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Case report

Combined modality therapy including cytoreductive surgery and heated intraperitoneal chemotherapy for synchronous low volume peritoneal carcinomatosis from adenocarcinoma of the tail of pancreas in a BRCA-2 carrier resulting in long-term disease-free survival: A case report

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ABSTRACT

Introduction: A BRCA-2 mutation carrier with a metachronous pancreatic adenocarcinoma (PC) and established peritoneal metastases is presented. Combined modality therapy including Cytoreductive Surgery (CS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) was associated with long-term disease-free survival.

Case presentation: A 62-yr. old female underwent successful treatment for stage IIIa carcinoma of the right breast at age 48. 11 years later a cystic adenocarcinoma of the tail of the pancreas with peritoneal metastases was diagnosed. Platin based neoadjuvant chemotherapy followed by definitive resection of the pancreatic mass with cytoreductive surgery (CS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) with mitomycin C was performed. Postoperatively, a retro-gastric fluid collection developed from a pancreatic duct leak, successfully managed non-operatively. Maintenance poly ADP ribose polymerase (PARP) inhibitor therapy was initiated after recovery from surgery. The patient experienced a 30-month disease free survival and was subsequently found to have oligometastases to the brain.

Discussion: CR and HIPEC have not been reported to be efficacious in patients with pancreatic carcinomatosis. However, PC arising in BRCA-2 carriers has a DNA repair defect, which is sensitive to platin based chemotherapy and mitomycin C. HIPEC has more severe postoperative complications following distal pancreatectomy. Isolated brain metastases from PC are rare. BRCA-2 mutation carriers are at significantly increased risk for PC.

Conclusion: Leveraging the DNA Repair defect in BRCA-2 pancreatic adenocarcinoma, including CS and HIPEC, led to long-term disease-free survival and good locoregional control in this patient. Complications from HIPEC are more severe. BRCA-2 carriers should undergo annual pancreatic cancer screening.

1. Introduction

A BRCA-2 Mutation Carrier developed a cough, and after an extensive work-up, was found to have a metachronous pancreatic adenocarcinoma with limited peritoneal spread. Management targeted the defect in DNA repair seen in these tumors and aggressive surgery resulting in good disease-free survival with rare brain only metastases.

This report was developed using SCARE 2020 criteria [1].

1.1. Patient information

This 62-yr. old Caucasian female's medical history includes diet-controlled Type II Diabetes Mellitus, obesity, degenerative joint disease and Stage IIIA, pT1b, N2a, M0 invasive breast cancer diagnosed at age 48. A right modified radical mastectomy was performed. Adjuvant therapy included Cytoxan, Adriamycin, Taxol and chest wall irradiation. Genetic testing revealed BRCA-2 deleterious mutation (E97X517GT). A

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left prophylactic mastectomy with bilateral latissimus dorsi flap reconstructions and bilateral salpingo-oophorectomy without hysterectomy followed. Surveillance with oncology for 10 years found no recurrence. Family history included a maternal grandmother with breast cancer, and a maternal aunt with Hodgkin Lymphoma. Allergies include Penicillin. There is a 10-pack year history of smoking.

1.2. Clinical findings

Examination found a healthy appearing middle aged white female with a BMI of 36.3. There were postoperative changes from prior bilateral mastectomy and latissimus dorsi reconstructions, without chest wall mass or regional adenopathy. There was no abdominal or pelvic mass, no Sister Mary Joseph Lymph Node, and no ascites.

1.3. Diagnostic assessment

MRI of the abdomen (Fig. 1) revealed a 3.6 × 2.0 cm cystic lesion of the pancreas suspicious for malignant transformation (Fig. 1). CT of the abdomen and pelvis confirmed the pancreatic lesion and cholelithiasis. Endoscopic US guided needle biopsy of the cystic neoplasm revealed pancreatic adenocarcinoma. Serum CEA was 63.4 ng/ml, and serum Ca19-9 was 5052 U/ml. Staging laparoscopy revealed no overt peritoneal metastases, but washings recovered adenocarcinoma (Fig. 2).

