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Ovarian Serous Carcinoma With a Novel HSP90AB1 Mutation in a Patient With Synchronous Primary Fallopian Tube Serous Carcinoma

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Abstract. *Background/Aim: Ovarian carcinoma is the fifth leading cause of cancer-related deaths in women in the United States. Serous papillary carcinoma is the most common histological type of ovarian carcinoma that often goes undetected until it has spread within the pelvis and abdomen leading to poor prognosis. Translation of next-generation sequencing (NGS) technology into personalized medicine and identification of new potential targets for therapeutic applications may be helpful. Case Report: We report a case of a 59-year-old female who initially presented in the emergency department with increasing abdominal girth, and bloating. Computed tomography showed ascites and omental and pelvic masses. Fine needle biopsy of the omental mass showed high-grade papillary adenocarcinoma consistent with high-grade ovarian serous carcinoma. She was treated with chemotherapy followed by debulking surgery. Primary ovarian serous carcinoma and synchronous primary fallopian tube serous carcinoma with multiple leiomyomas were identified in the surgical specimen. Pleural biopsy was also positive for carcinoma. NGS and programmed death-ligand 1 (PD-L1) expression testing were performed in the ovarian serous carcinoma. The results showed mutations of breast cancer type 1 (BRCA1) and type 2 (BRCA2), tumor protein p53 (TP53) (c.524G>A at pR175H), and heat shock protein 90 alpha family class B member 1 (HSP90AB1) (p.R456C), as well as low RNA expression score of PD-L1. Conclusion: Identification of these mutations and PD-L1 abnormality at the diagnosis of ovarian carcinoma may shed light for clinicians to provide targeted therapy with poly (ADP-ribose) polymerase (PARP) inhibitors and immune checkpoint inhibitors for ovarian serous carcinoma. This is the first documented case of ovarian serous carcinoma to have found a HSP90AB1 (p.R456C) mutation.*

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Key Words: Ovarian serous carcinoma, synchronous carcinoma, fallopian tube serous carcinoma, immunohistochemistry, next generation sequencing, chemotherapy, PD-L1 immunotherapy, targeted therapy, HSP90AB1 mutation.

Ovarian carcinoma is the fifth leading cause of cancer-related deaths in women in the United States, with an estimated 13,770 ovarian cancer-related deaths in 2021 (1). Serous papillary carcinoma is the most common histological type of ovarian carcinoma that often goes undetected until it has spread within the pelvis and abdomen. At this late stage, ovarian carcinoma is more difficult to treat and most women diagnosed with stage 4 ovarian carcinoma have a five-year survival rate of approximately 17%. Targeted genomic sequencing revealed novel in-frame deletion mutations of TP53 leading to p53 overexpression in tubo-ovarian high-grade serous carcinoma (HGSC) (2). This discovery of previously unreported somatic TP53 mutations provides insight into the translation of next generation-sequencing (NGS) technology into personalized medicine and identifies new potential targets for therapeutic applications (2).

Serous tubal intraepithelial carcinoma (STIC) is currently considered the precursor lesion of pelvic high-grade serous carcinoma (3). The incidence of STIC has been reported to range from 0.6% to 7% in *BRCA* mutation carriers. Synchronous carcinomas refer to cases in which the second primary cancer is diagnosed within 6 months of the primary cancer (4). Cases with synchronous primary ovarian serous

