Case Report

Homologous recombination deficiency score decreased after neoadjuvant chemotherapy in ovarian cancer patient: a case report

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Background: Homologous recombination deficiency (HRD) confers sensitivity to poly(ADP-ribose) polymerases inhibitor (PARPi) and DNA-damaging agents. Clinical tests predict the presence of HRD based on genomic features caused by HRD, which are generally considered permanent "genomic scars". We are the first to report a case of high-grade serous ovarian cancer (HGSOC) whose homologous recombination (HR) status changed from HRD positive to HRD negative after neoadjuvant chemotherapy (NAC).

Case Description: A 65-year-old Chinese woman who presented with bloating and weight loss for 2 months but had no relevant prior medical history was diagnosed with HGSOC after laparoscopic biopsies. She received NAC followed by interval debulking surgery (IDS) and standard chemotherapy combined with bevacizumab. Due to the HRD positivity measured using pre-NAC samples, she received PARPi plus bevacizumab as first-line maintenance therapy, followed by single PARPi maintenance. However, reassessment of the HRD using post-NAC tumor samples showed that the HR status changed from positive to negative after NAC. In the most recent follow-up visit, her cancer antigen 125 (CA-125) was 3.8 U/mL, and no tumor activity was detected on the computed tomography (CT) scan.

Conclusions: This surprising finding indicated that the HR status's phenotypic measurements might change after NAC, affecting therapeutic decisions. Tumor heterogeneity and NAC response heterogeneity may explain the observed HRD status change. Precautions need to be taken when interpreting HRD test results for HGSOC patients receiving NAC, especially for *BRCA*-negative patients. Further studies, including multi-sampling, are required to assess HRD dynamics and determine whether residual tumors after NAC will respond to PARPi.

Keywords: Case report; homologous recombination deficiency (HRD); ovarian cancer; neoadjuvant chemotherapy (NAC); homologous recombination change (HR change)

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Introduction

Background

Ovarian cancer is the seventh most commonly diagnosed cancer among women and is the leading cause of death amongst women with gynecological cancers (1). A 5-year survival among patients with advanced disease [International Federation of Gynecology and Obstetrics (FIGO) stage

III–IV] is <30% (2). Epithelial ovarian cancer is the most common type of ovarian cancer and has four main histological subtypes: serous, endometrioid, mucinous, and clear cell. Almost 70% of all epithelial tumors are aggressive high-grade serous ovarian cancer (HGSOC) and present in advanced stages (3). Cytoreductive surgery followed by platinum-based chemotherapy has remained the mainstay of treatment for decades (4). Homologous recombination deficiency (HRD) is a functional defect in the homologous recombination (HR) DNA repair pathway. Approximately 50% of HGSOC exhibit HRD, which confers sensitivity to poly(ADP-ribose) polymerases inhibitor (PARPi) and DNA-damaging agents (5). In addition, HRD tumors have been suggested to be more immunogenic, therefore, more susceptible to immunotherapy (6,7).

Rationale and knowledge gap

Clinical tests aim to predict the presence of HRD by detecting genomic features caused by HRD, such as loss of heterozygosity (LOH) (8), telomeric allelic imbalance (TAI) (9), and large-scale state transitions (LSTs) (10). These assays measure the consequence of HRD, irrespective of the underlying etiology. Although genomic alterations induced by HRD are considered permanent "genomic scars", tumoral HRD status has been recognized to be dynamic over time, such as the acquisition of *BRCA* reversion mutations that restore HR function in *BRCA*-mutant cancer cells (11,12). Studies have shown that 25% to 50% of patients treated with PARPi will have relapsed by 30 months from diagnosis, the *BRCA* reversion may be the underlying mechanism of PARPi resistance (13,14). Neoadjuvant chemotherapy (NAC) is widely applied in routine practice for ovarian cancer. However, it is still unknown whether the phenotypic measurement of HRD remains the same after NAC and whether residual tumors after NAC respond to PARPi based on synthetic lethality.

