Title

Use of platinum-based chemotherapy and pembrolizumab to treat squamous cell carcinoma arising in a mature teratoma of the ovary in a pre-menopausal woman with negative response: A case report.

Authors

Martel, Rachel
Marsh, Leah
Lai, Tiffany
et al.

Publication Date

2023-06-01

DOI

10.1016/j.gore.2023.101192

Peer reviewed

Gynecologic Oncology Reports 47 (2023) 101192

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Use of platinum-based chemotherapy and pembrolizumab to treat squamous cell carcinoma arising in a mature teratoma of the ovary in a pre-menopausal woman with negative response: A case report

Rachel A. Martel [a,*], Leah Marsh [a], Tiffany Lai [a], Valentina M. Rodriguez-Triana [a], Neda A. Moatamed [b], Joshua Cohen [c]

[a] Ronald Reagan UCLA Medical Center Department of Obstetrics and Gynecology, United States
[b] Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, United States
[c] Department of Surgery Division of Gynecologic Oncology, City of Hope, United States

ARTICLE INFO

Keywords:
Mature teratoma
Ovarian squamous cell carcinoma
Immunotherapy

ABSTRACT

Squamous cell carcinoma of the ovary (SCC) is a rare and aggressive disease and optimal treatment is unknown. Here we report the case of a 29- year-old woman who presented with abdominal pain and was ultimately found to have a multi-septate, gas containing pelvic mass with mixed fat, soft tissue, and calcified components concerning for a ruptured teratoma with fistulization to the distal ileum and cecum on imaging. Operative findings included a 20 cm pelvic mass arising from the right ovary with frank invasion into the ileum and cecum and dense adhesion to the anterior abdominal wall on surgical exploration. Pathologic specimens were remarkable for stage IIIC SCC of the ovary arising in a mature teratoma, with a tumor proportion score of 40%. She progressed on first line treatment with cisplatin, paclitaxel and pembrolizumab as well as second line treatment with gemcitabine and vinorelbine. She died nine months after her initial diagnosis.

1. Introduction

Squamous cell carcinoma (SCC) of the ovary is a rare disease that most commonly arises from a mature teratoma of the ovary, but also develops in the setting of endometriosis, a Brenner tumor, or independently (Roxburgh and Glasspool 2014). Mature teratomas are relatively common, accounting for approximately 10%-20% of ovarian neoplasms (Gadducci et al 2018), however only 0.5–2% (Gadducci et al 2018, 2019) of these develop a malignant transformation. Of those that do, SCCs are the most common, at approximately 80% of cases (Roxburgh and Glasspool 2014). The disease is most prevalent in post-menopausal women (Chen et al 2008; Dos Santos et al 2007; Gadducci et al 2018; Hackethal et al 2008), is associated with large cysts (>10 cm) (Chen et al 2008; Dos Santos et al 2007; Gadducci et al 2018) and is generally unilateral (Chen et al 2008; Gadducci et al 2019). As they are difficult to diagnose based on symptoms and imaging, ovarian SCCs are generally discovered post-operatively on review of pathologic specimens (Gadducci et al 2018, 2019).

As SCC of the ovary is rare, there is little consensus regarding optimal treatment including adjuvant chemotherapy or radiotherapy. While primary surgery is generally accepted as standard (Gadducci et al. 2019), there are no guidelines to inform subsequent management. Platinum-based chemotherapy is reported to be superior to other chemotherapy regimens (Li et al 2019), however given the poor prognosis of the disease even when adjuvant therapy is administered (Roxburgh and Glasspool 2014) additional strategies are needed. Here, we present the case of a 29-year- old woman with SCC of the ovary arising in a mature teratoma, who was treated with pembrolizumab in addition to platinum-based chemotherapy.

