Case Report

Malignant transformation of ovarian teratoma responded well to immunotherapy after failed chemotherapy: a case report

Xiaohong Li[1], Xuefeng Tang[2], Wenlei Zhuo[1]

[1]Department of Oncology, Second Affiliated Hospital of Army Military Medical University, Chongqing, China; [2]Department of Pathology, Second Affiliated Hospital of Army Military Medical University, Chongqing, China

Correspondence to: Wenlei Zhuo, PD. Department of Oncology, Second Affiliated Hospital of Army Military Medical University, Chongqing, China. Email: zhuowenlei@gmail.com.

Abstract: Mature cystic teratomas (MCTs), also known as dermoid cysts, are the most common ovarian germ cell tumors and the most common ovarian neoplasms in patients younger than 20 years. MCTs mainly appear as pelvic masses that are made up of different types of well differentiated derivates of at least two germinative cell types. MCT of the ovary is always benign lesions with slow growth and good prognosis. Unfortunately, in about 1–2% of cases, it may undergo malignant transformation. At present, surgical treatment is the preferred option for the early stage of malignant transformation of teratomas, while with a high postoperative recurrence rate. For advanced or recurrent malignant ovarian teratomas, the effect of conventional chemotherapy or radiotherapy is poor, leading to high mortality. Thus, identifying novel treatment for malignant transformed MCTs is an urgently need in clinic. Recently, PD-1 antibody-based immunotherapy has achieved great success in treatment of lung cancer, melanoma, and other malignant tumors. However, its effect on the malignant transformation of ovarian teratomas has not yet been reported. Here we reported a patient who suffered malignant transformation of ovarian teratoma and responded well to camrelizumab, an anti-PD-1 inhibitor.

Keywords: Immunotherapy; camrelizumab; ovarian teratoma

Submitted Dec 04, 2020. Accepted for publication May 13, 2021.
doi: 10.21037/apm-20-2429
View this article at: http://dx.doi.org/10.21037/apm-20-2429

Background

Ovarian teratomas are tumors originated from primordial germ cells, and occur frequently in women of childbearing age. However, postmenopausal women with an ovarian mass should be suspected of malignant ovarian germ cell tumors (MOGCTs). Their prognosis is poor, even for patients with early-stage disease (1). The non-epithelial ovarian cancers include MOGCTs and sex-cord stromal tumours, each of which is subdivided into several histological subtypes. MOGCTs are rare accounting for approximately 5% of all ovarian malignancies. Based on histopathology, MOGCTs consist of dysgerminoma, immature teratoma, yolk sac tumor, embryonal carcinoma, non-gestational choriocarcinoma, and mixed MOGCTs, but all are derived from primordial germ cells of the ovary. Ovarian small cell cancers and sarcomas are rarer (2). The most common type of mature teratomas is mature cystic teratomas (MCTs) (also known as dermoid cyst) (3). The majority of MCT are benign with malignant transformation being rare and reported in only 1–2% of cases, with squamous cell carcinoma (SCC) accounting for 80–90% of the transformed histology (4-6). Malignant transformation confers a significantly worse prognosis and only 1–2% of the SCC cases can be diagnosed preoperatively (7). Several risk factors and clinical features have been associated to MCT transformation into SCC, including patient age, tumor size, ultrasound characteristics, sonar tumor vessel wave form, computed tomography, and levels of SCC and CA-125 tumor markers. Due to the scarcity of literature, adjuvant treatment has yet to be defined. Here, we report a case of SCC arising from MCT and responded well

