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BRCA2 Reversion Mutation Identified by Liquid Biopsy After Durable Response to FOLFIRINOX in *BRCA2*-Associated Pancreatic Cancer

To the Editor:

The cancer predisposition genes *BRCA1/2* for pancreatic and hereditary breast and ovarian cancers have recently become important therapeutic targets after the emergence of poly(ADP-ribose)polymerase (PARP) inhibitors.[1] Latest National Comprehensive Cancer Network guidelines recommend germline testing or genomic profiling of tumor tissues when initiating palliative chemotherapy for patients with pancreatic cancer.[2] Although *BRCA1/2*-associated pancreatic cancer is sensitive to platinum-based chemotherapy, including FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin),[3] the resistance mechanism of FOLFIRINOX remains to be clarified.

BRCA reversion mutations restore protein function and are one of the key resistance mechanisms of PARP inhibitors and platinum-based chemotherapies.[4,5] Theoretically, *BRCA* reversion mutations emerge during tumor evolution in response to chemotherapy. Liquid biopsies have an advantage over tumor biopsy for detecting *BRCA* reversion mutations.[6] Herein, we report the first case of a pancreatic cancer patient whose *BRCA2* reversion mutation was detected by a second tumor profiling using liquid biopsy.

CASE REPORT

A 38-year-old woman with jaundice visited an academic hospital. After detailed examination, the patient was diagnosed with locally advanced pancreatic adenocarcinoma (cT4N1M0, Stage III, Union for International Cancer Control, Eighth Edition), and chemoradiotherapy using gemcitabine (GEM) plus nab-paclitaxel was initiated. After chemoradiotherapy, her disease became potentially resectable, so curative surgery was attempted. However, because laparotomy revealed para-aortic lymph node metastases, the surgical team discontinued the operation and systemic chemotherapy using GEM monotherapy was started. At this time, genomic profiling test (Oncomine Comprehensive Assay Version 3; Thermo Fisher Scientific, Waltham, Mass) using a tissue sample obtained from para-aortic lymph node metastases revealed pathogenic mutations in *BRCA2* S2835*, *TP53* E285K, *STK11* P281L, and *EIF3R-RSPO2* fusion. Four months later, the disease became refractory to GEM monotherapy and the treatment was switched to a modified FOLFIRINOX regimen. The patient showed an exceptional response to FOLFIRINOX, and the disease was well controlled for 18 months.

After developing resistance to FOLFIRINOX, the patient was referred to our hospital to undergo a liquid biopsy test (Guardant 360; Guardant Health, Redwood City, Calif). The test results reported *BRCA2* S2835*, *BRCA2* S2835L, and *BRCA2* E2846fs. The latter 2 mutations were not reported in the first genomic profiling test, and their allele frequency of cell-free DNA (cfDNA) was consistent with the somatic origin (1.9% and 3.4%, respectively). *BRCA2* S2835* mutation was consistent with the results of the first genomic test and could confer sensitivity to PARP inhibitors. Although her family history did not disclose the presence of pancreatic and hereditary breast and ovarian cancer, this mutation was highly suspected to be of germline origin given its high allele frequency of cfDNA (43.7%).[7] In contrast, *BRCA2* S2835L mutation could restore the *BRCA2* translation, which was interrupted by S2835* mutation; it was considered to be a *BRCA2* reversion mutation (Fig. 1). The patient strongly wished to receive a PARP inhibitor, which was approved for deleterious germline *BRCA*-mutated breast or ovarian cancers at that time. Unfortunately, the patient's general condition

