

## CASE REPORT

## Vaginal epithelioid angiosarcoma: a rare case

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### Abstract

Epithelioid angiosarcoma of the vagina is a rare variant, easily misdiagnosed as other epithelial neoplasms. On Hematoxylin–Eosin-stained sections, the pathologist encounters sheets of large, mildly to moderately pleomorphic epithelioid cells, with abundant eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli. We report the case of a 22-year-old woman initially diagnosed with condiloma-like tumor of the left vaginal wall, which turned out positive at immunostaining for epithelioid angiosarcoma. In her case, after the failure of chemotherapy in controlling the relapse of the disease, the only treatment option was radical hysterectomy with bilateral salpingo-oophorectomy.

**Keywords:** rare malignancy, vagina, epithelioid, angiosarcoma.

### ✉ Introduction

Vaginal epithelioid angiosarcoma is an extremely rare type of cancer, which can be easily misdiagnosed considering the much higher frequency of epithelial neoplasms in this particular site [1]. Most cases of epithelioid angiosarcoma are soft tissue angiosarcomas, with a minority falling into the visceral and cutaneous categories. Epithelioid angiosarcoma has a male predilection and, although isolated pediatric cases have been reported, they generally occur in adult life, with the highest incidence in the seventh decade [2, 3]. Endothelial malignancies are derived from mesenchymal cells, which undergo blood vessel and/or lymphatic endothelial differentiation, composed of large epithelioid cells arranged in solid sheets. Conventional angiosarcomas may show a focal epithelioid appearance, but a true epithelioid angiosarcoma is almost exclusively composed of epithelioid cells. Minimal vasoformative differentiation is observed [4]. Clinical suspicion and prompt diagnosis are essential for successful multimodal therapy. Initial surgical resection with adjuvant chemotherapy provides survival advantage. A delay in the diagnosis of angiosarcoma can affect the survival rate. Because of its rarity, no definite treatment could be suggested [5, 6]. Pathological diagnosis was obtained and multiple prognostic factors were evaluated for the survival rate. Moreover, their rarity and histopathological diversity may also contribute to the lack of consensus on risk factors for poor outcome and optimal treatment [4–8]. Histologically, the tumors were characterized by sheets of large polygonal cells with copious cytoplasm and centrally or slightly eccentrically placed vesicular nuclei. Nucleoli were usually present and mitotic activity was generally brisk. Additional aspects were geographic-

type tumor necrosis, mixed inflammatory infiltrates, and fibrosclerotic changes of the ground substance. In some cases, the observations suggested a vascular neoplasm included architectural (patent spaces containing red cells with papillary projections or angiomatoid spaces) and/or cytological findings (cytoplasmic vacuolation, in transcellular red blood cells). The staining quality of the cytoplasm ranged from basophilic to slightly eosinophilic [9–11]. Therapeutic options include surgery, radiotherapy and chemotherapy, singly or in association. The small number of reported cases up to date precludes determination of the optimum treatment regimen at this stage, although where possible, wide excision is recommended. The need for adjuvant therapy is determined on an individual basis [7, 9, 11].

We report the case of a 22-year-old woman, two times diagnosed with a benign condition, but whose clinical evolution suggested a more aggressive histological type, confirmed by positive immunostaining markers as vaginal epithelioid angiosarcoma.

### ✉ Case presentation

In our case, a gynecological examination requested for persistent pelvic pain during the past two months evidenced on speculum exam a 2 cm purple plane lesion situated in the upper third segment of the left vaginal wall. Vaginal tact revealed a retractile indurated vaginal wall at the lesion site. Her past medical history showed nothing remarkable. The biopsy of the excised vaginal tumor showed a plane condiloma-like lesion, emphasizing the importance of a second opinion due to the presence of adenocarcinoma-like structures embedded in the vaginal submucosa. The immunohistochemical tests did not support

the carcinomatous origin of the atypical cells, suggesting another type of tumor with more aggressive potential – angiosarcoma.

The patient refused any type of further diagnosis procedure, returning after six months accusing severe abdominal pain, with normal biological, cerebral and thoracic computed tomography (CT) findings. The magnetic resonance imaging (MRI) demonstrated a small left ovarian cyst and a left paravaginal nodule.

The surgical exploration of the peritoneal cavity revealed an extensive adhesional process involving the uterus, the left adnexa, the anterior wall of the rectum and the Douglas pouch peritoneum. Two endometriosis-like nodules, measuring up to 1.5 cm each were found, located on the left vaginal fornix and left parametrial tissue, with marked dilatation of the left ureter. The surgical intervention was limited to adherence dissection and nodules excision, followed by a ureteral pigtail stent insertion on the left side.

