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Primary angiosarcoma of the breast with metastasis to the ovary and axilla: an uncommon pattern of metastatic disease

(Angiosarcoma primario de mama con metástasis en ovario y axila: un patrón inusual de enfermedad metastásica)

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[CASO CLÍNICO]

Resumen (español)

El angiosarcoma primario de mama es una neoplasia infrecuente y agresiva con una etiología desconocida. Presentamos el caso de una mujer joven que inicialmente desarrolló un angiosarcoma primario de mama, y posteriormente un angiosarcoma de ovario y metástasis en la axila 20 meses después. Sólo han sido descritos unos pocos casos confirmados de angiosarcoma primario de mama que metastatice en el ovario. Sin embargo, los casos previos descritos tuvieron metástasis ovárica en la presentación o poco después del diagnóstico inicial. Este caso es infrecuente ya que las metástasis ocurrieron dentro de un intervalo próximo a los dos años desde el tratamiento del tumor primario. Discutimos este raro fenómeno y los posibles factores que contribuyen a la recurrencia.

Palabras clave (español)

Angiosarcoma, axila, mama, metástasis, ovario.

Abstract (english)

Primary angiosarcoma of the breast is an uncommon, aggressive neoplasm with an unknown etiology. In this paper, we present a case of a 28 year woman who initially developed primary angiosarcoma of the breast and ovary, followed twenty months later by metastasis to the axilla. Only a few cases of primary angiosarcomas of the breast have reported metastasis

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to the ovary. Of these cases, all had ovarian metastasis at presentation or shortly after initial diagnosis. This particular case is unusual, the metastases occurred two years following treatment of the primary tumor. This paper will address possible factors contributing to metastasis.

Keywords (english)

Angiosarcoma, axillae, breast, metastasis, ovary.

Introduction

Angiosarcomas (AS) are rare, usually aggressive soft tissue neoplasms which originate from endothelial cells. Primary breast AS (PBAS), although accounting for less than 0.1% of all malignancies, are one of the most common sarcomas. Risk factors include: trauma radiation; lymphoedema; breast implants; xeroderma pigmentosum; neurofibromatosis; and vinyl chloride. Secondary breast AS appears in older women, either following radiotherapy for breast cancer or due to chronic lymphoedema. The average time interval after radiotherapy is 10.5 years (1). The development of breast conservation therapy has caused an increasing incidence of secondary AS after adjuvant radiotherapy. PBAS is usually seen in women under 40 who have no previous history of malignancy or other known risk factors. Between 6% and 12% of cases appear during pregnancy or shortly afterwards, suggesting hormonal involvement.

Primary and secondary breast AS have similar malignant behaviour and both carry a poor prognosis. PBAS generally arise within the parenchyma. PBAS is considered histologically and clinically distinct from radiation-induced breast AS. Secondary AS differ from primary AS in their pathogenesis by showing high level amplifications of: MYC proto-oncogene; fms-related tyrosine kinase 4 (FLT4); and vascular endothelial growth factor receptor 3 (VEGFR3) (2,3). This vascular endothelial growth factor stimulates cellular responses by binding to tyrosine kinase receptors (VEGFRs) on cell surfaces, causing them to dimerize and activate through transphosphorylation (4). Hypoxia inducible factor 1 (HIF-1) is a heterodimeric transcription factor; it is regulated by changes in cellular oxygen concentration, growth factors, oncogenic activation, or loss of tumour suppressor function. Over expression of HIF-1α can lead to the production of various hypoxia inducible mRNAs encoding VEGF, platelet-derived growth factor B, erythropoietin, Galectin-3, and transforming growth factor alpha (5). In addition, the over expression leads to the production of *Wilms* tumour protein WT-1, a protein capable of activating vascular gene transcription (6).

PBAS initially presents as a painless, smooth, deep, mobile mass greater than 4 cm. 17% of cases include red discoloration and skin involvement (bluish overlying skin discoloration). In contrast, secondary cases present as ill-defined or multifocal cutaneous patches or nodules. PBAS shows a poorer outcome than other histological types of primary breast sarcomas.

Mammograms and ultrasounds do not have pathognomonic characteristics in angiosarcomas. Diagnosing angiosarcomas prior to surgery, using fine needle aspiration (FNA) or needle core biopsy (NCB) can be difficult and these procedures often cause excessive bleeding. Chen *et al.* reported a percutaneous biopsy false-negative rate of 37% (7). Surgical resection and microscopic examination of a sample of the tumour are often necessary to confirm a diagnosis. Immunohistochemical examination (factor VIII and CD31 positivity) will confirm the vascular nature of the tumour (8).

Previous studies have reported a varied five year overall survival rate (40% to 85%) (9). Certain factors are commonly accepted as affecting the survival of patients with soft tissue sarcomas. These include pathologic grade, tumour size at diagnosis and margin status, of which pathologic grade is the most important factor. However, it is not clear that these are prognostic factors in breast AS.