2. Initial presentation

The patient is a 29-year-old gravida zero who presented for care in February of 2022 with symptoms of persistent mild to moderate right lower abdominal pain, bloating, and occasional nausea and vomiting. Review of systems was otherwise negative without further gynecologic concerns. Her past medical history was significant for gastric ulcers and asthma. Her most recent pap smear in December of 2021 was HPV negative, ASCUS. Her family history was negative for malignancies of the breast, colon, uterus, or ovaries. Upon bimanual exam, non-mobile,

* Corresponding author at: 10833 Le Conte Avenue, CHS 27-139, Los Angeles, CA 90095, United States.
E-mail address: rmartel@mednet.ucla.edu (R.A. Martel).

https://doi.org/10.1016/j.gore.2023.101192
Received 21 March 2023; Received in revised form 10 April 2023; Accepted 13 April 2023
Available online 20 April 2023

tender pelvic masses were palpated without other gross abnormalities. Ultrasound of the abdomen and pelvis showed bilateral adnexal masses (14 cm left, 9 cm right) most consistent with dermoid tumors (Fig. 1).

The patient was scheduled for laparoscopic bilateral ovarian cystectomy. However, two weeks before her scheduled surgery, she presented to the emergency department with fever/chills and diarrhea and was found to have *Clostridium sordelli* bacteremia. On imaging, she had a multi-septate, gas containing pelvic mass with mixed fat, soft tissue, and calcified components concerning for a ruptured teratoma with two sites of frank fistulization with the distal ileum and cecum, focal bowel thickening in the transverse colon, and minimal pelvic free fluid (Fig. 2). She was started on broad spectrum antibiotics, and gynecologic oncology and general surgery were consulted for operative assistance in the setting of cyst fistulization to bowel.

Intraoperatively, findings included a 20 cm pelvic mass arising from the right ovary with frank invasion into the ileum and cecum and dense adhesion to the anterior abdominal wall, normal left ovary and fallopian tube, and nodularity involving the right lower anterior abdominal wall peritoneum. Rapid frozen section showed SCC arising within a right ovarian mature teratoma (Fig. 3). She underwent an exploratory laparotomy, lysis of adhesions, right salpingo-oophorectomy, right pelvic lymphadenectomy, omentectomy, ileocecectomy with ileocolonic anastomosis, and radical resection of retroperitoneal tumor. The uterus and left ovary and fallopian tube were left in-situ given her desire for fertility preservation. At the end of the procedure, she was optimally cytoreduced to no gross residual disease.

Final pathology resulted with stage IIIC SCC of the ovary arising in a mature teratoma, invading ileocecal valve bowel wall with associated fistula formation and bowel perforation (Fig. 3). The tumor was HPV negative. Somatic next generation sequencing revealed a tumor proportion score (TPS) of 40%, MS-stable, TMB 9 Muts/Mb, CD274 (PD-L1) amplification, CDKN2A D108H, EGFR amplification, JAK2 amplification, PDCD1LGS (PD-L2) amplification, TP53 R213. Claudin 6 negative. Germline genetic testing was negative for deleterious mutations.

She was discharged home on post-operative day nine. After consultation, the patient declined oocyte cryopreservation given the need for urgent initiation of chemotherapy.

3. Clinical course and treatment

CT scan four weeks after surgery and before initiation of adjuvant chemotherapy demonstrated no evidence of intrathoracic disease, but development of new peritoneal carcinomatosis. CA-125 was within normal limits at 25 U/mL. The patient started treatment with cisplatin, paclitaxel, and pembrolizumab followed by pembrolizumab maintenance. Pembrolizumab was added given supporting data in patients with SCC of the head and neck and given the patient's TPS of 40% (Burtness et al 2019). Given the patient's initial presentation with fistulization between bowel and tumor requiring bowel resection, she was deemed high risk for future fistula formation and Avastin was not added. CT scan after three cycles of chemotherapy demonstrated disease progression with multiple masses in the right pelvis and increased peritoneal carcinomatosis. With this, the decision was made to stop cisplatin and paclitaxel while continuing pembrolizumab, of which she received a fourth cycle (the decision to continue pembrolizumab was made with the patient after discussing the remote possibility of pseudoprogression).