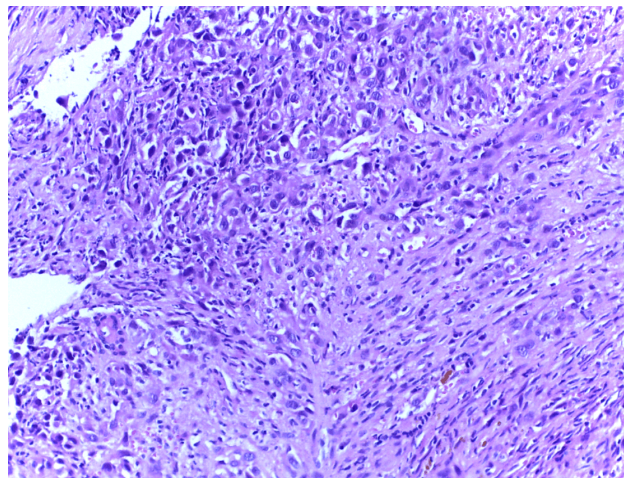
The tumor biopsy was processed automatically and embedded in paraffin block. On microscopic evaluation, the main tumor cellular type was represented by rounded large cells with reduced amphophilic cytoplasm and large polymorphous hyperchromatic nuclei layering small pseudovascular spaces. Among these pseudovessels were disposed large spindle cells crowded in irregular fascicles (Figures 1 and 2). The tumor cells realized a scarcely small network occupied by erythrocytes (Figure 3). Isolated mitotic cells (mostly spindle cells) were observed. Necrosis was absent. Inflammatory infiltrates were present in the superficial area of the tumor.

The immunohistochemistry (IHC) tests were performed on 3 µm 10% formalin-fixed paraffin-embedded samples using an indirect bistadial technique performed with a polymer based detection system (Max Polymer Detection System – Leica Ref. RE7280-k). The tissue samples were spread on poly-L-lysine-coated slides, immersed in three changes of xylene and rehydrated using series of graded alcohols. Antigen retrieval was performed using a microwave oven. In each section, endogenous peroxidase was blocked by 20 minutes incubation in 3% hydrogen peroxide. The primary antibody incubation was performed at room

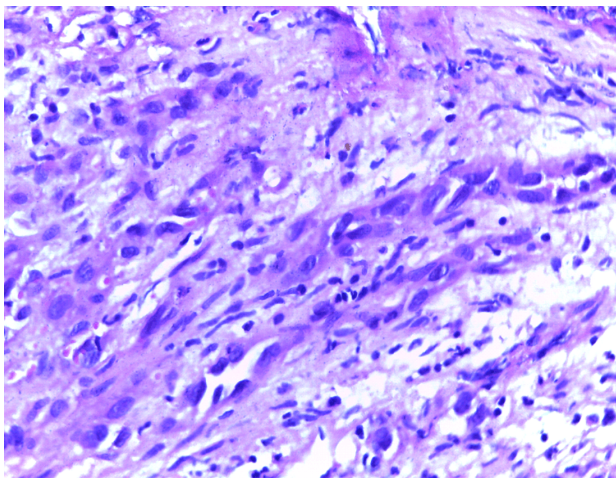
temperature for one hour for: CD31 (clone JC70A, 1:100 dilution, DAKO, Carpinteria, CA, USA), CD34 (clone QBEnd/10, 1:100 dilution, Leica, UK), vimentin (clone V9, 1:100 dilution, DAKO),  $\alpha$ -smooth muscle actin (1:100 dilution, DAKO) and Ki67 (clone MIB-1, 1:100 dilution, DAKO). The Max Polymer Detection System (Leica Ref. RE7280-k) was then applied for 30 minutes. Finally, the sections were incubated in 3,3'-Diaminobenzidine for 5 minutes, counterstained with Mayer's Hematoxylin and mounted. The slides were examined and photographed using a Leica DM750 microscope. Negative controls were obtained using a non-immune serum during the primary antibody incubation. As a positive control, a soft tissue sample was used. The immunohistochemical stains revealed a strong and diffuse positivity for vimentin (Figure 4) and for CD31 (Figure 5), certifying the vascular nature of the tumor. However, other vascular markers such as CD34 that was positive in all mature vessels and only in isolated tumor cells (Figure 6) and actin, which stained mostly the muscle coats of the vessels (Figure 7) were evidenced. The proliferative activity of the tumor showed by Ki67 was reduced (~10% of the tumor cells) and was expressed mainly in the rounded cells (Figure 8).

