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LETTER TO THE EDITOR

BRCA-associated pancreatico-biliary neoplasms: Four cases illustrating the emerging clinical impact of genotyping

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Three hundred thousand patients worldwide are diagnosed with pancreatic cancer (PC) each year. Most cases are sporadic; however 5–10% may be associated with inherited factors [1,2]. The risk of developing PC increases up to 30-fold if other family members are affected [1]. Biliary malignancies are less common [3].

Among known genetic predisposing factors are mutations in the *BRCA1* and *BRCA2* genes [4]. Surveillance and prophylactic surgery (mastectomy, oophorectomy) of women carrying mutations in *BRCA1* or *BRCA2* reduce the risk of death from neoplasms of the breast and ovaries [5]. As a result, other cancers are accumulating in these patients. Prostate, pancreatico-biliary, and gastric cancers occur with increased incidence in BRCA mutation carriers [6,7]. PC is particularly sinister with an overall five-year survival less than 5%.

High-risk germline or somatic mutations in *BRCA1* or *BRCA2* result in defective repair mechanisms for double strand DNA breaks [8]. Clinical studies in breast and ovarian cancers suggest that tumors with BRCA mutations are more likely to respond to certain treatments, particularly platinum-based chemotherapy [9]. In addition, a new class of molecules, PARP [poly (ADP-ribose) polymerase] inhibitors, has demonstrated clinical effect in BRCA mutation-associated ovarian cancer [10], but not in breast cancer [11]. PARP inhibitors are currently under clinical investigation for treatment of other BRCA mutation related malignancies, including PC [12–14]. There is emerging clinical awareness of the importance of performing a genetic work up of patients with PC with unusual disease presentation or family history in order to identify BRCA mutations, as there is accumulating evidence of differentiated response to therapy [2,13,15].

We present four patients with pancreatico-biliary cancer and germline BRCA mutations from a single institution. These cases illustrate the emerging clinical impact of genotyping.

Cases

Clinical factors, treatments, and response are shown in Table I. The family histories of the four cases are shown in Appendix 1 (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1044023).

Case 1

A 45-year-old Caucasian woman with a known *BRCA1* mutation was diagnosed with a 40 mm tumor in the pancreatic body. Nine years earlier she had had a bilateral mastectomy having been diagnosed with an invasive, triple negative ductal adenocarcinoma. The pancreatic tumor involved the gastric artery and was considered unresectable (Figure 1). Three core needle biopsies showed infiltrating ductal adenocarcinoma positive for cytokeratin (CK) 7 and CDX2, and negative for CK20, TTF1, and ER. She received eight cycles of chemotherapy with Folfirinox (leucovorin, fluouracil, irinotecan, and oxaliplatin) in standard dosage resulting in pronounced regression of the tumor, which was then deemed resectable (Figure 1). Serum CA 19-9

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Table I. Summary of findings and treatment of four cases of pancreatico-biliary cancer associated with germline BRCA-mutation.

CASE	Pathology	Stage	Gender	Age	Mutation	Metachroneous cancers	Antineoplastic treatment	Best response to treatment	Duration of treatment	Outcome
1	Ductal type adenoc.	locally advanced	female	45	*BRCA1 c.5557-?_c.6295+?del*	IDC at age 36	Neoadjuvant Folfirinox Adjuvant Gem	pCR NE	3 months 1 month	Alive with NED 11 months after diagnosis
2	Ductal type adenoc.	metastatic	male	35	*BRCA2 c.6601delA*	None	Folfirinox PARP-inhibitor Gem+ Nab-Paclitaxel Cisplatin	PR (11 months)[a] SD SD NE	6 months 7 months 3 months 1 treatment	Died 21 months after diagnosis
3	Neuroendocrine tumor	localized	female	41	*BRCA2 c.3237_3238delCA*	None	IFNa+ SA Ytt-DOTATOC + SA Carbo-eto + SA Sunitinib+ SA Temozolomide+ SA Everolimus+ SA Oxa+ capecitabine + SA Capecitabine+ SA Capecitabine+ Bev+ SA PARP-inhibitor+ SA	PD NE[a] PD SD SD[a] PR (9 months) PR (5 months) PR SD NE	5 months 3 months 2 months 4 months 1 month 11 months 6 months 4 months 5 months 1 month	Died 72 months after diagnosis
4	Intestinal type adenoc. Ductal type adenoc.	localized metastatic	female	39 68	*BRCA2 c.9181+1G>T*	IDC at age 36	Cisplatin+ Gem[b]	PR	Ongoing	Alive

adenoc, adenocarcinoma; Bev, bevacizumab; BRCA, Breast cancer susceptibility gene; Carbo, carboplatin; Eto, etoposide; Folfirinox, leucovorin/fluorouracil/irinotecan/oxaliplatin; Gem, Gemcitabine; IDC, invasive ductal cancer of the breast; Oxa, oxaliplatin; SA, Sandostatin analogue; IFNα, Interferon-α; NE, not evaluated; NED, no evidence of disease; pCR, pathological complete response; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Toxicity-related treatment change; [b]Palliative chemotherapy for metastatic bile duct cancer.

was normal after three cycles. A Whipple procedure was performed; pathological examination of the surgical specimen showed only focal fibrosis of the pancreatic body without residual tumor, i.e. a complete pathological response. Subsequently, she received adjuvant gemcitabine until dose-limiting liver toxicity occurred after five cycles. She had no evidence of relapse at the latest follow-up with thoraco-abdominal computer tomography (CT) scans six months after surgery.