The decision was then made to pursue palliative external beam radiation to the right pelvis to relieve symptoms of increasing pain, followed by second line systemic treatment with gemcitabine and vinorelbine (extrapolated from data of treatment of squamous cell carcinoma of the lung (Ozkaya et al 2012)). The patient received one week of radiation therapy and one cycle of gemcitabine and vinorelbine. CT scan at initiation of chemotherapy demonstrated decreased size of the pelvic masses with persistent carcinomatosis, and interval development of internal air and enteric contrast within several of the tumors concerning for fistulization with bowel.

Given concern for tumor fistulization, the patient underwent palliative laparoscopic loop ileostomy for diversion. Her post-operative

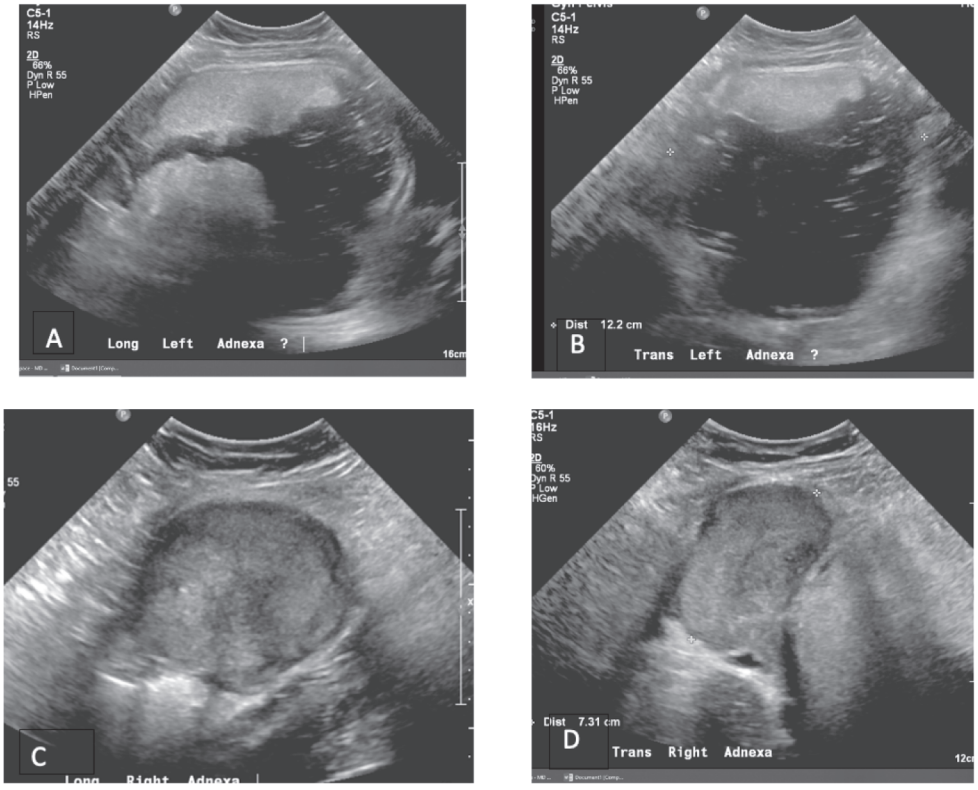

Fig. 1. Ultrasound imaging of the patient at her initial presentation for care demonstrating bilateral adnexal masses consistent with dermoid cysts A) Long view of the left adnexa B) transverse view of the left adnexa C) long view of the right adnexa D) transverse view of the right adnexa.

