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Angiosarcomas of Primary Gynecologic Origin – A Case Series and Review of the Literature

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Abstract. *Background/Aim: Angiosarcoma of primary gynecologic origin is an extremely rare and highly malignant tumor of endothelial origin with a 5-year survival rate of less than 35%. To date, only 61 cases have been described in the literature. The aim of this study was to present more cases and discuss potential therapy options. Case Report: The following case series presents three cases of gynecologic angiosarcomas that were under therapy at the Charité – University medicine of Berlin from June 2014 to February 2018. Results: Two of the cases deal with primary angiosarcomas of the uterus whereas the third case was diagnosed after the suspicion of a recurrence of a poorly differentiated squamous cell carcinoma of the cervix uteri. In case one a 75-year old patient with initial postmenopausal bleeding and a tumor mass of the uterus is described. After surgery a hemangiosarcoma of the uterus was confirmed. After two months the patient presented with a presacral peritoneal sarcomatosis. Chemotherapy of weekly paclitaxel was administered. Case two deals with a patient presenting with abdominal pain. A uterine sarcoma with infiltration of the parametry and angiosarcomatosis peritonei was diagnosed during an emergency laparotomy because of spontaneous peritoneal bleeding. Moreover, osseous metastasis was found. The patient underwent weekly paclitaxel. Due to tumor progression, chemotherapy was changed to doxorubicin and olaratumab and radiotherapy was induced. The patient died 33 months after initial diagnosis. Case three describes a 34-year old patient with suspected local recurrence of cervical cancer with infiltration of the bladder. During TURB an angiosarcoma was found. Following laparoscopy revealed peritoneal metastasis. The patient underwent weekly paclitaxel followed by a paclitaxel and pazopanib maintainance therapy which showed a regression. Due to progression afterwards, chemotherapy was changed to gemcitabine and docetaxel and gemcitabine monotherapy. The patient died 33 months after initial diagnosis. Conclusion: Even though there is no evidence on standard treatment of this extremely rare and aggressive tumor entity of the female genital tract the patients showed the longest stability of disease during chemotherapy with weekly paclitaxel.*

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Angiosarcomas are rare and highly aggressive endothelial-cell tumors, mainly occurring in elderly men (1). Although the most frequent manifestation site is the skin, it can develop in any organ. Chronic lymphedema, previous radiation, exogenous toxins and familial syndromes such as neurofibromatosis type 1 are considered as risk factors (1). Interestingly, a mutation in the *BRCA1* or *BRCA2* gene is a predisposition towards development of angiosarcoma after breast cancer treatment (2). To date, only 61 cases appearing in the female genital tract (FGT) have been described in the English literature (3-12) (Figure 1). With a 5-year survival rate of less than 35%, it is comparable to angiosarcomas of other origins (1, 3). Due to the lack of experience with this extremely rare tumor entity a standardized therapy has not been yet established. We present a case series of three cases of angiosarcomas of the FGT treated at the Charité - University Medicine Berlin.

