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Postoperative Adjuvant Therapy for Uterine Epithelioid Angiosarcoma: A Case Report and Review of the Literature

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Abstract: ***Background:*** ***Uterine epithelioid angiosarcoma is an extremely rare malignant neoplasm and has a poor prognosis. Therapeutic options that significantly contribute to the survival and prognosis of patients are still being explored.*** ***Objective:*** ***We hope that by reviewing the literature and sharing our own case can find out the postoperative treatments methods that may be beneficial to the prognosis of patients, especially postoperative adjuvant chemotherapy.*** ***Method:*** ***We report a new case and reviewed the literature. According to the current diagnostic criteria, we retrieved and identified 15 qualifying cases from PubMed, Scopus, and Web of Science. Moreover, we found a case from China Science and Technology Journal Database (CNKI), which was never reported in the English literature.*** ***Results:*** ***A 53-year-old female presented with abdominal pain and distension to find to pelvic mass. She was taken for a total abdominal hysterectomy, bilateral salpingo-oophorectomy, sigmoidectomy and sigmoidostomy returned a diagnosis of epithelioid angiosarcoma of the uterus. She was still alive but with suspected metastasis at the time of this report, 6 months after diagnosis.*** ***Conclusion:*** ***In the future, molecular and immunological deciphering of angiosarcomas may open up avenues for precision medicine to help patients to improve the recognition of the tumor, to avoid potential misdiagnosis and gain better therapeutic strategies for well-established survival benefit.***

Keywords: Epithelioid angiosarcoma, Uterine, Immunohistochemistry, Therapy**.**

1. Introduction

Epithelioid angiosarcoma (EAS) is a rare and aggressive soft tissue sarcoma that consists mainly of epithelioid cells in histomorphology and is considered as a special histologic subtype of angiosarcoma (AS) [1,2], accounting for less than 2% of all sarcomas [3]. Clinically, it can occur at any anatomic site, most commonly in the scalp, breast and extremities, characterized by high recurrence and metastatic rates as well as a poor prognosis [4,5].

Currently, the accurate diagnosis of epithelioid angiosarcoma is mainly based on histopathological and immunohistochemical findings [6]. Current updated diagnostic criteria for a tumor qualifying as EAS include: (1) malignant endothelial cells with exclusively or predominantly (> 90% of the tumor area) an epithelioid morphology; and (2) positive immunohistochemical staining for at least 1 endothelial marker including Factor VIII (FVIII), platelet endothelial cell adhesion molecule (CD31), Cluster of differentiation 34 (CD34), or ETS-related gene (ERG) [7]. Unfortunately, there was no information on immunohistochemical findings in most of the early reported cases before the 1980s, mainly due to the fact that immunohistochemistry (IHC) just has been routinely used to assist in pathological diagnosis until the early 1980s [8,9].

Up to date, in the uterus, there have reported 16 valid cases (Table 1) diagnosed by morphology and IHC in the literature. Nevertheless, sporadic case reports alone failed to explore effective treatment and identify the pathogenesis, which has seriously impeded progress in the treatment of the disease [10].

Herein, we present a case of uterine epithelioid angiosarcoma and a review of previously reported valid cases, hoping to provide clinical experience for postoperative adjuvant treatment of this disease.

Table 1: Summary of reported cases of Epithelioid uterine angiosarcomas

Case No.	Author (Year)	Age (years)	Presentation	Tumor Size(cm)	Primary treatment	Follow up (months)
1	Majeed et al. [39] (1990)	76	abdominal swelling vaginal bleeding weight gain constipation dysuria anemia	18×17×13 uterus	TAH/BSO	6, DOD (Metastasis had occurred at initial diagnosis; Recurrence [a] at 2.5mos)
2	Tallini et al. [16] (1993)	56	vaginal bleeding	30×24	TAH/BSO+LN	7, Metastasis and DOD (Recurrence [b] at 2mos)
3	Drachenberg et al. [17] (1994)	58	vaginal bleeding anemia	12-uterus	TAH/BSO+RT+CT (unspecified type)	2 (Recurrence and DOD at 2mos)

