Journal of Cancer Research and Practice

journal homepage: www.ejcrp.org

Case Report

Germline BRCA2 Mutation Pancreatic Adenocarcinoma

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Abstract

Pancreatic adenocarcinoma is one of the most challenging malignancies. Its surgical resection is regarded as the only potential curative treatment. However, most patients present with advanced stages, associated with very poor prognosis. Germline BRCA1 and BRCA2 (BRCA1/2) mutations account for few advanced pancreatic adenocarcinomas and thus present as disease-specific entities. Cancers harboring BRCA1/2 mutations are relatively more chemosensitive and have exhibited survival benefits with platinum-containing combination treatments. FOLFIRINOX has been evaluated in various trials and is a well-established first-line chemotherapy for metastatic pancreatic cancer in patients with good performance status. Here, we report the case of a patient with germline BRCA2-mutation pancreatic adenocarcinoma who exhibited a good response to modified FOLFIRINOX, achieving an 18-month complete response.

Keywords: BRCA, olaparib, pancreatic cancer

Introduction

Pancreatic cancer is a highly lethal malignant disease. Germline *BRCA1* and *BRCA2 (BRCA1/2)* mutations account for approximately 4%–7% of pancreatic adenocarcinomas[1,2] and are considered to be a different disease entity. Clinical studies have suggested that tumors harboring a *BRCA* mutation are more likely to respond to platinum-containing combination treatments and to have a more favorable prognosis.[3-6] Herein, we present the case of a patient with germline *BRCA2*-mutated metastatic pancreatic adenocarcinoma who successfully achieved a complete response with FOLFIRINOX treatment.

Received: 28-Jul-2019 **Revised:** 05-Sep-2019
Accepted: 09-Sep-2019 **Published:** 02-Mar-2020

Access this article online

Quick Response Code:

Website: www.ejcrp.org

DOI: 10.4103/JCRP.JCRP_20_19

Case Report

A 78-year-old man presented to our Medical Oncology Department in June 2017 with high levels of tumor markers, including carcinoembryonic antigen (8.2 ng/dL) and carbohydrate antigen (CA 19-9; 4818 U/mL), detected during a regular health checkup. He did not report a history of weight loss, loss of appetite, changes in bowel habits, or other specific discomfort, and a physical examination revealed only mild upper abdominal tenderness. His family history included type 2 diabetes mellitus, and his two daughters had breast cancer with *BRCA2* mutation.

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How to cite this article: Chen WC, Chen MH. Germline BRCA2 mutation pancreatic adenocarcinoma. J Cancer Res Pract 2020;7:29-33.

A positron emission tomography-computed tomography (CT) scan revealed fluorodeoxyglucose-avid focus in the pancreatic tail with at least two focal uptakes in the liver; a pancreatic neoplasm with liver metastasis was suspected. Magnetic resonance imaging (MRI) of his abdomen subsequently revealed a mass lesion measuring 4.2 cm in the pancreatic tail, with several nodular lesions in the liver [Figure 1a]. Based on laboratory examination and radiological findings, a multidisciplinary tumor conference consensus was that it was a resectable pancreatic tail tumor. He subsequently received laparoscopic distal pancreatectomy and splenectomy in June 2017. At the time of surgery, the lesion was well defined and measured 3.5 cm (length) ×2.5 cm (diameter). Pathological findings indicated a moderately to poorly differentiated adenocarcinoma without lymph node metastasis, and the tumor was stage pT3N0M1. However, the postoperative CA 19-9 level was elevated to 6740 U/mL, and liver CT demonstrated multiple liver metastases [Figure 1b]. To actively seek further treatment, the patient was then referred for genetic testing. A specimen from the primary pancreatic tumor and a blood sample were sent for a next-generation sequencing assay (ACT Genomics), which identified a somatic *KRAS* Gly12Asp mutation along with an effective target drug (sorafenib). Furthermore, the copy number variants of heterozygous deletions over *ARID1A* and *FLCN* were revealed. Notably, a germline *BRCA2* single nucleotide mutation (c. 809C> G) over exon 10 on chromosome 13, leading to Ser270Ter amino acid change, was detected in both the primary lesion and blood sample [Table 1].

