Case Report

Exceptional response to FOLFIRINOX in a patient with pancreatic cancer and a germline *RAD51C* mutation

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Abstract: Pancreatic cancer is projected to become the second leading cause of cancer death in the United States by 2030. Deleterious germline mutations can contribute to pancreatic cancer susceptibility. Herein we report a case of a patient with metastatic pancreatic adenocarcinoma to the lung and liver who was found to have a deleterious germline mutation in *RAD51C* who had a remarkable response to chemotherapy with FOLFIRINOX, a platinum-containing regimen.

Keywords: Pancreatic adenocarcinoma; *RAD51C*; oxaliplatin

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Introduction

Current guidelines for germline genetic testing in patients with pancreatic cancer are limited compared to guidelines available for breast, ovarian, and colon cancer patients. However, identification of heritable deleterious mutations can guide treatment decisions for patients and can impact screening recommendations for family members. *BRCA1*, *BRCA2* and *PALB2* are genes, which encode proteins that are part of the Fanconi Anemia pathway and are involved in DNA repair. Germline mutations in these genes are known to be associated with increased risk for pancreatic adenocarcinoma in addition to other types of cancers. Proteins in the Fanconi Anemia pathway function together with a family of proteins known as the *RAD51* paralogs which consist of five proteins (*RAD51B*, *RAD51C*, *RAD51D*, *XRCC2* and *XRCC3*). The *PALB2* protein acts as a hub to join *RAD51* with *BRCA1* and *BRCA2* to repair double stranded DNA breaks via homologous recombination (1).

We report a patient with a germline *RAD51C* mutation with pancreatic adenocarcinoma. We pay special attention to his response to systemic therapy with the cross-linking agent oxaliplatin, which supports a causal relationship between the *RAD51C* mutation and the pathogenesis of his cancer.

Case presentation

A 60-year-old Hispanic man with a past medical history of hypertension, dyslipidemia and gout presented with new onset dyspepsia, and given persistence of his symptoms and an associated 14-pound weight loss. His family history was positive for prostate cancer in his father in his 80s, a paternal cousin with ovarian cancer in her 60s, and a maternal cousin with endometrial cancer. He was referred for an ultrasound of the abdomen. The ultrasound showed a cystic mass in the tail of the pancreas, as well as multiple liver masses and retroperitoneal adenopathy. A computed tomography (CT) scan revealed a hypo-enhancing mass in the pancreatic distal body and tail measuring 6.2×4.6 cm^2, encasing the splenic artery and celiac trunk, extensive abdominal lymphadenopathy, numerous scattered pulmonary nodules and numerous hypo-enhancing liver tumors consistent with metastatic pancreatic cancer. He underwent percutaneous biopsy of a liver tumor, which was positive for metastatic poorly differentiated adenocarcinoma, compatible with pancreatobiliary primary.

Next generation sequencing of the tumor biopsy using a commercially available panel revealed alterations in *KRAS*, *ASXL1*, *EP300* loss, *KMT2C* (MLL3), and *TP53*. The tumor was microsatellite stable and the tumor mutation

Table 1 Germline and Somatic genetic sequencing data

Alterations detected	Germline panel	Somatic next-generation sequencing
Known deleterious alterations	*RAD51C* gene (c.709C>T, p.Arg237Ter)	KRAS (G12R)
		ASXL1 (C594*)
		EP300 loss (exons 4-6)
		KMT2C (MLL3) (D1371fs*7)
		TP53 (F134V)
		Microsatellite stable
		Tumor mutation burden Intermediate (8 Muts/Mb)
Variants of unknown significance	BRCA2 (c.3262C>T, p.Pro1088Ser) MUTYH (c.1234C>T, p.Arg412Cys)	BRCA2 (P1088S)
		MUTYH (R412C)
		JAK1 (I62V)
		CBL (S739F)
		CD79A (P78S)
		PBRM1 (R1561S)
		CDKN2A rearrangement
		POLD1 (A769S)
		FANCA (F419S)
		PREX2 (N1224S)
		FLT1 (R133K)
		TGFBR2 (N490fs*26)

