Case Report

CHEK2 mutation in a patient with pancreatic adenocarcinoma—a rare case report

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Abstract: Pancreatic cancer (PaCa) is very aggressive malignancy with poor prognosis. Individuals with a family history of PaCa have a higher risk of developing cancer which points to a hereditary component. Here, we report a unique case of CHEK2 mutant PaCa in a patient with no medical but significant family history. A 59-year old female presented with 3-month history of worsening epigastric pain and jaundice. CT abdomen/pelvis with contrast showed pancreatic head mass which was confirmed by endoscopic ultrasound guided biopsy. She was diagnosed with pancreatic adenocarcinoma harboring CHEK2 mutation. She had extensive surgery followed by adjuvant chemotherapy. Follow up imaging in 3 months obtained after surgery and adjuvant chemotherapy showed extensive liver metastasis and patient decided to pursue hospice. Germline testing in all PaCa patients has become essential as mutations in CHEK2 and other DNA repair genes constitute a unique subset of PaCas. Not only does it help in assessment of cancer risk in the individual and family members but also guide anticancer therapy selection. PaCa patients harboring CHEK2 mutations do not usually respond to chemotherapeutic agents such as gemcitabine. However, new treatment strategies such as PARP inhibitors targeting defective DNA repair mechanism are currently being investigated and showed some promise in treating CHEK2 mutant PaCa patients.

Keywords: Pancreatic cancer (PaCa); CHEK 2; PARP inhibitor

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Introduction

Pancreatic cancer (PaCa) has the worst prognoses, with 92% of the patients succumbing to their disease within 5 years (1). It is the eighth most commonly diagnosed cancer in the developed world (2). Death rates are on the rise (3) as more than half of PaCa cases are diagnosed at a later stage. This may be partially responsible for the low five-year survival rates for PaCas, which are currently 8%. Today, research is continuing to elucidate the molecular events that promote PaCa development and disease progression. However, an understanding of the etiology of PaCa remains poor, due to a scarcity of information regarding the risk factors associated with PaCa (4). Despite decades of effort, mortality and incidence rates for PaCa remain similar, thus research towards early detection of this devastating disease is crucial.

PaCa is very aggressive and has a poor prognosis. Mostly commonly PaCa is attributed to sporadic causes, especially to modifiable risk factors such as tobacco and alcohol abuse (5). Individuals with a family history of PaCa carry an increased risk of developing the disease, which points to an underlying hereditary component. Gene mutations predisposing to PaCa can be either acquired or hereditary in nature. The main histological subtype of PaCa is pancreatic ductal adenocarcinoma (PDAC) (6). The second most common type is pancreatic neuroendocrine tumors, which are more indolent in nature. Genes implicated thus far in hereditary PDAC include *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2* and

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PMS2 (6). *CHEK2* mutation, as noted in our patient, is rarely observed in PaCa. Recent data generated by The Cancer Genome Atlas (TCGA) Research Network concluded that CHEK2 mutations are observed in 0.7% of PaCa cases. We present the following case in accordance with CARE reporting checklist (7) (available at http://dx.doi.org/10.21037/acr-20-83).

Case presentation

A 59-year-old female with no significant medical history and tobacco use presented to the emergency department with 3-month history of epigastric pain and yellowish discoloration of skin. Her family history is significant for breast cancer in her sister, maternal grandmother, PaCa in her sister and prostate cancer in her father and brother. Vital signs were stable and physical examination was remarkable for scleral icterus and mild epigastric tenderness on palpation. Laboratory tests were significant for elevated liver function enzymes including bilirubin. Her Aspartate transaminase (AST) was 736, Alanine transaminase (ALT) was 253, alkaline phosphatase (ALP) was 358, total bilirubin was 4.7 and CA 19-9 was 1,356. Computerized tomography (CT) abdomen/pelvis with contrast showed 4.4 cm × 3.0 cm heterogeneous pancreatic head mass with common bile duct dilatation concerning for malignancy. Gastroenterology was consulted for further workup and they recommended endoscopic ultrasound (EUS) for further characterization of the mass. EUS confirmed the hypoechoic pancreatic head mass and biopsies were obtained by fine needle aspiration. Biopsy was positive for pancreatic adenocarcinoma. Given the elevation of liver enzymes in a cholestatic pattern, differential diagnosis included biliary obstruction secondary to stone or stricture, cholangiocarcinoma and pancreatic carcinoma.