Objective

Here, we reported one HGSOC case whose HR status changed from HRD positive to HRD negative after NAC. To our knowledge, there is no report documenting the decrease of HRD score in HGSOC patients after NAC. Tumor heterogeneity (intratumoral, intertumoral), and NAC response heterogeneity may explain the HRD status change. This finding indicated that the HR status's phenotypic measurements of the post-NAC tumor might differ from the original tumor, and extra precautions must be taken when interpreting HRD test results. To make optimal clinical decisions, whether the HRD status of HGSOC patients receiving NAC should be detected from either treatment naïve biopsies, treated tumor samples, or multiple tumor lesions needs thorough study in the future. We present this case in accordance with the CARE reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-23-19/rc).

Highlight box

Key findings

- We reported one high-grade serous ovarian cancer case whose homologous recombination status changed from homologous recombination deficiency (HRD) positive to HRD negative after neoadjuvant chemotherapy (NAC).

What is known and what is new?

- Clinical tests aim to predict the presence of HRD by detecting genomic features, which are considered permanent "genomic scars" and confer sensitivity to poly(ADP-ribose) polymerases inhibitor (PARPi). However, it is still unknown whether the HRD remains unchanged and whether residual tumors respond to PARPi after NAC.
- The phenotypic measurements of HRD might change between original tumors and post-NAC tumors, affecting treatment decisions.

What is the implication, and what should change now?

- Our discovery suggests that extra precautions need to be taken when interpreting HRD score results for patients receiving NAC, especially for *BRCA*-negative patients. It is important to design future studies that include multi-sampling to allow the assessment of HRD status dynamically.

Case presentation

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This research proposal was covered by approval for data use and clinical studies from the General Ethics Commission, West China Second University Hospital. Additional ethical approval was not necessary from the Ethics Commission of West China Second University Hospital, as only anonymized data were analyzed in this study. Written informed consent to participate was given by the patient prior to examination and documentation. A copy of the written consent is available for review by the editorial office of this journal.

The patient was a 65-year-old Chinese woman with no

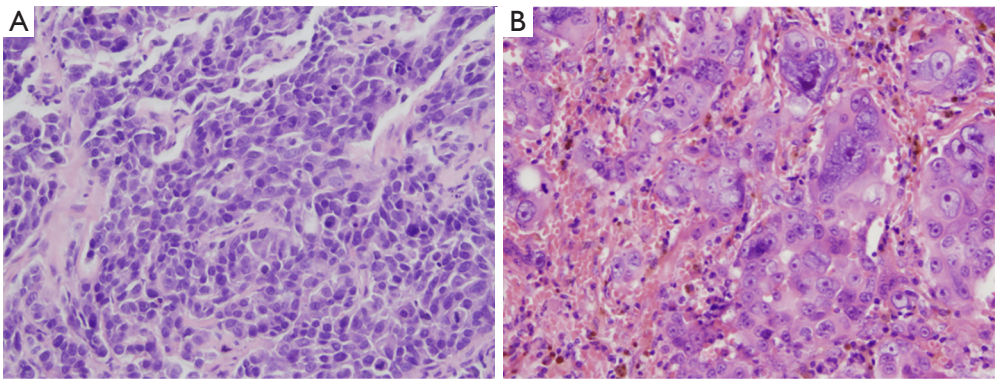

Figure 1 Representative H&E images from pre-NAC (A) and post-NAC (B) tumor sections (magnification 400×). Altered cell morphology indicates tumor cell apoptosis and necrosis in post-NAC tumor specimens in both cases. NAC, neoadjuvant chemotherapy; H&E, hematoxylin and eosin.

