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Case report

Pazopanib treatment of a platinum-resistant recurrence of a high-grade Sertoli cell tumor and assessment of the treatment response by FDG-PET/CT: A case report

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ABSTRACT

Ovarian Sertoli cell tumors (SCTs) are rare sex cord tumors (Oliva et al., 2005). The standard treatment for high-grade SCTs is surgery followed by platinum-based chemotherapy. Although platinum-based chemotherapy is also an option for recurrent SCTs (Sigismondi et al., 2012), there is no established chemotherapy regimen for platinum-resistant recurrent SCTs. The effectiveness of pazopanib in treating epithelial ovarian cancer has recently been reported (du Bois et al., 2014; Pignata et al., 2015). In the case described herein, pazopanib was used to treat the platinum-resistant recurrence of a high-grade Sertoli cell tumor, and the response was evaluated by 18F-fluoro-deoxyglucose positron emission tomography (FDG-PET)-computed tomography (CT). Written informed consent to reporting the case was obtained from the patient.

1. Case report

A 32-year-old, gravida 1 woman with Marfan syndrome was referred to our institution owing to rapidly growing pelvic tumors. Imaging results suggested disseminated ovarian cancer. Laparotomy revealed two solid yellow tumors in the ovaries (12 cm and 8 cm in diameter, respectively) and widespread bulky disseminations mainly in the Douglas pouch and the peritoneum under the right diaphragm. Debulking procedures including bilateral salpingo-oophorectomy were performed, but most of the disseminated lesions remained. The pathology report was delayed because of difficulty in making a final diagnosis. The patient underwent 2 cycles of adjuvant chemotherapy with paclitaxel and carboplatin, but the disease progressed. The final diagnosis was made by the central pathology review board and was high-grade SCT. The Ki-67 index was 40%, and immunohistochemical staining of CD99 was negative (Fig. 1A–C). The chemotherapy regimen was immediately changed to bleomycin, etoposide, and cisplatin (BEP). After 5 cycles of BEP, CT showed a complete response. Second-look surgery revealed no macroscopic disease, and pathological examination of multiple biopsies and material obtained from peritoneal stripping of the right diaphragm showed no active microscopic residual tumors. Two additional cycles of BEP were administered.

The patient remained disease-free for the next 5 months, at which point she complained of abnormal genital bleeding, a dark-colored umbilicus, and upper abdominal pain requiring non-steroidal anti-inflammatory drugs (NSAIDs). Transvaginal ultrasonography revealed bulky masses and ascites in the pelvis and umbilicus indicative of a metastatic tumor. FDG-PET/CT findings suggested tumor recurrence in the pelvis, the umbilicus, and the peritoneum under the right diaphragm. Endometrial biopsy revealed metastases of the SCT in the endometrial cavity (Fig. 1D).

Owing to limited treatment options, and after discussion with the patient and her family, pazopanib was chosen for disease control. Pazopanib (800 mg) was administered orally to the patient. One month of pazopanib treatment relieved the upper abdominal pain, eliminating the need for NSAIDs. The skin lesion in the umbilical tumor had mostly disappeared 1 month after initiating treatment (Fig. 2), and genital bleeding had stopped. The largest tumor was located under the right diaphragm. As visualized by FDG-PET/CT, the tumor diameter was 7 cm before treatment and 5 cm 1 month after treatment began; the maximum standardized uptake value (SUVmax) at these times was 10.53 and 5.41, respectively (Fig. 3A, B). The diameter of the umbilical tumor was 3 cm and 2 cm in FDG-PET/CT scans before and 1 month after treatment initiation, respectively, and the SUVmax at these times was 9.55 and 4.51, respectively. The mass in the pelvis also decreased in size (Fig. 3C, D).

The side effects of pazopanib were mild appetite loss and changes in hair color. There were no grade 2 or higher hematologic or non-