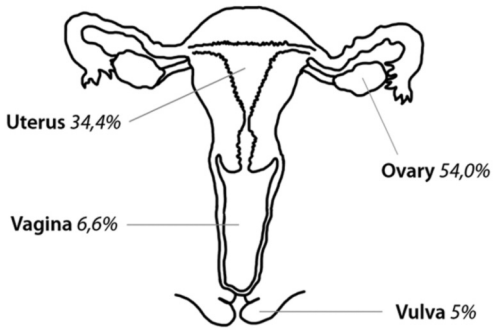

Figure 1. *Distribution of angiosarcomas of the female genital tract.*

Case Report

Case one. A 75-year old patient was admitted to the Charité hospital due to postmenopausal bleeding. A transvaginal ultrasound showed solid and cystic lesions throughout the whole uterus. A hysteroscopy and fractionated curettage were performed, reveling a suspect endometrium. The laboratory results showed an elevated LDH with 303 U/l and normal values of the tumor markers cancer antigen 125 (CA-125), human epididymis protein 4 (HE4), and carcinoembryonic antigen (CEA). A magnetic resonance imaging (MRI) of the thorax, abdomen and pelvis (Figure 2) showed an inhomogeneous contrast-enhancing tumor of the corpus uteri and furthermore no evidence for tumor spread. A laparotomy with hysterectomy, bilateral salpingo-oophorectomy and peritonectomy of the douglas cavity was performed. The histologic findings confirmed the manifestation of a hemangiosarcoma of the uterus, which was classified as FIGO stage IA (Figure 3). On the second postoperative day the patient developed a pulmonary artery embolism, which could be treated properly. Two months later the patient represented herself with reoccurring vaginal bleeding. The bleeding could be arrested with electrocoagulation. A histopathological biopsy showed recurrence of the tumor and computed tomography (CT) showed presacral peritoneal sarcomatosis surrounding the rectum. The case was discussed in our interdisciplinary online tumor conference (13). It was evaluated to start chemotherapy with paclitaxel 80 mg/m^2 weekly. The tumor response is still pending (Table I).

Case two. A 61-year old patient was admitted to our hospital due to abdominal pain. In a subsequent CT scan a cystic lesion inside the liver (5.5 cm), a lesion on the right lateral side of the cervix uteri (1.5 cm) and small pulmonal nodes were detected. A diagnostic laparoscopy was performed and peritoneal biopsies were obtained. The histological findings could not reveal a primary tumor. Further diagnostic steps such as sonography, gastroscopy and mammography were performed, but showed no evidence of primary tumor formation.

The patient was then referred to our hospital for a second opinion and further treatment concerning the cancer of unknown primary (CUP-syndrome). Initial laboratory results showed no elevation of tumor markers carbohydrate antigen (CA-125), human epididymis protein (HE4), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and squamous cell carcinoma antigen (SCC). Further diagnostics were initiated and a ^{18}F-FDG-positron emission tomography/CT scan (^{18}F-FDG PET/CT) as well as a bone scintigraphy result was indicative of osseous metastasis in the os sacrum, the distal part of the femur and the cervical spine. Additionally, in a colonoscopy an external compression of the caecum could be detected.

A further MRI scan of the pelvis showed a cystic lesion of the right pelvis (8×6 cm), partly filled with blood, a lesion ventral of the uterus (2 cm) as well as a suspected peritoneal carcinomatosis. A hysteroscopy and a fractionated abrasion were performed but in histological examination, no malignancy could be found.

A few weeks later, the patient presented in our emergency department with persistent anaemia and suspected bleeding of the peritoneal lesions. An emergency laparotomy with peritonectomy of the right diaphragm, right hemicolectomy with creation of an ileostoma and ascendostoma, en-bloc resection of the uterus, adnexa and peritoneum of the pelvis was performed. The postoperative residual tumor mass was larger than one cm.

The pathologic examination revealed a high-grade hemangiosarcoma of the parametrium (Figure 4). After being presented in our interdisciplinary online tumor conference (13), the patient underwent adjuvant chemotherapy with twelve courses of paclitaxel 60 mg/m^2 weekly. In a follow-up CT scan the initially described right lesion in the pelvis decreased in size, but multiple new lesions of the peritoneum occurred. Due to the deterioration of the patient's general condition and newly-diagnosed macrohematuria with a suspected tumor infiltration of the bladder multiple stays at hospital were necessary. Radiation of the femur and operative stabilization by a mark brand were conducted. A transurethral resection of the bladder (TURB) showed a circular invasion of the tumor around the right ostium. Three courses of doxorubicin and two courses of olaratumab were administered. However, in a subsequent CT scan a significant progression of the peritoneal carcinomatosis and new osseous metastasis could be seen. The patient died of disease 17 months after being first diagnosed with an angiosarcoma (Table I).