relevant past medical history who presented to hospital on July 2020 with bloating, poor appetite, fatigue, and weight loss (2 kg) for 2 months. Pelvic examination showed healthy external genitalia and cervix. Irregular cystic solid mass could be palpated on both side adnexa. A computed tomography (CT) scan revealed a cystic tumor in the pelvic cavity that involved both side ovaries, with peritoneal carcinomatosis and nodules in the right lobe of the liver. Her cancer antigen 125 (CA-125) level was 584.7 U/mL (normal range of CA-125 level <35 U/mL). A standard laparoscopic procedure was performed for pelvic biopsies under general anesthesia conditions. The endoscopic evaluation of the pelvis showed bloody peritoneal fluid (200 mL), a cystic solid mass involving bilateral adnexa, and extensive peritoneal dissemination. Tissue samples from the cystic solid mass and omental nodules were biopsied for pathologic examination, and ascites were sent for cytology test. The biopsies confirmed high-grade serous adenocarcinoma in the fimbriae end of the fallopian tube, omentum, and ascites (*Figure 1*). After genetic counseling and informed consent, we assessed her HRD score [PARP inhibitor CDx genetics testing (HRD), BGI, Shenzhen, China] using samples from the biopsy and detected mutations of HR repair (HRR) pathway genes [PARP inhibitor CDx genetics testing (HRR), BGI, Shenzhen, China]. The HRD score comprehensively evaluated LOH, TAI and LST scores with correction of ploidy and purity of tumor by BGI, and the calculation formula of HRD score was preliminarily determined as follows: HRD_{score} = LOH + TAI + (LST – K × Ploidy) (15). The results showed that her HRD score was 42.57 (LOH 21, TAI 10, LST 43, Ploidy 2.03, K 15.5), and no deleterious mutation of any HRR gene was detected either in the germline testing (*Table 1*) or the somatic testing (*Table 2*). HRD positive was defined as a high HRD score (above the HRD threshold, ≥30) and/or harmful mutations were detected in tumor *BRCA1/2*. HRD negative was defined as a low HRD score (below the HRD threshold, <30), and no harmful mutations were detected in tumor *BRCA1/2* (15). Based on this, we concluded that her tumor was HRD positive and that she would potentially benefit from PARPi.

After being evaluated by a gynecological oncologist and calculating the predictive value score using the Multivariate Model of Significant Clinical and Radiologic Criteria Predictive of Suboptimal Cytoreduction system (Suidan score 4, *Table 3*) (16), the patient was deemed to receive NAC because she was unlikely to achieve residual disease <1 cm only through cytoreduction. Therefore, she was treated with two cycles of carboplatin [area under the curve (AUC) 5] plus paclitaxel (175 mg/m^2) (TC, q3w) during July and August 2020, and she had good responses, with the CA-125 level dropping to 14.5 U/mL. Next, the patient received interval debulking surgery (IDS) on October 2020 with the help of a hepatobiliary surgeon (R0 resection), consisting of total hysterectomy with bilateral adnexectomy, pelvic and para-aortic lymph node dissection, omentectomy, appendectomy, and cytoreductive procedure. The postoperative pathology confirmed HGSOC with liver parenchymal metastasis, thus her final diagnosis was stage IVB HGSOC. She recovered well from the surgery and symptoms such as bloating and poor appetite were largely alleviated. She received one cycle of TC (dose same

