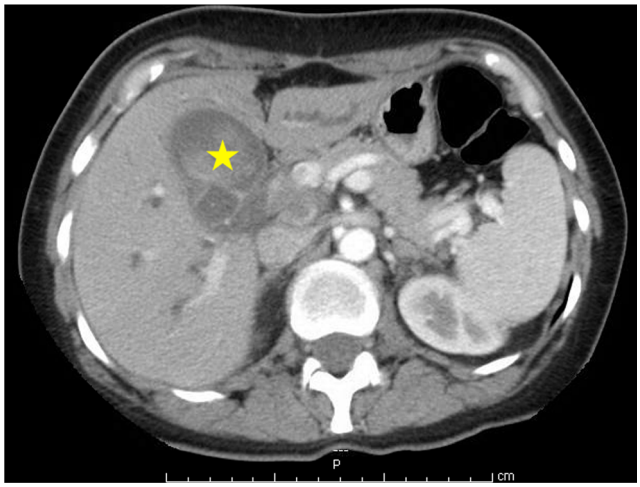

Fig. 1 Axial-computed tomography of the abdomen showing a 6 × 5-cm hypodense mass in the left hepatic lobe (yellow star)

family history (Fig. 3). Given the personal history of two malignancies diagnosed under the age of 50 and limited family history, she underwent genetic testing for the following genes: APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53, VHL, and XRCC2. The patient tested positive for BRCA1 (c.5177_5180delGAAA (p.Arg1726LysfsX3)). She later underwent prophylactic hysterectomy and bilateral salpingo-oophorectomy.

Discussion

Gallbladder adenocarcinoma (GBAC) is the most common cancer of the biliary tract and the sixth leading cause of digestive tract malignancies [1]. Geographic and ethnic variations were noted as relatively high incidence rates were observed in central European, Indian American, and Chilean-Mapucho populations [2]. It affects females up to six times more frequently than men [1]. Risk factors include cholelithiasis, gallbladder polyps, porcelain gallbladder, and primary sclerosing cholangitis [1, 3]. Except for female gender, our patient lacked any notable risk factor. GBAC is usually diagnosed incidentally after routine cholecystectomy [4]. It can also present with non-specific symptoms such as abdominal pain, jaundice, and weight loss that often appear late in the course of the disease. Therefore, delayed diagnosis which was the case with our patient is common [1, 2]. Overall, GBAC carries an unfavorable prognosis with only 10% of tumors are amenable to surgical resection with a curative intent [4].

BRCA1 genes are tumor suppressor genes that are involved in repair of damaged DNA. Mutations of the BRCA1 genes have been shown to interfere with the ability of cells to repair double-stranded DNA breaks by homologous recombination [5]. Germline mutations in BRCA1 are common in certain ethnic populations such as Ashkenazi Jews. They are inherited in an autosomal dominant fashion with incomplete penetrance and are associated with a significantly increased risk of breast and ovarian cancers as well as others [6].

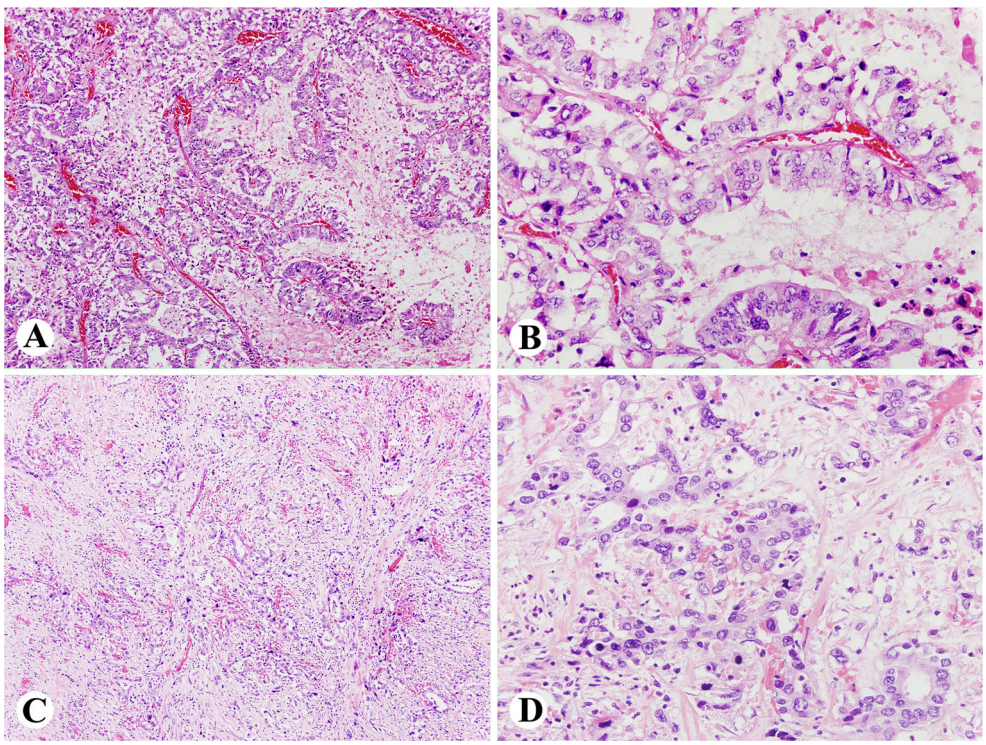

Fig. 2 Gallbladder adenocarcinoma with papillary features (**a**–**b**) and deep invasion (**c**–**d**) (H&E stain and C, 100×; B and D, 400×)