A reduced dose of a modified FOLFIRINOX regimen (i.e., 120 mg/m^2 irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 folinic acid, and 2000 mg/m^2 5-fluorouracil through continuous intravenous infusion over 40 h) was selected as first-line adjuvant treatment, considering his good performance status 1 and genetic results. He received 12 cycles with prophylactic granulocyte colony-stimulating factor support for 6 months (June 2017–March 2018). In January 2019 (6 months after the diagnosis), a repeat abdomen CT revealed complete regression of the metastatic tumors over his liver without evidence of disease at the primary site [Figure 1c]. He then

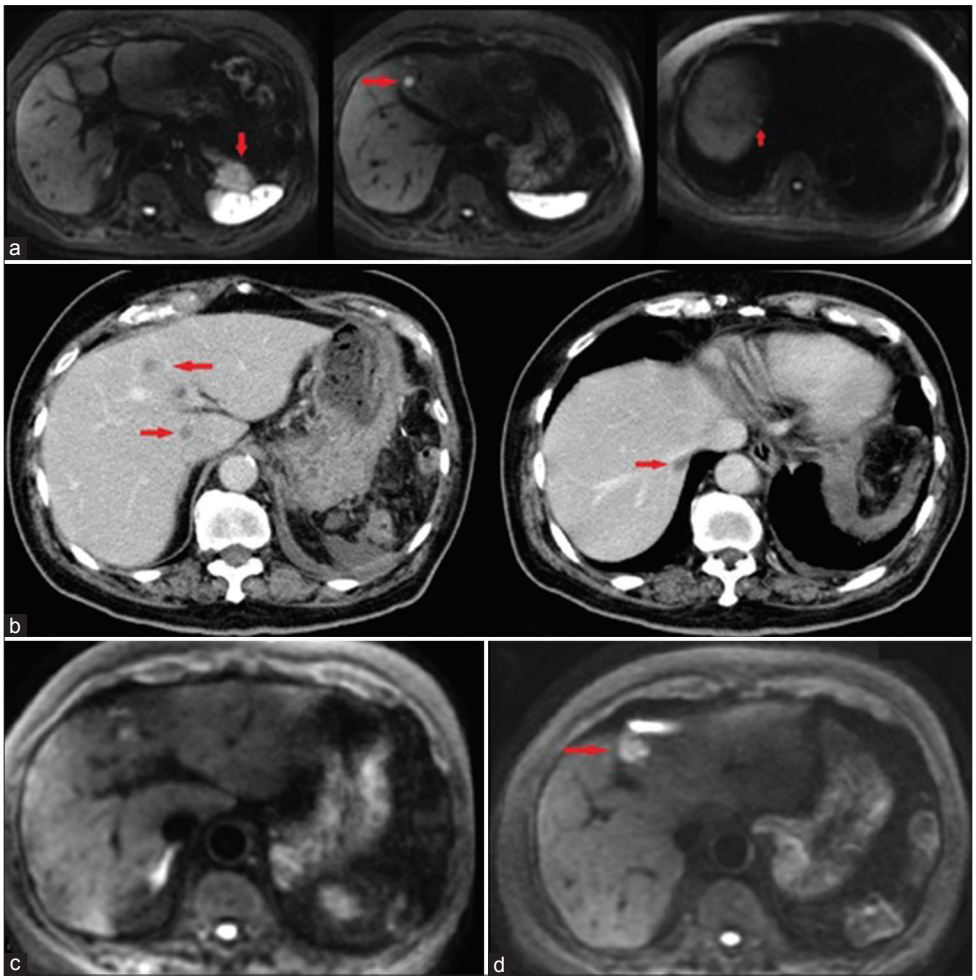

Figure 1: (a) Abdominal magnetic resonance images revealed a heterogeneous lesion with enhancement at the pancreatic tail along with liver metastasis. (b) Abdominal computed tomography revealed multiple liver metastases 1 month after surgical resection. (c) A 16-month complete response of the liver metastases and primary tumor in follow-up magnetic resonance images. (d) Solitary liver recurrent metastasis was noted in March 2019, 18 months after surgery

Table 1: Next-generation sequencing assay results

Tissue	Gene	Genomic alternation	Coverage	Allele frequency (%)	cDNA change
Pancreas	BRCA2	Ser270Ter	345	51.9	c.809C>G
	KRAS	Gly12Asp	2784	17.0	c.35G>A
	ARID1A	Heterozygous deletion			
	FLCN	Heterozygous deletion			
Blood	BRCA2	Ser270Ter	345	49.4	c.809C>G

received maintenance treatment with TS-1 (oral tegafur/gimeracil/oteracil) for 12 months (April 2018–March 2019). This treatment was discontinued when recurrence was noted on follow-up MRI in March 2019 [Figure 1d], with a 1.8-cm nodule at S4a of the liver with low signal intensity on T1-weighted and high signal intensity on T2-weighted MRI with arterial enhancement and isointensity in the delayed phase, which led to peripheral focal bile duct dilatation and perfusion change. Furthermore, his CA 19-9 level increased synchronously to 968 U/mL. He underwent radiofrequency ablation under the impression of solitary liver metastasis and was again treated with the combination FOLFIRINOX regimen in April 2019. Three months after the liver metastases had been discovered, a repeat MRI scan revealed complete remission, and a reduced CA 19-9 level of 357 U/mL was noted.