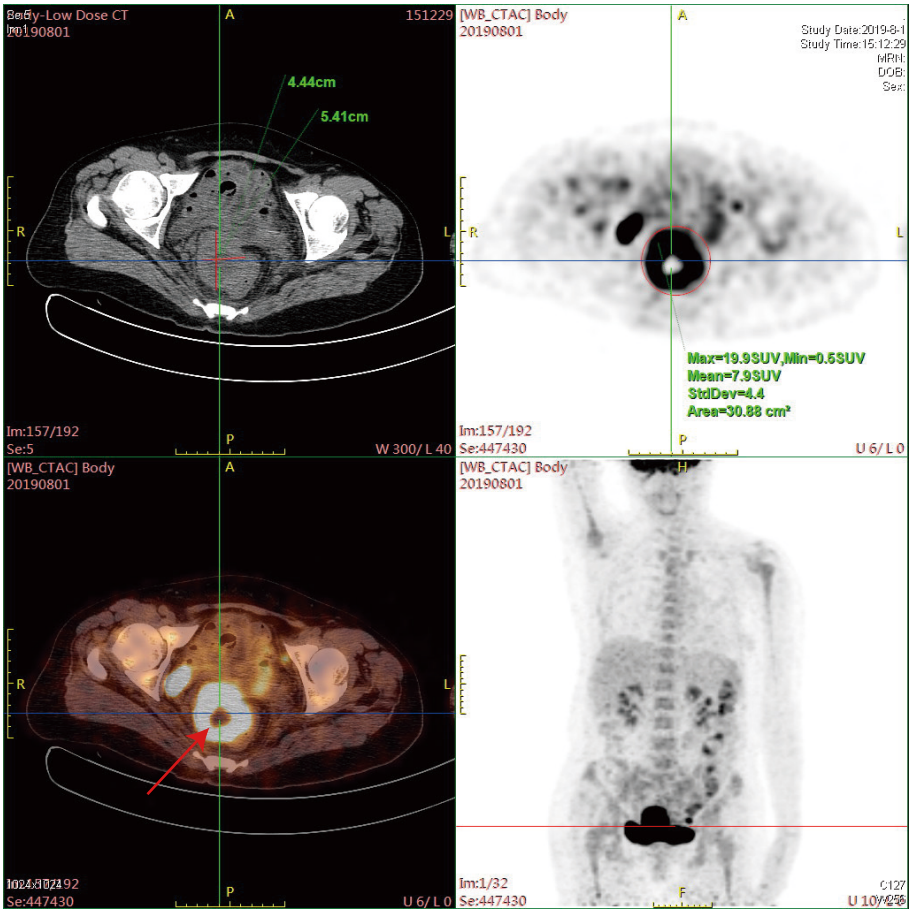

Figure 1 Positron emission tomography (PET)/computed tomography (CT) imaging showed multiple pelvic metastases with increased fluorodeoxyglucose (FDG) activity, meaning recurrence occurred 2 months after the first operation. The arrow indicates the location of the lesion.

to immunotherapy. We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2429).

Case presentation

A 54-year-old female presented to Second Affiliated Hospital of Army Military Medical University, Chongqing, China to take routine examination. On May 21, 2019, a cystic mass in the right adnexa (6.3 cm × 6.1 cm × 6.1 cm) was found by a vaginal ultrasound scan. Tumor marker carbohydrate antigen CA-199 was 188.65 U/mL, CA-125 was 23.2 U/mL and SCC was 1.9 ng/mL. She underwent total laparoscopic hysterectomy and double adnexal resection on May 29. Postoperative pathology revealed a malignant transformation of the teratoma (SCC) in the right ovary, with extensive necrosis. Immunohistochemistry showed 35BH11 (weak+), CK7 (–), CK20 (–), CK5/6 (+), P63 (+), WT-1 (–), P53 (+), ER (–), PR (–), PAX-8 (–), PAX-2 (–), GATA3 (–), GCDFP-15 (–), Ki-67 (80–90%), and TTF-1 (–). After surgery, two cycles of TP (paclitaxel and cisplatin) were performed as postoperative adjuvant treatment.