4	Schammel and Tavassoli [40] (1998)	49	pelvic mass anemia	29.1×28.7×19	TAH/BSO	3, DOD
5	Schammel and Tavassoli [40] (1998)	75	vaginal bleeding	6.3×6×4.5	TAH/BSO	7, DOD
6	Olawaiye et al. [34] (2008)	54	weight loss	11.6-uterus	TAH/BSO	12, ANED (Recurrence [c] at 2mos)
7	Donnez et al. [41] (2011)	58	abdominal discomfort chronic cystitis	2500-g uterus.	TAH/BSO+CT (Ifosfamide, Doxorubicin) + zoledronic acid	53, DOD (Metastasis had occurred at initial diagnosis)
8	Hwang and Lim [28] (2013)	61	lower abdominal pain vaginal bleeding	12×10×9	TAH/BSO+LN+RT	NA (Metastasis had occurred at initial diagnosis)
9	Suzuki et al. [23] (2014)	62	uterine bleeding	3	TAH/BSO	50, Metastasis [d]
10	Yunqi Xiong and Xia Wu [42] (2015)	57	vaginal bleeding	4 ×3× 3	TAH/BSO+LN+CT (Cisplatin, Epirubicin and Ifosfamide)	NA (alive at time of report)
11	Liu et al. [43] (2016)	56	lower abdominal pain pelvic mass anemia	11× 8×7	TAH/BSO	Withdrew
12	Strickland et al. [18] (2017)	67	vaginal bleeding weight loss pelvic mass anemia	24×20×12	TAH/BSO	2, DOD
13	Hara et al. [19] (2018)	48	abdominal distention weight loss anemia	28×23	TAH/ RSO+CT (Paclitaxel, Epirubicin and Carboplatin)	10, ANED
14	Majeed et al. [20] (2020)	56	weight loss pelvic pain	10.2×9.3×5.5	TAH/BSO+CT (unspecified type)	3, DOD
15	Deb et al. [10] (2022)	57	vaginal bleeding haematuria	2.1×1.3×0.7	NC+TAH/BSO (Paclitaxel, Carboplatin)	14, ANED
16	Present case (2022)	53	abdominal pain abdominal distention pelvic mass constipation dysuria anemia	12×10×10	TAH/BSO+CT (Paclitaxel and Carboplatin)	12, ANED, then lost to follow up (Metastasis had occurred at initial diagnosis)
17	Sevim et al. [44] (2023)	55	vaginal bleeding	3. 5	TAH/BSO+CT (Paclitaxel and Carboplatin)	16 (Recurrence [e] at 2mos; ANED at about 16mos and alive at time of report)

Note. Abbreviations: TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; RSO, right salpingo-oophorectomy; DOD, dead of disease; CT, chemotherapy; RT, radiotherapy; NC, neoadjuvant chemotherapy; ANED, alive with no evidence of disease; NA, not available/reported.
a. The disease relapsed at 2.5 months after surgery and the treatment after recurrence was not available
b. The disease relapsed at 2 months after surgery, then the patient started on CT (doxorubicin, ifosfamide and mesna) and RT
c. The disease relapsed at 3 months after surgery, then the patient started on CT (gemcitabine, taxotere and bevacizumab) and later changed to albumin-bound paclitaxel (ABI-007, Abraxane™) and bevacizumab.
d. The disease metastasized at 50 months after surgery, then the patient accepted adjuvant chemotherapy (unspecified type).
e. The disease relapsed at about 3 months after surgery, then the patient continued with the original CT regimen (paclitaxel and carboplatin)

2. Case Report

The patient, a 53-year-old multiparous (G5P3) and perimenopausal female, was admitted with progressively aggravating lower abdominal pain and distension of 2 weeks which was accompanied by dizziness, dysuria and constipation. In the past year, she started having menstrual disorder and had been aware of a soft mass in her lower abdomen which increased slowly in size since then, but she didn't take it seriously. Retrospecting the patient's medical history revealed a surgical history of ectopic pregnancy 26 years ago and a history of pregnancy hypertension to placental abruption 23 years ago. She denied the history of radiotherapy, chemical exposure and malignant tumors.

Physical examination showed that the uterus was enlarged to an approximate 12-week pregnancy size with irregular shape and uneven surface in medium texture. It was poor in mobility and pressed with tenderness. Ultrasonography observed a 108mm×86mm irregular isohypoechoic subserosal mass in the fundus of the ante-positioned uterus (88mm×65mm× 60mm) and a 62mm×52mm poorly demarcated irregular heterogeneous isohypoechoic which was no distinct demarcation with uterus including hyperechoic nodules inside it on the left side of the uterus. A subsequent pelvic contrast-enhanced magnetic resonance imagining (CE-MRI), in Figure 1, showed multiple nodules and masses of varying sizes with oval shapes are visible in the myometrium of the uterine fundus and the left adnexal region. The largest lesion, located in the uterine fundus, measures approximately 10.4 cm×8.5cm×9.5 cm with well-demarcated borders and demonstrates heterogeneous enhancement, with some areas showing no significant enhancement. No significant abdominal lymphadenopathy nor peritoneal deposits were identified but presence of ascites within the pelvic cavity. The MRI findings were suggestive of uterine leiomyoma possibly with degeneration, warranting distinction from malignant transformation, and further evaluation was recommended.

