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Mismatch repair deficiency in ovarian cancer

Lam and colleagues present a case report in this issue of Gynecologic Oncology Reports entitled "Off-label use of paclitaxel and pembrolizumab in a case of platinum refractory epithelial ovarian cancer and extensive thromboembolism" (Lam et al., 2022). This patient had a germline MSH2 mutation who presented with bilateral DVTs and PEs with a pelvic mass. Given worsening DVTs after 6 cycles of carboplatin and paclitaxel, she received a total of nine cycles of carboplatin and paclitaxel until the CT scan showed progression of disease. She then had pegylated liposomal doxorubicin (PLD) for a total of seven cycles until progression of disease with increasing size of the pelvic mass and increasing peritoneal and omental disease. She was then initiated on pembrolizumab and weekly paclitaxel. After the sixth cycle, her CA-125 normalized and CT scan after the seventh cycle showed interval decrease in the size of the pelvic mass. She has been on this regimen for 16 months with no evidence of disease progression.

This case highlights key questions in the treatment of ovarian cancer particularly within the context of mismatch repair deficiency.

Mismatch repair (MMR) deficiency in ovarian cancer It has been described that MMR deficiency is seen 10–15% of epithelial ovarian cancers (Murphy and Wentzensen, 2011; Pal et al., 2012, 2008; Xiao et al., 2014). In particular, Pal et al. published in 2008 on a systematic review with 18 studies on 977 cases with the following subtypes: serous (32%), endometrioid (29%), mucinous (19%), and clear cell (18%). Overall 12% were noted to have somatic MMR deficiency, and the subtypes with loss of MMR expression included 35% with clear cell, 34% with endometrioid, 26% mucinous histology, and 0 serous histology (Pal et al., 2008). Pathogenic germline MMR mutations are found in less than 1% of unselected ovarian cancer cases with a higher frequency in those with invasive cancers of the endometrioid and clear cell subtypes. Of the nine pathogenic mutations clearly identified in *MLH1, MSH2,* and *MSH6* genes, the majority (55%) were detected in the *MSH6* gene (Pal et al., 2012). The case presented here noted that the histology of the CT-guided core biopsy of the mass was adenocarcinoma of Mullerian origin. Thus, the specific histotype may be one that is more highly associated with pathogenic mutations in MMR genes.

Response to pembrolizumab and paclitaxel in MMR deficient tumors. The authors noted that the patient's response to pembrolizumab and paclitaxel may have been due to a MSH2 mutation. Le et al. investigated treatment-refractory progressive metastatic colorectal and non-colorectal cancers with MMRd. This study found that the objective response rate was 71% in MMRd noncolorectal cancer compared to 0 in the MMRp colorectal cancer (Le et al., 2015). Of note, the tumor types represented in this study were colon, rectal, cholangiocarcinoma, endometrial, small bowel, and gastric origin. There was a subsequent study that did include ovarian cancers. Marabelle and colleagues found in the Phase II KEYNOTE-158 study that of the 15 MSI-H/MMRd advanced ovarian cancer tumors that received pembrolizumab, there was an objective response rate of 33.3% with a median PFS of 2.3 months (95% CI: 1.9–6.2 months) and median OS that was not reached (95%CI: 3.8 to NR) (Marabelle et al., 2020). The median time to response was 2.1 months with a range of 1.3–10.6 months.

The authors cite another case report from Jing et al. of a patient with MSI-H tumor who had a complete response after combination pembrolizumab and nab-paclitaxel in recurrent, metastatic, platinum-sensitive epithelial ovarian cancer (Jiang et al., 2020). These case reports highlight that testing for mismatch repair deficiency, especially in the non-serous histotype ovarian cancers, can lead to additional treatment options not traditionally considered in ovarian cancer. The question of whether combining pembrolizumab with paclitaxel versus pembrolizumab alone remains to be determined in the MMRd tumors. This case report highlights the importance of sharing these cases of MMRd in ovarian cancers treated with pembrolizumab-based therapy.

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