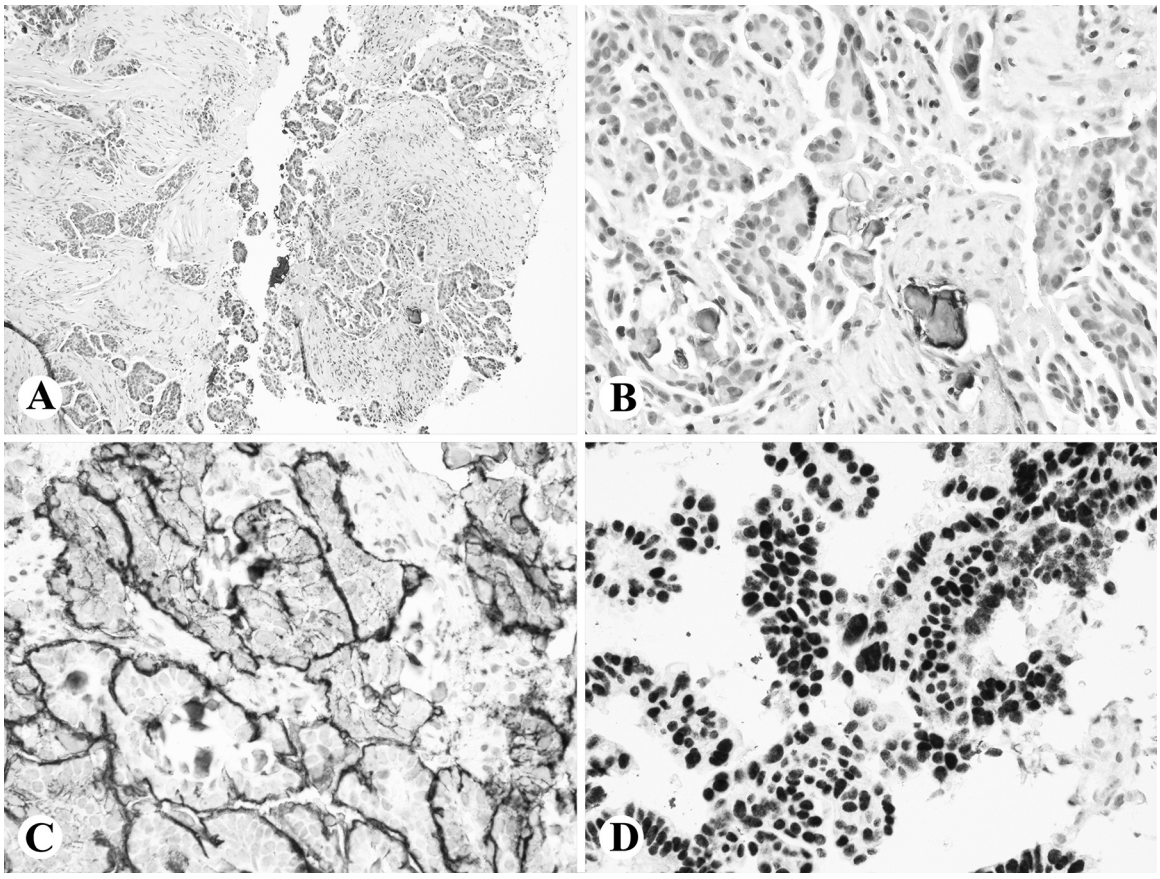

Figure 1. *Omental metastatic high-grade ovarian serous carcinoma. (A, B) Fine needle biopsy showing high-grade papillary carcinoma with psammoma bodies (H&E stain); (C, D) Immunohistochemistry showing that tumor cells are positive for CA125 (C) and Pax8 (D) (A, 100×; B-D, 400×).*

carcinoma and primary fallopian tube serous carcinoma are rarely reported. We report such a case and the patient was diagnosed at stage 4 ovarian serous carcinoma at the initial presentation in an emergency setting. She was treated with neoadjuvant chemotherapy followed by debulking surgery. The patient expired at 49 months after diagnosis. NGS was performed in her ovarian serous carcinoma. Despite the common mutations in BRCA1, BRCA2, and TP53, a novel mutation of HSP90AB1 was also identified. PD-L1 expression analysis showed low RNA expression score. The pathogenesis, diagnosis, treatment and prognosis of this entity are discussed.