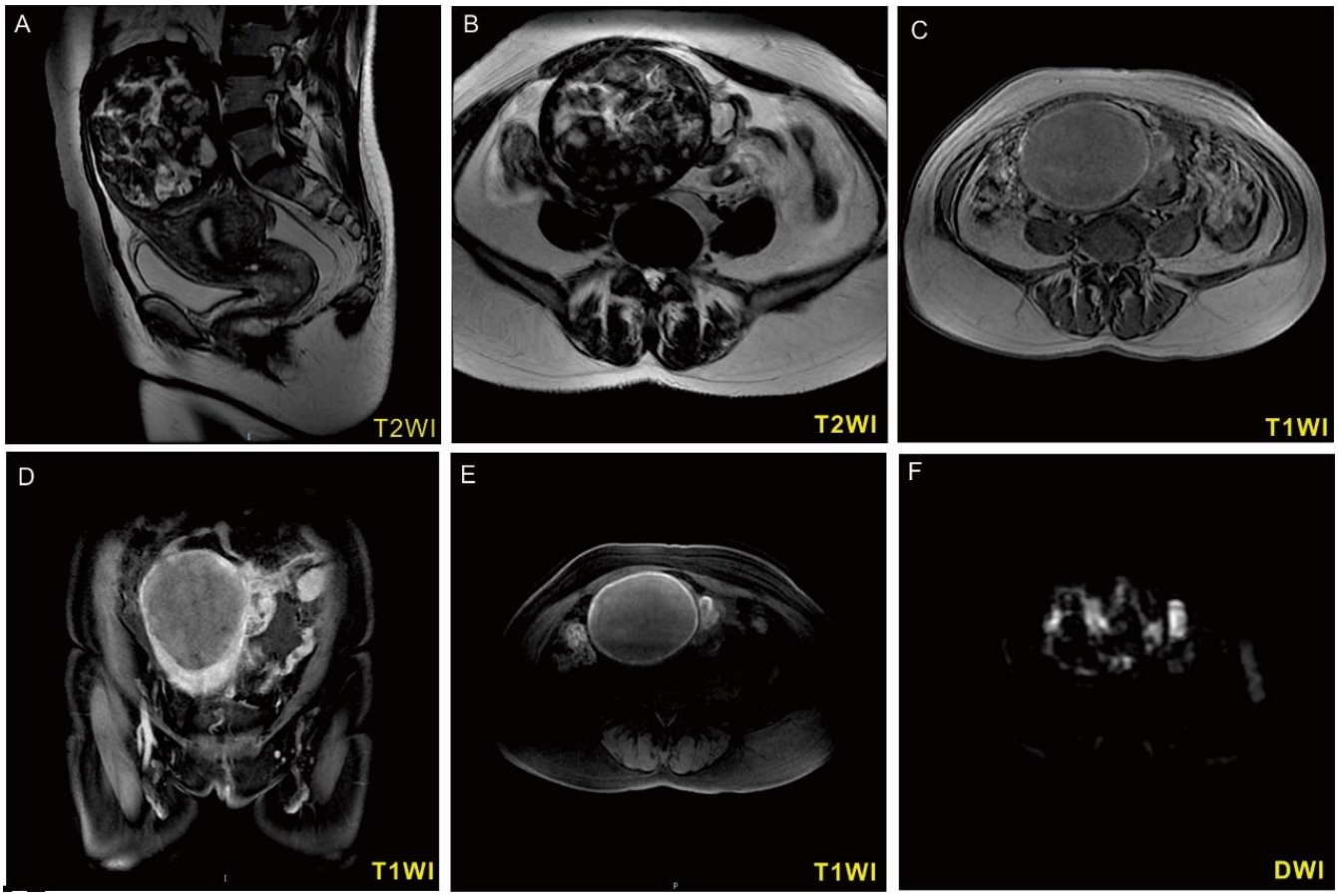

Figure 1: Findings of CE-MRI images of the pelvis previous to operation showed that the largest mass in the myometrium of the uterine fundus, approximately 10.4 cm × 8.5 cm × 9.5 cm, comparing to the myometrium, appeared as isointense to slightly hyperintense on T1-weighted imaging (T1WI) and heterogeneous hypointense to hyperintense on T2-weighted imaging (T2WI). (A) Oblique sagittal T2-weighted fast spin-echo (FSE) image, (B) Oblique axial T2-weighted FSE image, (C) Axial breath-hold T1-weighted gradient-echo (GRE) image, (D) Coronal Liver Acquisition with Volume Acceleration (LAVA)+ Contrast, (E) Axial LAVA Mask, (F) Axial Diffusion-weighted image (b-value=1000 s/mm²)

The preoperative laboratory examination showed that the patient had anemia (hemoglobin 98g/L; hematocrit 29.8%). The preoperative serum level of CA125 was 213.40 U/mL, significantly higher than the normal level(0-35U/mL). Other tumor markers including AFP, CA199, HE4, ProGRP (Pro-gastrin-releasing peptide) and CYFRA21-1 (cytokeratin 19 fragment antigen21-1) in serum were within normal limits. Preoperatively, gynecological oncologists suspected the tumor was a multiple uterine leiomyoma or leiomyoma with degeneration, even uterine malignancy and suggested surgical resection for clear diagnosis and treatment.