As she had no evidence of extra-pancreatic involvement, decision was made to opt for surgery. She underwent pancreaticoduodenectomy with pancreatojejunostomy, hepaticojejunostomy, gastrojejunostomy along with cholecystectomy (Whipple procedure) for PaCa. She was found to have 4.2 cm × 3.6 cm × 2.3 cm moderately differentiated invasive ductal adenocarcinoma of the pancreas invading ampulla of Vater, duodenal, peripancreatic and retroperitoneal soft tissues. Pathological staging was Stage II T3N0M0. Her post-operative course was complicated by pancreatic fluid leak which was treated with the appropriate antibiotics. Based on her pathological staging, decision was made to start her on adjuvant chemotherapy after she recovered from surgery. Her performance status was not good enough to undergo adjuvant treatment with mFOLFIRINOX. Hence, she underwent 6 cycles of adjuvant chemotherapy with Gemcitabine and Capecitabine (Xeloda) to treat micro metastasis and delay recurrence based on European study group for pancreatic cancer trial (ESPAC-4) (8). She tolerated chemotherapy well without any side effects. Repeat CT imaging showed no evidence of recurrence. She underwent germline testing after consultation with a genetic counsellor. She was found to be positive for deleterious mutation in *CHEK2* gene (c.433, C>T, p. R145W). Following completion of adjuvant treatment and one negative scan, patient's CA 19-9 trended up at 3 months follow up. Repeat imaging found liver metastases and patient opted to pursue hospice and passed away after.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was not obtained from the patient for publication of this Case report. Patient passed away and we were unable to contact patient's next of kin despite reaching out multiple times.

Discussion

This is one of the few cases reporting pancreatic adenocarcinoma harboring CHEK2 mutation, found in a patient with no significant medical history, but a strong family history. Her young age, absence of risk factors and family history of cancer suggested an underlying genetic predisposition. Hence, the patient underwent germline testing. Cancers harboring the CHEK2 mutation might respond to DNA damaging agents such as Poly ADP-Ribose Polymerase (PARP) inhibitors (9). PARP inhibitors target tumor cells with homologous recombinant repair deficiency (HRR) due to synthetic lethality with most prominent gene being BRCA. If tumor cells possess BRCA mutations, HRR loss would result in cell death. PaCa was known to have strong relationship with BRCA gene mutations. BRCA gene mutations cause HRR deficiency, and are the most studied target of PARP inhibitors. *CHEK2* gene has been shown to interact with BRCA, and hence mutations in *CHEK2* gene can also create an HRR deficient state in the cancer (10,11).

CHEK2 is a multi-organ cancer susceptibility gene (12). The CHEK2 protein participates in DNA damage response in many cell types and is therefore a good candidate for a

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multisite cancer susceptibility gene. Activation of CHEK2 in response to DNA damage prevents the cell from entering into mitosis (12). The *CHEK2* gene (MIM +604373) encodes the human analogue of the yeast checkpoint kinases Cds1 and Rad53 (13). Activation of CHEK2 in response to DNA damage prevents the cell from entering into mitosis. CHEK2 is activated by phosphorylation by ATM in response to double strand DNA breaks (13,14). Activated CHEK2 activates p53, which triggers cell cycle arrest at G1 or apoptosis (15,16). Thus CHEK2 plays an important role in cell cycle regulation and DNA damage repair, both crucial processes in preventing cancer development (16).

Research over the years has elucidated some of our understanding of the CHEK2 mutation's effect on cancer development. A study published in 2006 by Bartsch and colleagues provided the first hint that the germ line variant CHEK2*1100delC could be rarely associated with the predisposition to Familiar Pancreatic Cancer (FPC), though it is not a major determinant of the disease (17).