Case 2

A 35-year-old Caucasian man was diagnosed with a pancreatic tumor and multiple liver lesions. Two core needle biopsies from the liver showed a relatively well differentiated adenocarcinoma, positive for CK7, CDX2, CEA, and CA125, but negative for CK20. He received Folfirinox and achieved a partial response (PR) after four cycles preceded by a rapid improvement in his general condition from WHO Performance Status (PS) 2 to PS 0. Serum CA 19-9 remained high (> 10 000 kU/l) throughout the course. Genetic testing for a mutation in *BRCA2*, previously identified in the mother of the patient, revealed that he carried the mutation. Following eight cycles of Folfirinox with sustained PR, the patient was enrolled in a phase I trial with a PARP-inhibitor and had stable disease (SD) for seven months. At progression, he was offered gemcitabine

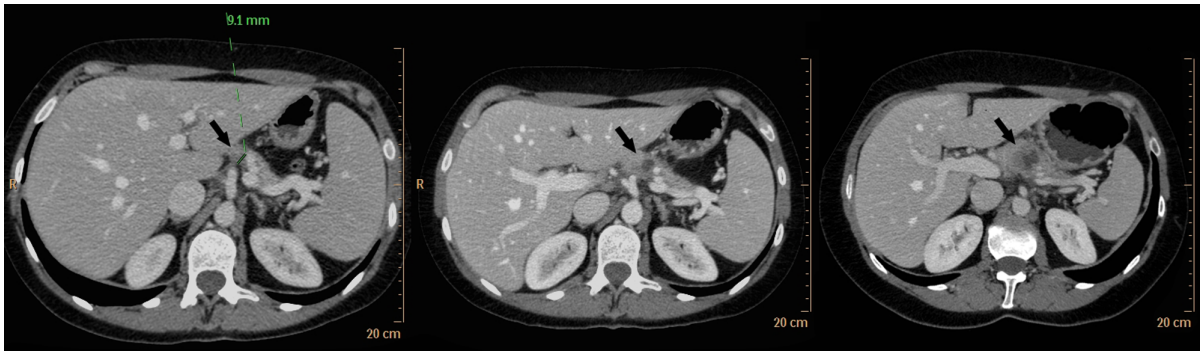

Figure 1. CT images of locally advanced pancreatic adenocarcinoma (arrow) at baseline (right), after four cycles of Folfirinox (middle), and after eight cycles with tumor shrinkage to 9 mm in a 45-year-old female (Case 1) with BRCA1 germline mutation, showing complete pathological response after radical pancreatectomy.

and nab-paclitaxel at reduced dose. Evaluation after three series showed progressive disease (PD). In spite of a further treatment attempt with single-drug cisplatin, the patient's condition rapidly deteriorated and he succumbed 21 months after diagnosis.

Case 3

A 41-year-old Caucasian woman presented with a 50 mm cystic tumor in the body of the pancreas. A core biopsy revealed a primary pancreas neuroendocrine tumor (NET), immunohistochemically positive for pan CK marker and the neuroendocrine markers synaptophysin, CD56, and chromogranin A (CgA), with a Ki67-proliferation index below 2% (grade 1). Immunostaining for CK7, CK20, ER, and GCDFP15 were negative. Serum CgA was elevated to 532 μg/l (ULN 94 μg/l). Initially, she was treated with interferon-α and a sandostatin analog (Octreotide LAR), the latter being continued during her subsequent treatment. A Whipple procedure resulted in an R0-resection of a moderately differentiated pT3pN1 NET with a Ki67-proliferation index of 20% (grade 2). Recurrence occurred in cervical lymph nodes two months after surgery with a Ki67-index of 15%. A neck lymph node dissection was followed by two cycles of somatostatin-receptor-targeted radioimmunotherapy with Yttrium-90 DOTATOC. As a result of a family history of relatives carrying a *BRCA2* mutation, genetic testing of the patient was performed and revealed that the patient carried the mutation. Six months after DOTATOC-treatment, multiple octreoscan-negative liver metastases were observed. Two core needle biopsies showed neuroendocrine carcinoma with Ki67-indexes of 10% and 25%, respectively. She subsequently received multiple regimens of systemic antineoplastic treatment (see Table I). She had a progressing 25 mm metastasis in the left upper abdomen with a Ki67-index of 10% removed. Of special interest, the patient had an uncommon objective response to everolimus and sixth line treatment with capecitabine and oxaliplatin resulted in an unexpected PR with a 50% decrease in serum CgA and an improvement in PS from 1 to 0. At PD after 20 months with sustained response, the patient was enrolled in a phase I-study of a PARP-inhibitor, but died from liver failure three months after phase I treatment initiation and six years after diagnosis.