Following multidisciplinary team (MDT) evaluation by gynecologic oncology specialists, determined surgical intervention to be the optimal treatment strategy. Initially, single-port multi-channel laparoscopic exploration was performed and it was found that a firm tumor was present in the uterine fundus where multiple blood-rich tumor tissues could be seen protruding out of the serosa and about 500ml bloody ascites in the abdominal-pelvic cavity. In addition, the left uterine adnexa, sigmoid colon, intestinal mesentery and appendix were invaded by the tumor to form a caky crispy bleeding-prone metastasis with multiple vascular openings on the surface adhering to the uterine horn on the left side of the uterine tumor. The pelvic peritoneum and bladder surface are also scattered with many lesions with a diameter of about 0.5 to 3 cm. No obvious neoplasm metastasis was found in the right uterine adnexa, the upper abdomen, liver, pancreas, stomach and greater omentum. At the same time, we immediately switched to laparotomy and intraoperatively invited two gastrointestinal surgeons together to perform total abdominal hysterectomy, bilateral salpingo-oophorectomy, sigmoidectomy, sigmoidostomy, appendectomy, tumor cytoreduction and pelvic adhesiolysis with the consent of the patient's family. The operation went well.

The postoperative histopathological report confirmed uterine epithelioid angiosarcoma with left adnexa, sigmoid colon, mesentery and peritoneum invasion, stage IIIB (FIGO). Specifically, there are two nodules in the myometrium, the smaller one and the left adnexa confirmed to epithelioid angiosarcoma by morphology and IHC, but the larger one showed massive necrotic hemorrhage without clear tumor component. The surgical resection margins of both ends of the sigmoid colon, the parametrium and the uterosacral ligaments were all free of malignancy. The right accessory, appendix and the resected periintestinal lymph nodes had no evidence of metastasis.

Subsequently, adjuvant chemotherapy with TP regimen (paclitaxel 240 mg and carboplatin 600 mg) was started on the thirteenth postoperative day, scheduled for 8 courses (every 21 day a course). Initially, she experienced only occasional itching with no other discomfort, but five months after the

operation, she developed minor vaginal bleeding. On examination, we found a 0.5-cm cauliflower-like grey-white and taupe soft tissue in her right vaginal vault, then the biopsy showed inflammatory cell infiltration with atypical cells. Reexamination of contrast-enhanced MRI displayed two annular enhanced nodules (hyperintensity on T2 and isointensity on T1WI) in the left pelvic iliac vascular area, approximately 17mm and multiple lymph nodes around the abdominal aorta, suggesting possible metastasis. The patient was still alive at 12 months after the initial diagnosis, but subsequently lost to follow-up.

2.1 Materials AND Methods

Histopathologic and immunohistochemical examination. All the tissues underwent fixation in 10% neutral-buffered formalin for optimal tissue preservation and embedded in paraffin after routine processing, sectioning, and staining with hematoxylin-eosin (H&E). Immunostaining employed monoclonal/polyclonal antibodies directed against the following molecular markers: CD31 (PECAM-1, MX032), CD34 (QBEnd/10), ERG (MXR004), FVIII (F8/86), Vimentin (V9), Cytokeratin (CK, AE1/AE3), Friend leukemia integration 1 transcription factor (FLI-1, MX045), Ki-67 antigen (Ki-67, MIB-1), tumor protein 53 (P53, MX008), human chorionic gonadotropin (HCG, CG04+CG05), estrogen receptor (ER, SP1), progesterone receptor (PR, ER2), Tumor protein p63 (P63, MX013), Cyclin-dependent kinase inhibitor 2 (P16, MX007), Podoplanin (D2-40), Carcinoembryonic antigen (CEA, COL-1), Epithelial membrane antigen (EMA, E29), Wilms tumor protein 1 (WT-1, MX012), CK7 (ov-TL12/30), CK5/6 (MX040), GATA binding protein 3 (GATA-3, L50-823), Naphthalene aspartic protease A (Napsin A, MX015), Paired box gene 8 (PAX-8, MRQ-50), Hepatocyte nuclear factor 1-beta (HNF1β, OTIR2E9), Mucin 4 (MUC4, 8G7), α-Methylacyl-CoA racemase (P504S, 13H4).

3. Results

3.1 Gross Findings

Macroscopically, the mass was under the serosa of the uterine fundus, measuring about 12cm×10cm×10cm. Its shape was irregular with multiple blood-rich tumor tissues protruding outside the serosa and outer surface was yellowish-white in color. In addition, the left uterine adnexa, sigmoid colon, intestinal mesentery and appendix were adhered together to form a 16×14×14-cm sized caky reddish crisp adhesion with multiple vascular openings visible on the surface. On sectioning, the mass displayed a spongy hemorrhagic cut surface just like cooked beef-like tissues with massive reddish brown necrotic tissues and blood clots as well as the aforementioned adhesion. The endometrium, uterine cervix, right uterine adnexa showed no gross abnormalities.