1.4. Therapeutic intervention

Neoadjuvant FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin, irinotecan) chemotherapy for twelve cycles was given. Repeat abdominal MRI defined the pancreatic tail mass smaller, measuring 3.1 × 1.8 × 3.9 cm. Serum CEA was 8.5 ng/ml and serum Ca19-9 was 373 U/ml, also significantly improved. Six weeks after chemotherapy an exploratory laparotomy, greater omentectomy, distal pancreatectomy/splenectomy, partial cecectomy, umbilectomy, CS including resection of meso-rectal nodule, para-aortic tissue, and small bowel mesenteric nodule, and HIPEC with Mitomycin-C 30 mg for a total of 120 min at 41 to 42 degrees Celsius was done. An R0 resection with complete cytoreduction was achieved with a Peritoneal Cancer Index (PCI) of [2]. The procedure was performed by authors CO and RAH in an academically affiliated community hospital, which developed a HIPEC Program in 2005. The senior surgeon (RAH) has performed over 100 CS and HIPEC procedures.

Pathology confirmed a ductal adenocarcinoma of the pancreatic tail, histologic grade 2 with evidence of treatment effect measuring 4.5 × 2.5 × 1.4 cm. The margins were negative (R0). Lymph-vascular invasion was not found, and 20 regional nodes were negative. Metastatic disease was found in a peri-cecal soft tissue nodule and a mesorectal nodule (Pathologic stage ypT3, ypN0, ypM1).

1.5. Follow-up and outcomes

The patient had a 12-week postoperative course with an unplanned hospital re-admission for delayed gastric emptying from a controlled pancreatic duct leak and retro-gastric fluid collection (Fig. 3). This was managed with Sandostatin, supportive TPN, and percutaneous G-Tube placement. Ultimately endoscopic trans-gastric stent placement was required with complete resolution of the retro-gastric fluid collection (Fig. 4).

5 months after surgery the patient was home and had reached her preoperative functional status. Repeat CA19-9 and CT of Chest/Abdomen and Pelvis at six months postoperatively were normal. 15 months post-op the PARP inhibitor Olaparib was begun without side effects. Serial CT scans and CA19-9 surveys were continued at six-month intervals without recurrence. 28 months following surgery a surveillance CA19-9 was elevated at 51.93 U/ml and repeat CA19-9 at 29 months confirmed the elevation at 67.47 U/ml. CT scans of the Chest/Abdomen/Pelvis at 30 months were normal, and PET/CT Scan at 32 months was normal. A subsequent MRI of the brain found 2 rim-enhancing masses within the right frontal lobe associated with vasogenic edema (Fig. 5).

Biopsy confirmed metastatic pancreatic adenocarcinoma. The patient underwent craniotomy with resection of two right frontal lobe metastases followed by Gamma Knife Radiosurgery. CT of the chest, abdomen and pelvis at 36 months following her HIPEC still found no evidence of extracranial metastatic disease. The patient subsequently developed leptomeningeal spread and died 39 months following surgery.

2. Discussion

The National Comprehensive Cancer Network (NCCN) recommends annual screening for pancreatic cancer in BRCA-2 patients with a family history of pancreatic cancer [2]. Underscreening for pancreatic adenocarcinoma in BRCA1 and BRCA2 gene mutation patients without a