Case Report

A 59-year-old female initially presented in the emergency department with increasing abdominal girth, constipation and bloating for three months. Her past history included hypothyroidism and reflux esophagitis. Her family history included one maternal cousin dying of unknown cancer at 30 years old, her mother died of colon cancer at 87 years, and her father died of prostate cancer at 90 years. Physical exam showed abdominal distension with tenderness. There was no rebound or guarding. Ultrasound examination showed moderate ascites and paracentesis showed nearly 3 liters, cytology showed malignant cells. Serology test of Cancer antigen 125 (CA125) was elevated to 3,238 U/ml. Computed tomography showed a large omental mass (14.7 cm) and a pelvic solid and cystic pelvic mass (9.5 cm). Needle core biopsy of the omental mass revealed metastatic serous papillary adenocarcinoma with psammoma bodies (Figure 1A and B) with positive immunoreactivity for CA125 (Figure 1C), Paired box 8 protein (PAX8) (Figure 1D), P53, Keratin-7 (CK7) and Wilms' tumor 1 (WT-1), negative for Keratin-20 (CK20), Caudal type homeobox 2 protein (CDX2), and transcription termination factor 1 (TTF1), consistent with ovarian primary. She was treated with 3 cycles of neoadjuvant chemotherapy with dose-dense carboplatin and taxol followed by diagnostic laparoscopy, exploratory laparotomy, extensive lysis of adhesions, total abdominal hysterectomy, bilateral salpingo-