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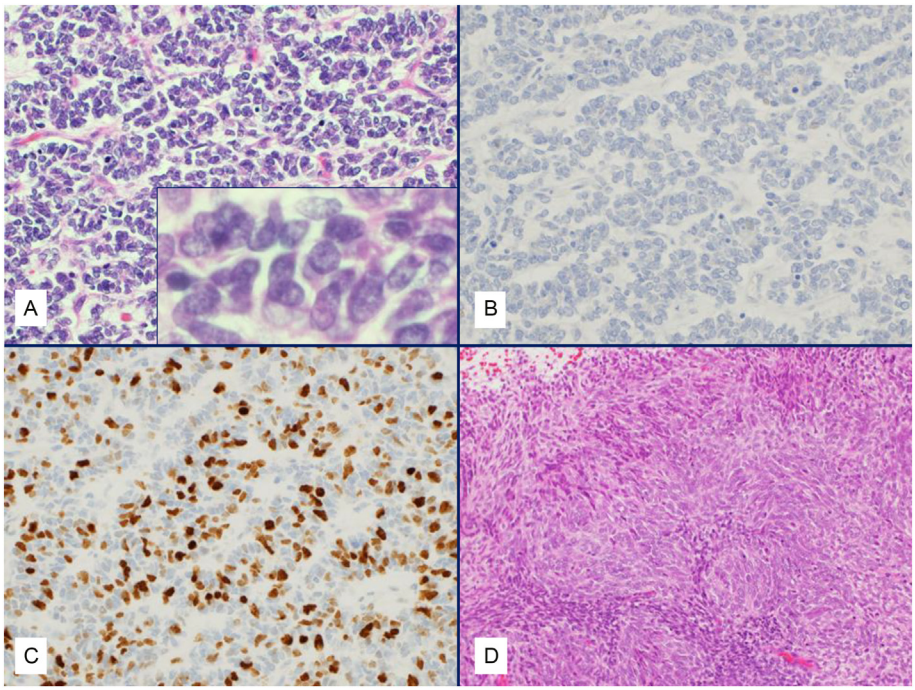

Fig. 1. Microscopic findings of the primary ovarian Sertoli cell tumor (SCT) (A–C). A: Hematoxylin and eosin (H&E) staining, magnification ×20 and ×40 (inset). B: Immunohistochemical staining of CD99 was negative. Magnification ×20. C: Immunohistochemical staining of Ki-67; 40% of the cells were positive. Magnification ×20. D: Microscopic examination of the endometrial biopsy at the time of recurrence shows metastasis of the SCT. H&E, magnification, ×20.

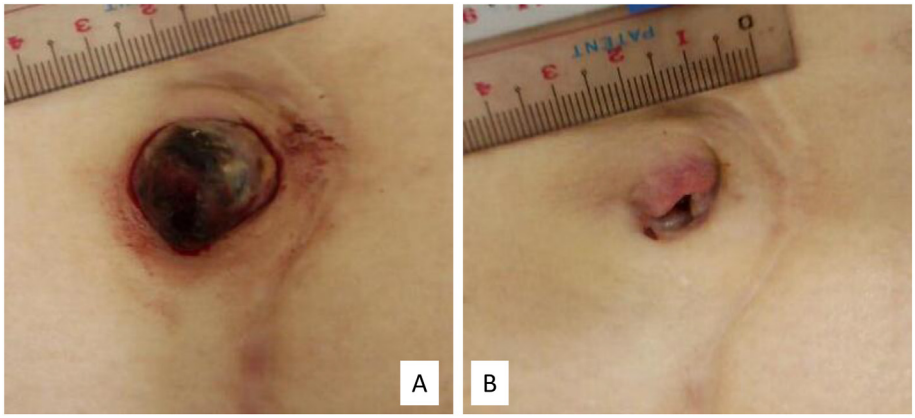

Fig. 2. Gross images obtained before (A) and 1 month after (B) the initiation of pazopanib treatment.

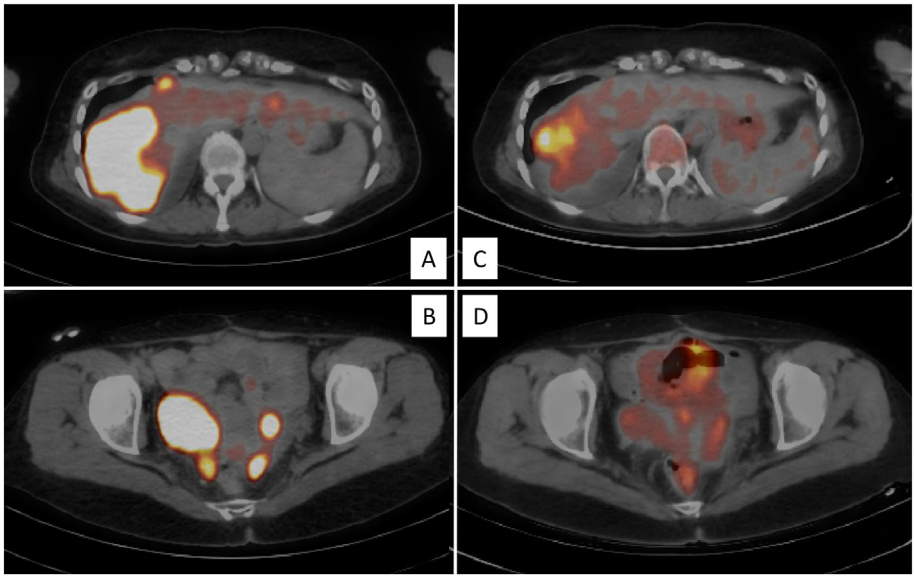

Fig. 3. A: 18F-fluoro-deoxyglucose positron emission tomography-computed tomography images before (A, C) and 1 month after (B, D) the initiation of pazopanib treatment. A: Before treatment, the largest tumor, which was under the right diaphragm, had an SUVmax of 10.53 and a diameter of 7 cm. B: After treatment, this tumor shrank to 5 cm, and the SUVmax decreased to 5.41. C: The image shows the tumor in the pelvis near the uterus and in the Douglas pouch before treatment. D: After treatment, this tumor had decreased in size.