On July 29, 2019, a positron emission tomography (PET)/computed tomography (CT) scan revealed a recurrent mass of 4.44 cm × 5.41 cm in pelvic, with increased fluorodeoxyglucose (FDG) activity and blurred margin of the adjacent rectal wall. Some pelvic lymph nodes also showed increased FDG activity (*Figure 1*). Tumor marker CA-199 was 3.12 U/mL, CA-125 was 10.2 U/mL and SCC was 9.10 ng/mL. On August 9, 2019, the patient underwent a second surgery, included laparoscopic para-aortic lymph node dissection, pelvic lymph node dissection, pelvic mass resection, omentectomy, appendectomy,

enterolysis and pelvic adhesiolysis. Postoperative pathology proved moderately differentiated SCC with treatment response and necrosis in the mass of pelvis and mesentery. Besides, multiple metastases were found in the lymph nodes of the left pelvic area [1/4].

Based on the specimens obtained from the second surgery, a genetic testing using the next generation sequencing technology was performed and identified *TP53* p.R273C and *JAK2* p.E1024G mutation. Moreover, the percentage of PD-L1 protein positive tumor cells was less than 1%, and the percentage of PD-L1 protein positive immune cells was 2%. In addition, tumor mutation burden (TMB) was 19.07 mutations/Mb and microsatellite state was stable (MSS).

Unfortunately, on September 2, pelvis magnetic resonance imaging (MRI) indicated multiple pelvic metastases (approximately 8.45 cm × 5.9 cm for the larger mass) (*Figure 2A*). Serum tumor marker CA-199 was <2.00 U/mL, CA-125 was 59.8 U/mL and SCC was 12.9 ng/mL. Besides, the neutrophil-to-lymphocyte ratio (NLR) is 6.1. Based on the patient's TMB and gene mutation, the treatment was converted to immunotherapy combined with antiangiogenic therapy: camrelizumab (200 mg intravenous infusion for 1/2 weeks) plus anlotinib (12 mg oral 1/day for 14 consecutive days) for 2 cycles of treatment. On October 23, pelvic MRI showed the pelvic metastasis was significantly reduced and shrunk (approximately 2.3 cm × 2.0 cm in size) (*Figure 2B*). The tumor regression degree was 72.8%. Serum tumor markers decreased with CA-199 to <3.04 U/mL, CA-125 to 6.6 U/mL, SCC to 0.6 ng/mL and NLR is 1.5. For unexpected gastrointestinal bleeding happened on October 6, 2019, anlotinib was discontinued, and camrelizumab was continued as monotherapy for 4 cycles until December 16.

On November 29, pelvic MR indicated further shrinkage of the mass (approximately 1.0 cm × 0.9 cm in size) (*Figure 2C*). Camrelizumab had been administered for 17 cycles until October 2020. During this period, all the serum tumor markers including CA-199, CA-125, and SCC were within the normal range. In February 2020, pelvic MRI suggested further shrinkage of the mass (nodule diameter of approximately 1.1 cm), through a telephone follow-up performed in October 2020, the patient reported she was in a good condition without obvious signs of recurrence.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Discussion

Malignant transformation of MCTs is rare and only occurred in about 1–2% of all the cases. It has been reported that middle-aged and elderly population (>45 years old), preoperative tumor size (>9.9 cm), elevated levels of CA-125 (35 IU/mL), and characteristic imaging changes are independent risk factors for the malignant transformation of MCTs (4,8). This case presents a 54-year-old female with large tumor mass (6.3 cm × 6.1 cm × 6.1 cm) and elevated CA-199, CA-125, and SCC, indicating high risk factors for malignancy. Actually, postoperative pathology proved a teratoma with malignant transformation. It is reported that expression of sex determining region Y-box 2 (SOX2) has been recognised in primitive neuroectoderm of teratoma. Furthermore, Sal-like protein 4 (SALL4) is positive in some immature teratomas (9). Immunohistochemistry in this patient indicated P63 expression, suggesting the presence of squamous differentiation (10). This suggests that teratomas should be followed up closely although they are benign in most cases. If the risk factors or signs of deterioration are present, prompt surgery should be considered as soon as possible.