Case three. A 34-year old patient was admitted to hospital due to increased abdominal girth, nausea, vomiting and hematuria. The patient's medical history included a cervical

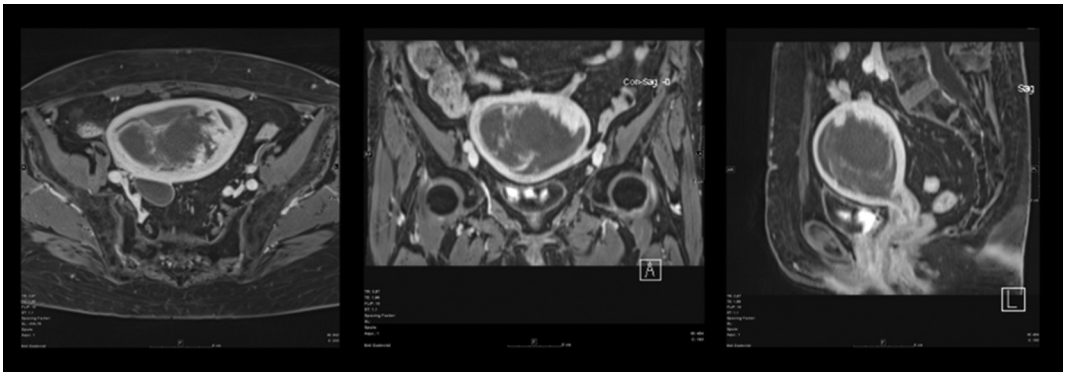

Figure 2. *Diagnostic MRI previous to operation in case 1. T1-weighted MRI image with contrast (6 ml Gardovist intravenously), (A) axial, (B) coronar, (C) sagittal position.*

Table I. *Summary of outcomes, therapy, follow-up and histopathological findings of all cases.*

Case	Age	Localization	Metastasis	Surgical treatment	Systemic treatment	Follow-up	Ki-67
1	75	Uterus	None	HE, AE, PE of the douglas cavity	None	NED, 3 months	90%
2	61	Parametrium	Uterus, ovaries, bone	HE, AE, PE of the pelvis and right diaphragm, right hemicolectomy with ileostoma and ascendostoma	PXW, Doxo/Olara	DOD, 17 months	40%
3	34	Vagina	Peritoneum, omentum, liver, bone	none	PXW/Pazo, Gemci/Doce, MTX, vinblastine, propranolol	DOD, 33 months	40%

Ki-67, Antigen KI-67 proliferation index; HE, hysterectomy; AE, adnectomy; PE, peritonectomy; PXW, paclitaxel weekly; Doxo/Olara, Doxorubicine and Olaratumab; Pazo, Pazopanib; Gemci/Doce, Gemcitabine and Docetaxel; MTX, methotrexat; NED, no evidence of death; DOD, death of disease.

carcinoma FIGO stage Ib1 (pT1b1 pN0 (0/25) M0 L0 V0 G3 R0) that was diagnosed seven years before. Back then, she had received a total mesometrial resection (TMMR) with therapeutic pelvic lymphadenectomy. Due to recurrence in the vagina and pelvis of the cervical carcinoma one year after primary treatment the patient was treated with three courses of chemotherapy with paclitaxel, ifosphamide and cisplatin as well as a subsequent radiation with tele- and brachytherapy.

Upon admittance, another recurrence of the cancer was suspected. Laboratory results showed elevated CA-125 (102.5 U/l) as well as elevated creatinine (1.49 mg/dl). A CT scan of the abdomen verified a local recurrence in the vagina with infiltration of the bladder wall and the left ostium and suspected peritoneal carcinosis. In conclusion, a TURB was performed and the histological report showed an angiosarcoma of the vagina. No further metastasis could be found in a subsequent PET/CT scan (Figure 5). However, in a diagnostic laparoscopy sampling of the pelvic wall showed histological evidence of peritoneal metastasis of the angiosarcoma. Intraoperative findings were an omental cake with fragile tissue, contact bleeding and superficial peritoneal carcinosis in the pelvis (Figure 6). The case was discussed in our interdisciplinary online tumor conference (13) and ten courses of chemotherapy with paclitaxel 80 mg/m^2 weekly were initiated. The patient's condition improved under this therapy and a good tumor response on paclitaxel was seen. Two courses of paclitaxel with a course length of 21 days and pazopanib 800 mg/day followed as a maintenance therapy. A few weeks later the patient represented again with abdominal pain, fast abdominal girth growth and a recurrence of the angiosarcoma in the vagina. A CT scan of the abdomen revealed hepatic metastasis. She then received six courses of docetaxel 70 mg/m^2 and gemcitabine 700 mg/m^2. After a three-month period of maintenance therapy with gemcitabine monotherapy the chemotherapy was discontinued due to the patient's wish.