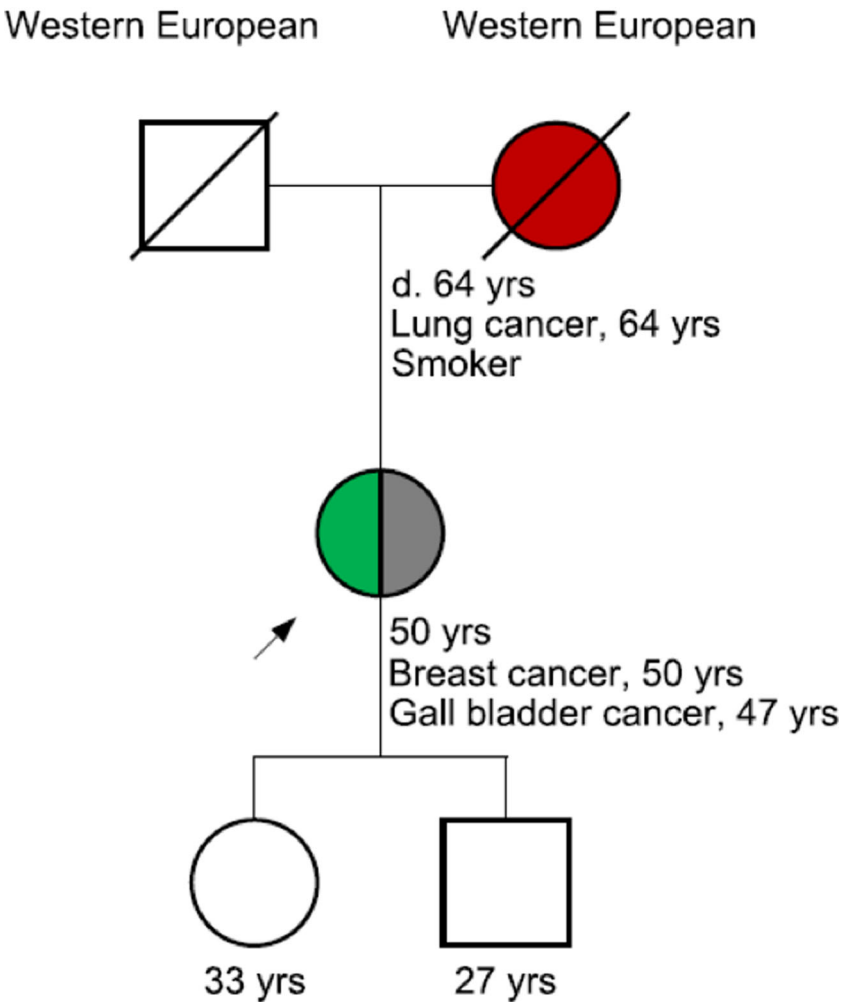

Fig. 3 Pedigree of the proband (represented by the arrow). No information was available about grandparents, aunts and uncles, cousins, and possible half siblings

Several digestive malignancies, especially pancreatic adenocarcinoma, have been previously described in patients with germline BRCA1 mutations [7, 8]. A number of population-based and epidemiologic studies have reported an increased incidence of gallbladder carcinoma in carriers of BRCA mutations [9, 10]. Risch et al. reported an eightfold increased risk of hepatobiliary cancers among first-degree relatives of patients with BRCA mutations [9]. Another study by the Breast Cancer Linkage Consortium reported a fivefold increased risk of gallbladder and bile duct cancers in 173 breast-ovarian cancer families with BRCA2 mutations [10].

Our patient was managed with surgical resection and adjuvant chemotherapy with cisplatin and gemcitabine. Previous reports have shown that several BRCA1-related tumors may be more responsive to cisplatin-based or gemcitabine-based regimens [11, 12], as well as to a newer class of medications known as poly ADP Ribose Polymerase (PARP) inhibitors [13, 14]. Surveillance imaging did not show recurrence of disease 5 years after diagnosis of GBAC in our patient. Like other BRCA-related malignancies, BRCA1-related GBAC may be more responsive to cisplatin-based or gemcitabine-based regimens.

Genetic testing was offered based on the patient's clinical history alone as the family history was limited. Like in adopted individuals, the limited family history poses challenges in providing a comprehensive and appropriate plan for prevention and detection of concomitant malignancies [15]. Unfortunately, the mode of transmission (paternal or maternal) or if other family members had unusual malignancies will likely never be clear. Both offspring were offered testing but declined. The social complexities and dynamics of families can often confuse and limit the usefulness of genetic testing. Therefore, limited family history should not discourage clinicians from pursuing genetic testing in patients with features suggestive of an inherited cancer syndrome.

Association of hepatobiliary tumors with BRCA1 mutations has been reported in several population studies. However, GBAC in the setting of BRCA1 mutation has been previously described in only one case report. Unique to our patient with germline BRCA1 mutation is the diagnosis of GBAC as the patient's first malignancy. Therefore, germline BRCA1 mutations need to be considered in patients with GBAC and atypical features such young age, absence of

typical risk factors, and presence of other malignancies. Referral to a geneticist is appropriate in such cases as this can reduce future risk of other malignancies by genetic counseling, enhanced screening, and prophylactic surgeries.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Patient Consent Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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