The microscopic and immunohistochemical examination supported the diagnosis of vaginal epithelioid angiosarcoma. When facing this diagnose, the patient accepted and started chemotherapy with Paclitaxel and Cisplatin.

Although the initial response to adjuvant chemotherapy was promising, seven months later, after six cycles of chemotherapy, the clinical examination found a pelvic tumor, invasive into the left vaginal wall, showing a vegetant exophytic aspect on speculum examination. Magnetic resonance imaging with gadolinium-enhancing T2 showed a 2/1.5 cm heterogeneous left paravaginal nodule, surrounding the pelvic segment of the left ureter. The surgical management was radical abdominal hysterectomy with excision of the upper two thirds of the vagina, bilateral salpingo-oophorectomy and reimplantation of the ureter using the psoas hitch technique. The patient did not develop any postoperative complications and underwent three more cycles of chemotherapy.

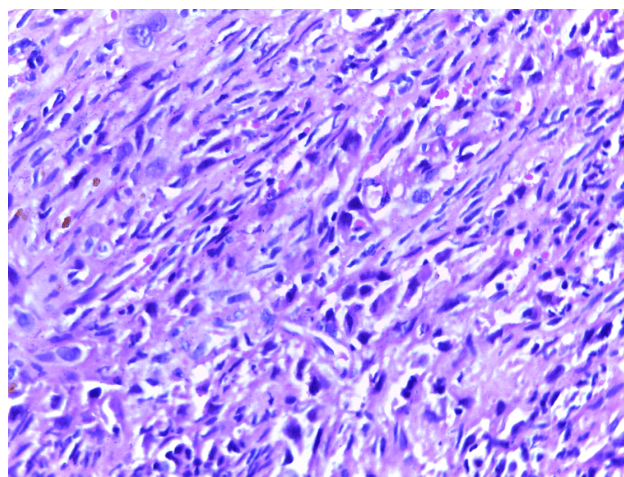


**Figure 1 – Tumor sample composed of spindle cells with fascicular disposition and rounded cells with hobnail appearance layering vascular spaces, with rare erythrocytes and hemosiderin deposits. Hematoxylin-Eosin (HE) staining, ×200.**

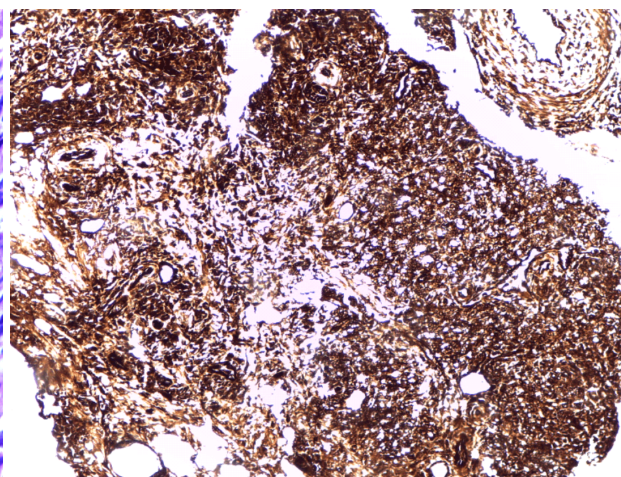


**Figure 2 – The tumor presents vascular spaces with rounded cells protruded into the lumina and presenting hobnail aspects. HE staining, ×400.**