The patient underwent total hysterectomy and bilateral adnexectomy according to standard surgical treatment. In terms of postoperative adjuvant chemotherapy, it has been reported that cisplatin-based chemotherapy can be administered for a grade 1 non-FIGO stage IA immature teratoma (11). However, the components of mature teratoma and immature teratoma are quite different. An immature teratoma contains several embryonic components (usually immature primitive neuroectoderm), while a mature teratoma does not contain primitive neuronal components.

SCC comprises 80% of all malignant transformations of mature teratomas, for which the role of chemotherapy is uncertain. Since the common chemotherapy for SCC such as lung or head and neck squamous carcinoma is taxanes combined with platinum (TP), the patient was empirically treated with TP as a postoperative adjuvant chemotherapy. However, within a short time (after 2 months), pelvic lesions recurred and significantly increased, suggesting resistance to chemotherapy.

After the first recurrence, because the lesion could not be completely resected, a cytoreductive surgery was performed as second operation. However, less than one month later, pelvic MRI showed a second recurrence of the tumor with

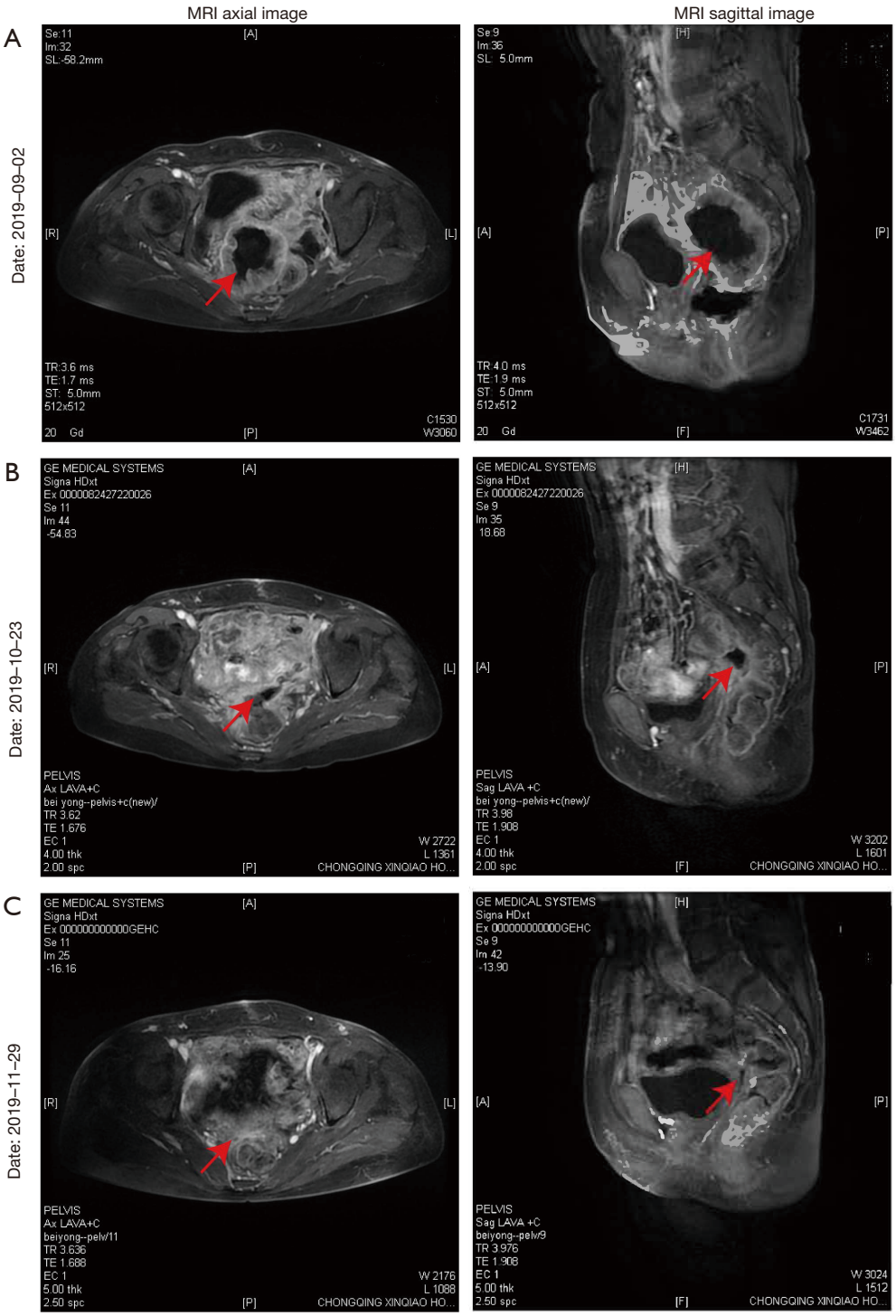

Figure 2 A series of magnetic resonance imaging (MRI) images showed the effect of immunotherapy combined with antiangiogenic drug therapy on the pelvic metastases. (A) On September 2 (nearly a month after the second operation), obvious multiple pelvic metastases (approximately 8.45 cm × 5.9 cm for the larger mass) indicated recurrence happed after the second operation; (B) on October 23, the pelvic metastasis was significantly reduced and shrunk (approximately 2.3 cm × 2.0 cm in size), showing the efficacy of the two cycles of immunotherapy combined with antiangiogenic drugs therapy; (C) on November 29, the pelvic metastasis was further reduced and shrunk (approximately 1.0 cm × 0.9 cm in size), showing further efficacy after the two more cycles of immunotherapy. The arrow indicates the location of the lesion.

multiple pelvic metastasis. Because the first chemotherapy treatment failed, and the patients could not tolerate a second chemotherapy, it was difficult to choose new drugs. Fortunately, the results of gene detection in tumor tissues from the second operation revealed high TMB with 19.07 mutations/Mb and *TP53* p.r273c mutation. This suggests that immune checkpoint inhibitor therapy based on the programmed death 1 (PD-1) antibody may provide better clinical benefits.