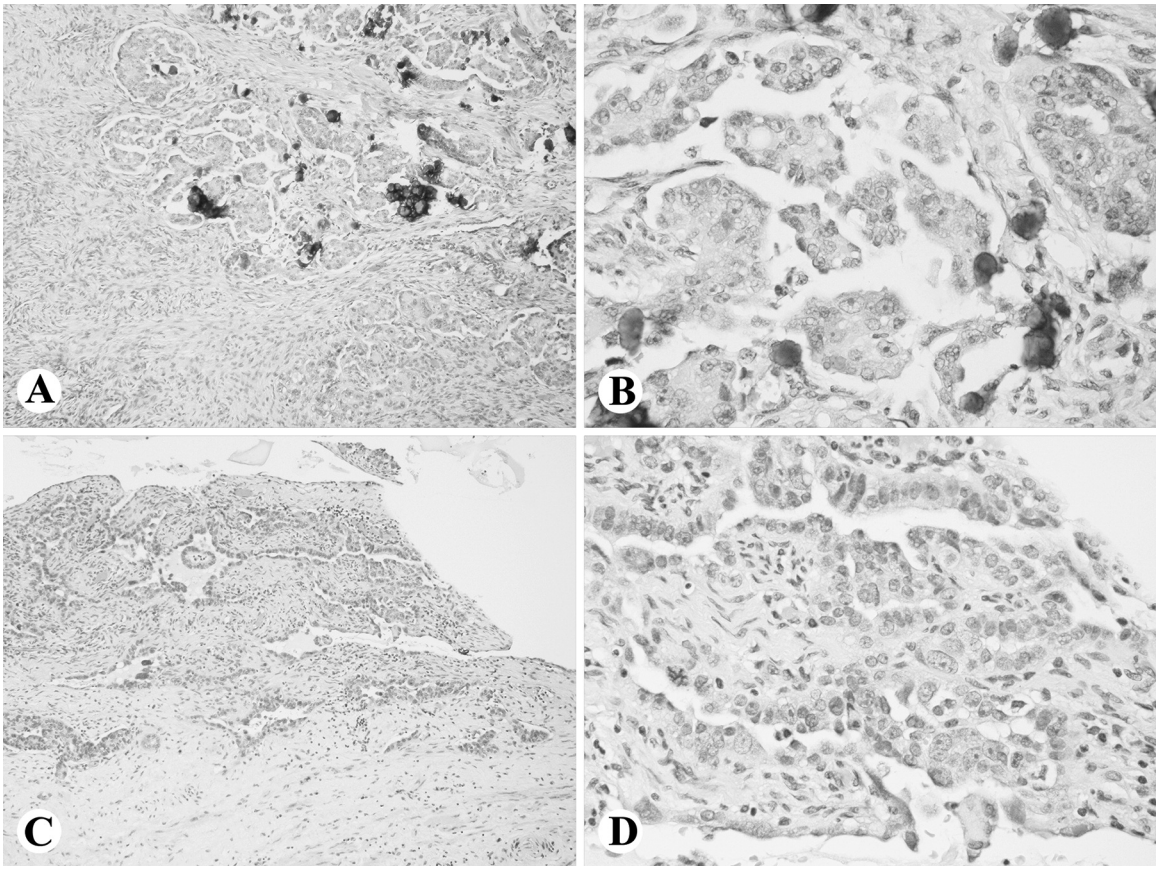

Figure 2. *Synchronous ovarian serous carcinoma and primary tubal serous carcinoma. (A), (B), a section of the tumor from the cystic and solid ovarian mass showing high-grade serous carcinoma with psammoma bodies; (C), (D), a section of the primary fallopian tube serous carcinoma in situ and associated invasion (H&E stain, A and C, 100×; B and D, 400×).*

oophorectomy, appendectomy, infragastric omentectomy, splenectomy with en bloc resection of splenic flexure colon and tail of pancreas and primary side-to-side colonic anastomosis, optimal cytoreduction to <2 mm residual disease. The specimen was submitted for pathology evaluation.

In pathology, grossly, the right ovarian mass was 5.5 cm with cystic and solid component and a 0.8 cm mass was present at the right distal fallopian tube. The omental mass was 4.5 cm. Multiple nodules in the spleen parenchyma and serosal nodules of stomach, appendix, and sigmoid colon were also present. Microscopically, the ovarian mass showed high-grade serous carcinoma with numerous psammoma bodies (Figure 2A and B) and carcinoma *in situ* arising from serous cystic component while the gross separate right fallopian tube mass also showed serous carcinoma *in situ* and associated invasive component (Figure 2C and D). Tumor infiltrating lymphocytes were present in carcinoma components. Pleural biopsy was also positive for serous carcinoma. Immunohistochemistry for mismatch Repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2) showed intact expressions. The final pathology diagnosis was synchronous high-grade primary ovarian serous carcinoma and primary fallopian tubal serous carcinoma with pleural, peritoneal and splenic parenchymal metastases. The tumor stage was ypT3cN1 (AJCC, 7th ED) and FIGO stage IIIC status post chemotherapy with moderate response (score 2). The patient also had synchronous multiple leiomyomas (up to 2.8 cm in the greatest dimension) and adenomyosis in her uterus.

Post-surgery the patient recovered well and her serum CA125 was decreased to 96 U/ml and was given additional cycle of dense dose of carboplatin and Taxol chemotherapy. At the five-month follow-up she was found to have a small chest wall nodule. It was resected and diagnosed as metastatic serous carcinoma. Although more chemotherapy was given to the patient, at the 45 months post-surgery follow up the patient was found to have gastric and cerebellum metastasis (Figure 3). She agreed with hospice care and expired one month later.

Tumor molecular characteristics and novel mutation. NGS for the ovarian serous carcinoma was performed based on

