

# World Journal of *Gastrointestinal Oncology*

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## Pancreatic mucinous cystadenocarcinoma in a patient harbouring *BRCA1* germline mutation effectively treated with olaparib: A case report

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### Abstract

#### BACKGROUND

Pancreatic mucinous cystadenocarcinoma (MCAC) is a rare malignancy with a poor prognosis when it presents metastases at diagnosis. Due to its very low incidence, there are no clear recommendations for the treatment of advanced

and Rizzo A reviewed the literature; Ricci C, Ingaldi C, Alberici L, Minni F and Casadei R were the patient's surgeons and reviewed the literature; Santini D and Turchetti D performed pathological examinations and BRCA testing, respectively, and reviewed the literature; Di Marco M was responsible for revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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disease. Olaparib (an oral PARP inhibitor) has been approved for the maintenance treatment of patients with metastatic pancreatic adenocarcinoma harbouring germline *BRCA1/2* mutations. Herein, we report the first case of a germline *BRCA1* mutated unresectable MCAC which was effectively treated with olaparib.

### CASE SUMMARY

A 41-year-old woman, without personal or family history of cancer, was diagnosed with ovarian and peritoneal metastases of MCAC. She underwent 12 cycles of gemcitabine plus oxaliplatin (GEMOX) obtaining a partial response and allowing radical surgery. One year later, local recurrence was documented, and other 12 cycles of GEMOX were administered obtaining a complete response. Seven years later, another local recurrence, not amenable to surgical resection, was diagnosed. She started FOLFIRINOX (oxaliplatin, irinotecan, leucovorin and fluorouracil), obtaining a partial response after 8 cycles. Given the excellent response to platinum-based chemotherapy, *BRCA* testing was performed, and a *BRCA1* germline mutation was detected. She was switched to maintenance olaparib due to chemotherapy-related toxicities and achieved an almost complete metabolic response, with a reduction in the diameter of the lesion, after three months of therapy.

### CONCLUSION

The current case suggests the beneficial effect of olaparib in *BRCA* mutated MCAC. However, further studies are required.

**Key Words:** Mucinous cystadenocarcinoma; Pancreatic cancer; *BRCA1* gene; Olaparib; Case report

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**Core Tip:** Pancreatic mucinous cystadenocarcinoma (MCAC) is a rare malignancy with a poor prognosis when it presents metastases at diagnosis. Due to its very low incidence, there are no clear recommendations for the treatment of advanced disease. Olaparib (an oral PARP inhibitor) has remarkable curative effects in *BRCA* mutated pancreatic ductal adenocarcinoma, breast and ovarian cancers. However, there are few data on its efficacy in the treatment of other types of pancreatic malignancies. Herein, we report the first case of a germline *BRCA1* mutated MCAC which was effectively treated with olaparib. We also provide a brief overview of the most relevant clinical features of MCAC.

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## INTRODUCTION

Mucinous cystic neoplasms (MCNs) of the pancreas range from benign mucinous cystadenoma to malignant cystadenocarcinoma, and they represent 23% of all resected pancreatic cysts<sup>[1]</sup>. Lou *et al*<sup>[2]</sup> estimated that pancreatic mucinous cystadenocarcinoma (MCAC) accounts for approximately 0.5% of all pancreatic malignancies, using the Surveillance, Epidemiology and End Results program database. Surgery represents the first choice of treatment for patients with resectable disease. The prognosis of resectable MCAC seems to be significantly more favourable compared to that of pancreatic ductal adenocarcinoma (PDAC)<sup>[3]</sup>. However, locally advanced and metastatic MCACs have a poor prognosis. Due to the very low incidence of MCAC, both controlled prospective studies and clear recommendations for the treatment of

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advanced disease are lacking<sup>[4]</sup>.

*BRCA1* and *BRCA2* genes code for proteins that are involved in homologous recombination repair of double-strand DNA breaks, and their mutations are associated with an increased risk of several types of cancer<sup>[5]</sup>. In pancreatic adenocarcinoma, the prevalence of germline *BRCA1/2* mutations among patients with apparently sporadic forms of the disease ranges from 1.8% to 4.6%<sup>[6,7]</sup>. Recently, maintenance olaparib (an oral PARP inhibitor) has been approved for the treatment of patients with metastatic pancreatic adenocarcinoma harbouring germline *BRCA1/2* mutations based on the results of the POLO trial<sup>[8]</sup>. Nevertheless, the prevalence of germline *BRCA1/2* mutations in pancreatic MCAC is unclear, and there are no data on the efficacy of PARP inhibitors in the treatment of *BRCA1/2* mutated MCAC.