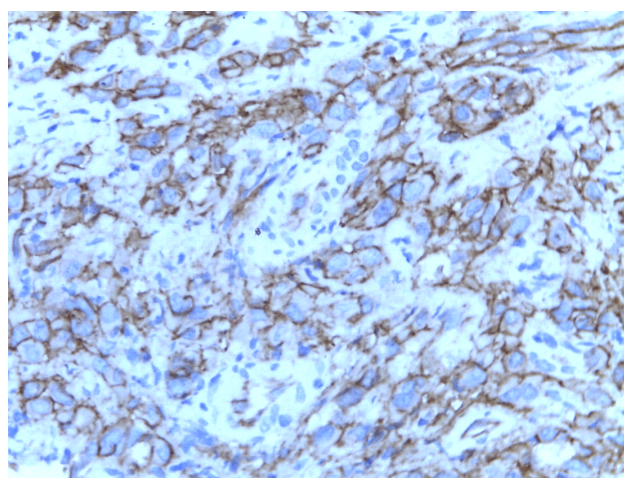




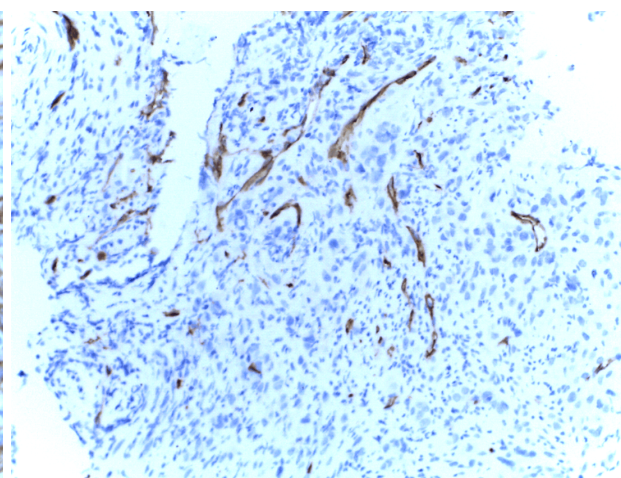
**Figure 3** – Intermingled spindle and round cells with hemosiderin deposits and erythrocytes in small pseudo-lumina. HE staining,  $\times 400$ .



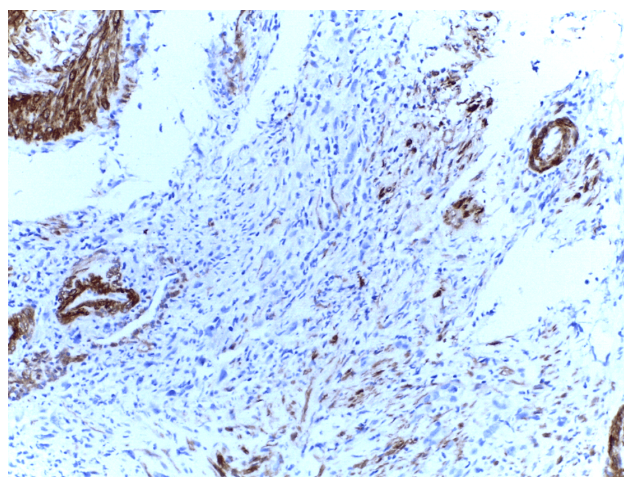
**Figure 4** – Immunohistochemical staining. All types of cells are positive for vimentin,  $\times 100$ .



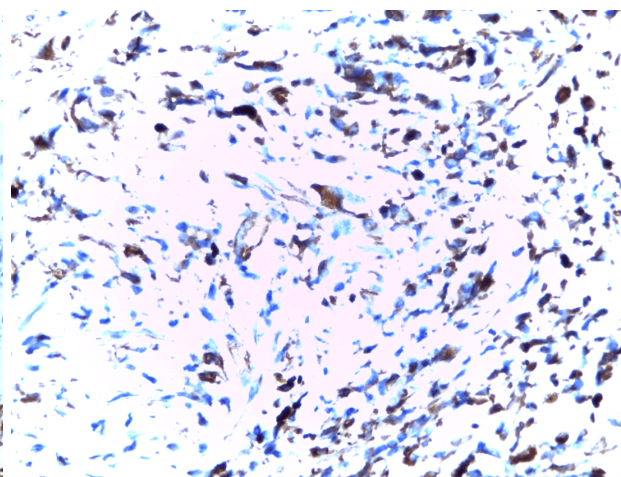
**Figure 5** – Immunohistochemical staining. All tumor cells strongly expressing CD31 in the cell membrane,  $\times 400$ .



**Figure 6** – Immunohistochemical staining. CD34 present in the normal small vessels and only in isolated tumor cells,  $\times 200$ .



**Figure 7** – Immunohistochemical staining.  $\alpha$ -Smooth muscle actin is positive in the muscular wall of small vessels and in rare spindle tumor cells,  $\times 200$ .



**Figure 8** – Ki67 immunostaining showing a low rate of proliferating cells,  $\times 400$ .

At the follow-up session, nine months later, the patient was found free of disease, with normal aspect of the kidneys and no signs of pelvic or vaginal tumor relapse on clinical examination, ultrasound (US) or MRI.

