



Searching for a Germline Etiology in Cancer: A Case Report of a Man with Synchronic Pancreatic and Colo-Rectal Cancer

Almudena Callejo Goena^{1*}, Sergio Carrera Revilla^{1,2}, Aintzane Sancho Gutiérrez¹, Cristina Martínez Bouzas³, Silvia Ibáñez Alonso⁴, Eider Azkona Uribebarrea¹, Ane Lopetegui Aizpurua¹ and Guillermo López Vivanco¹

¹Department of Medical Oncology, Cruces University Hospital, Spain

²Department of Medical Oncology, Hereditary Cancer Genetic Counseling Unit, Cruces University Hospital, Spain

³Molecular Genetics Laboratory of Service of Biochemistry, Cruces University Hospital, Spain

⁴Department of Radiology, Cruces University Hospital, Spain

Abstract

Pancreatic Cancer (PC) is an aggressive disease with a poor outcome, not only because of the advanced stage at the time of diagnosis in most cases but also because of the difficulty in achieving a complete resection in many cases, the low chemo sensitivity of this tumor and the lack of mutational drivers for a targeted therapy. Even if the sporadic PC is the most prevalent one, mostly due to different external factors such as cigarette smoking, alcohol abuse or diabetes, the hereditary PC, with rather well-defined germline pathogenic variants, exists. We must take this into account when considering the underlying etiology of the tumor and the therapeutic options in these patients.

We describe a case report of a 56-year-old man simultaneously diagnosed with a Colorectal Cancer (CRC) and an advanced pancreatic adenocarcinoma, whose familial history made us suspect of a hereditary causative component, and in whom we found a pathogenic variant in the *BRCA2* gene. The response to the chemotherapeutic treatment observed in this patient was also congruent with this genetic finding, and it could lead us to a more personalized treatment with platinum containing regimens or Poly-ADP Ribose Polymerases (PARP) inhibitors.

Keywords: Pancreatic adenocarcinoma; Colorectal cancer; Hereditary cancer; Genetic testing; *BRCA2*

Case Presentation

The patient is a 56-year-old man with a history of limited tobacco consumption and whose mother and sister had respectively been diagnosed at 70 and 45 years-old with breast cancer. Due to a positive Fecal Occult Blood Test (FOBT), he underwent a large colonoscopy, finding a proliferative lesion in the upper rectum, compatible with a tubulovillous adenoma with low grade of dysplasia and more than twenty adenomatous polyps through the whole colon. We conducted a Tomography Computerized (TC) scanner, revealing no distant metastases, a pelvic Magnetic Resonance (MR), which showed a clinical cT1-2N0 rectal neoplasm, and a blood analysis, which showed altered Glutamate Pyruvate Transaminase (GPT) and bilirubin. A later cholangiopancreatography MR and a liver ultrasound showed some little hepatic metastases, probably secondary to another pathological lesion observed in the head of the pancreas, narrowing the coledochus duct and producing a retrograde dilatation of the biliary duct. A hepatic biopsy obtained surgically, in the context of a cholangitis, confirmed a pancreatic metastatic adenocarcinoma.

With a normal Carcinoembryonic Antigen (CEA) level but high Carbohydrate Antigen 19-9 (CA 19.9), the patient started a chemotherapeutic treatment consisting of Nab-paclitaxel (125 mg/m²) followed by Gemcitabine (1,000 mg/m²) endovenous on days 1, 8 and 15 every four weeks. The best observed radiological response was stable disease, with oscillating levels of CA 19.9, but he presented hepatic progression after seven cycles of treatment.

A second chemotherapeutic line with endovenous Oxaliplatin (130 mg/m²) day 1 and oral Capecitabine (1,000 mg/m²) twice daily for 14 days every three weeks was initiated. The biggest

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*Correspondence:

Almudena Callejo Goena, Department of Medical Oncology, Cruces University Hospital, Baracaldo, Spain, E-mail: mariaalmudena.callejogoena@osakidetza.eus

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Figure 1: Scanner at baseline of treatment.