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## CASE PRESENTATION

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### **Chief complaints**

A 41-year-old Caucasian woman was referred to our centre. She had a history of nausea, constipation and epigastric pain for several months.

### **History of present illness**

The patient had no relevant events in her medical history.

### **History of past illness**

The patient had no relevant events in her medical history.

### **Personal and family history**

No significant personal or family history.

### **Physical examination**

Unremarkable.

### **Laboratory examinations**

The serum cancer antigen (CA) 125 level was 150 IU/mL (reference range 0.00–35.00 IU/mL), while serum CA19-9 level was 354 IU/mL (reference range 0.00–37.00 IU/mL) and serum carcinoembryonic antigen (CEA) level was 13.4 ng/mL (reference range 0.00–5.00 ng/mL for non-smokers).

### **Imaging examinations**

She underwent computed tomography (CT) which revealed two bilateral ovarian masses 145 mm and 71 mm in diameter, respectively, and a lesion measuring 40 mm in the body of the pancreas.

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## FINAL DIAGNOSIS

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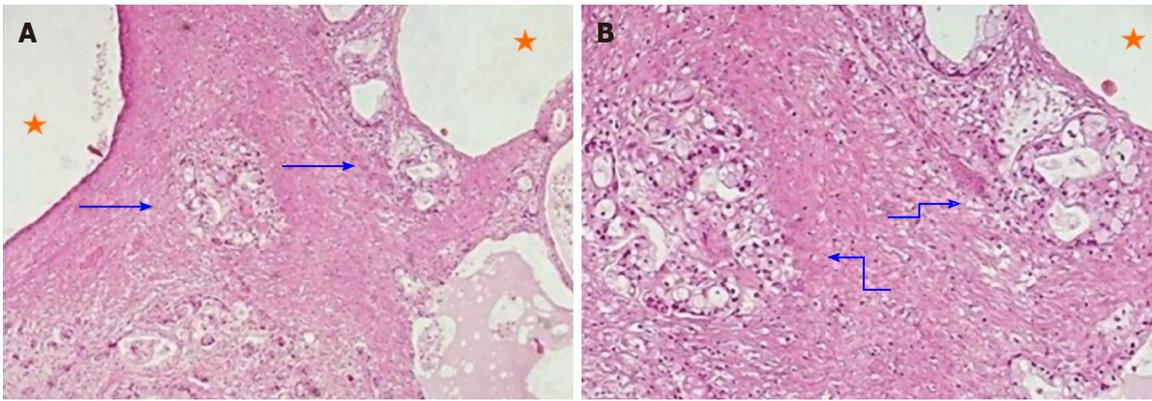
Pathology revealed ovarian and peritoneal metastases of pancreatic MCAC.

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## TREATMENT

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Suspecting two different tumours, she underwent surgery with radical intent in November 2008. The surgeons immediately detected a previously unrecognized peritoneal carcinosis during the exploratory laparotomy. Nonetheless, they still performed a hysterectomy and a bilateral salpingo-oophorectomy to resolve the associated symptoms caused by these masses. The surgical specimen included the uterus and ovaries, which were macroscopically infiltrated by two cystic lesions measuring 65 mm × 60 mm × 40 mm and 100 mm × 90 mm × 50 mm, respectively. Pathology revealed ovarian and peritoneal metastases of pancreatic MCAC (Figure 1). One month later, she started chemotherapy with gemcitabine plus oxaliplatin (GEMOX, gemcitabine 1000 mg/sm/d1 and oxaliplatin 100 mg/sm/d2 every two weeks) obtaining a partial response after 12 cycles. Given the excellent response to chemotherapy, we performed a second exploratory laparotomy in October 2009 during which no peritoneal carcinosis was found. She underwent distal pan-



**Figure 1** Histological examination of the ovarian metastases. A: Hematoxylin-eosin staining ( $\times 10$ ) of the resected specimen showing glandular areas (arrows) next to cystic spaces (stars); B: Higher-power view ( $\times 20$ ) of the glands shown before displaying malignant cytology and an infiltrating pattern.