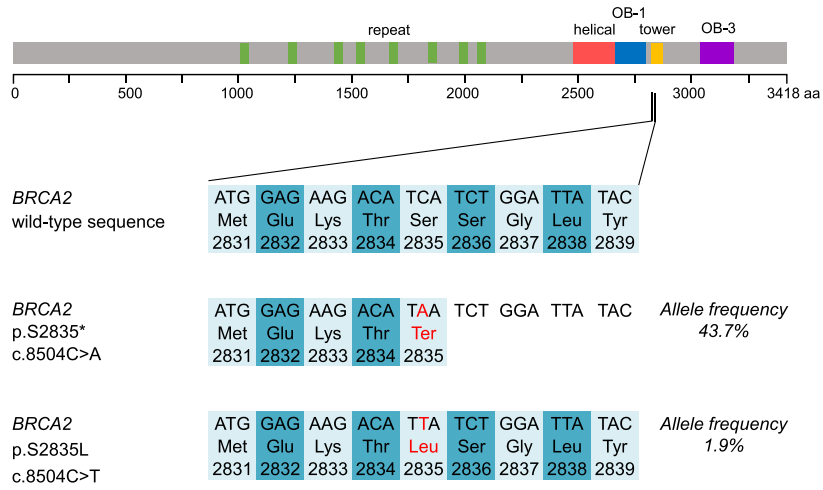

FIGURE 1. *BRCA2* reversion mutation detected using liquid biopsy after developing resistance to FOLFIRINOX treatment. *BRCA2* S2835* was identified by initial genomic profiling test using a tissue sample. After developing resistance to FOLFIRINOX, liquid biopsy revealed that *BRCA2* S2835L mutation could restore the *BRCA2* translation, which was interrupted by S2835* mutation and was considered to be a *BRCA2* reversion mutation. aa, amino acid; helical, helical domain; OB-1, oligonucleotide/oligosaccaride binding domain 1; OB-3, oligonucleotide/oligosaccaride binding domain 3; repeat, BRC repeats; Tower, tower domain.

rapidly deteriorated and she could not receive PARP inhibitor or genetic counseling.

DISCUSSION

To the best of our knowledge, this is the first report of a *BRCA* reversion mutation after developing resistance to FOLFIRINOX treatment, identified by liquid biopsy in a patient with advanced pancreatic cancer.

BRCA reversion mutation was first reported as a secondary mutation that restores the wild-type *BRCA2* reading frame, which could be a major clinical mediator of acquired resistance to platinum-based chemotherapy and PARP inhibitor.[4,5] *BRCA* reversion mutations are defined as follows[6]: (1) a base substitution that changes a nonsense mutation to a missense mutation and (2) an insertion or deletion that restores the open reading frame.

According to a recent study by Lin et al,[6] *BRCA* reversion mutations were identified in pretreatment cfDNA from 18% of platinum-refractory and 13% of platinum-resistant cancers compared with 2% of platinum-sensitive ovarian cancers who are carriers of germline *BRCA* mutations. They also found an association between *BRCA* reversion mutations and decreased clinical benefits from a PARP inhibitor.[6] However, their accurate prevalence in patients with pancreatic cancer remains unknown.

Recently, the efficacy of maintenance olaparib for patients with pancreatic cancer who harbor deleterious germline *BRCA* mutations has been proven by an international, phase III POLO (Pancreas cancer OLaparib Ongoing) trial,[1] and olaparib has been approved by the US Food and Drug Administration for this indication. However, no data are available regarding the efficacy of olaparib for patients who develop *BRCA* reversion mutations during tumor evolution in response to platinum-based chemotherapy in patients with metastatic pancreatic cancer; hence, further data are needed.

In conclusion, we reported the first case of a patient with pancreatic cancer whose liquid biopsy test disclosed a *BRCA2* reversion mutation. Because olaparib has been approved for use among patients with pancreatic cancer with deleterious germline *BRCA* mutations, monitoring *BRCA* reversion mutation using liquid biopsy could be a relevant option to guide clinical decisions when selecting PARP inhibitors. Further studies are warranted to clarify the clinical validity and utility of monitoring *BRCA* reversion mutation using liquid biopsy in patients with advanced pancreatic cancer who harbor deleterious germline *BRCA* mutations.

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All procedures followed during our study involving human participants were in accordance with ethics committee of Kyoto University Graduate School of Medicine (G692) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The authors obtained written informed consent from the patient.