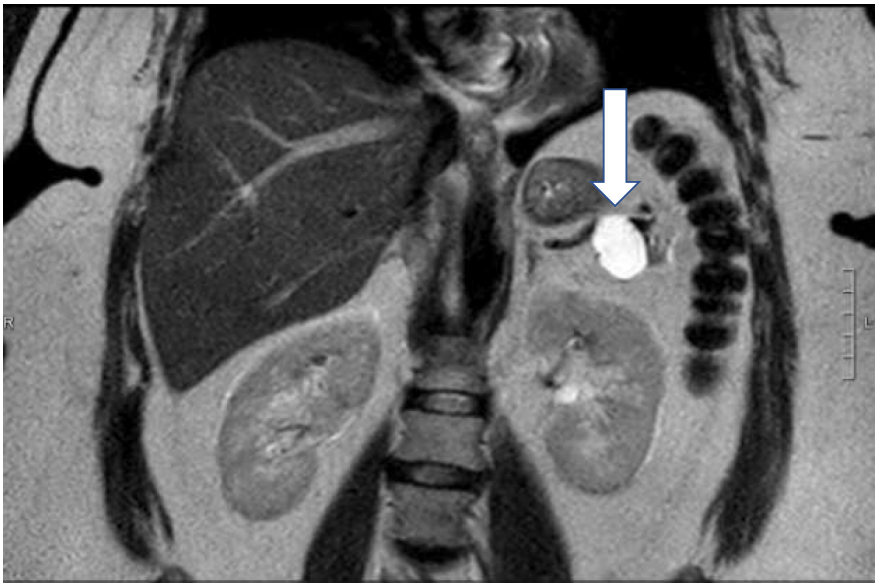

Fig. 1. MRI of abdomen revealing a 3.6 × 2.0 cm cystic lesion of the tail of the pancreas.

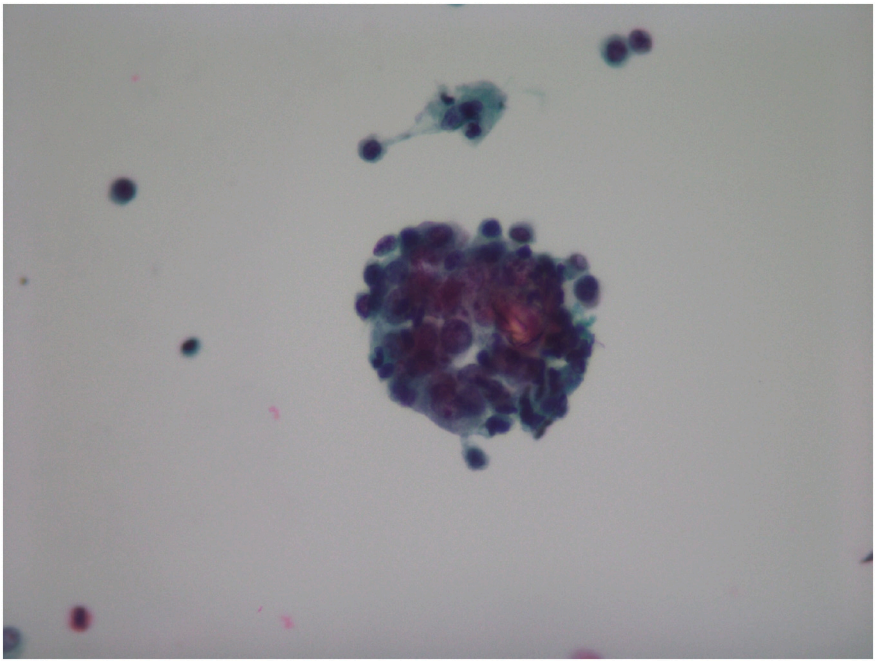

Fig. 2. Intraperitoneal washings and cytology obtained at Staging Laparoscopy showing Adenocarcinoma.