A progression of peritoneal metastasis was notified. Chemotherapy with gemcitabine was reinitiated. However, further tumor progression could be detected with diffuse

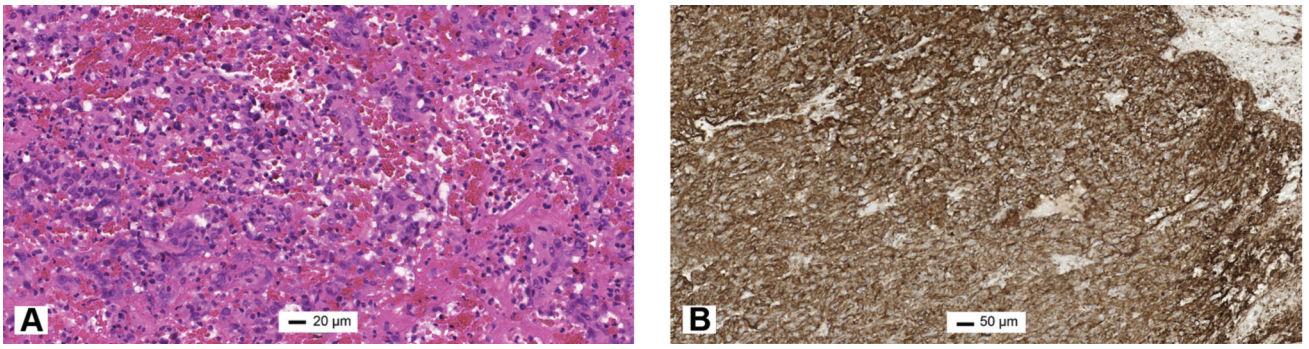

Figure 3. *Histopathological findings in Case 1. (A) Angiosarcoma with solid growth pattern of spindle cells with slit like, blood filled spaces, H&E staining. (B) Spindle cells proving strong positivity for CD31 immunohistochemistry.*

