Case report

Elevated tumor mutational burden and prolonged clinical response to anti-PD-L1 antibody in platinum-resistant recurrent ovarian cancer

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1. Introduction

Among gynecologic malignancies, ovarian cancer is the second most common and the leading cause of mortality. Studies have demonstrated that immunologic response can impact prognosis, and with the rapid development of cancer immunotherapy, clinicians must determine how to identify patients most likely to benefit. Here, we report the case of a patient with platinum-resistant ovarian cancer who had a durable response to avelumab, an anti-programmed death-ligand 1 (PD-L1) antibody, with comprehensive genomic profiling (CGP) obtained before and after treatment. We highlight the role of immune checkpoint inhibition in ovarian cancer, associated toxicities, and genetic factors that may have contributed to her response.

2. Case report

A 71-year-old female presented with abdominal pain, bloating, and dyspnea. A computed tomography (CT) scan showed large volume ascites, peritoneal carcinomatosis, bilateral pleural effusions, and a pulmonary embolism. Cytologic examination of the paracentesis specimen revealed adenocarcinoma of Mullerian origin. Given the patient's advanced disease and medical comorbidities, she was started on neoadjuvant weekly carboplatin (AUC 2 mg/mL/min) and paclitaxel (60 mg/m²). Cancer antigen 125 (CA-125) declined from 3866 U/mL to 58 U/mL and after treatment. We highlight the role of immune checkpoint inhibition in ovarian cancer, associated toxicities, and genetic factors that may have contributed to her response.

3. Discussion

Over the past two decades, growing evidence has established that critical interactions occur between the immune system and ovarian...
cancer. The presence of tumor infiltrating lymphocytes has a significant positive impact on both progression-free and overall survival (Zhang et al., 2003). Furthermore, The Cancer Genome Atlas (TCGA) defined four distinct clusters of ovarian cancer based on gene expression, demonstrating that the immunoreactive subgroup has the best survival (Cancer Genome Atlas Research Network et al., 2011). However, significant obstacles remain in harnessing the immune system to treat ovarian cancer.

Many cancers escape elimination by the immune system via binding of programmed death 1 (PD-1) to its ligand PD-L1, which is expressed on the surface of many tumors (Yang et al., 2011). Additionally, BRCA2-mutated cases were associated with higher chemotherapy response rates and longer PFS. ADAMTS-mutated cases of ovarian cancer are associated with higher genome-wide mutation rates and higher chemotherapy response rates, longer platinum-free duration, and better PFS and overall survival (Liu et al., 2015). There is growing evidence that ovarian cancers with a higher somatic mutation burden also respond better to cytotoxic chemotherapy.

Ultimately, our patient developed pneumonitis, which responded to steroid treatment and she was allowed to continue avelumab after pulmonology consultation since she was benefiting from therapy per study protocol. However, six months later she developed recurrent pneumonitis, confirmed on bronchoscopy, and pulmonology recommended stopping therapy. After discontinuation of avelumab, she developed bulky retroperitoneal lymphadenopathy and elevated CA-125. Pulmonary disorders such as pneumonitis are uncommon but have been reported with ICPI (Topalian et al., 2012). More common side

Table 1
Somatic tumor mutations from peritoneal fluid (initial diagnosis) and from pelvic lymph node (recurrent disease) detected by next-generation sequencing assay.

| Specimen | NGS panel | Mutations detected |
|----------|-----------|--------------------|
| Peritoneal fluid (prior to chemotherapy and anti-PD-L1 therapy) | FoundationOne* (315 genes) | BRCA2, c.5079delT, p.R1694*12, EGR, c.940G > A, p.D314N, TET2, c.3768_3769insACGGC, p.L1256*10, TP53, c.394A > C, p.K132Q, MAP2K4 splice site c.115_115+62del63, NOTCH1 splice site c.5638 + 21 > G, FGFR4 amplification, TERC amplification, PRKCI amplification, RB1 loss exons 19–26, BRCA2, c.5079delT, p.R1694*12, TET2, c.3768_3769insACGGC, p.L1256*10, TP53, c.394A > C, p.K132Q |
| Pelvic lymph node biopsy (after chemotherapy and anti-PD-L1 therapy) | NCI-MATCH (167 genes) | BRCAX, c.5079delT, p.R1694*12 |

Differences in the testing results can be attributed to the relative sizes of the gene panels, test sensitivities, and the types of alterations each assay is designed to detect. Abbreviations: NGS, next-generation sequencing; PD-L1, programmed death-ligand 1; NCI-MATCH, National Cancer Institute Molecular Analysis for Therapy Choice.

Avelumab, a fully human anti-PD-L1 IgG1 monoclonal antibody inhibits the immunosuppressive effect of antigen-specific T-cell activation by blocking PD-1/PD-L1 binding. In a cohort of 75 pretreated patients with recurrent or refractory ovarian cancer, avelumab demonstrated clinically activity with a 33.3% progression-free survival (PFS) rate at 24 weeks and a median PFS of 11.9 weeks (Disis et al., 2015). The PD-1 inhibitor nivolumab has also shown activity in platinum-resistant ovarian cancer in a recent phase II trial reporting a 15% ORR and a 45% disease control rate among 20 patients (Hamanishi et al., 2015). This patient with platinum-resistant ovarian cancer experienced a durable response to single-agent avelumab therapy for 16.5 months, much longer than the 3–4 month responses typically observed with single-agent chemotherapy (Pujade-Lauraine et al., 2014). Interestingly, CGP of DNA extracted from cells in peritoneal fluid collected at initial diagnosis showed a TMB of 10.2 mutations/Mb in comparison to 10.6 mutations/Mb at the end of carboplatin/paclitaxel chemotherapy; red arrows indicate the start/end of avelumab treatment. The presence of tumor in pelvic lymph node (recurrent disease) detected by next-generation sequencing assay.

Somatic tumor mutations from peritoneal fluid (initial diagnosis) and from pelvic lymph node (recurrent disease) detected by next-generation sequencing assay.
effects of PD-L1 inhibitors are diarrhea, fatigue, arthralgia, rash, nausea, pruritus, headache, and infusion-reactions (Brahmer et al., 2012). Among ovarian cancer patients specifically, endocrine disorders, including hypothyroidism and autoimmune thyroiditis, may occur in 40% of patients (Hamanishi et al., 2015).

This case highlights an impressive and prolonged response to anti-PD-L1 antibody in an ovarian cancer patient with a relatively high number of somatic tumor mutations, suggesting that, similar to melanoma and other carcinomas, TMB may be a biomarker that identifies patients who will respond to ICPi. In contrast to other carcinomas, which generally demonstrate higher median TMB and ICPi response thresholds, an ovarian-specific threshold may be considerably lower. Broader evaluation of samples from ovarian ICPi clinical trials with correlation to TMB scores would be useful to validate this hypothesis and set an appropriate clinical threshold. This case also reinforces the potential clinical value of CGP for ovarian tumor samples. In addition to germline mutation testing for all ovarian cancer patients, further analysis by tumor-based sequencing may reveal somatic alterations in known biomarkers, such as BRCA, and identify those patients more likely to respond to immunotherapy.

Conflicts of interest

Christopher B. Morse reports no conflicts of interest. Julia A. Elvin and Laurie M. Gay report employment by Foundation Medicine, Inc. John B. Liao reports research funding from Merck through his institution.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

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