Table 1 Summary of germline HRR gene mutation

Number	Gene	Transcript	Nucleotide change	Amino acid change	Gene subregion	Heterozygosity	Mutation type	Variant classification
1	*ATM*	NM_000051.3	c.1236-3dupT	–	IN9	Het	Splice	Benign
2	*BARD1*	NM_000465.3	c.216-14delT	–	IN2	Het	Splice	Benign
3	*BLM*	NM_000057.3	c.2555+7T>C	–	IN12	Het	Splice	Benign
4	*BRCA1*	NM_007294.3	c.4837A>G	p.Ser1613Gly	EX16	Het	Missense	Benign
5	*BRCA1*	NM_007294.3	c.3548A>G	p.Lys1183Arg	EX11	Het	Missense	Benign
6	*BRCA1*	NM_007294.3	c.3113A>G	p.Glu1038Gly	EX11	Het	Missense	Benign
7	*BRCA1*	NM_007294.3	c.2612C>T	p.Pro871Leu	EX11	Het	Missense	Benign
8	*BRCA2*	NM_000059.3	c.943T>A	p.Cys315Ser	EX10	Het	Missense	Likely benign
9	*BRCA2*	NM_000059.3	c.7806-14T>C	–	IN16	Hom	Splice	Benign
10	*BRIP1*	NM_032043.2	c.2755T>C	p.Ser919Pro	EX19	Hom	Missense	Benign
11	*BRIP1*	NM_032043.2	c.587A>G	p.Asn196Ser	EX6	Het	Missense	Likely benign
12	*CDH1*	NM_004360.4	c.48+6C>T	–	IN1	Hom	Splice	Benign
13	*CDH1*	NM_004360.4	c.2164+17dupA	–	IN13	Het	Splice	Benign
14	*CFTR*	NM_000492.3	c.1408G>A	p.Val470Met	EX11	Het	Missense	Benign
15	*CHEK1*	NM_001274.5	c.1411A>G	p.Ile471Val	EX13	Hom	Missense	Benign
16	*EPCAM*	NM_002354.2	c.344T>C	p.Met115Thr	EX3	Het	Missense	Benign
17	*ERCC2*	NM_000400.3	c.2251A>C	p.Lys751Gln	EX23	Het	Missense	Benign
18	*ERCC2*	NM_000400.3	c.934G>A	p.Asp312Asn	EX10	Het	Missense	Benign
19	*ERCC2*	NM_000400.3	c.477+9A>C	–	IN6	Het	Splice	Benign
20	*ERCC4*	NM_005236.2	c.974-7G>A	–	IN5	Hom	Splice	Benign
21	*ERCC5*	NM_000123.3	c.3310G>C	p.Asp1104His	EX15	Hom	Missense	Benign
22	*FANCA*	NM_000135.2	c.3935-16C>T	–	IN39	Het	Splice	Benign
23	*FANCA*	NM_000135.2	c.2426G>A	p.Gly809Asp	EX26	Hom	Missense	Benign
24	*FANCA*	NM_000135.2	c.2151+8T>C	–	IN23	Hom	Splice	Benign
25	*FANCA*	NM_000135.2	c.1826+15T>C	–	IN20	Hom	Splice	Benign
26	*FANCA*	NM_000135.2	c.1501G>A	p.Gly501Ser	EX16	Hom	Missense	Benign
27	*FANCA*	NM_000135.2	c.1226-20A>G	–	IN13	Hom	Splice	Benign
28	*FANCA*	NM_000135.2	c.796A>G	p.Thr266Ala	EX9	Hom	Missense	Benign
29	*FANCA*	NM_000135.2	c.710-12A>G	–	IN7	Hom	Splice	Benign
30	*FANCD2*	NM_001018115.2	c.378-6_378-5delTT	–	IN5	Het	Splice	Benign
31	*FANCD2*	NM_001018115.2	c.439-16A>G	–	IN6	Het	Splice	Benign
32	*FANCD2*	NM_001018115.2	c.695+16G>C	–	IN9	Het	Splice	Benign
33	*FANCD2*	NM_001018115.2	c.784-19C>T	–	IN10	Het	Splice	Benign
34	*FANCD2*	NM_001018115.2	c.1278+1delG	–	IN15	Het	Splice donor	Benign
35	*FANCD2*	NM_001018115.2	c.1278+3_1278+5delAAG	–	IN15	Het	Splice	Benign

Table 1 (*continued*)