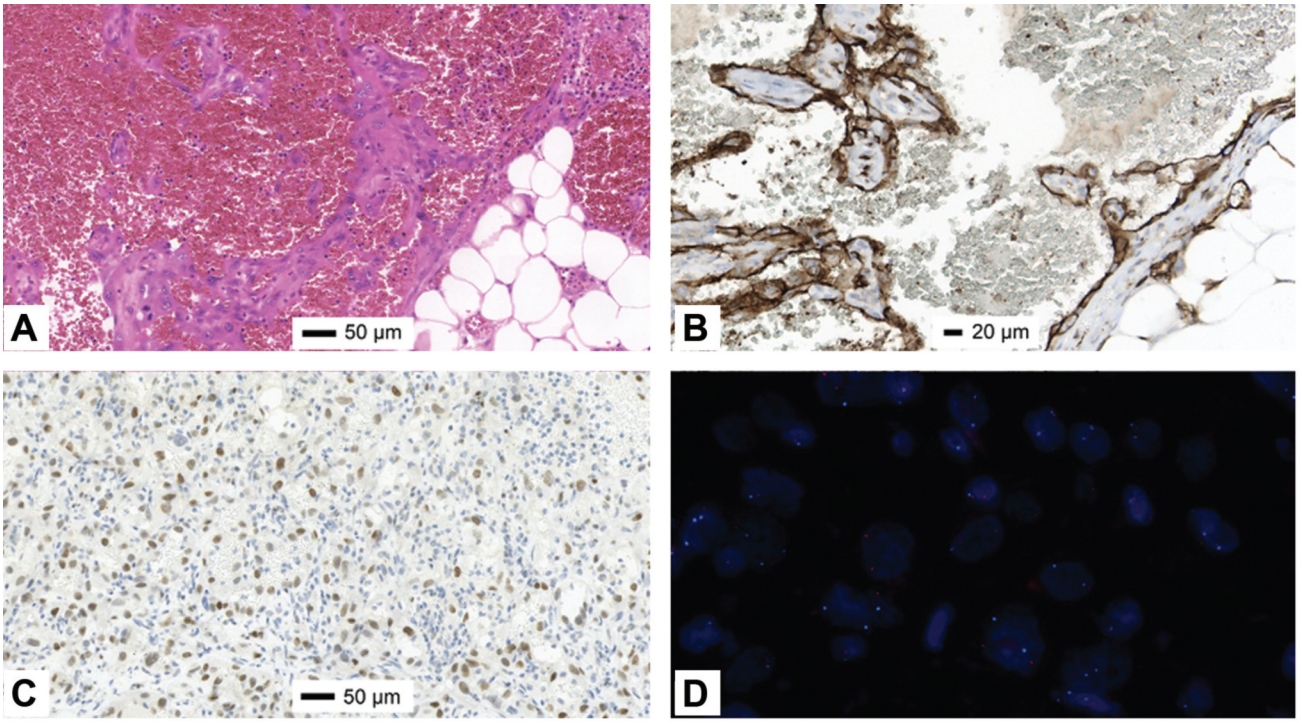

Figure 4. *Histopathological findings in Case 2. (A) Angiosarcoma with typically enlarged blood vessels lined by atypical endothelial cells, H&E staining. (B) Atypical endothelial cells proving strongly positive for CD31 immunohistochemistry. (C) Nuclear expression of myc immunohistochemically. (D) No amplification of c-myc in FISH diagnosis.*

osseous metastasis in the pelvis and infiltration of the L5 nerve radix. Due to macrohematuria and progression of the tumor masses with infiltration of the bladder, chemotherapy was changed to methotrexate, vinblastine and propranolol. Despite more chemotherapy, the patient died of disease 33 months after initial diagnosis (Table I).

Pathological findings. Macroscopically, the tumors were partially white-colored and partially cystic modified. The tissue seemed rough and hemorrhagic. In case two, the ovaries and both adnexa also showed superficial peritoneal sarcomatosis.

In all cases, microscopical findings showed spindle cell epitheloid neoplasia with partly solid growth and partly growing as blood filled cavities or as well as net-like, cohesive cells (Table II). The cytoplasm seemed light eosinophil and the nuclei showed moderate to severe atypia. Nuclei were enlarged, deformed eventually bizarre with prominent nucleoli. The mitotic activity was strong with 9 mitoses per 10 high-power fields, FN 20, atypical mitoses were frequent.