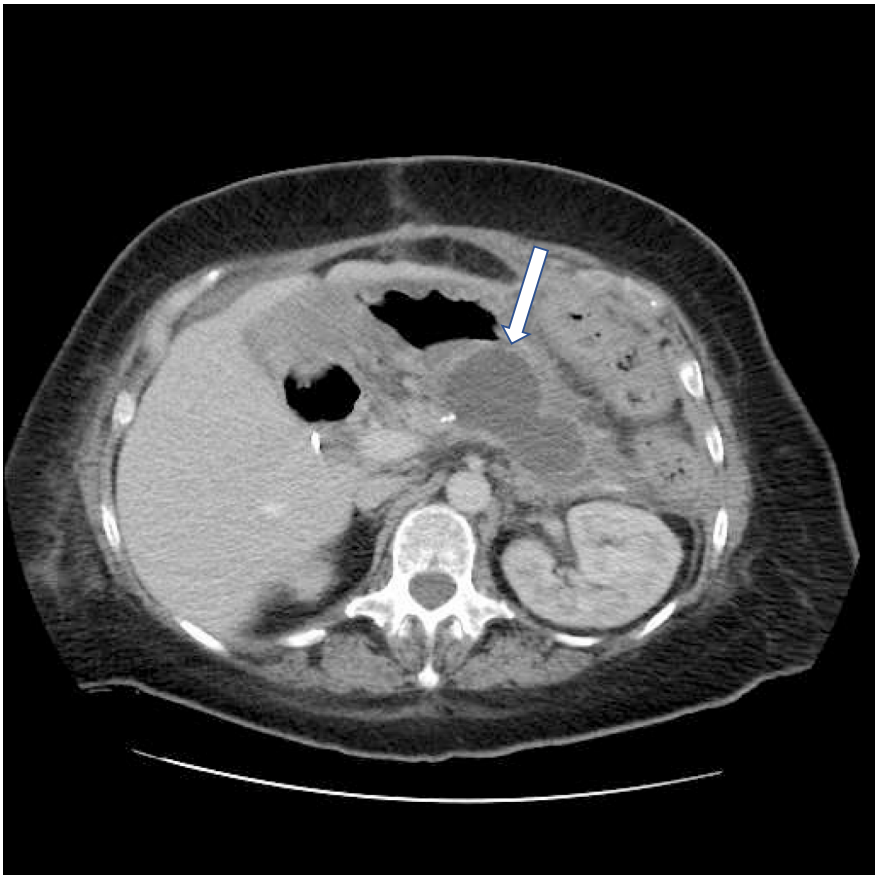

Fig. 3. Retro-gastric Fluid Collection from controlled pancreatic duct leak causing delayed gastric emptying.

family history for pancreatic cancer represents an emerging problem [3]. Had annual screening with Endoscopic EUS, or Pancreatic MRI and MRCP been done in our case, a cystic neoplasm of the pancreas would likely have been found, and resected.

This case provides a template for exploiting the DNA repair defect that pancreatic adenocarcinomas arising in BRCA-2 carriers exhibit. FOLFIRINOX neoadjuvant chemotherapy was chosen because these tumors are sensitive to Platin based multiagent chemotherapy [4,5].

