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.

BRCA2 reversion mutations restore protein function and are one of the key resistance mechanisms of PARP inhibitors and platinum-based chemotherapies.4,5 Theoretically, BRCA1 reversion mutations emerge during tumor evolution in response to chemotherapy. Liquid biopsies have an advantage over tumor biopsy for detecting BRCA1 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 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-RSQP2 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 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 worsened and the patient declined further treatment and passed away from recurrent disease.

Zsuzsanna Nemeth, MLIS, CCRC
Department of Health Informatics
University of Miami
Leonard M. Miller School of Medicine
Miami, FL

Jamie S. Barkin, MD
Division of Gastroenterology
Department of Medicine
University of Miami
Leonard M. Miller School of Medicine
Miami, FL

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OPEN

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

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Letters to the Editor

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routinely 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. BRCA2 S2835* was identified by initial genomic profiling test using a tissue sample. After developing resistance to FOLFIRINOX, liquid biopsy revealed that BRCA2 S2835 mutation could restore the BRCA 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/oligosaccharide binding domain 1; OB-3, oligonucleotide/oligosaccharide binding domain 3; repeat, BRCT repeats; Tower, tower domain.

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 S2835 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/oligosaccharide binding domain 1; OB-3, oligonucleotide/oligosaccharide binding domain 3; repeat, BRCT repeats; Tower, tower domain.

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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, whereas triglyceride (TG)-lowering therapy is crucial in early HTG-AP. Glyceride (TG)-lowering therapy is crucial to the treatment of HTG-AP patients. 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 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                     | Yes                     | Yes                     |
| T2DM                    | Yes                     | No                      | No                      | No                      | No                      |
| HTG                     | Yes                     | Yes                     | Yes                     | Yes                     | Yes                     |
| Ca²⁺, 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, μU | 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                      | Yes                     | No                      | No                      |
| CRRT                    | No                      | No                      | Yes                     | 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                    |
| Maximum 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.

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