hematologic toxicities, as assessed according to the Common Terminology Criteria for Adverse Events (version 4.0). A slight rise in blood pressure to 135 mmHg (systolic) was well controlled by administration of an antihypertension drug. CT performed 3 months after initiating pazopanib treatment showed stable disease, as evaluated according to the Response Evaluation Criteria in Solid Tumors (version 1.1). Pazopanib was given for another 2 months, and it was discontinued because of oozing bleeding from the umbilical tumor. The patient received best supportive care for 3 months, and then died of disease.

2. Discussion

SCT is rare sex cord tumor, and high-grade SCT is even more rare. The SCT in this case was highly malignant based on both its pathology and clinical characteristics. Although ovarian SCTs are usually unilateral (Oliva et al., 2005), the SCT in this case was bilateral. Robust mitotic activity is associated with the recurrence of SCTs (Oliva et al., 2005), and the Ki-67 index in this case was 40% (Fig. 1C), which predicted an adverse outcome. Sertoli cells express CD99, but in this case, immunohistochemical staining of CD99 was negative (Fig. 1B), perhaps because expression is related to the degree of differentiation (Gordon et al., 1998). Although BEP chemotherapy was an effective treatment for the initial disease, the patient relapsed within 6 months after BEP treatment. Platinum-based chemotherapy is also an option for recurrent SCTs (Sigismondi, Gynecol Oncol, 2012), there is no established chemotherapy regimen for platinum-resistant recurrent SCTs.

Pazopanib, an oral tyrosine kinase inhibitor, exhibits anti-angiogenic effects by inhibiting signaling by the vascular endothelial receptor, the platelet-derived growth factor receptor, and c-kit. Several studies have demonstrated the efficacy of pazopanib in treating epitherial ovarian cancer (EOC). In a single arm phase 2 trial of recurrent EOC, pazopanib monotherapy yielded serological response in 28% patients (Friedlander et al., 2010). Combination chemotherapy with pazopanib and low dose oral cyclophosphamide demonstrated antitumor activity, which was considered as synergistic anti-angiogenic effect by pazopanib and metronomic chemotherapy (Dinkic et al., 2017). In a randomized phase 2 MITO-11 trial of platinum-resistant EOC, combination with pazopanib and weekly paclitaxel showed 3 month improvement of progression free survival (PFS) over weekly paclitaxel alone (hazard ratio [HR], 0.42; p = 0·0002) (Pignata et al., 2015). In a randomized phase 3 AGO-OVAR16 trial of EOC, maintenance pazopanib following the first-line chemotherapy significantly improved PFS over placebo (HR, 0.77; p = 0.0021) (du Bois et al., 2014). In East Asian patients, however, maintenance pazopanib showed a disadvantage in overall survival (Kim et al., 2018).

However, pazopanib treatment of ovarian SCTs has not been assessed previously. Bevacizumab administration is a treatment option for recurrent granulosa cell tumors according to the guidelines of the National Comprehensive Cancer Network and it might have been one of the treatment options in this case. However, recurrent tumors in the Douglas pouch have a high risk of gastrointestinal perforation in administration of bevacizumab (Cannistra et al., 2007). Therefore, pazopanib was chosen for treatment.

In our case, the patient's symptoms disappeared 1 month after initiating pazopanib treatment. Response assessment to anti-angiogenic therapy by FDG/PET-CT has been performed in tumors other than SCTs (Kayani et al., 2011, Farnebo et al., 2014, Prior et al., 2009;27). The PAZPET-1 trial is evaluating the use of 18F-fluciclatide as a biomarker in platinum-resistant ovarian cancers treated by weekly administration of pazopanib and paclitaxel (PAZPET-1 http:~). In our case, FDG-PET/CT was used to monitor the response to pazopanib in platinum-resistant SCT metastases. The imaging results for the largest tumor showed a 48% reduction in the SUVmax and a 40% reduction in tumor size (diameter of the major axis) after 1 month of pazopanib treatment. This finding suggests that early assessment of the treatment response to pazopanib may predict the effectiveness of the treatment (Young et al., 1999).

3. Conclusion

This is the first report of the effectiveness of pazopanib in treating a platinum-resistant recurrence of a high-grade SCT and of treatment evaluation by FDG-PET/CT. Pazopanib may be a viable treatment option for platinum-resistant high-grade SCTs that recur and metastasize.

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