3.2 Microscopic Findings

Microscopically, the lesion was composed of sheets or nests of epithelioid or spindled tumor cells exhibiting marked cytologic atypia, accompanied by geographic necrosis and hemorrhage (Figure 2a, b). The epithelioid tumor cells accounted for approximately 90% of the tumoral cellular population, while the spindled tumor cells constituted about 10%. The tumor cells exhibited abundant eosinophilic cytoplasm with discernible nuclear membranes and prominent macronucleoli (Figure 2c). In some areas, vascular differentiation and mitotic figures are readily identified could be seen (Figure 2c). In the nonnecrotic areas, irregular vascular channels lined by conspicuous epithelioid tumor cells were extensively distributed, demonstrating intervascular anastomoses and containing intraluminal erythrocytes (Figure 2b).

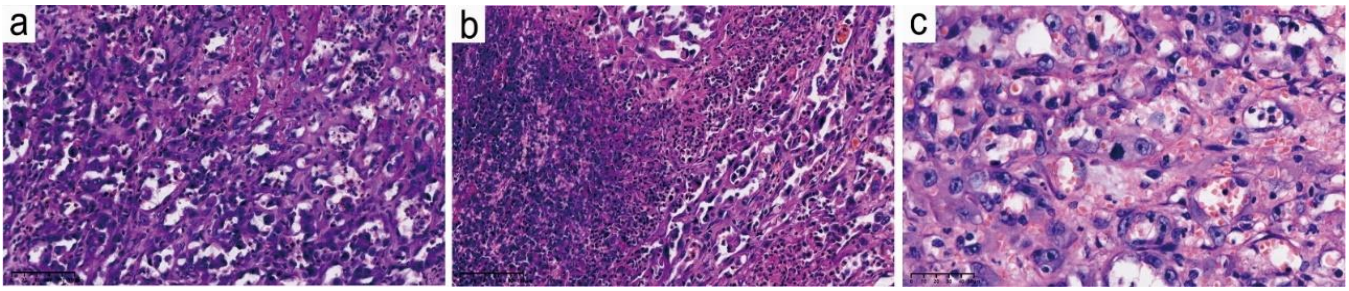

Figure 2: Histologic features of uterine mass (H&E, ×200 magnification): a) Sheets or nests of epithelioid or spindled tumor cells with discernible nuclear membranes, prominent nucleoli, vesicular nuclei and eosinophilic cytoplasm were observed. b) Geographic necrosis and hemorrhage were observed in the left part, while irregular vascular channels lined by conspicuous epithelioid tumor cells containing intraluminal erythrocytes is observed in the right part. c) Mitotic figure (arrow)

3.3 Immunohistochemical Findings

Immunohistochemically, in Figure 3, tumoral cells in the angiosarcoma component were diffuse positivity for CD31, CD34, ERG, FLI-1, CK and Vimentin. Ki-67 showed a 40% proliferation index in tumor cells. P53 was immunolabeled in 20% neoplastic cells. Moreover, scattered positive staining was also detected for FVIII. Stains for ER, PR, P63, P16, CEA, EMA, WT-1, CK7, CK5/6, GATA-3, Napsin A, PAX-8, HNF1β, MUC4, P504S, HCG, D2-40 were negative. Overall, the immunohistochemical and histologic findings supported for neoplasm of endothelial origin and a diagnosis of epithelioid angiosarcoma was rendered.