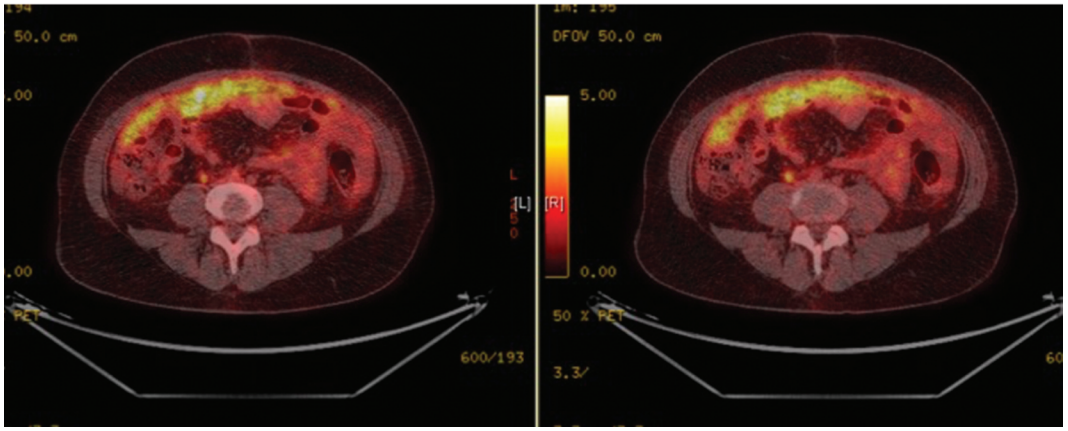

Figure 5. *Diagnostic PET-CT previous to treatment in case 3. Omental cake.*

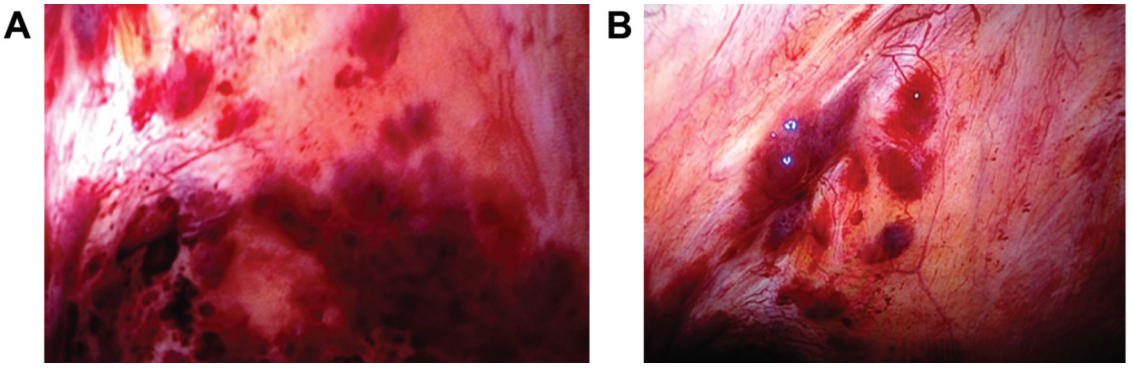

Figure 6. *Intraoperative findings in case 3. Peritoneal tumor infiltration with hemorrhage.*

Immunohistochemically, the tumors proved to be of endothelial origin with strong CD31 positivity. The proliferation rate of Ki-67 was found to be approximately 90% (case one), 40% (case two) and 40% (case three). CD34 had only been positive in case three. In some regions the marker CD10 showed minimal positivity in case one. Vimentin and Fli-1 showed positivity in case two. Pancytokeratine, estrogene receptor, progresterone receptor, actine and inhibine markers were all negative. EpCam, Calretinin, PanCK, MNF116, AE1/AE3, CK7/18/20 and EMA were all negative in case two. Although immunhistochemically there was some nuclear positivity for myc, the *C-MIC* gene was not amplified in case two.

Discussion

This case series presents three patients with angiosarcomas of different origins within the FGT. Two patients underwent surgery and three patients were treated with weekly paclitaxel as first-line chemotherapy in a palliative setting.

Angiosarcoma is a very rare disease. Even though the main organ of manifestation is the skin, a small percentage can also evolve within the female genital tract localized in the uterus, ovaries, vagina or vulva (3). So far, evidence-based therapy is limited to nonexistent. Primary surgery and adjuvant therapy, as in chemotherapy or radiation, are widely acknowledged. Due to its aggressiveness, the 5-year overall survival rate approximates only 27-35% (1, 3). Radical surgery is still seen as the primary treatment of choice. The benefit of adjuvant chemotherapy has not been evaluated completely. Respectively, there is no evidence for a better survival rate after adjuvant chemotherapy in localized angiosarcomas of the skin (14). A clear improvement of the survival rate could only be shown in patients with ovarian angiosarcomas (3). Whether adjuvant chemotherapy is indicated depends on the stage of disease.

Nevertheless, a high percentage of angiosarcomas develop metastasis. In metastatic angiosarcomas, chemotherapy is considered the first-line treatment of choice (1). There has been no consensus on the choice of chemotherapy with more

Table II. *Histopathological findings*.

Case	Localization	Microscopic features	CD31	CD34	Ki-67	PanCK	Follow-Up
1	Uterus	Spindle cell, epitheloid	+	–	90%	–	NED, 3 months
2	Parametrium	Spindle cell, hemorrhage	+	–	40%	–	DOD, 17 months
3	Vagina	Spindle cell, hemorrhage	+	+	40%	–	DOD, 33 months

CD31, Cluster of differentiation 31; CD34, cluster of differentiation 34; Ki-67, antigen KI-67 proliferation index; PanCK, pancytokeratine; +, positive; –, negative; NED, no evidence of death; DOD, death of disease.

benefits for patients. Different studies show a better survival rate from using anthracyclines, taxanes and tyrosine kinase inhibitors (15-29). Therefore, anthracyclines are considered the first-line treatment in advanced and metastatic angiosarcomas. In a more experimental setting, some case reports show a highly effective use of propranolol (30-33). Monoclonal antibodies for anti-PDGFRa like olaratumab could not show a beneficial effect on overall survival in combination with doxorubicin in patients with advanced soft-tissue sarcomas (16, 34, 35). Different patterns with paclitaxel, gemcitabine and pegylated-liposomal doxorubicin may be used in a palliative setting (17, 18, 24, 36). Comparable to angiosarcomas of other origins, a review of angiosarcomas of the FGT showed that adjuvant chemotherapy can improve the survival rate (3).