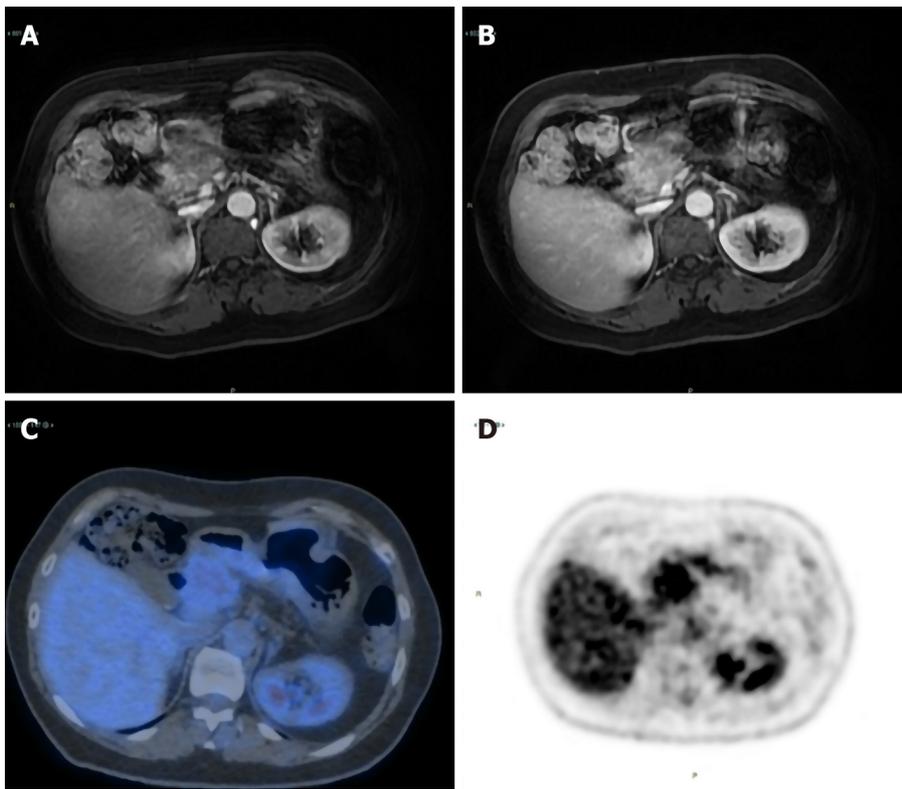
createctomy and pathological examination confirmed the initial diagnosis of pancreatic MCAC. The patient remained disease-free until September 2011, when both CT and 18F-fluoro-D-glucose positron emission tomography/X-ray computed tomography (18F-FDG PET-CT) showed a local recurrence and GEMOX was restarted obtaining a complete response after 12 cycles (confirmed both by CT and 18-FDG PET-CT). In June 2019, during the follow-up program, laboratory tests documented an increase of serum CEA (14.2 ng/mL), while serum CA125 and CA19-9 were normal. We performed magnetic resonance imaging and 18F-FDG PET-CT (Figure 2) which showed a local recurrence not amenable to surgical resection (invasion of the hepatic artery and superior mesenteric vein). The diagnosis was confirmed with an endoscopic ultrasound-guided biopsy. She started FOLFIRINOX (oxaliplatin 85 mg/sm, irinotecan 180 mg/sm, leucovorin 400 mg/sm and fluorouracil 400 mg/sm given as a bolus followed by 2400 mg/sm as a 46 h continuous infusion, every two weeks) obtaining a significant response, with a decrease of 18F-FDG uptake (SUV = 3.9 vs 6) and reduction in CEA level (2.78 ng/mL) after 8 cycles (Figure 3). However, toxicities were observed and included febrile neutropenia and grade 3 vomiting. Considering the excellent radiological response to platinum-based chemotherapy, we performed BRCA testing. Constitutional DNA of the patient was analyzed for BRCA1 and BRCA2 variants using Next Generation Sequencing (ION Torrent S5) and the variant c.4117G>T (p.Glu1373Ter) was detected in the BRCA1 gene. In January 2020 she was switched to maintenance olaparib tablets (300 mg twice daily) with good tolerance, except for anaemia G2 and fatigue G1.