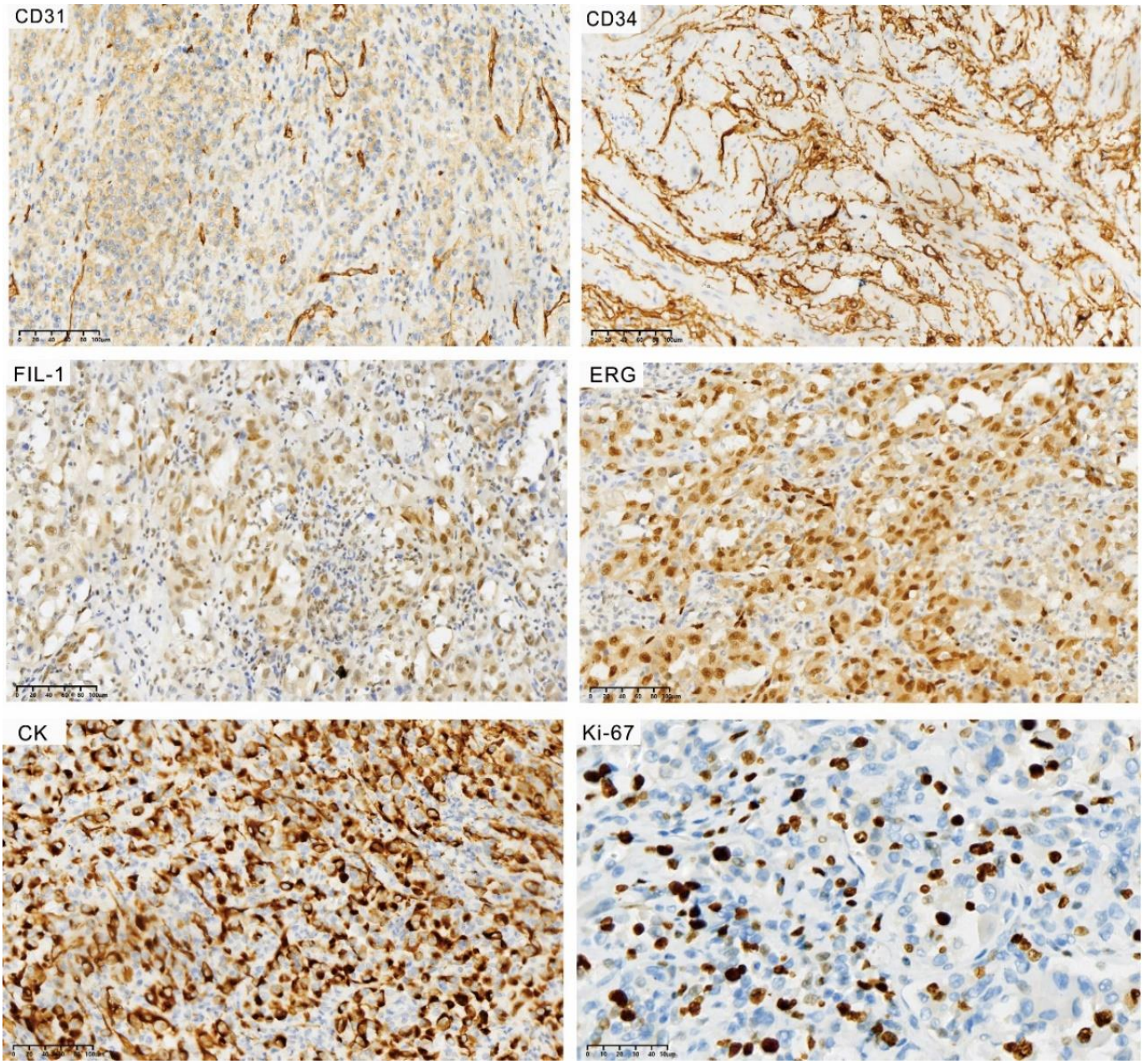

Figure 3: Immunohistochemical findings (Original magnification ×20): tumoral cells showed diffuse strong membranous-cytoplasmic positivity for CD31 and CD34, nuclear positivity for ERG and FIL-1, cytoplasmic positivity for CK and FVIII.

4. Discussion

Uterine angiosarcoma is an extremely rare malignancy and a highly malignant disease, with approximately 30 cases reported in the English literature [10], among which those the epithelioid variants are even rarer. According to the latest diagnostic criteria for epithelioid angiosarcoma [7], some previous cases that were diagnosed as uterine epithelioid angiosarcoma without histological or immunohistochemical evidence are not considered to be valid in the present study. Therefore, we finalized 16 reported cases of uterine epithelioid angiosarcoma and analyzed them in combination with the case diagnosed at our institution, as shown in Table 1.

Notably, the patients (Table 1) were predominantly in postmenopausal or perimenopausal at initial diagnosis, with a median age of 57 years (range, 48 to 76 years), in distinct contrast to ovarian epithelioid angiosarcoma, which usually affects premenopausal women or even children [11]. Regarding clinical manifestations, of 17 reported cases of uterine epithelioid angiosarcomas, approximately 50% patients presented with abnormal genital bleeding (10/17) or anemia (7/17); less than a third of patients were aware of a pelvic mass or suffered from pelvic abdominal pain or abdominal distension or weight loss. In addition, individual patients may complain of compressive or invasive symptoms, such as dysuria, constipation, hematuria, cystitis, etc.

Epithelioid angiosarcomas, once commonly misdiagnosed as carcinoma, melanoma or mesothelioma due to its rarity and similarity to carcinoma, and also easily missed [12,13]. Positive staining for endothelial markers (Factor VIII, CD31, CD34, ERG, FLI1 and VEGF) and negative staining for melanoma (S100 and SOX10) and carcinoma markers (CAM 5.2 and AE1/AE3) are helpful for the correct diagnosis of EAS [14,15]. In the present case, epithelial angiosarcoma was

confirmed by positive immunostaining for several endothelial markers, including FVIII, CD31, CD34, FLI-1 and ERG. Consequently, the ultimate diagnosis requires immunohistochemical results to support the histopathological findings in order to confirm the vascular endothelial origin of the tumor and perform a differential diagnosis.