Discussion

BRCA1 and *BRAC2* are tumor suppressor genes that protect cells by maintaining chromosomal stabilization and genome integrity, thereby enabling an error-free DNA repair process through the homologous recombination pathway following double-strand DNA breaks.[7] Thousands of types of mutations in these genes have been identified, with some being recognized as pathogenic variants that may lead to malignancy development. Germline *BRCA1/2* mutations are inherited in an autosomal-dominant fashion and are considered to be susceptibility genes for breast and ovarian cancers.[8-10] The prevalence of BRCA2 mutations in Asian populations varies among countries and studies, ranging from 3.1% to 13.5%. Most Asian studies have reported more frequent mutations in *BRCA2* than in *BRCA1*. According to a cross-sectional study of 68 hospitals with women with hereditary breast and ovarian cancer (HBOC) in Taiwan, among the 272 patients analyzed, the prevalence of *BRCA2* pathogenic mutation was 6.8% (16/236). The Korean hereditary breast cancer study included a total 2953 individuals with HBOC and reported a prevalence of *BRCA2* pathogenic mutations of 3.1% (90/2953). Another study enrolled 260 individuals with HBOC in Japan, of whom 13.5% (35/260) were *BRCA2* positive. In addition, another analysis of 94 individuals with breast and ovarian tumors conducted in Singapore revealed a prevalence rate of *BRCA2* mutations of 11.1%.[11-13] Moreover, *BRCA1/2* mutations represent a major genetic predisposition to pancreatic adenocarcinoma, with a 2- to 6-fold increased risk in such patients. *BRCA1/2* mutations are estimated to occur in approximately 4%–7% of patients with pancreatic adenocarcinoma.[1,2] Patients with germline *BRCA1/2* mutations are more likely to develop cancers at a younger age with a more aggressive disease compared to those without germline *BRCA1/2* mutations.[5,14-16] However, the prognosis varies according to the origin of the cancers. Germline *BRCA1/2* mutations have been associated with a higher risk of nodal involvement, distant metastasis, and poor survival in prostate cancer. However, the prognosis is equivocal or may even be better in patients with pancreatic and ovarian cancers.[5,15] *BRCA1/2* mutation tumors typically present with a later clinical stage, a greater possibility of developing metastatic lesions, and a higher pathological grade. In our patient, we detected a single-nucleotide *BRCA2* mutation, *BRCA2* c.809C>G over exon 10 on chromosome 13, leading to Ser270Ter amino acid change. This variant allele is predicted to encode a truncated nonfunctional protein product and to be related to a hereditary cancer-predisposing syndrome according to the BRCA exchange. The BRCA exchange is a database that aggregates data consisting of the international evidence-based network for the interpretation of germline mutant alleles consortium expert panel, along with expert clinicians, diagnosticians, researchers, and database providers to advance the understanding of *BRCA1* and *BRCA2* variations.[17,18]

Mutations of *BRCA1/2* interfere with normal cellular function, leading to not only the onset and progression of cancer but also the impaired ability of tumor cells to repair platinum-induced double-strand breaks. Thus, these tumors may be more chemosensitive to DNA-damaging agents or ionizing radiation and cause subsequent cell apoptosis.[19,20] In addition, a large body of clinical evidence suggests that such patients may exhibit survival benefits when exposed to platinum-based chemotherapy regimens, including cisplatin, oxaliplatin, and carboplatin, compared to those who receive nonplatinum combinations.[4,21] Six-month treatment with FOLFIRINOX, a platinum-containing combination therapy (oxaliplatin, irinotecan, fluorouracil, and leucovorin), has been suggested as a standard of care for advanced pancreatic adenocarcinoma with *BRCA1/2* mutations.[22,23]

Novel agents such as poly(ADP-ribose) polymerase (PARP) enzyme inhibitors are molecules that inhibit the activity of PARPs involved in various DNA damage repair pathways, which separate histones from DNA and enable DNA repair. The accumulation of DNA damage

due to the lack of DNA repair mechanisms by PARP inhibitors has been shown to result in mitotic catastrophe and subsequent tumor cell death.[24] In clinical trials on patients with a germline *BRCA2* mutation, response rates of approximately 40% have been recorded with olaparib for recurrent breast and 31% for ovarian cancers.[25-28] Pancreatic cancer cells with *BRCA2* mutations are also sensitive to PARP inhibitors. A randomized, double-blind, placebo-controlled phase 3 (POLO) trial which evaluated the efficacy of olaparib as maintenance therapy in patients with a germline *BRCA1*/2 mutation showed no progression of metastatic pancreatic cancer or disease during first-line platinum-based chemotherapy. In addition, the median progression-free survival was significantly longer in the patient group (7.4 months) than in the placebo group (3.8 months).[29] The antitumor activity of PARP inhibitor maintenance treatment after first-line chemotherapy was demonstrated in this population and may have been considered as an onward treatment option for our patient.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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