Figure 2: Scanner at 5th month of treatment. Minor response.

hepatic lesion (45 mm in its largest diameter), Figure 1 showed significant radiological changes at the 5th month of treatment (6 cycles); namely, even though the tumor size was higher due to the cystic component (45 mm × 61 mm) Figure 2, the tumor density had decreased significantly. Considering that CA 19.9 had also decreased, these findings were interpreted as a minor response, which was maintained after ten cycles (9th month) of treatment. At that moment, we decided to make a break-treatment due to the related-to-Oxaliplatin grade 2 neurotoxicity. The patient continues without treatment at this time, with stable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

In parallel, the patient was evaluated in our Hereditary Cancer Genetic Counseling Unit. First, considering that the patient had been diagnosed with a pancreatic adenocarcinoma and a synchronous rectal neoplasm, both of them belonging to the tumor spectrum of Lynch Syndrome (LS), we performed the immunochemistry of the DNA Mismatch Repair genes (MMR) *MLH1-MSH2-MSH6-PMS2* in the rectal biopsy, given that the pancreas sample was not available for that procedure. The result obtained (MMR proficient), and the fact that no other LS-related tumors were described in the family, gave us the clue to stop the screening for this syndrome.

Additionally, given the fact that our patient presented a complete cytoreduction and more than twenty colorectal adenomas, thus fulfilling the criteria for screening of MUTYH Associated Polyposis (MAP) [1], we analyzed the most prevalent variants in the *MUTYH* gene in our country (c.536 A>G, c.1187 G>A, c.1227_1228 dup). Again, we did not find here a pathogenic variant.

Finally, taking into account that in his family there were two cases of breast cancer (his mother at 70 years old and his sister at 47 years old), one of them triple-negative, we decided to analyze the mutational status of *BRCA1* and *BRCA2* genes. In this case, we found a pathogenic variant (a frameshift one) in exon 11 of the *BRCA2* gene, specifically c.5213_5216delCTTA (p.Thr1738Ilefs*2) (HGVS nomenclature), which leads to a deletion of four bases, with a consecutive change in the pattern of reading and producing a non-functional altered protein. This meant that we had identified a plausible underlying genetic cause of the tumors he presented, and that the patient and his maternal family belonged to the 8% tumors that are hereditary, specifically to the Hereditary Breast and Ovarian Cancer (HBOC) syndrome [2,3]. Moreover, now we could presume that this genetic finding could have favored the minor radiological response observed in the patient with the second treatment, which contained Oxaliplatin.

Discussion

PC remains an aggressive disease, with poor outcome because of its silent nature, the lack of reliable secondary prevention measures and the frequent advanced-stage at diagnosis; the 1-year survival rate of people with pancreatic cancer who do not have surgery is 29%, and the 5-year survival rate is 7% [4]. It is urgent to identify risk factors for developing PC and mutational drivers for a targeted therapy.

The most important identified risk factors for developing a PC are older age, tobacco consumption, alcohol abuse, diabetes, chronic pancreatitis, dietary factors and family history, but only 5% to 10% of PC is related to a hereditary alteration [5]. Germline mutations in *BRCA1/2*, *PALB2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *ATM*, *APC*, *STK11*, *PRSS1* and *TP53* genes are associated with varying degrees of increased risk for Pancreatic Ductal Adenocarcinoma (PDAC), the most frequent histological subtype of PC [6]. Hence, the more remarkable hereditary cancer predisposition syndromes with increased risk of PDAC are the HBOC syndrome, Familial Melanoma (FM), Lynch Syndrome (LS), Familial Adenomatous Polyposis (FAP), Peutz-Jeghers Syndrome (PJS) and Li-Fraumeni Syndrome (LFS) [4]. They account for almost 10% to 15% of PDAC familial cases.

Among them, HBOC syndrome is the best-defined hereditary syndrome cancer, caused mainly by germline mutations in *BRCA1/2* genes, which increase especially the risk of developing breast and ovarian cancer but also pancreatic and prostatic cancer [3]. Both of them are inherited in an autosomal dominant manner and must be suspected in those families with multiple breast-ovarian cancer cases, especially when they are diagnosed at an early age. Whereas the relationship between the *BRCA1* mutations and PDAC are less clear, increased risk of PDAC in patients with germline mutations in *BRCA2* genes is well defined, with a relative risk in the range of 2.3 to 7 across different published studies [7,8]. Mutations in *BRCA2* gene is probably the most common inherited disorder in familial pancreatic cancer [9], being the median age of diagnosis in these carriers 60 years old, namely 8-10 years younger than the median age for sporadic PC in Europeans.