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Number	Gene	Transcript	Nucleotide change	Amino acid change	Gene subregion	Heterozygosity	Mutation type	Variant classification
36	*FANCD2*	NM_001018115.2	c.1278+15C>T	–	IN15	Het	Splice	Benign
37	*FANCD2*	NM_001018115.2	c.3466+34_3466+36dupTTT	–	IN34	Het	Splice	Benign
38	*FANCD2*	NM_001018115.2	c.3849+13A>G	–	IN38	Het	Splice	Benign
39	*FANCI*	NM_001113378.1	c.257C>T	p.Ala86Val	EX4	Het	Missense	Benign
40	*FANCI*	NM_001113378.1	c.1698+15C>T	–	IN17	Het	Splice	Benign
41	*FANCI*	NM_001113378.1	c.2225G>C	p.Cys742Ser	EX22	Het	Missense	Benign
42	*FANCI*	NM_001113378.1	c.3006+15A>C	–	IN27	Het	Splice	Benign
43	*GEN1*	NM_001130009.2	c.274T>A	p.Ser92Thr	EX3	Hom	Missense	Benign
44	*GEN1*	NM_001130009.2	c.2039C>T	p.Thr680Ile	EX14	Hom	Missense	Benign
45	*GEN1*	NM_001130009.2	c.2515_2519delAAGTT	p.Lys839Glufs*2	EX14	Het	Frameshift	Benign
46	*MRE11A*	NM_005590.3	c.403-6G>A	–	IN5	Het	Splice	Benign
47	*MSH2*	NM_000251.2	c.211+9C>G	–	IN1	Het	Splice	Benign
48	*MSH2*	NM_000251.2	c.1661+12G>A	–	IN10	Het	Splice	Benign
49	*MSH2*	NM_000251.2	c.2006-6T>C	–	IN12	Het	Splice	Benign
50	*MSH6*	NM_000179.2	c.3438+14A>T	–	IN5	Het	Splice	Benign
51	*MUTYH*	NM_001128425.1	c.1014G>C	p.Gln338His	EX12	Het	Missense	Benign
52	*NF1*	NM_000267.3	c.730+32dupT	–	IN7	Het	Splice	Benign
53	*PMS2*	NM_000535.6	c.1621A>G	p.Lys541Glu	EX11	Hom	Missense	Benign
54	*PMS2*	NM_000535.6	c.1408C>T	p.Pro470Ser	EX11	Hom	Missense	Benign
55	*PMS2*	NM_000535.6	c.706-4delT	–	IN6	Het	Splice	Benign
56	*PMS2*	NM_000535.6	c.705+17A>G	–	IN6	Hom	Splice	Benign
57	*POLE*	NM_006231.3	c.6657+16C>T	–	IN47	Hom	Splice	Benign
58	*POLE*	NM_006231.3	c.6330+15G>A	–	IN45	Hom	Splice	Benign
59	*POLE*	NM_006231.3	c.3582+17A>G	–	IN29	Hom	Splice	Benign
60	*PPP2R2A*	NM_001177591.1	c.1095-10A>G	–	IN9	Het	Splice	Benign
61	*PRSS1*	NM_002769.4	c.508A>G	p.Lys170Glu	EX4	Het	Missense	Benign
62	*PTEN*	NM_000314.6	c.802-3dupT	–	IN7	Het	Splice	Benign
63	*RAD52*	NM_134424.3	c.186+13A>G	–	IN3	Het	Splice	Benign
64	*RAD52*	NM_134424.3	c.-18-20delT	–	IN1	Het	Splice	Benign
65	*RAD54L*	NM_003579.3	c.408G>C	p.Lys136	EX6	Het	Missense	VUS
66	*SLX4*	NM_032444.3	c.3812C>T	p.Ser1271Phe	EX12	Het	Missense	Benign
67	*STK11*	NM_000455.4	c.33G>A	p.Met11Ile	EX1	Het	Missense	VUS
68	*TP53BP1*	NM_001141980.1	c.5306-8delT	–	IN24	Het	Splice	Benign
69	*TP53BP1*	NM_001141980.1	c.3421A>C	p.Lys1141Gln	EX17	Het	Missense	Benign
70	*TP53BP1*	NM_001141980.1	c.1249G>A	p.Gly417Ser	EX11	Het	Missense	Benign
71	*TP53BP1*	NM_001141980.1	c.1074C>G	p.Asp358Glu	EX9	Het	Missense	Benign

Table 1 (*continued*)

Table 1 (*continued*)

Number	Gene	Transcript	Nucleotide change	Amino acid change	Gene subregion	Heterozygosity	Mutation type	Variant classification
72	*WRN*	NM_000553.4	c.1720+15A>G	–	IN14	Het	Splice	VUS
73	*WRN*	NM_000553.4	c.1982-5delT	–	IN17	Hom	Splice	Benign
74	*WRN*	NM_000553.4	c.3138+7G>A	–	IN25	Hom	Splice	Benign
75	*WRN*	NM_000553.4	c.3222G>T	p.Leu1074Phe	EX26	Hom	Missense	Benign
76	*XRCC3*	NM_001100119.1	c.722C>T	p.Thr241Met	EX8	Het	Missense	Benign
77	*XRCC3*	NM_001100119.1	c.-354-9A>G	–	IN1	Hom	Splice	Benign

HRR, homologous recombination repair; Het, heterozygous mutation; Hom, homozygous mutation; VUS, variant of unknown significance.