Case 4

A 39-year-old Caucasian woman with known *BRCA2* mutation underwent a Whipple procedure for a tubulovillous adenoma of the papilla of Vater, which showed foci of moderately differentiated adenocarcinoma of intestinal type, pT1pN0R0. Adjuvant therapy was not considered. Three years after the diagnosis of papillary cancer, she had a left mastectomy for an ER-positive invasive ductal carcinoma. She received adjuvant radiotherapy and CMF (cyclophosphamide, methotrexate and 5-fluoruracil). She subsequently underwent prophylactic bilateral oophorectomy. Twenty-nine years after the first, and 26 years after the second cancer diagnosis, she was diagnosed with bile duct cancer with multiple intrahepatic and regional lymph node metastases. A core needle biopsy from the liver revealed adenocarcinoma, morphologically and immunohistochemically distinct from the previous cancers. Serum CA-19-9 level was very high (> 10 000 kU/l). The patient is currently undergoing palliative treatment with gemcitabine and cisplatin. Evaluation after four months has shown PR of liver metastases and abdominal lymph nodes, and an improvement in PS from 2 to 1.

Discussion

The cases we present illustrate that PC in patients with BRCA mutations often show unusual clinical presentations and may have a favorable response to systemic antineoplastic treatment. The median age at time of diagnosis of pancreatic adenocarcinoma is 71 years [1], and diagnosis before the age of 40 is rare. Genetically predisposed patients present with PC at an earlier age [1,2], this being consistent with the relatively young age of our cases.

One patient carried a mutated allele of *BRCA1*; three carried a mutated allele of *BRCA2*. The connection between *BRCA2* mutation and PC is well described with a relative risk of 3.5 [7]. In contrast, Brose et al. [6] were the first to report the increased risk of PC associated with germline *BRCA1* mutation with a relative risk of 2.8. *BRCA1* and *BRCA2* both encode for proteins related to repair of double-strand breaks of the DNA. Deficiency in these genes result in derouting repair mechanisms to error-prone pathways, which eventually lead to chromosomal instability in the cell [8,16].

Most BRCA related PCs are ductal type adenocarcinomas, histopathologically indistinct from sporadic cases [2,15]. An unusual case of acinar cell carcinoma of the pancreas associated with germline *BRCA1* mutation was reported by Lowery et al. [15]. Although several studies lack histopathological evaluation, to our knowledge neuroendocrine pancreatic tumors or intestinal type papillary carcinomas have not been reported earlier in BRCA-mutated patients (see Cases 3 and 4).

Patients with BRCA mutations have a better response to certain chemotherapeutic agents [2,15]. There is increasing focus on PARP inhibitors, as they have showed remarkable response rates in phase I and II studies of BRCA-associated breast, ovarian, prostate and PC [13,17]. The PARP-inhibitor olaparib has recently been approved by the European Medicines Agency (EMA) for use in relapsing, platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancers related to BRCA mutations [18]. PARP is a nuclear enzyme involved in single-strand break repair, whose inhibition increases cell death in BRCA proficient cells [19]. All the patients we presented had an objective response to platinum containing chemotherapy. In particular, Case 1 achieved pathological complete response (pCR) by Folfirinox. pCR is exceedingly rare in PC, and has been reported in only a few cases in the literature [20,21]. Accumulating evidence from clinical trials and case reports suggests, that platinum-based therapies are effective in treatment of tumors related to BRCA mutations [2,9,15], and platinum-based first-line treatment should therefore be considered in pancreatico-biliary cancers associated with this genotype.

With emerging therapeutic modalities, it is increasingly relevant to consider screening of patients with PC for BRCA mutations. Mutation screening should always be conducted in the context of a genetic work up and genetic counseling. Obtaining a family history of patients with PC in order to detect suspect patterns is important since this may indicate a familial risk even if no pathogenic variants are detected. Currently there is no evidence that supports the benefit of surveillance for PC [1]; the relative risk of PC in carriers of mutation in a BRCA gene is increased, but the annual incidence rate of PC is low [4] and BRCA mutation screening in order to prevent PC by prophylactic measures is, therefore, presently not relevant. Genetic analysis in patients diagnosed with PC and a relevant family history or unusual clinical presentation may provide useful information as PC related to BRCA mutation carries potential for individualized treatment including targeted therapy and the possibility of a better outcome.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Appendix to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1044023.