Interestingly, six of the seventeen reported cases of uterine epithelioid angiosarcoma were coexistent with uterine leiomyomas [6,16–20], whereas the others were pure lesions. Under this circumstance, it is debated whether there is a connection between hysteromyoma and epithelioid angiosarcoma, especially in postmenopausal and perimenopausal women. Following the research by Chan et al. (1991), Drachenberg et al. (1994) speculated that leiomyomata may be involved in the pathogenesis of angiosarcoma by generating mechanical pressure leading to lymphatic vascular obstruction and thus causing benign vascular transformations [17,21]. In addition, another possible explanation offered by Schammel and Tavassoli (1998) [17] is that this may be smooth muscle proliferation of the adjacent myometrium in response to an epithelioid angiosarcoma rather than a true uterine leiomyoma. On the other hand, a US population-based study of uterine leiomyomas showed that the proportion of women with uterine leiomyomas was highest in the 50 to 54 years (15.9%) [22], similar to the median diagnostic age of EAS in uterus which seems to better explain the coexistence of uterine leiomyomas and EAS in uterus. Therefore, when uterine epithelioid angiosarcoma and uterine leiomyomas have no anatomical relationship, we tend to regard their coexistence in surgical specimens as an epidemiological feature of uterine leiomyomas that is not strongly related to the occurrence of epithelioid angiosarcoma.

To date, the pathogenesis of uterine epithelioid angiosarcoma is obscure, still in the initial stage of exploration. In the past decade, only two cases to research on the molecular genetics in uterus. Initially, Japanese scholars Suzuki et al. (2014) unexpectedly identified breakages at three loci, i.e. YWHAE (17p13), FAM22A (10q23) and FAM22B (10q22) by fluorescence in situ hybridization analysis in the course of the procedure of differential diagnoses [23]. Subsequently, Chinese scholars Liu et al. (2016) also performing the fluorescence in situ hybridization for their case according to the same protocol of Suzuki et al. however, neither breakage nor fusion of these genes was detected in their case [6]. However, relatively specific molecular alterations have been identified in other sites. For example, in the breast, more than 90% of secondary breast angiosarcomas have characterized MYC amplification which may trigger oncogenesis via autocrine activation of VEGF [24,25]. Therefore, MYC-overexpressing AS may be susceptible to targeted therapy with VEGF pathway inhibitors [25].

Furthermore, a patient collaboration project on angiosarcoma reported that a subset of patients with head and neck angiosarcoma have a high tumor mutation burden (TMB) and dominant UV-damage mutant features that may be apt for checkpoint immunotherapy, and revealed recurrently mutated genes in angiosarcoma that included KDR, TP53, and PIK3CA by Whole-exome sequencing (WES) [26]. Therefore, it is necessary to perform molecular analysis, if possible, to explore the unique molecular expression and immune milieu and to enrich the gene spectrum of EAS originating from uterus in order to obtain novel potential therapeutic strategies.

Frustratingly, there has never been a consensus on the optimal therapy for epithelioid angiosarcoma of uterus. The therapeutic modalities vary among individual cases, including primary treatment with surgery with or without adjuvant chemotherapy or radiotherapy. Accurate preoperative diagnosis of EAS is a significant challenging due to the non-specific clinical presentation and paucity of imaging and laboratory diagnostic characteristics [13]. Thus, the starting treatment time is almost after the diagnosis confirmed by biopsy of the post-operative specimen. There is only one case was diagnosed preoperatively by chance on bladder biopsy, then received neoadjuvant chemotherapy prior to surgery. Compared to at least half of the patients, this case achieved a better survival benefit of more than 14 months [10]. This suggests that neoadjuvant chemotherapy may improve the outcome of EAS and highlights the importance of pre-operative diagnosis.

However, despite all cases initially have undergone total abdominal hysterectomy and salpingo-oophorectomy and strived to achieve optimal debulking at metastasis. The overall prognosis remains poor, with most patients achieving only a short disease-free interval and then deteriorating rapidly, with five-year survival rates of less than 20%. In the table 1, almost 50% patients (8/17) died of the disease within 1 year of diagnosis and the peak of recurrence is 2 to 3 months postoperatively; a quarter of the patients had metastasized at diagnosis. It is mainly through haematogenous metastases to distant organs or direct spread to adjacent sites, whereas lymphatic metastasis is uncommon [27]. It remains controversial whether lymph node dissection is routine, as the majority of patients with abdominal metastases have negative lymph node biopsies [28], as was our patient.