Table 2 Summary of somatic HRR gene mutation identified from tumor samples

Sample	Gene	Mutation	Gene subregion	Transcript	Variant frequency (%)	Variation level
Pre-NAC	*TP53*	p.Tyr107Serfs*10 (c.320_338delACGGTTTCCGTCTGGGCTT)	EX4	NM_000546.5	31.66	Tier II
Post-NAC	*TP53*	p.Tyr107Serfs*10 (c.320_338delACGGTTTCCGTCTGGGCTT)	EX4	NM_000546.5	9.35	Tier II
	GEN1	p.V781L (c.2341G>C)	EX14E	NM_001130009.1	10.83	Tier III

HRR, homologous recombination repair; NAC, neoadjuvant chemotherapy; Tier II, variants with potential clinical significance; Tier III, variants of unknown clinical significance.

Table 3 Multivariate model of significant clinical and radiologic criteria

Criteria	Score
Clinical criteria	
Age ≥60 years	1*
CA-125 ≥600 U/mL	1
ASA 3–4	3
Radiologic criteria	
Retroperitoneal lymph nodes above the renal hilum (including supradiaphragmatic) >1 cm	1
Diffuse small bowel adhesions/thickening	1*
Perisplenic lesion >1 cm	2
Small bowel mesentery lesion >1 cm	2*
Root of the superior mesenteric artery lesion >1 cm	2
Lesser sac lesion >1 cm	4

*, criteria that fit for the patient. Score 0–2: PDS; Score ≥3: NAC + IDS. CA-125, cancer antigen 125; ASA, American Society of Anesthesiologists; PDS, primary debulking surgery; NAC, neoadjuvant chemotherapy; IDS, interval debulking surgery.

as NAC and frequency), followed by five cycles of TC combined with bevacizumab (7.5 mg/kg) from October 2020 to April 2021. After first-line chemotherapy, her CA-125 level returned to normal (4.0 U/mL), and no tumor activity was seen on the CT scan. According to the National Comprehensive Cancer Network (NCCN) guidelines and the results from the PAOLA-1 trial, which showed improvement in progression-free survival (PFS) when olaparib was added to maintenance bevacizumab in BRCA wild type but HRD positive patients who had a complete response/partial response (CR/PR) after first-line chemotherapy plus bevacizumab (17). The patient received olaparib (150 mg, bid) plus bevacizumab (7.5 mg/kg, q3w) as first-line maintenance therapy from July 2021 to June 2022, followed by single olaparib maintenance with mild adverse events, mainly grade I–II leukopenia and fatigue, without specific interventions. We expect a significant survival benefit from the maintenance therapy due to her HRD positivity. In the most recent follow-up visit (July 2023), her CA-125 was 3.8 U/mL, and no tumor activity was detected on the CT scan (*Figure 2*). We reassessed the HRD score and HRR pathway genes mutation using the non-necrotic tumor specimen from the IDS after she provided informed