## OUTCOME AND FOLLOW-UP

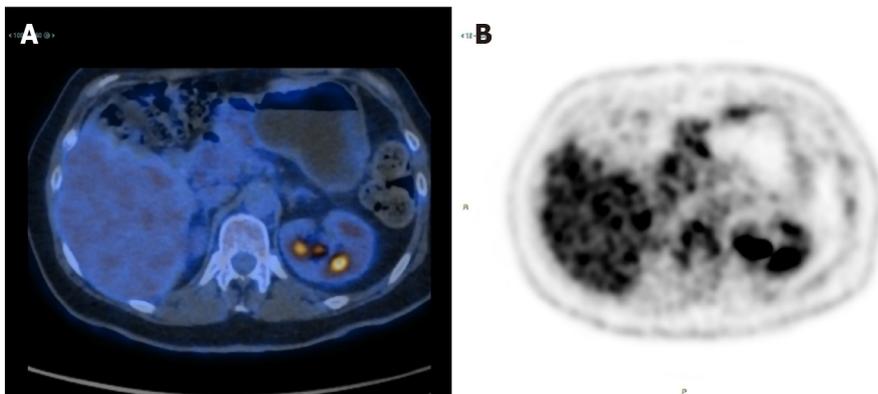
An 18F-FDG PET-CT performed in May 2020 documented an almost complete metabolic response (SUV = 2.1) with a reduction in the diameter of the lesion (Figure 4). Over the next three weeks, treatment was discontinued due to drug shortage related to the COVID-19 pandemic. In June 2020, treatment was restarted and another 18F-FDG PET-CT performed in September 2020 revealed 18F-FDG uptake similar to that shown in May 2020 (SUV = 2.3), while CEA level was 1.45 ng/mL. The patient is still well and receiving olaparib.

## DISCUSSION

Mucin-producing cystic tumours of the pancreas are classified into two different entities: Intraductal papillary mucinous neoplasms (IPMNs) and MCNs, which are defined by the presence of ovarian-type stroma and do not communicate with the ductal system, unlike IPMNs<sup>[9-13]</sup>. MCNs represent 23% of all resected pancreatic cysts with a mean age at diagnosis of 51 years<sup>[1]</sup>, whereas the mean age at diagnosis for MCAC is higher with a difference of more than ten years (mean 64 years)<sup>[2]</sup>. MCAC represents the malignant form of a mucinous cystic neoplasm; approximately 70% of all patients are female presenting with a relatively large tumour (median size 5.5 cm) which is mainly located in the body/tail of the pancreas<sup>[14]</sup>. MCAC is usually

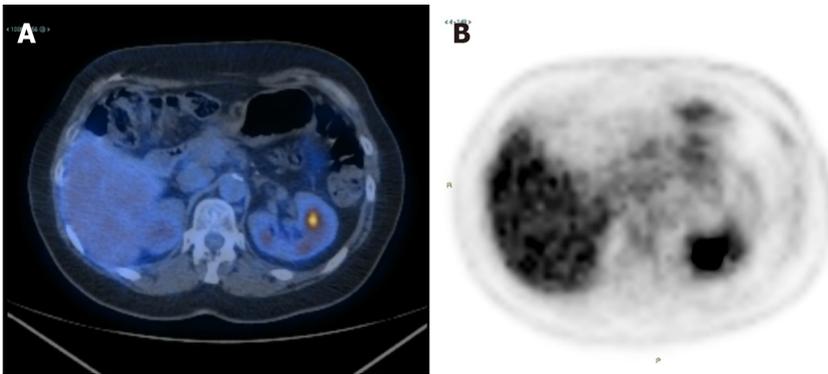


**Figure 2** Magnetic resonance imaging and 18F-fluoro-D-glucose positron emission tomography/X-ray computed tomography. June 2019, Magnetic resonance imaging (MRI) shows the presence of a lesion approximately 4.4 cm × 3.2 cm in the cephalopancreatic area, with MRI characteristics compatible with local recurrence of the basic neoplastic pathology; A: Arterial phase; B: Portal phase; C and D: 18F-fluoro-D-glucose (FDG) positron emission tomography/X-ray computed tomography confirms the diagnostic suspicion of disease recurrence showing a pathological 18F-FDG uptake.