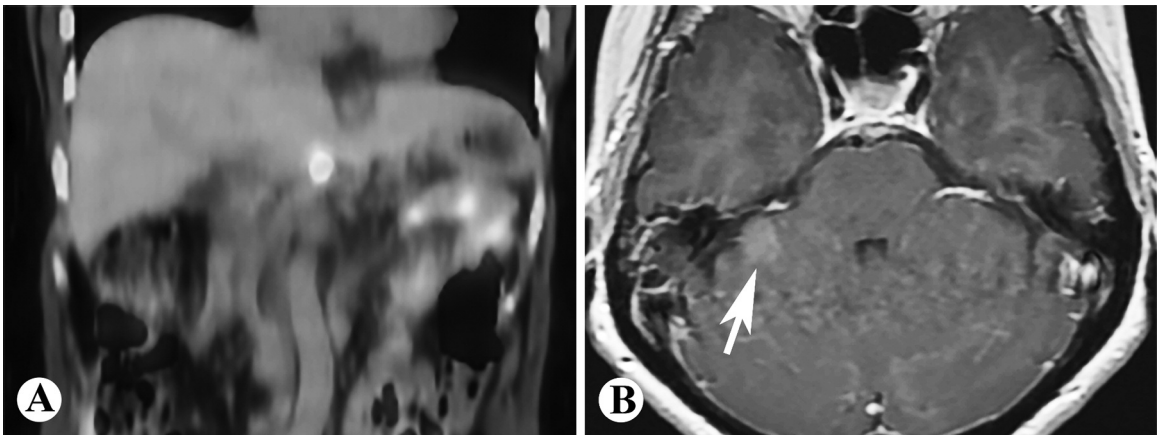

Figure 3. *Imaging findings showing the ovarian serous carcinoma metastasis to the liver ligaments and stomach (A, PET/CT, coronal) and cerebellum (B, MRI, axial, arrow).*

the protocol of STRATA NGS panel and PD-L1 analysis. The NGS test assayed for 429 cancer-related genes including selected specific predefined single nucleotide variants, multinucleotide variants, small insertions and deletions, gene fusions, exon skipping mutations, copy number changes, microsatellite instability status, tumor mutation burden (TMB) and PD-L1 (CD274) expression status, and de novo deleterious mutations in tumor suppressor genes including ATM, BRCA1, BRCA2, CDKN2A, MSH2, MSH6, PTEN, RB1, TP53. Among 429 selected genes, mutations of TP53 (p. R175 H, NM_00546.5:c.524G>A), BRCA1 (deep deletion and hotspot), BRCA2 (deep deletion and hotspot), and TMB (low with 2 mutations per Mb) were identified. HSP90AB1 mutation at p.R456C was identified from TMB mutation analysis. PD-L1 abnormality (low with RNA expression score 7) was also identified in this patient.

Discussion

This is an unusual case of primary high-grade ovarian serous carcinoma with synchronous primary fallopian tube serous carcinoma with a novel HSP90AB1 mutation of tumor mutational burden (TMB) identified from the ovarian serous carcinoma. Synchronous multiple uterus leiomyomas and adenomyosis were also present. The primary ovarian tumor showed solid and cystic changes with numerous psammoma bodies. Serous carcinoma *in situ* with invasion was morphologically identified in both origins. The patient with clinical stage 4 disease received regular neoadjuvant therapy followed by debulking surgery and her serum CA125 decreased from 3,238 to 96 U/ml. Although her overall survival 49 months after diagnosis through our treatments was longer than that reported in the literature (33 months) with similar treatment (5), NGS was performed to explore the possible targeted therapy for the patients with stage 4 disease. Interestingly mutations including novel mutation of HSP90AB1 (p.R456C) and common mutations of TP53 (c.524G>A at p.R175H), BRCA1 and BRCA2 were identified in this case. In addition, there were increased tumor infiltrating lymphocytes (TIL) seen in our case, consistent with a recent study that mutated TP53 at p.R175H is shared among a subset of patients with metastatic colorectal cancer (6). To the best of our knowledge, this has not been documented in ovarian carcinoma.

Although NGS in ovarian cancer has been reported in many cases, the exact tumor molecular pathogenesis remains to be elucidated for further targeted therapy. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases (7). Among patients with invasive ovarian carcinoma, family history is not sufficiently accurate to predict mutation status. In this case, although the patient's parents died of colon cancer and prostate cancer at old age, respectively, and there was a cousin died at age 30 with unknown cancer, no family history of cancers arising from gynecologic organs and breast was identified. Recent studies showed that somatic mutation of tumor protein TP53 is a hallmark of tubo-ovarian high-grade serous carcinoma and is observed in almost all such cases and TP53 remains as the most frequently altered gene in high-grade serous ovarian cancer (2, 8). AB Mutalib *et al*. compared high-grade serous ovarian carcinoma to normal ovarian tissue by NGS and found that eight genes were altered in both the tumor and normal groups (APC, EGFR, FGFR3, KDR, MET, PDGFRA, RET and SMO) while four genes (TP53, PIK3CA, STK11 and KIT) were exclusively altered in the tumor group. TP53 alterations were present in all the tumors but not in the normal group. Six deleterious mutations in TP53 (p.R175H, p.H193R, p.Y220C, p.Y163C, p.R282G and p.Y234H) were identified in eight serous ovarian carcinoma samples and none