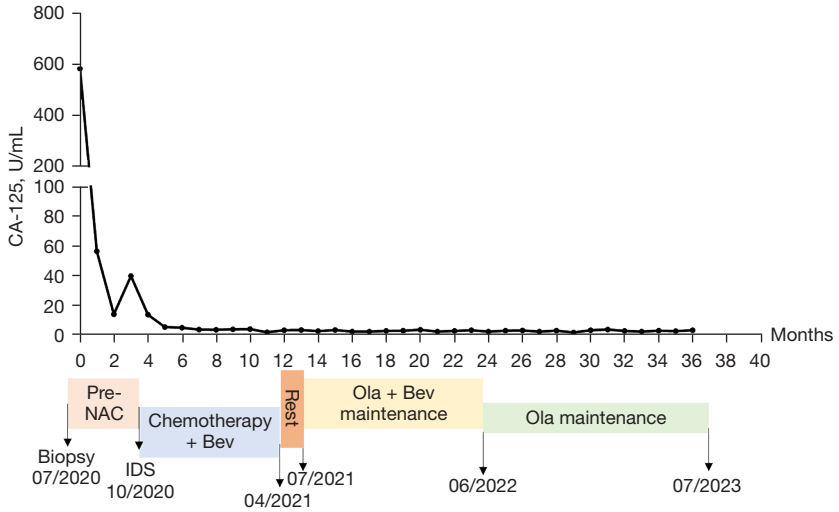

Figure 2 The level of CA-125 for patient during the course of the treatment. Due to the local COVID-19 lockdown situation, the treatment frequency was not always 21 days. CA-125, cancer antigen 125; NAC, neoadjuvant chemotherapy; IDS, interval debulking surgery; Bev, bevacizumab; Ola, olaparib; COVID-19, coronavirus disease 2019.

consent for testing. No pathogenic mutation of any HRR gene was detected; however, surprisingly, the HRD score calculated from the tumor sample was less than one (LOH 1, TAI 0, LST 0, Ploidy 2.00, K 15.5) and determined as HRD negative. The tumor purity of the tested samples was evaluated by an experienced pathologist, which is 40% pre-NAC and 20% post-NAC. Although tumor purity both fulfilled the quality control requirements for the HRD score assessment, a concern was raised about whether the HRD score change was caused by lower tumor content in the post-NAC sample. To further clarify this issue, we reassessed the HRD score in the post-NAC sample by using tumor materials specifically scraped from tumor sections that an experienced pathologist marked. The results showed that the tumor purity was 50% and an HRD score of –8.93 (LOH 11, TAI 7, LST 5, ploidy 2.06, K 15.5). The average sequencing depths of the three samples are more than 150×, and the capture efficiencies are more than 45% for all samples. These details exclude our concern that the HRD status change observed in this patient was due to lower tumor purity and unqualified quality control.

Discussion

Key findings

In this study, we reported one HGSOC case whose HR status changed from HRD positive to HRD negative after NAC. This surprising finding indicated that the HR status's phenotypic measurements might change after NAC, therefore affecting therapeutic decisions.

Strengths and limitations

This report has merits as it is the first report showing the HR status changed from HRD positive to HRD negative after NAC and has educational values. This finding has drawn our attention to the fact that extra precautions need to be taken when interpreting HRD score results for patients receiving NAC. The limitation of our study is that one case was inadequate to draw any statistically meaningful conclusions, and it may lack the ability to generalize.

Comparison with similar researches

To represent, there is no comparable clinical studies reported. Only a previous study (18) reported that concordance in functional HR status between ascites and solid tumor subcultures was seen in only half of the patients which partially supported our theory that intratumoral and intertumoral heterogeneity may be responsible for our discovery.

Explanations of findings

HRD is defined by an impaired error-free HR pathway for repairing DNA double-strand breaks caused by germline/

somatic mutations or epigenetic modifications of genes involved in the HR pathway (19). Approximately 50% of HGSOCs exhibit HRD, and the recognition of HRD as a biomarker for HGSOC has transformed treatment paradigms for advanced ovarian cancer. Mechanistically, it is expected that PARPi will be most active in HRD-positive tumors, while HRD-negative tumors are unlikely to respond to PARPi. Although clinical trial results showed that niraparib could provide a longer duration of PFS than placebo in the overall population, niraparib provides a significant clinical benefit for HRD-positive patients over HRD-negative patients (20). Identifying HRD positivity in clinical specimens is critical to patient selection for PARPi, especially for *BRCA*-negative patients. To date, no uniformly accepted gold standard for HRD assessment exists. Present clinical methods for detecting HRD are limited to direct measuring HR gene mutations, detecting genomic scars reflecting genomic instability, or assessing HR functionality by RAD51 foci formation assays.