**Figure 3** 18F-fluoro-D-glucose positron emission tomography/X-ray computed tomography performed after eight courses of FOLFIRINOX. A and B: 18F-fluoro-D-glucose positron emission tomography/X-ray computed tomography shows a metabolic reduction in cephalopancreatic disease.

symptomatic at the time of diagnosis with pain (59%) and jaundice (32%) being the two most frequent symptoms. Also, serum CA19-9 level is often increased<sup>[15]</sup>. The prognosis of resectable MCAC seems to be significantly more favourable compared to pancreatic ductal adenocarcinoma<sup>[2,3]</sup>. In a retrospective study involving 507 patients with MCAC, the median observed survival for patients with resectable disease was 111.0 mo *vs* 14.0 mo and 4.0 mo for those with regional and metastatic disease, respectively<sup>[14]</sup>. Interestingly, the performance of curative-intent surgery and the tumour stage were independent predictors of survival. Instead, tumour size seemed to have an insignificant impact on the disease-specific survival of patients with localized MCAC, different to pancreatic ductal adenocarcinoma<sup>[16]</sup>. Due to the very low incidence of this malignancy, there are no prospective studies focusing on chemotherapy for MCAC, and data are available from only case series and case



**Figure 4** 18F-fluoro-D-glucose positron emission tomography/X-ray computed tomography performed after three months of maintenance olaparib. A and B: 18F-fluoro-D-glucose positron emission tomography/X-ray computed tomography shows complete metabolic normalization of the pancreatic lesion, which is also reduced in size.

reports. Thus, it is unclear what is the most appropriate therapeutic approach for advanced disease<sup>[4,17,18]</sup>. This fact is reflected in the poor prognosis of advanced MCAC, especially when compared with that of resectable disease.

BRCA1 and BRCA2 proteins play a crucial role in repairing double-strand DNA breaks *via* the homologous DNA repair mechanism. Deleterious mutations within these genes are associated with an increased risk of breast, ovarian and prostate cancer<sup>[19,20]</sup>. In addition, germline *BRCA1* and *BRCA2* mutations are associated with a relative risk of 2.26 and 3.51 for developing pancreatic adenocarcinoma, respectively<sup>[21,22]</sup>. PARP inhibitors interfere with base excision repair, a crucial pathway in the repair of DNA single-strand breaks, causing an accumulation of single-strand DNA breaks which result into DNA double-strand breaks. Inactivation of *BRCA1* or *BRCA2* genes sensitizes cells to the inhibition of PARP, causing cell cycle arrest and apoptosis when cells are exposed to PARP inhibitors<sup>[23]</sup>. Olaparib (an oral PARP inhibitor) has recently been approved for the maintenance treatment of patients with metastatic pancreatic adenocarcinoma that had not progressed during first-line platinum-based chemotherapy<sup>[6]</sup>. To date, there are no reports of *BRCA*-mutated MCAC treated with PARP inhibitors.

At the time of diagnosis, our patient had metastatic disease, but an aggressive surgical approach associated with a marked response to platinum-based chemotherapy allowed a complete response. Although her family history was negative for cancer, given the impressive response to platinum-based chemotherapy, we investigated and detected a *BRCA1* germline mutation. Historically, screening for *BRCA* mutations was offered only to those patients with a family history highly suspicious for a genetic predisposition syndrome<sup>[24]</sup>. However, this strategy fails to identify a relevant proportion of patients with germline *BRCA1/2* mutations<sup>[24]</sup>. Given the results of the POLO trial, and emerging evidence on the efficacy of platinum-based chemotherapy in *BRCA* mutated PDAC, National Comprehensive Cancer Network guidelines now recommend germline testing for all patients with PDAC<sup>[25-27]</sup>.

To our knowledge, this is the first report on the efficacy of a PARP inhibitor in a MCAC patient harbouring a germline *BRCA* mutation. After three months of treatment with maintenance olaparib, we documented a deep metabolic response with a reduction in the diameter of the lesion and after seven months of therapy 18F-FDG PET-CT still shows an almost complete metabolic response. Treatment was well tolerated except for anaemia G2 and fatigue G1, and it was discontinued for only one week due to fatigue. Reported toxicities in our case are in line with previous studies, with fatigue (60%), nausea (45%) and anaemia (27%) being the three most common adverse events reported in the POLO trial<sup>[6]</sup>.

## CONCLUSION

Increased use of *BRCA* testing, not based only on personal or family history of cancer, may help to identify a higher number of patients which could benefit from target therapies. As previously demonstrated in the treatment of patients with other types of cancers harbouring a germline *BRCA* mutation, we suggest that maintenance olaparib should also be considered for MCAC patients as it is safe and effective. However,

further studies are needed to confirm our results.

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