Tumor neoantigens are important factors triggering anti-tumor and immunotherapy responses. The TMB has the potential to predict the production of tumor neoantigens, thus becoming an important marker for predicting the therapeutic response of some tumors to the PD-1/programmed death ligand 1 (PD-L1) (PDx) pathway inhibitors. Furthermore, changes in the NLR may be a useful predicting factor in patients treated with anti-PD-1/PD-L1 agents. Increased NLR has been reported as an independent poor prognostic indicator and its normalisation following treatment has been found to predict survival. Baseline NLR is easily obtainable in daily clinical practice (12). In previous research, Checkmate 227 study on non-small cell lung cancer (NSCLC) showed that high TMB is a positive predictor for the efficacy of PD-1 antibodies (13). When PD-1 antibodies are used to treat melanoma (14) and triple negative breast cancer (15), high TMB also predicts longer OS and PFS. However, PD-1 antibody did not improve the survival rate of glioma patients with high TMB, suggesting that the immune response against glioma is less dependent on TMB (16). As for the significance of high TMB in malignant teratomas, it has not yet been reported.

The malignant transformation of a teratoma was the result of progressive accumulation of genetic mutations. During this process, tumor neoantigens might be produced and accumulated. In this case, the high TMB may indicate more mutation loads and neoantigens production, therefore lead to stronger immunotherapy response. Additionally, the *TP53* mutation was also found by genetic testing in this patient, which may be a favorable factor for the application of immunotherapy. It has been reported that the *TP53* mutation enhances the immunogenicity of the tumor, which may lead to cytotoxic T lymphocytes infiltrating into the tumor stroma, thereby enhancing the efficacy of immunotherapy (17). Moreover, studies have also noted that the immunotherapeutic effect may be increased in patients with the *TP53* mutation by increasing TMB (13,18). Recently, Assoun *et al.* also found that among NSCLC patients treated with immune checkpoint inhibitors, those harbored *TP53* mutation exhibited significantly better OS, PFS, and objective response rate (ORR) as compared to *TP53* wild-type patients (19). Thus, we considered that PD-1 antibody may be an excellent option for treating this patient.