Cancer genomes often harbor chromosomal aberrations arising from defective DNA repair, leading to gross chromosomal rearrangements (21) and certain genomic signatures. This leads to the development of assays to evaluate the "genomic scars" as an indirect measure of HRD, such as the presence of LOH, TAI, LST, signature 3 (22), and HRDetect (23). These assays measure the consequence of HRD, irrespective of the underlying etiology. The combination of LOH, TAI and LST performed best at distinguishing HRD-positive tumors from HRD-negative tumors (24,25). More assays are currently commercially available, among them, the 'myChoice CDx' assay by Myriad (24), and 'FoundationFocus CDx BRCA LOH' by Foundation Medicine (26) have been approved by the Food and Drug Administration (FDA). In this study, the HRD score comprehensively evaluated LOH, TAI, and LST scores with correction of ploidy and purity of tumor by BGI. The HRD score threshold in this study was predefined by analyzing HRD scores in a training cohort of 195 ovarian and breast tumor samples with known *BRCA1/2* status and identifying a cutoff with 95% sensitivity to detect those tumors with *BRCA1/2* deficiency. HRD positive, defined as an HRD score ≥30 and/or tumor with harmful *BRCA1/2* mutation, was tested for its ability to identify which tumors responded to platinum-based chemotherapy in Chinese epithelial ovarian cancer patients (15).

The most likely explanations for HR status change could be intratumoral and intertumoral heterogeneity, and NAC response heterogeneity. First, the HRD score is assessed using core-needle biopsy samples or a few tissue sections from a tumor resection specimen representing only a small fraction of a large tumor mass. Several studies have reported differences in the mutation landscape of the same tumor depending on where the tumor was sampled (27,28). These findings suggest that spatial genomic heterogeneity exists within a single tumor, which might account for the HR status change. Second, tumor cells harboring HRD are more sensitive to platinum-based chemotherapy (29), which results in surviving chemo-resistant clones. These chemo-resistant clones are most probably HRD negative which remained until the surgery and were used for our second test. Last, the tumor tissues analyzed from biopsy and surgery were most probably obtained from different sites of lesions in the same patient. It is likely that biopsy from a single site of lesion may not be representative of the tumor elsewhere genetically and therefore may lead to inconsistent HR status. Recently, single-cell RNA sequencing has been applied to examine how ovarian cancer cells change before and after chemotherapy. No copy number alterations predicted from single-cell RNA sequencing were found, which may imply a stable HR status during chemotherapy. However, direct evidence by measuring HRD on a single cell level is needed (30).

Implications and actions needed

Intertumoral and intratumoral heterogeneity will lead to different prognoses when patients are treated according to the same molecular markers. However, limited by technology and economic costs, tumor molecular tests are usually carried out with samples from a single site. We often test the latest samples in current clinical practice, because previous treatment may affect the tumor genome. This will enable us to consider the follow-up treatments of the patient based on HRD negative status. However, Patel *et al.* reported that HRD was maintained between the primary and recurrent samples of HGSOC (31). This reminds us that there are still residual tumor cells which are HRD positive, and these cells may predominate at relapse. Thus, we considered treating the patient based on the HRD tested pre-NAC. We will follow up on her treatment and prognosis, which may be presented in the future.

Conclusions

Our discovery suggests that a pre-NAC biopsy sample may

be considered for HRD scoring when clinicians encounter the situation we presented here. NAC is widely applied in routine practice, and residual tumors remaining after NAC are believed to be resistant to chemotherapy. However, whether residual tumors after NAC respond to PARPi based on synthetic lethality is still unclear, and this issue needs thorough study in the future. Although repeated tumor testing has not been shown to be of any utility in therapeutic decision-making for patients who have already undergone somatic testing, our finding indicated that it is important to design future studies, including multi-sampling, to allow the assessment of HRD status dynamically.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This research proposal was covered by approval for data use and clinical studies from the General Ethics Commission, West China Second University Hospital. Additional ethical approval was not necessary from the Ethics Commission of West China Second University Hospital, as only anonymized data were analyzed in this study. Written informed consent to participate was given by the patient prior to examination and documentation. A copy of the written consent is available for review by the editorial office of this journal.

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