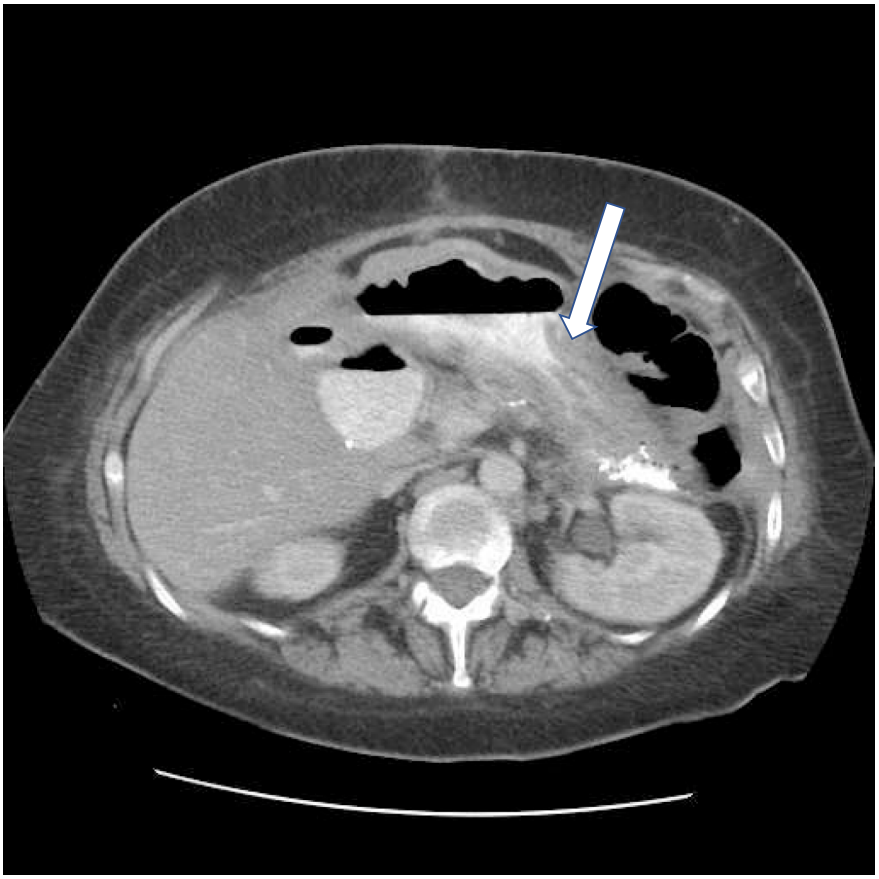

Fig. 4. Retro-gastric fluid collection resolved after endoscopic trans-gastric drainage.

Complete pathologic responses have been reported in similar settings [6]. Proving chemo-sensitivity was one essential foundation upon which to recommend CS with HIPEC in this case. The Mitomycin C for the HIPEC was chosen as it too exploits the DNA repair defect of these tumors [7]. In December 2019 the FDA approved use of PARP inhibitors as maintenance therapy for metastatic pancreatic adenocarcinoma arising in the BRCA-2 patients who had shown response to platin based chemotherapy. Additionally, Vyas and others have reported that platinum derivatives, mitomycin-C, and PARP inhibitors targeting DNA defect show efficacy [4,5,6,7,8].

This case highlights the importance of accurate staging. Knowing there were peritoneal metastases at the time of diagnosis guided informed application of neoadjuvant chemotherapy. It also allowed an opportunity to confirm the tumor was "chemosensitive".

Several authors have shown significant elevation of the serum CEA and Ca19-9 tumor markers is associated with metastatic disease and helpful in tailoring diagnostics [9,10,11]. This patient's initial CEA was 63.4 ng/ml and Ca 19-9 was 5052 U/ml both markedly elevated, prompting the staging laparoscopy. DeRosa reviewed 149 articles in the literature from 2000 to 2014, and developed an algorithm for staging laparoscopy including: CT scan revealing resectable tumor, Ca 19-9 greater or equal to 150 U/ml, and tumor size of greater than 3 cm [12].

Patients with positive cytology for pancreatic adenocarcinoma are classified in the The American Joint Committee on Cancer (AJCC) staging system as stage IV disease and have a guarded prognosis. Ferrone reported patients with positive peritoneal cytology, 37% had metastatic disease, 11% had locally advanced disease and only 5% of patients had a resection with a median overall survival of 8 months [13].

There are few reports of CS and HIPEC for pancreatic adenocarcinoma. Tentes reported on 6 patients with established peritoneal metastases who underwent 8 procedures, with only one surviving to 36 months [14]. Tentes also reported on 33 patients undergoing adjuvant HIPEC for resectable pancreatic cancer. The 5-year survival was 24%, the mean survival was 33 months, and the median survival was 13 months [15].

Our patient developed oligometastases in the brain, with long term control of her locoregional and peritoneal disease (36 months). Brain only metastases from pancreatic carcinoma are rare. Lemke reviewed the literature and found 12 cases from 1990 to 2012 [16]. 75% of these metastases were metachronous, and all symptomatic. These authors reported benefit from complete resection of brain metastases in carefully selected patients [16].

Multiple authors have reported the number of visceral resections performed with CS and HIPEC is associated with increased morbidity [17,18]. Downs-Canner reported a 26% overall incidence of postoperative pancreatic fistula after performing a distal pancreatectomy. The addition of HIPEC to a distal pancreatectomy during CS was associated with development of more severe pancreatic fistulas, but no increase in the overall fistula rate [19]. Our patient required readmission for a retro-gastric collection attributed to a pancreatic leak classified as a Grade "B" Fistula according to the updated 2016 definition of the International Study Group of Pancreatic Fistula [20]. This was drained internally and did not require reoperation.