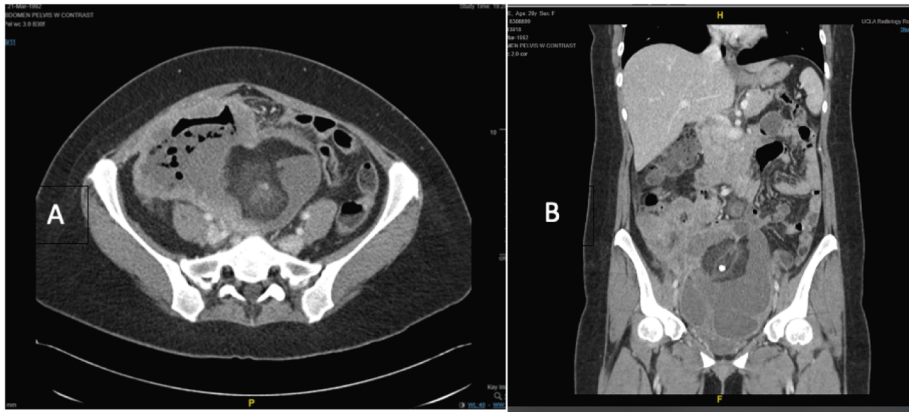

Fig. 2. CT Imaging of the patient at her initial presentation to the emergency department, demonstrating a multi-septate, gas containing pelvic mass with mixed fat, soft tissue, and calcified components concerning for a ruptured teratoma with two sites of frank fistulization with the distal ileum and cecum, focal bowel thickening in the transverse colon, and minimal pelvic free fluid. A) Axial view B) Coronal view.

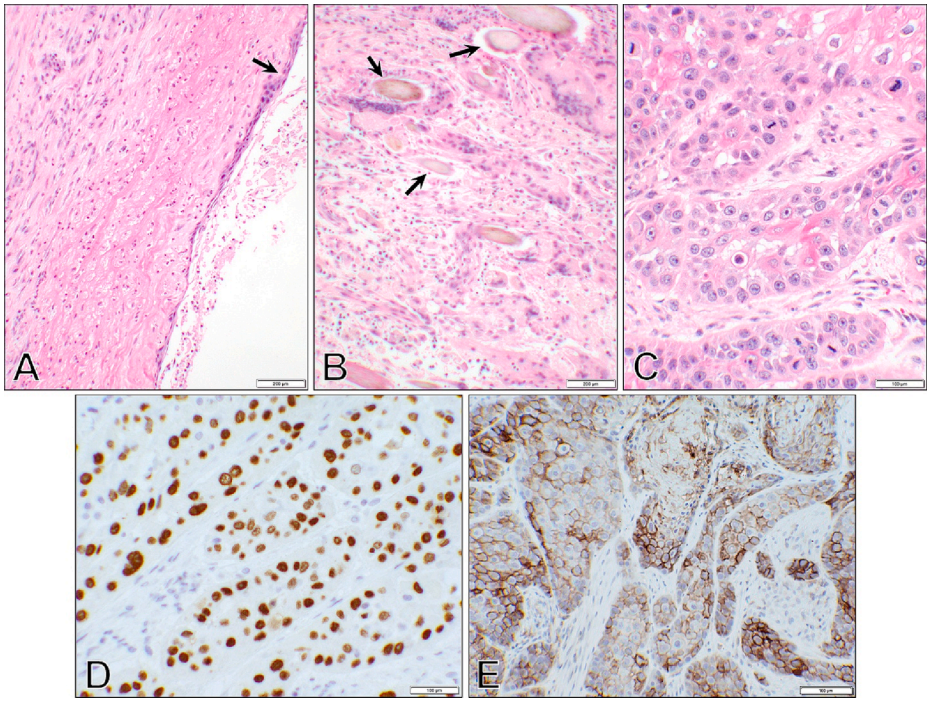

Fig. 3. Malignant squamous cell carcinoma arising in a background of preexisting teratoma with squamous lined cyst and hair. (A) The photomicrograph shows a portion of the mass with benign squamous cyst lining (arrow). (B) Few hair shafts (arrows) are seen in the cyst contents (10x objective). (C) Invasive squamous cell carcinoma showing infiltrative nests of malignant cells into the stroma (40x objective). (D) P63 immunohistochemical stain showing positive nuclear staining which confirms squamous cell origin of the tumor (40x objective). (E) PD-L1 immunostain shows positive staining of the tumor cells (40x objective).

course was complicated by development of a five-centimeter infraumbilical anterior abdominal wall abscess with apparent fistulization to underlying small bowel loops in the anterior pelvis. She was started on broad spectrum antibiotics and interventional radiology was consulted for image guided drainage. During this admission, after extensive goals of care discussion with the palliative care team, the patient decided to forgo further chemotherapy. She was discharged on a course of oral antibiotics with drain in situ and with her ostomy functioning well.