In retrospective studies investigating angiosarcomas of the skin, such as ANGIOTAX, ANGIOTAX PLUS or EORTC, chemotherapy with weekly paclitaxel showed a significant increase of overall survival (OS) (8 to 19.5 months) (17, 21, 25, 26). The overall response rate differed from 19% to 62% (17, 18, 21, 25, 26) and progression-free survival ranged from 4 to 7.6 months.

Only four cases of angiosarcomas of the vagina are described in the literature (3, 8, 37, 38). Two of these cases underwent solely adjuvant radiotherapy. The OS were 4 and 48 months. Chemotherapy with weekly paclitaxel and paclitaxel and cisplatin were conducted in the other two cases. The patient with initial weekly paclitaxel treatment showed the longest OS with 24 months. These findings seem equal to our two cases with weekly paclitaxel treatment. Considering these findings, weekly paclitaxel seems to be the most effective treatment for angiosarcomas of the FGT if adjuvant or primary chemotherapy is indicated. Limiting this conclusion is the lack of retro- or prospective studies and the overall small number of cases.

The reason for these different responses on chemotherapy, may be caused of the heterogeneity of the histopathological characteristics. Angiosarcomas usually present as malignant endothelial cells with a great variety of expression. The more aggressive a tumor is, the more unorganized the cell architecture becomes. Immunohistochemically angiosarcomas express von Willebrand factor, CD34, CD31, vascular endothelial growth factor (VEGF) and ulex europaeus agglutinin 1. To distinguish the angiosarcoma from a malignant melanoma S100, human melanoma black-45 and the melanoma antigen can be used (1). Kruse *et al*. state in their case report review that CD31, CD34 and cytokeratins are strongly expressed immunohistochemically (3). In our cases only CD31 was positive. Pancytokeratine has not been expressed in any angiosarcoma even though the uterine one was declared as being epitheloid. All three showed spindle cells and hemorrhage.

The proliferation rate of Ki-67 was approximately 40% in two of our cases. These two cases also showed good response to paclitaxel. Another case report showed comparable results with good tumor response to paclitaxel in a uterine angiosarcoma with a Ki-67 proliferation index of 50% (39). In analogy to breast cancer treatment, the Ki-67 proliferation index may be discussed as a prognostic marker for the tumor response on chemotherapy (40, 41). Thus far, the Ki-67 index had only been analyzed as a diagnostic tool to distinguish between hemangioma and angiosarcoma of the breast (42). A correlation between the Ki-67 proliferation index and tumor response on different cytostatic substances should be considered in future studies.

Conclusion

Angiosarcomas of the gynecological tract are very rare tumor entities. The ideal therapy has not been yet established. Therefore, further studies have to be performed to evaluate the profitability of different chemotherapies on overall survival. In conclusion, based on the experience of our three reported cases, weekly paclitaxel can be considered an effective adjuvant therapy for angiosarcoma of the gynecological tract.

Conflicts of Interest

Dr. Sehouli reports research funding and adboard from Bayer, Lilly and PhamaMar, outside the submitted work; Dr. Pietzner reports personal fees from AstraZeneca, personal fees and travel support from Roche, personal fees from MSD, personal fees from PharmaMar, personal fees and travel support from Tesaro/GSK, outside the submitted work; Mr. Chinczewski, Dr. Taube, Dr. Feldhaus, Dr. Chekerov, Dr. Dröge, Dr. Muallem and Dr. Alavi have nothing to disclose.

Authors' Contributions

Lukas Chinczewski and Sara Alavi were responsible for the study coordination, analysis and interpretation of data and drafting of the manuscript. Lisa Dröge, Klaus Pietzner, Radoslav Chekerov and Jalid Sehouli were involved in the acquisition of data as well as the analysis and interpretation of data and critical revision. Eliane Taube was responsible for the pathological findings and Felix Feldhaus for the radiological findings. All Authors discussed the results and contributed to the final manuscript.

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