burden was intermediate (8 Muts/Mb). Somatic variants of uncertain significance are shown in *Table 1*. Multigene panel testing of germline DNA revealed that he carries a mutation in the *RAD51C* gene (c.709C>T, p.Arg237Ter). Additionally, two variants of uncertain significance were identified; BRCA2 (c.3262C>T, p.Pro1088Ser) and MUTYH (c.1234C>T, p.Arg412Cys), both of which have been reported by other labs as being benign or likely benign variants and therefore are not suspected to be associated with an increased risk for cancer.

Given his excellent performance status he was started on systemic palliative chemotherapy with FOLFIRINOX. Repeat CT imaging after 6 and 12 cycles showed progressive radiological improvement, with near complete resolution of the pulmonary nodules with one remaining residual measurable subpleural nodule in the left lower lobe measuring 0.6 cm (previously measuring 1 cm), as well as interval decrease in the size and number of his liver lesions (see *Figure 1*). His pancreatic mass also decreased in size. A PET/CT scan demonstrated near-complete resolution of his disease with remaining increased metabolic activity in the tail of the pancreas with an SUV 2.5–2.9 and in the liver with an SUV 3.7. He remains on chemotherapy and is currently being screened for a clinical trial of a PARP inhibitor as a maintenance strategy. His daughter inherited the *RAD51C* mutation and has been counseled on prophylactic salpingo-oophorectomy at the age of 45–50 years.

Discussion

The Fanconi Anemia and homologous recombination pathway are activated by replicative stress, particularly DNA damage caused by cross-linking agents or reactive oxygen species. Therefore, a germline mutation in any of the genes in this pathway leads to less effective DNA repair, as shown by its response to DNA damaging agents. Indeed, *BRCA1/2* mutation carriers with ovarian or pancreatic cancer show higher response rates to treatment with DNA damaging agents resulting in improved outcome (2,3).