In September of 2022 CT scan again demonstrated disease progression with continued invasion into the bowel and anterior abdominal wall. She presented to the emergency department with wound dehiscence of the incision from her initial laparotomy secondary to frank tumor invasion into the anterior abdominal wall. On further discussion, given her declining performance status, the patient decided to transition to hospice care. The patient died in November of 2022, nine months after her initial diagnosis.

4. Discussion

4.1. Presentation and diagnosis

Although our patient was younger than the average age of 55 typically reported for the onset of SCC of the ovary (Chen et al 2008; Dos Santos et al 2007; Gadducci et al 2018; Hackethal et al 2008), she otherwise presented with characteristic symptoms of abdominal pain and large palpable adnexal masses (Chen et al 2008; Gadducci et al 2019; Hackethal et al 2008; Li et al 2019). While CA-125 has been reported as a marker for the disease (Chen et al 2008) with higher levels indicating poor prognosis (Hackethal et al 2008), other studies contest this (Hurwitz et al 2007) and her levels were within normal limits. Studies also suggest that HPV may play a role in the malignant transformation of mature teratomas to SCC (Shi et al 2022), however this is debated (Cooke et al 2017; Gadducci et al 2018, 2019), and our patient's recent pap smear and tumor testing were negative for HPV. While evidence of bowel fistulization to the teratoma could be suspicious for

malignancy on imaging, in line with prior case reports the patient's disease was not diagnosed until the frozen section was performed intraoperatively (Hurwitz et al 2007; Roxburgh and Glasspool 2014).

4.2. Prognosis

Our case is consistent with literature demonstrating that SCC of the ovary is an aggressive disease with poor prognosis if the disease has spread beyond the ovary (Gadducci et al 2019; Roxburgh and Glasspool 2014). A review of 12 patients with SCC of the ovary arising in a mature teratoma found that women with stage IA disease generally have excellent prognosis (Hurwitz et al 2007). Observation alone after surgery may be appropriate in these patients (Chen et al 2008; Dos Santos et al 2007). However, a review of 277 patients with SCC arising in a mature teratoma found that tumor stage had a significant prognostic effect only when comparing early with advanced stage disease, with minimal difference in survival between those with stage II-IV disease (Hackethal et al 2008). And a review of 435 cases of ovarian SCC found that prognosis was significantly worse among those with stage II-IV disease compared to stage I. In this study, five-year overall survival was 85.8, 39.1, 26.2 and 0% for stage I, II, III, and IV, respectively (Li et al 2019). A review of 188 cases of SCC of the ovary arising from a mature teratoma similarly found an overall five- year survival rate of 48.5% (stage I 75.7%; stage II, 33.8%; stage III, 20.6%; and stage IV, 0%). The authors also concluded that tumor stage, age, tumor size, pre-operative SCC antigen levels, CA-125 levels, and optimal debulking were all prognostically significant, while only stage and optimal debulking significantly impacted survival (Chen et al 2008).

4.3. Treatment

While the recommendation for primary surgery for SCC of the ovary is generally with hysterectomy and bilateral salpingo-oophorectomy with optimal cytoreduction in advanced stage disease (Gadducci et al 2019; Hackethal et al 2008; Hurwitz et al 2007; Li et al 2019), in this case the uterus and contralateral ovary and fallopian tube were left in-situ given the patient's young age and desire for fertility preservation. The addition of lymphadenectomy has also been reported to improve survival (Hackethal et al 2008; Roxburgh and Glasspool 2014) although data are mixed (Li et al 2019). This patient had optimal cytoreduction and was determined to have stage IIIC disease.