Additionally, the pathology of the second operation founded a tumor with extensive necrosis. It was likely that the necrosis was caused by the relatively insufficient blood supply for the rapid growth of the tumor, rather than the response of chemotherapy with TP chemotherapy, because the tumor volume had increased rapidly before. Meanwhile, this suggests that tumor growth depends on its blood supply evidently. And thus, anti-angiogenesis therapy might be effective.

Anlotinib is a new oral small molecular multi-targeted tyrosine kinase inhibitor that effectively inhibits kinases such as vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and c-Kit, and has the dual effects of anti-tumor angiogenesis and inhibition of tumor growth (20,21). On the other hand, anlotinib can relieve the immunosuppressive state of the tumor microenvironment, positively regulates immune function, and enhances the therapeutic effect of immunotherapy drugs, through remodeling the tumor vascular microenvironment, blocking VEGF mediated dendritic cell inhibition, and activating T cells and other mechanisms (22,23). Therefore, in order to achieve a synergistic effect, we applied the combination of camrelizumab (humanized anti-PD-1 monoclonal antibody, Hengrui, Jiangsu, intravenous infusion) plus anlotinib (oral).

After two cycles of the combination treatment, pelvic MRI indicated that pelvic metastases were significantly reduced. Tumor markers such as CA-125 were also decreased significantly, suggesting obvious clinical benefits. Thereafter, anlotinib was discontinued due to gastrointestinal bleeding (not excluding the association with the side effects of anlotinib). Camrelizumab alone was continued to be applied and further reduction of the pelvic mass was observed. Until October 2020, follow-up indicated satisfactory status of the patient without obvious signs of recurrence or significant treatment side effects.

Conclusions

Selecting treatments based on genetic mutations is an option worth exploring, however, past research has shown that the lack of efficacy of imatinib in MOGCTs is probably

related to the frequent mutations in the KIT enzymatic site, which leads to reduced sensitivity to imatinib blockade. Investigation of CDK4/6 inhibition for the treatment of teratoma is required, based on the preliminary indication of safety and potential clinical benefit. Finally, embryonal carcinoma can originate from the ovaries and invariably express CD30 on their cell membranes. Targetable biomarkers for chimeric antigen receptor (CAR) T-cell therapy are expanding, but tumour rarity and heterogeneity are currently limiting the development of CAR T-cell therapy in MOGCTs (24). In this case, based on high TMB and *TP53* mutation, we confirmed that the application of Camrelizumab achieved a good effect. It is suggested that immunotherapy with PD-1 antibody may be a good option for some cases.

Acknowledgments

Funding: The Key Supporting Project of Talent Bank Funded by Army Medical University (2019R035).

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-2429

Peer Review File: Available at http://dx.doi.org/10.21037/apm-20-2429

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2429). The authors have no conflicts of interest to declare.

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. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