Germline mutations in the *RAD51* paralogs have

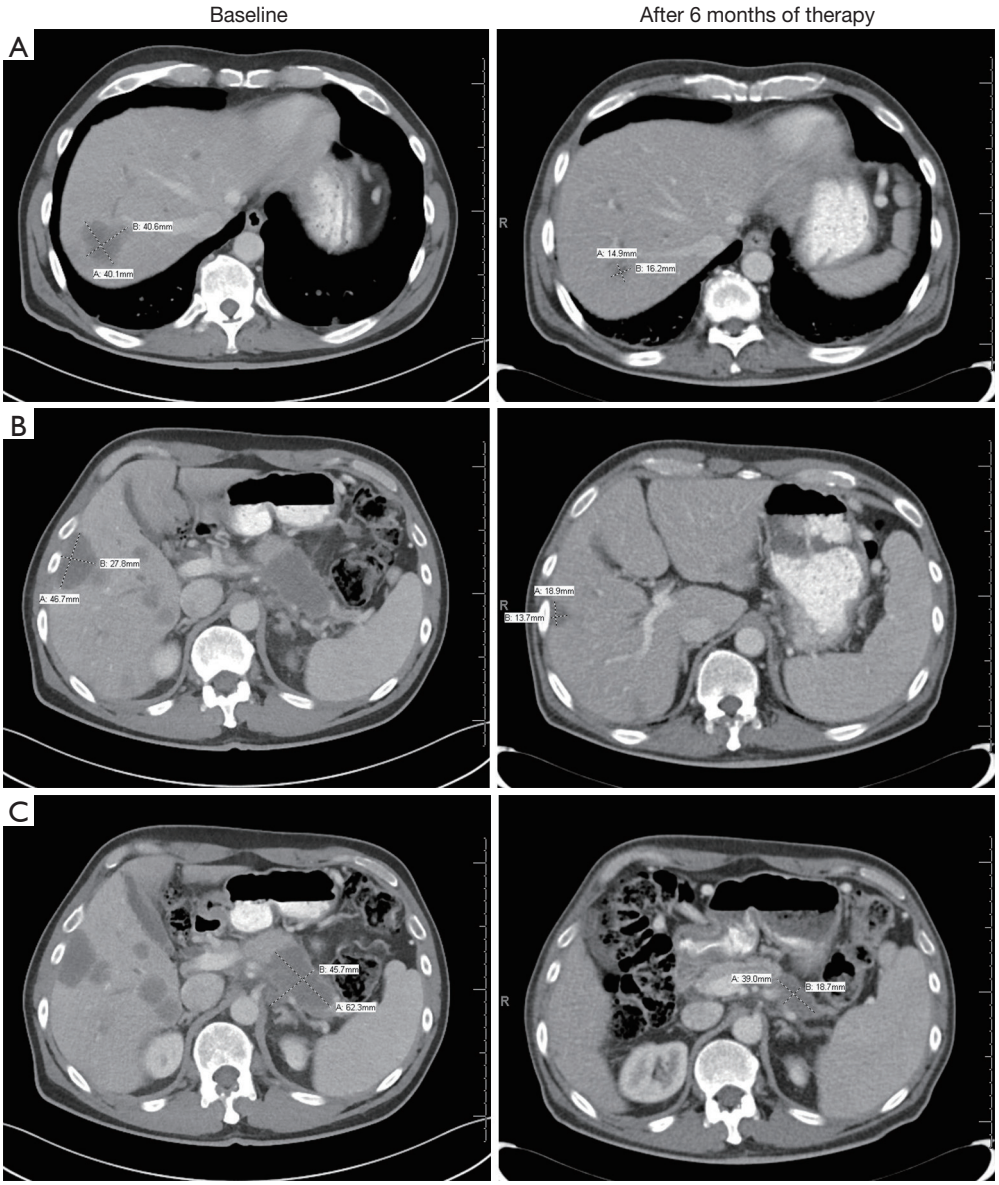

Figure 1 Computed axial tomography scans at baseline (pretreatment) and after 6 months of FOLFIRINOX chemotherapy showing target lesions in the liver (A and B) and pancreas (C) with a significant reduction in size.

been associated with susceptibility to cancer. Specifically, *RAD51C* mutations are associated with an estimated increased risk for ovarian cancer corresponding to 9% at age 80 years, with the mean age being approximately 60 years (4). Current NCCN guidelines recommend that prophylactic salpingo-oophorectomy be considered beginning at 45 to 50 years (5). At this time, there is unknown or insufficient evidence for increased risk of other cancer types, though some reports of its contribution to breast cancer in some families exist (3,6).

To our knowledge, this is the first reported case of a *RAD51C* germline mutation in a patient with pancreatic adenocarcinoma. There are reports of *RAD51C* mutations in patients with GIST and head and neck cancers (7,8). The patient's remarkable response to platinum-based therapy supports the hypothesis that the *RAD51C* mutation contributed to the development of his pancreatic cancer (9,10). Platinum agents exert their antineoplastic activity by causing DNA crosslinking. DNA repair of these crosslinks is dependent on both Fanconi anemia (FA) and

BRCA proteins, which act in homologous recombination repair pathways (1,11). Therefore, germline and somatic homologous recombination mutations may be predictive of platinum sensitivity (12). Therefore, the inability of the tumor cells to repair the damage cause by the oxaliplatin could explain his excellent response to FOLFIRINOX.

Conclusions

The case described suggests that carriers of *RAD51C* mutations may be at increased risk to develop pancreatic cancer and that platinum agents may be a useful therapeutic modality in patients with tumors associated with a germline *RAD51C* mutation. Germline genetic testing in patients with pancreatic adenocarcinoma might help select better agents for therapy and might also impact screening recommendation for family members.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images. A copy of the written consent is available for review.

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