One shortcoming of research and literature to date is that the prevalence of mutations and survival based on carrier status among PDAC patients has not been well described (18). Peters *et al.* assessed the prevalence of known heritable germline mutations in PDAC patients and found that only 6.6% of unselected PDAC patients carry a germline mutation in a gene known to increase PDAC risk, and that 4.3% have a mutation in genes not previously linked to PDAC (19). Petersen *et al.* conducted a study using a hereditary cancer panel and determined that with a 12% prevalence of deleterious mutations, susceptibility gene testing in PDAC patients with a positive family history is warranted regardless of a patient meeting FPC criteria (18).

Although any of these individual findings might be due to chance, on the whole these studies cumulatively show that mutations in CHEK2 increase the risk of cancer in many different organs (12). The mutation found in our patient is associated with an increased risk for cancers of the breast, colon, thyroid, and prostate, some of which were present in her family history.

Today we know the availability of cancer gene mutation panel-based screening will identify increasing numbers of patients who carry diverse germline mutations. CHEK2 is typical of a category of genes where mutations in the genes are rare and are associated with modest penetrance (12). The difficulty in studying these genes lies in the fact that very large sample sizes are needed to identify significant relative risks. Note also that different populations harbor carriers at a different frequency, and different cancer risks are associated with different mutations (12). Thus, breakthroughs in germline mutation research for PaCa can help clinicians to better inform family members during genetic risk counseling. The diversity of genetic susceptibility offers future opportunities for targeted therapies (18).

Current therapy for PaCa includes surgery and chemotherapy; PaCa is notorious for having resistance to many key chemotherapeutic agents and targeted novel therapies (20). Surgery was a good option in this patient's case, as there was no evidence of extra-pancreatic involvement. Adjuvant chemotherapy with Gemcitabine and Capecitabine (Xeloda) are approved for clinical use in patients with pancreatic adenocarcinoma. Both Gemcitabine and Capecitabine (Xeloda) are pyrimidine analogues. A study conducted by Duong *et al.* in 2013 found that inhibition of checkpoint kinase 2 (CHEK2) enhances sensitivity of pancreatic adenocarcinoma cells to Gemcitabine (20). In this study, co-treatment of NSC109555 (a potent and selective CHK2 inhibitor) potentiated the cytotoxic effect of gemcitabine (GEM) in PaCa MIA PaCa-2 cells (20). Furthermore the study found that genetic knockdown of CHEK2 by siRNA enhanced Gemcitabine-induced apoptotic cell death (20). The study suggests that inhibition of CHK2 could be a beneficial therapeutic approach for PaCa therapy in clinical treatment (20).

Following Gemcitabine our patient's CA 19-9 is trending up suggesting CHEK2 is responsible for resistance to Gemcitabine. Imaging after 3 months was found to have liver metastases and patient opted to pursue hospice. Based on our case experience, we suggest checking CA 19-9 more frequently might help in detection of cancer earlier than radiographic PaCas are divided into four different subsets by whole exome sequencing and the genomically unstable subtype (DNA damage pathway) may respond to PARP inhibitors (4). Germline testing in all PaCa patients has become essential as mutations in CHEK2 and other DNA repair genes constitute a unique subset of PaCas. Not only does it help in assessment of cancer risk in the individual and family members but also guide anticancer therapy selection. Gemcitabine based therapies may not be effective for PaCas with CHEK2 mutation. CHEK2 mutation cancer may respond to DNA damaging agents such as PARP inhibitors. Based on this case and other cases of PaCa with mutations in genes involved in DNA damage response pathway, we at Kansas University Medical Center have developed a clinical trial to explore PARP inhibitors in this setting (21).

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/acr-20-83

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/acr-20-83). The authors have no conflicts of interests to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was not obtained from the patient for publication of this Case report. Patient passed away and we were unable to contact patient's next of kin despite reaching out multiple times.

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