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Treatment of Hypertriglyceridemia-Induced Acute Pancreatitis With Plasma Diafiltration
A Pilot Study

To the Editor:

Severe hypertriglyceridemia-induced acute pancreatitis (HTG-AP) is a critical illness associated with high mortality rate and potentially fatal complications,[1,2] whereas triglyceride (TG)-lowering therapy is crucial in early HTG-AP.[1,3] Plasmapheresis and other extracorporeal filtration techniques were widely used for timely and fast reduction of TG levels. However, it is not an ideal procedure because of potential transfusion related complications or complex operation.[4,5]

Plasma diafiltration (PDF), which used high cutoff hemofilter and diluted plasma as replacement fluid, can significantly decrease middle– and high–molecule-weight mediator levels with low substitution flow, achieving approximately the same effect as that of conventional plasmapheresis.[6] However, no previous reports exist on the treatment of HTG-AP with PDF. Therefore, we designed a retrospective study to evaluate the efficacy and safety of PDF application in combination with routine treatments in 5 HTG-AP patients admitted to the intensive care unit (ICU).

MATERIALS AND METHODS

A total number of 5 HTG-AP patients with a mean age of 35.2 (standard deviation, 1.72; range, 32–37) years who received PDF as part of their treatment during their ICU stay between January 2017 and December 2018 were recruited. All patients received standard conventional treatment. Therapeutic PDF was also performed to rapidly reduce the TG levels, which was discontinued when the levels of serum TGs were less than 1000 mg/dL.

RESULTS

The patients' baseline characteristics are shown in Table 1. The Ranson criteria score values of all patients were greater than 3, indicating severity of pancreatitis. Mechanical ventilation was needed for 1 patient because of acute respiratory distress syndrome for 6 days. Another patient received continuous renal replacement therapy for acute kidney injury. All patients had a known history of hyperlipidemia, whereas 2 of them had alcohol consumption; 2 had hypertension; 1

TABLE 1. Baseline Characteristics and the Treatment of HTG-AP Patients

	Case 1	Case 2	Case 3	Case 4	Case 5
Baseline characteristics					
Sex	Male	Male	Male	Female	Male
Age, y	37	36	35	32	36
Alcohol use	No	No	Yes	No	Yes
T2DM	Yes	No	No	No	No
HP	No	No	Yes	No	No
HTG	Yes	Yes	Yes	Yes	Yes
Ca^{2+}, mmol/L	2.04	1.79	1.72	1.35	2.17
Cholesterol, mmol/L	11.56	12.12	12.66	18.59	14.2
HDL, mmol/L	0.88	0.75	0.77	0.99	0.9
LDL, mmol/L	10.68	11.37	11.24	16.38	7.02
Amylase on admission, μ/L	284	111	491	138	354
APACHE II score	3	5	5	12	7
Ranson score	3	4	5	5	3
Marshall score	3	1	2	3	2
TG on admission, mg/dL	2681.5	3291.3	3932.9	5928.83	3796.22
TG after one session, mg/dL	948.7	516.8	1115.9	1056.57	474.3
TG after PDF, mg/dL	948.7	516.8	493.6	945.07	474.3
TG on discharge from ICU, mg/dL	560.2	613.7	167.3	836.2	324.6
Local complications	None	None	None	None	None
Systematic complications	None	None	None	None	None
Mechanical ventilation	No	No	No	Yes	No
CRRT	No	No	No	Yes	No
LOS in ICU, d	3	3	4	10	2
Total LOS, d	13	21	19	23	12
PDF treatment					
No. PDF sessions	1	1	2	2	1
Duration of apheresis, h	6	3	6 + 6	6 + 6	6
Heparin dosage, U/h	750	500	No	No	No
Blood flow rate, mL/min	180	180	180	180	180
Dialysate flow rate, mL/min	3000	3000	3000	3000	3000
Replacement flow rate, mL/min	600	600	600	600	600
Removal rate for TC after one session, %	57.8	57.9	31.9	49.2	4.8
Removal rate for TG after one session, %	64.6	84.3	71.6	82.2	87.5
Maximal TMP, mm Hg	10	10	10	10	10
Maximal arterial pressure, mm Hg	−110	−160	−90	−100	−85
Maximal venous pressure, mm Hg	80	500	80	120	101

APACHE II indicates Acute Physiology and Chronic Health Evaluation; CRRT, continuous renal replacement therapy; HP, hypertension; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LOS, length of stay; T2DM, type 2 diabetes mellitus; TC, total cholesterol.