2.1. Conclusion

Patients with BRCA-2 mutations should be considered for annual pancreatic screening for pancreatic cancer to include MRI and MRCP or Endoscopic US. Accurate staging is essential once an adenocarcinoma is diagnosed to allow for appropriate therapy and treatment sequencing. Pancreatic adenocarcinoma in BRCA-2 patients is more sensitive to combined modality therapy because of the defect in DNA repair, and this

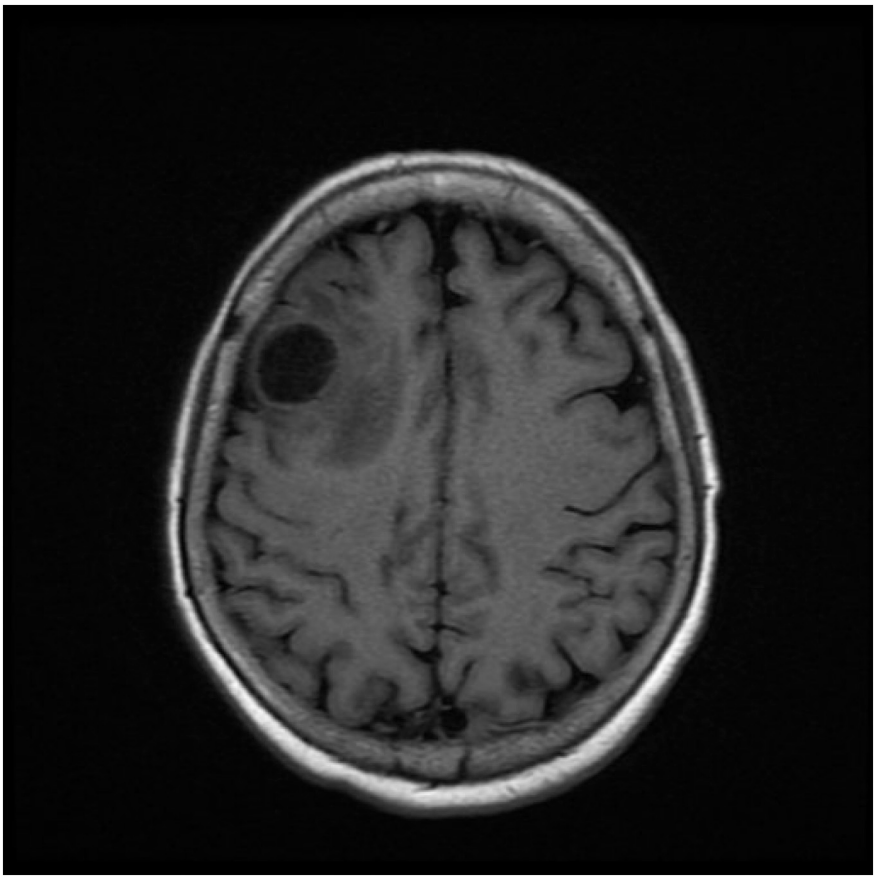

Fig. 5. One of two cerebral metastases defined by MRI of Brain.

defect can be exploited leading to better survival. CS and HIPEC obtained good locoregional and peritoneal control in this patient, but certainly more studies need to be performed before applying HIPEC more broadly because of the associated morbidity of this therapy.

2.2. Patient perspective

28 months after surgery our patient reported she "was doing great!" She had regained her weight, was eating well with no abdominal pain. She was walking daily without difficulty. Her wound had healed "perfectly". She experienced no side effects from long-term PARP Inhibitor maintenance therapy.

Written consent was obtained from the patient.

Provenance and peer review, not commissioned, externally peer-reviewed.

Ethical approval

Ethical approval has been exempted by my institution for this case report.

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CRediT authorship contribution statement

1. Richard A Hoefer, DO, FACS was co-surgeon and contributed to the concept of this report, and writing of this paper.
2. Chukwuemeka Obiora, MD, FACS was co-surgeon for this case, and contributed to the concept of this report.
3. Basem Azab, MD contributed to the concept of this report and provided careful review of the paper.
4. Elizabeth A Harden, MD cared for this patient, and contributed to the concept of this report and helped edit the manuscript.
5. John F. Kessler cared for this patient and contributed to the concept of this report.

Guarantor

Richard A Hoefer, DO, FACS accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Consent

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

Declaration of competing interest

The authors have no conflicts of interest to declare.

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