## Discussion

Angiosarcomas are rare malignant neoplasms of endothelial origin [2], representing less than 1% of sarcomas [4, 5–7]. Most angiosarcomas arise spontaneously without

recognized associated risk factors [5, 6], but there are described predisposing conditions such as: previous radiation therapy, chronic lymphedema, familial syndromes [5], exogenous toxins [7–9] or foreign bodies [4]. These vascular lesions can arise anywhere in the body [7], developing mostly in the skin of the head and neck [1], soft tissues and breast [1–4], and rarely involving the female genital tract [7, 9, 10]. A morphological subtype of angiosarcoma is the epithelioid angiosarcoma, in which the malignant endothelial cells have a predominantly or exclusively epithelioid appearance [2, 11].

Vaginal angiosarcoma is a very rare encounter [1, 5], the first case being reported in the medical literature in 1983 by Prempre *et al.* [5]; the epithelioid subtype is even rarer, the first case being reported in 1998 by McAdam *et al.* [4], while in 2014 Richer *et al.* reported the third case of this kind [1].

When a less experienced pathologist faces an epithelioid lesion of the vagina, angiosarcoma is not the first pathological diagnosis that comes to mind, because angiosarcomas have a propensity for a varied histological appearance that initially do not suggest a vascular neoplasm [7, 11–17].

Vaginal epithelioid angiosarcoma can easily be mistaken for squamous cell carcinoma (especially if vascular features are subtle) or metastatic epithelial tumors [1, 4, 6]. Endothelial malignancies are derived from mesenchymal cells, which undergo blood vessel and/or lymphatic endothelial differentiation; epithelioid angiosarcomas follow either or both (vascular and lymphatic) endothelial cell lines [2, 18].

The microscopic appearance of the tumor is the first to draw attention to an experienced pathologist about the vascular and malignant type of the investigated tumor: mildly to large pleomorphic epithelioid cells arranged in sheets, islands or cords; the cells are filled with abundant eosinophilic cytoplasm, showing a vesicular appearance of the nucleus due to the peripheral situation of the chromatin contrasting with the large nucleoli [2]. The distinction from an epithelial tumor is made by the presence of cleft-like areas, intracytoplasmic lumina that often contain erythrocytes [2–4]. Focal areas of irregularly anastomosing vessel formation are usually present [2, 18, 19]. The positive immunostain for Ki67 sustains the malignant type of the tumor, while the positive immunohistochemical tests for markers widely expressed in angiosarcomas (such as CD31, CD34, factor VIII and vimentin) and the immunonegative results for cytokeratin 34AE12, S100, myogenin, desmin, EMA, human herpesvirus type 8 (HHV-8), calretinin, WT-1, Melan-A, CD34 make it easy to differentiate this pathology from melanomas, carcinomas, Kaposi sarcomas, malignant mesotheliomas, lymphomas or malignant peripheral nerve sheath tumors [2, 7, 13–19].

In rare cases when the diagnosis of epithelioid angiosarcoma is not clearly elucidated by routine HE staining in correlation with immunohistochemical techniques, electron microscopy can help confirm the endothelial differentiation. Ultrastructurally, large round to oval cells (endothelial cells), adjacent to smaller polygonal to spindle cells (pericytes) are seen. Red blood cells are seen in vascular canals formed by closely approximated,

circumferentially orientated endothelial cells [2, 13, 19–21].

The genetics of this malignancy is poorly understood, no specific genetic aberration being reported in primary angiosarcoma so far [4, 21–23].

Most cases of female genital angiosarcoma have an aggressive behavior, with a five-year survival of about 35% and a median survival of seven months [7, 23]. Unfortunately, no evidence-based treatment recommendations are available for specific angiosarcoma subtypes [7]. The main factor in determining survival in angiosarcomas is the accessibility of the tumor to complete surgical excision [4, 20–23]. Radical surgery with complete resection is considered as the main curative option. Wide resection margins are required because of the invasive and multifocal nature of angiosarcomas [4, 7, 10] and local control is improved with adjuvant radiotherapy with wide treatment fields [7]. There is no compelling evidence for adjuvant chemotherapy [7, 10, 20, 23], although there are some cases reported in the literature with good evolution following chemotherapy.

## Conclusions

Vaginal epithelioid angiosarcoma is a rare, aggressive and with poor prognosis vascular malignancy which can mimic multiple other epithelioid malignancies. Knowledge of its clinicopathological and immunohistochemical features is required for diagnosis and to avoid confusion with other tumors with epithelioid histomorphology. The use of a wide spectrum immunohistochemical panel involving several markers, including CD31, CD34, actin, vimentin, Ki67 is helpful. Furthermore, initial evaluation of HE-stained sections and appropriate immunostaining can usually provide a final diagnosis.

## Conflict of interests

The authors declare that there are no conflicts of interests.

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