References

1. Boussios S, Attygalle A, Hazell S, et al. Malignant Ovarian Germ Cell Tumors in Postmenopausal Patients: The Royal Marsden Experience and Literature Review. Anticancer Res 2015,35:6713-22.
2. Boussios S, Moschetta M, Zarkavelis G, et al. Ovarian sex-cord stromal tumours and small cell tumours: Pathological, genetic and management aspects. Crit Rev Oncol Hematol 2017;120:43-51.
3. Kurman RJ, Carcangiu ML, Herrington CS, et al. WHO Classification of Tumours of Female Reproductive Organs. 4th edition. World Health Organization, 2014.
4. Yamaguchi K, Mandai M, Fukuhara K, et al. Malignant transformation of mature cystic teratoma of the ovary including three cases occurring during follow-up period. Oncol Rep 2008;19:705-11.
5. Al-Rayyan ES, Duqoum WJ, Sawalha MS, et al. Secondary malignancies in ovarian dermoid cyst. Saudi Med J 2009;30:524-8.
6. Kido A, Togashi K, Konishi I, et al. Dermoid cysts of the ovary with malignant transformation: MR appearance. AJR Am J Roentgenol 1999;172:445-9.
7. Comerci JT Jr, Licciardi F, Bergh PA, et al. Mature cystic teratoma: a clinicopathologic evaluation of 517 cases and review of the literature. Obstet Gynecol 1994;84:22-8.
8. Kikkawa F, Nawa A, Tamakoshi K, et al. Diagnosis of squamous cell carcinoma arising from mature cystic teratoma of the ovary. Cancer 1998;82:2249-55.
9. Boussios S, Zarkavelis G, Seraj E, et al. Non-epithelial Ovarian Cancer: Elucidating Uncommon Gynaecological Malignancies. Anticancer Res 2016;36:5031-42.
10. Rekhi B, Parikh P, Deodhar KK, et al. Squamous carcinoma coexistent with teratoma of ovary: a clinicopathological study of 12 cases diagnosed over a 10-year period at a tertiary cancer referral center. J Cancer Res Ther 2015;11:211-5.
11. Faure-Conter C, Pashankar F. Immature Ovarian Teratoma: When to Give Adjuvant Therapy? J Pediatr Hematol Oncol 2017;39:487-9.
12. Moschetta M, Uccello M, Kasenda B, et al. Dynamics

of Neutrophils-to-Lymphocyte Ratio Predict Outcomes of PD-1/PD-L1 Blockade. Biomed Res Int 2017;2017:1506824.
13. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med 2018;378:2093-104.
14. Park C, Kim M, Kim MJ, et al. Clinical Application of Next-Generation Sequencing-Based Panel to BRAF Wild-Type Advanced Melanoma Identifies Key Oncogenic Alterations and Therapeutic Strategies. Mol Cancer Ther 2020;19:937-44.
15. Barroso-Sousa R, Keenan TE, Pernas S, et al. Tumor Mutational Burden and PTEN Alterations as Molecular Correlates of Response to PD-1/L1 Blockade in Metastatic Triple-Negative Breast Cancer. Clin Cancer Res 2020;26:2565-72.
16. Samstein RM, Lee CH, Shoushtari AN, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet 2019;51:202-6.
17. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science 2015;348:69-74.
18. Rizvi NA, Hellmann MD, Snyder A, et al. Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer. Science 2015,348:124-8.
19. Assoun S, Theou-Anton N, Nguenang M, et al. Association of TP53 mutations with response and longer survival under immune checkpoint inhibitors in advanced non-small-cell lung cancer. Lung Cancer 2019;132:65-71.
20. Lin B, Song X, Yang D, et al. Anlotinib inhibits angiogenesis via suppressing the activation of VEGFR2, PDGFR and FGFR1. Gene 2018;654:77-86.
21. Sun Y, Niu W, Du F, et al. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. J Hematol Oncol 2016;9:105.
22. Jain RK. Abstract IA03: Antiangiogenesis strategies revisited: From starving tumors to alleviating hypoxia. Mol Cancer Ther 2015;14:IA03.
23. Dirkx AE, oude Egbrink MG, Castermans K, et al. Anti-angiogenesis therapy can overcome endothelial cell anergy and promote leukocyte-endothelium interactions and infiltration in tumors. FASEB J 2006;20:621-30.
24. Boussios S, Mikropoulos C, Samartzis E, et al. Wise Management of Ovarian Cancer: On the Cutting Edge. J Pers Med 2020;10:41.

Cite this article as: Li X, Tang X, Zhuo W. Malignant transformation of ovarian teratoma responded well to immunotherapy after failed chemotherapy: a case report. Ann Palliat Med 2021;10(7):8499-8505. doi: 10.21037/apm-20-2429