The *PALB2* gene has been recently added to the list of familial PC genes, with an estimated risk of PDAC still not well defined [10]; it codes for a protein that connects to the *BRCA2* protein and helps to localize it to the nucleus. Initial data suggest that the *PALB2* gene accounts for 1% to 3% of familial PC [11].

Differential diagnosis of PC tumors in families or individuals with a suspected inherited/germline component can be highly difficult and potential algorithms based on a gen-by-gen strategy have been proposed [5].

Regarding the therapeutic approach, a genetic finding could also lead us to a more personalized treatment, especially if it constitutes a potential driver, as we have observed in other tumors with germline mutations, such as breast-ovarian cancer *BRCA* mutated or deficient-MMR tumors [12-16].

Within advanced PDAC, two chemotherapy treatment schemes (5-Fluorouracil, Oxaliplatin, and Irinotecan (FOLFIRINOX) or Gemcitabine plus Nab-paclitaxel) have showed improvements in overall survival compared with Gemcitabine alone, which was considered, until 2011, as the standard of care for patients with metastatic pancreatic cancer. The intense chemotherapeutic regimen of FOLFIRINOX has been shown to be superior to Gemcitabine alone in Progression Free Survival (PFS) and Overall Survival (OS) [17]. The combination of Gemcitabine and Nab-paclitaxel has also demonstrated superiority in terms of efficacy for metastatic pancreatic cancer compared to Gemcitabine monotherapy [18]. Thus, nowadays, FOLFIRINOX and/or Gemcitabine and Nab-Paclitaxel are standard first-line schedules for metastatic disease in patients with ECOG scale of Performance Status (PS) 0-1.

There is no standard chemotherapy for second-line treatment. In patients progressing to Gemcitabine-based combinations, 5-Fluorouracil/Oxaliplatin or 5-Fluorouracil/liposomal Irinotecan (nal-IRI) combinations could be considered in selected patients with good PS [19]. Also, as we did with our patient, the combination of Capecitabine and Oxaliplatin has demonstrated activity after failure of first-line Gemcitabine-based therapy [20,21].

Patients with a pathogenic variant in *BRCA1/2* or *PALB2* genes would be especially sensitive to the FOLFIRINOX combination or a platinum-containing regimen, an issue that should be prospectively tested [22,23]. The reason for this is that tumors harboring somatic or germline pathogenic variants in genes related to DNA double strand damage repair, such as *BRCA1/2*, which are associated with homologous recombination deficiency, are more susceptible to apoptosis after exposure to chemotherapy (e.g., platinum agents), because double DNA strand breaks cannot be repaired [24]. This benefit in platinum-based schedules has also been reported in patients with PDACs related to HBOC syndrome and clinical trials with platinum-containing regimens are on-going [25-27].

Additionally, Poly-ADP Ribose Polymerases (PARP) inhibitors provide a promising avenue of treatment for cancers associated with *BRCA1/2* mutations. PARP are involved in single DNA strand break repair, so inhibition of their mediated pathway could lead to tumor cell destruction in the presence of a pathogenic *BRCA* variant. Both Olaparib and Rucaparib (PARP inhibitors) have showed tumor response rates in patients with metastatic PC [12,28] and a phase III trial with Olaparib monotherapy following Cisplatin, Carboplatin or Oxaliplatin in these patients is currently in progress [29]. Other earlier randomized clinical trials with PARP inhibitors are ongoing [26,30-33].

Conclusions

Despite not having a high incidence in the population, PC remains as a major health problem due to its aggressive behavior and high mortality. Therefore, when evaluating these patients, it is crucial to analyze not only their performance status, their comorbidities and the disease-related characteristics, but also the underlying genetic features of the tumor, for the sake of finding or personalizing their therapeutic options.

Although it is thought that only a 10% of PC have a familial component, identifying a patient that belongs to a family with a hereditary cancer syndrome could lead us to a more personalized treatment, a better follow-up and adequate family advice.

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