in the normal group (8). In our case, despite the mutations of BRCA1 and BRCA2, we also found the mutation of TP53 (c.524G>A at p.R175H) that was recently reported as a novel TP53 mutation in some breast carcinoma cases (9) and two ovarian serous carcinoma cases (8).

The TMB refers to the total number of replacement and insertion/deletion (indel) mutations per basic group in the exon coding region of the assessed gene in the genome of a tumor cell. TMB may play an important role in the prognosis and guiding immunotherapy of ovarian carcinoma (10). By detecting the TMB of ovarian carcinoma, clinicians can more accurately treat patients with immunotherapy, thereby improving their survival rate (10). Per our protocol, qualitative TMB results include: Low: <10 mutations per Mb; Intermediate: 10-15 mutations per Mb; and High: >15 mutations per Mb. Therefore, searching for new treatment methods plays an important role in improving the prognosis of patients with ovarian carcinoma. In our case, a novel pathogenic mutation of HSP90AB1 (p.R456C) was identified through TMB analysis and this is the first documented case of ovarian serous carcinoma with HSP90AB1 (p.R456C) mutation. Although HSP90AB1 mutation is pathogenic, its significance among other mutated genes remains to be further elucidated through more case studies.

In recent years, immunotherapy, as a new treatment of ovarian cancer, has gradually attracted attention and achieved some results in the treatment of ovarian carcinoma, especially the inhibitors for immune checkpoint of PD1/PDL1. Unfortunately, the overall response rate of patients to these inhibitors is still low (11). Per our protocol, PD-L1 expression (normalized to multiple housekeeping genes and a common control) is reported as RNA expression score (RES, range=0-100) with a RES threshold >20.3 at least 50% of tumor content to define PD-L1 RNA high. This threshold was validated as 100% sensitive and 70% specific for predicting PD-L1 tumor proportion score (TPS) more than 50%. In our case, PD-L1 status was reported as low RES and anti-PD-L1 or PD-1 therapy was not offered to this patient. However, a recent study showed the prevalence of PD-L1 expression is variable in different types of tubo-ovarian carcinoma and is highest in high-grade serous carcinoma (HGSC). In high-stage HGSC, PD-L1 positivity in tumor cells is associated with an increased immune response and improved survival (12).

In addition, simultaneous germline and tumor sequencing is an efficient way to provide enhanced information to guide the care of patients with ovarian cancer. This approach can identify somatic BRCA mutations at diagnosis, allowing physicians to provide Poly (ADP-ribose) polymerase (PARP) inhibitor maintenance and improve outcomes for those patients (13).

In summary, our unusual case of high-grade ovarian serous carcinoma demonstrated molecular characteristics of the common mutations of BRCA1 and BRCA2, and TP53 (c.524G>A at pR175H), novel mutation of HSP90AB1 (p.R456C), as well as low RNA expression score of PD-L1. Identification of these mutations and PD-L1 abnormality at the diagnosis of ovarian carcinoma may shed light for clinicians to provide targeted therapy with PARP inhibitors and immune checkpoint inhibitors for ovarian serous carcinoma. The significance of novel HSP90AB1 (p.R456C) mutation in this entity remains to be further investigated through more case studies.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

J.L. designed the study, reviewed the slides, made the diagnosis, collected and analyzed the data, wrote and finalized the article. C.T. and J.R.C. critically reviewed the article.

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