While there is no established first line treatment regimen and the utility of both adjuvant chemotherapy and radiation therapy is debated (Hurwitz et al 2007), adjuvant chemotherapy is generally recommended for stage IB disease and above (Gadducci et al 2019). Studies have shown that adjuvant chemotherapy can improve survival in patients with advanced stage disease (Chen et al 2008, Li et al 2019). Hackethal et al (2008) found that in those with greater than stage IA disease, only regimens with alkylating agents significantly impacted survival. Platinum based chemotherapy with cisplatin or carboplatin and paclitaxel is the most commonly employed adjuvant regimen (Gadducci et al 2019; Koufopoulos et al 2019) and is reported to be more effective than other regimens (Li et al 2019). A report of a woman with stage III disease who received six cycles of cisplatin and paclitaxel following primary surgery reported good response with the patient disease free after four years (Powell et al 2003), and a 2007 review recommended platinum-based chemotherapy in those with stage III disease (Dos Santos et al 2007). Regimens of cyclophosphamide, doxorubicin and cisplatin, cisplatin with etoposide, cisplatin and fluorouracil, gemcitabine and carboplatin, and cisplatin alone have also been reported (Dos Santos et al 2007, Koufopoulos et al 2019). Limited data is available on second line chemotherapy regimens. Case reports of second line use of topotecan and cisplatin, gemcitabine, and irinotecan exist with only irinotecan demonstrating good response (Koufopoulos et al 2019). Multiple reviews have concluded that adjuvant radiation and chemoradiation may not be beneficial in the treatment of SCC of the ovary despite SCC generally being radiosensitive and may actually worsen prognosis (Chen et al 2008; Hackethal et al 2008). However, Dos Santos et al (2007) do suggest that whole pelvic radiation and platinum-based chemotherapy may be beneficial in those with stage I-II disease.

As informed by existing literature, our patient received cisplatin and paclitaxel as part of her first line adjuvant chemotherapy regimen. However, her treatment course differs from the majority of published case reports given the addition of pembrolizumab to her regimen. Prior studies have demonstrated that targeted therapies may play a role in the treatment of ovarian SCC. Ford and Timmins (2011) present the case of a 41-year-old woman with stage IIC disease who received 3 cycles of cisplatin, paclitaxel and pelvic and extended field radiation therapy with concomitant cisplatin and cetuximab sensitizers (borrowed from the treatment of advanced SCCs of the head and neck) followed by an additional three cycles of cisplatin and paclitaxel. The patient was disease free 65 months after diagnosis. Wu et al. (2021) report the case of a 36-year -old women with stage IVB SCC arising from a presumed mature teratoma who was not optimally cytoreduced and received adjuvant chemotherapy with carboplatin, paclitaxel and bevacizumab with disease progression. The authors explain that the patient had an ECOG score of two making her ineligible for clinical trials, and she was thus started on pembrolizumab as her tumor had 50–60% positivity for PDL-1. At time of publication, the patient had been on pembrolizumab for 15 months with stable disease and improvement to ECOG performance status of 0. Wu et al hypothesize that SCC arising from mature teratomas may overexpress the gene XCL1 which is associated with tumor expression of PD-L1 and CD8 + T-cell infiltration.

Unfortunately, our patient's disease progressed while on a regimen that included pembrolizumab despite evidence of PD-L1 expression on immunohistochemical staining (TPS 40%). This indicates that treatment may be dependent on factors beyond the presence of PD-L1 amplification. Future investigation is warranted to determine the role of immunotherapy in the setting of SCC arising in a mature teratoma (Cooke et al 2017).

Consent

Written informed consent was obtained from the patient's family for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

RM conceptualized the case report and wrote the original draft.

LM, TL, VR, and JC reviewed and edited the draft and supervised RM.

NM reviewed and edited the draft and reviewed pathologic specimens for inclusion in the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. There are no funding sources to report.

References

Burtness, B., Harrington, K.J., Greil, R., Soulières, D., Tahara, M., de Castro, G., et al., 2019. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet 394 (10212), 1915–1928.