As previously alluded to, EAS is a disease with dismal prognosis. Deb et al. (2022) performed survival analysis of uterine angiosarcoma for the first time and reported that primary tumor size may be a key prognostic factor, while treatment modalities used and age at diagnosis did not impact survival [10]. Additionally, p53 positivity (defined as >20% nuclear positivity) [29] and a high proliferative index (MIB-1≥10%) [30] are adversely correlated with prognosis. In our case, P53 and Ki-67 staining were respectively positive in 20% and 40% of the tumor cells. Based on these findings, we have closely followed our patient, observing the results of laboratory and ultrasound tests at each chemotherapy session. According to the data currently available, we found that our patient's CA125 change trend somewhat reflected the patient's condition. CA125 levels showed a tendency to decrease before her vaginal bleeding (213.40 U/ml, 13.0 U/ml, 7.8 U/ml, 6.40 U/ml and 7.3 U/ml for the first to fourth chemotherapy sessions, respectively) and to rise afterwards (7.3 U/ml and 8.7 U/ml for the first to fourth chemotherapy sessions, respectively). As we all know, good follow-up indicators are important for a good treatment plan. We speculate that CA125 may be one of potential laboratory indicators for the monitoring of the prognosis of EAS of uterus.

However, Cytotoxic chemotherapy has shown a marginal role in improving overall survival and local control [31,32]. Only 7 cases in Table 1 received adjuvant or neo-adjuvant chemotherapy, but some precise data about the treatment modalities (e.g. dose and time interval of adjuvant chemotherapy, chemotherapy modalities….) are not available in most these cases. There is evidence that paclitaxel-based chemotherapeutic regimens may improve survival [33]. Taxane and antiangiogenic combination given the previously observed activity of taxanes in angiosarcomas [34]. Initial responses to cytotoxic chemotherapy are common, but the duration of response is often limited, and most patients eventually succumb to metastatic disease. However, complete responses of angiosarcomas can occasionally occur with chemotherapy, including taxanes and doxorubicin-based regimens [35,36].

Recently, immunotherapy has shown promising results in the treatment of angiosarcoma. Immune checkpoint inhibitors are currently in clinical trials that include angiosarcoma patients (NCT02815995) [37]. The recent discovery for the role of the molecular-targeted immunotherapy with bevacizumab, pazopanib, sorafenib or sunitinib has uncovered a novel therapeutic synergy in treating angiosarcoma [37]. Case reports in the literature have shown remarkable response of visceral and cutaneous angiosarcoma involvement in patients treated with an anti-PD-1 antibody, this offers a potential hypothesis to explain early evidence of PD-1 blockade activity in cutaneous angiosarcomas with chemotherapy-refractory angiosarcomas who were treated with checkpoint inhibitors [38]. Rapidly deteriorating disease making it impossible to receive any cytotoxic chemotherapy and therefore whether to consider Immunotherapy.

5. Conclusion

In summary, multi-omic analysis and immune profiling reveal distinct subtypes of human angiosarcoma. In the future, molecular and immunological deciphering of angiosarcomas may open up avenues for precision medicine to help patients to improve the recognition of the tumor, to avoid potential misdiagnosis and gain better therapeutic strategies for well-established survival benefit.

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Financial Disclosure

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Conflict of Interest

The authors declare that there is no conflict of interest relevant to this article.

Informed Consent

Written informed consent was obtained from the patient's family for publication of this case report.

Author Contributions

Xin Ran and Dan Wang: study design, data collection, statistical analysis, data interpretation, manuscript preparation, and literature search; Xin Ran drafted the original manuscript. Qingshu Li, M. A., MA. Sc. performed the autopsy and described the histopathological findings. Youlin Deng and Qingshu Li, M.A., MA. Sc. are the corresponding authors. All authors reviewed and revised the manuscript draft and approved the final version for submission.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Abbreviations

EAS: epithelioid angiosarcoma;
AS: angiosarcoma;
CNKI: China Science and Technology Journal Database;
CD31: platelet endothelial cell adhesion molecule;
CD34: Cluster of differentiation 34;
CE-MRI: contrast-enhanced magnetic resonance imagining;
MDT: following multidisciplinary team;
FVIII: Factor VIII;
IHC: immunohistochemistry;
H&E: hematoxylin-eosin;
ERG: ETS-related gene;
CK: cytokeratin;
FLI-1: friend leukemia integration 1 transcription factor;
Ki-67: Ki-67 antigen;
HCG: human chorionic gonadotropin;
ER: estrogen receptor;
PR: progesterone receptor;
P63: tumor protein 63;
P16: cyclin-dependent kinase inhibitor 2;
D2-40: podoplanin;
CEA: carcinoembryonic antigen;
EMA: epithelial membrane antigen;
WT-1: Wilms tumor protein 1;
GATA-3: GATA binding protein 3;
Napsin A: napthalene aspartic protease A;
PAX-8: paired box gene 8;
HNF1β: hepatocyte nuclear factor 1-beta;
P504S: α-Methylacyl-CoA racemase;
MUC4: Mucin 4;
TIWI: T1-weighted imaging;
T2WI: T2-weighted imaging;
TAH, total abdominal hysterectomy;
BSO, bilateral salpingo-oophorectomy;
RSO, right salpingo-oophorectomy;

DOD, dead of disease;
CT, chemotherapy;
RT, radiotherapy;
NC, neoadjuvant chemotherapy;
ANED, live with no evidence of disease;
NA, not available/reported.

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