Chen, R.J., Chen, K.Y., Chang, T.C., Sheu, B.C., Chow, S.N., Huang, S.C., 2008. Prognosis and treatment of squamous cell carcinoma from a mature cystic teratoma of the ovary. J. Formosan Med. Assoc. 107 (11), 857–868.

Cooke, S.L., Ennis, D., Evers, L., Dowson, S., Chan, M.Y., Paul, J., et al., 2017. The Driver Mutational Landscape of Ovarian Squamous Cell Carcinomas Arising in Mature

Cystic TeratomaSquamous Cell Carcinoma Arising in Mature Cystic Teratoma. Clin. Cancer Res. 23 (24), 7633–7640.
Dos Santos, L., Mok, E., Iasonos, A., Park, K., Soslow, R.A., Aghajanian, C., et al., 2007. Squamous cell carcinoma arising in mature cystic teratoma of the ovary: a case series and review of the literature. Gynecol. Oncol. 105 (2), 321–324.
Ford, T.C., Timmins III, P.F., 2011. Successful treatment of metastatic squamous cell carcinoma of the ovary arising within a mature cystic teratoma. Clinical Ovarian Cancer 4 (1), 44–46.
Gadducci, A., Pistolesi, S., Guerrieri, M.E., Cosio, S., Carbone, F.G., Naccarato, A.G., 2018. Malignant transformation in mature cystic teratomas of the ovary: case reports and review of the literature. Anticancer Res 38 (6), 3669–3675.
Gadducci, A., Guerrieri, M.E., Cosio, S., 2019. Squamous cell carcinoma arising from mature cystic teratoma of the ovary: A challenging question for gynecologic oncologists. Crit. Rev. Oncol. Hematol. 133, 92–98.
Hackethal, A., Brueggmann, D., Bohlmann, M.K., Franke, F.E., Tinneberg, H.R., Münstedt, K., 2008. Squamous-cell carcinoma in mature cystic teratoma of the ovary: systematic review and analysis of published data. Lancet Oncol. 9 (12), 1173–1180.
Hurwitz, J.L., Fenton, A., McCluggage, W.G., McKenna, S., 2007. Squamous cell carcinoma arising in a dermoid cyst of the ovary: a case series. BJOG 114 (10), 1283–1287.
Koufopoulos, N., Kokkali, S., Antoniadou, F., Nasi, D., Goudeli, C., Terzakis, E., Pigadioti, E., Khaldi, L., 2019. EP895 Primary squamous cell carcinoma of the ovary: review of the literature. Int. J. Gynecol. Cancer 29.
Li, C., Zhang, Q., Zhang, S., Dong, R., Sun, C., Qiu, C., et al., 2019. Squamous cell carcinoma transformation in mature cystic teratoma of the ovary: a systematic review. BMC Cancer 19 (1), 1–12.
Ozkaya, S., Findik, S., Dirican, A., Atici, A.G., 2012. Long-term survival rates of patients with stage IIIB and IV non-small cell lung cancer treated with cisplatin plus vinorelbine or gemcitabine. Exp. Ther. Med. 4 (6), 1035–1038.
Powell, J.L., Stinson, J.A., Connor, G.P., Shiro, B.S., Mattison, M., 2003. Squamous cell carcinoma arising in a dermoid cyst of the ovary. Gynecol. Oncol. 89 (3), 526–528.
Roxburgh, P., Glasspool, R., 2014. Squamous carcinoma of the ovary. Curr. Oncol. Rep. 16 (12), 1–6.
Shi, Z., Yang, L., Bian, C., 2022. Squamous cell carcinoma in mature cystic teratoma of the ovary induced by human papillomavirus 16 infection: A case report and literature review. Medicine 101 (38), e30667.
Wu, M., Bennett, J.A., Reid, P., Fleming, G.F., Kurnit, K.C., 2021. Successful treatment of squamous cell carcinoma arising from a presumed ovarian mature cystic teratoma with pembrolizumab. *Gynecol.* Oncol. Rep. 37.