Total mastectomy is the preferred surgical treatment (10). Chemotherapy and radiation therapy may be used as adjuvant treatment.

Half of AS are associated with metastatic disease, with the metastasis occurring either at presentation or developing subsequently during the course of the disease. The lungs and the liver are the most common metastatic sites, followed by lymph nodes, bone marrow and, less frequently, the ovaries, kidneys, omentum, the adrenal gland, the stomach, the pancreas, peritoneum, the oesophagus and the skin.

This case report follows a 28 year old woman who had previously undergone a total mastectomy

due to a high grade PBAS. 20 months later she developed AS of the ovary and metastasis to the axilla. This is exceptionally rare. In previous studies, 100% of cases reporting metastasis documented it occurring within the first year of diagnosis of a high grade PBAS (11).

Case report

A 28 year old woman was admitted to the gynecological emergency department complaining of abdominal pain. The patient's past medical history included a radical right mastectomy 20 months previously, due to a poorly differentiated PBAS (T2aN0M0 G3), fibromyalgia and nuligesta. The patient was a smoker with a ten pack year history. Allergies included quinolones. This patient also had a relevant family history. A paternal aunt was diagnosed with breast cancer at the age of 50 and her maternal grandmother suffered from Hodgkin´s Lymphoma.

The PBAS was a rapidly growing lesion measuring 10 cm at diagnosis. After surgery it remained 2 cm from the nearest margin resection. The Ki67 protein had a value of 10%. She had an immediate breast reconstruction, using an expander implant, and six subsequent cycles of adjuvant chemotherapy. The chemotherapy regimen consisted of ifosfamide and epirubicin with granulocyte colony stimulating factor (G-CSF) support; it ended 15 months later. It was followed by adjuvant breast radiotherapy with a regimen of 50 Gy. The breast implant placement was carried out 14 months later.

The patient was hemodynamically stable on admission. On examination the patient had positive rebound tenderness in the right iliac fossa and hypogastrium. The Blumberg sign was positive and there were positive bowel sounds.

An abdominal ultrasound reported a distended pouch of Douglas occupied by echogenic material; it might have corresponded to hematic material, suggesting the possibility of a ruptured corpus luteum and a heterogeneous mass in the left ovary. A discrete amount of free fluid was detected. No signs of an appendicitis were detected.

A transvaginal ultrasound was performed and a solid vascularized neoplasm was found in the left ovary. A thoracic-abdominal-pelvic computed tomography (CT) with contrast revealed lymphadenopathy with punctuate calcifications in the right axillary region, the largest having a maximum diameter of 21mm. There were no pulmonary lesions, no hilar or mediastinal lymphadenopathy and no evidence of pleural effusion. The CT also revealed a left ovarian mass. The mass was retrouterine in location with high density areas of heterogeneous tissue. The mass measured approximately 68x41x69 mm in its transverse, sagittal and anteroposterior diameters respectively. Small amounts of free peritoneal fluid were present. There was no evidence of pelvic, retroperitoneal or mesenteric lymph nodes involvement, no focal lesions in the liver nor peritoneal implants. No bone lesions were seen. A pelvic nuclear magnetic resonance (NMR) with contrast was performed, revealing a solid tumour with a left parauterine-retrouterine location measuring 85x38x62 mm in its transverse, sagittal and anteroposterior diameters respectively. It presented a heterogeneous signal intensity with multiple T1-hyperintense areas, compatible with areas of bleeding. After a contrast medium was administrated, hyperintense necrotic areas were detected. The findings described are most compatible with metastatic ovarian neoplasm.

The full blood count and coagulation screen were normal. Due to the finding of an ovarian neoplasm and the personal history of breast angiosarcoma, it was decided to perform an exploratory laparotomy. An intraoperative biopsy of the left adnexa revealed a malignant mesenchymal tumour. Consequently, stage surgery was completed with a total hysterectomy, right adnexectomy, appendectomy, inframesocolic omentectomy and pelvic and paraaortic lymphadenectomy.

The histological results were as follows: absence of neoplastic cells in the ascitic fluid and a diagnosis of angiosarcoma in the left ovary. The immunohistochemical study was positive for CD34 and CD31, negative for monoclonal antibody D2-40 and pan cytokeratin CK, with a high Ki67 (> 60%). It was an angiosarcoma with different degrees of differentiation (figure 1). It had more than 20 mitoses/10 HPF (High Power Field), very few foci of tumour necrosis and abundant lakes of hematic material.

This particular tumour did not affect the ovarian capsule. No tubal, appendix, contralateral ovary, omentum or pelvic or paraaortic node involvement was identified. It was therefore classed as a stage Ia ovarian angiosarcoma.

Treatment by paclitaxel chemotherapy (90mg/m^2, 144mg weekly) was recommended at the weekly medical oncologist consultation. Examination showed a 4 cm hard and painful right axillary mass. A right axillary ultrasound revealed a 2.4x2.3cm solid, hypoechoic and lobulated mass, compatible with tumour recurrence. Three adjacent lymphadenopathies were identified whose sizes were

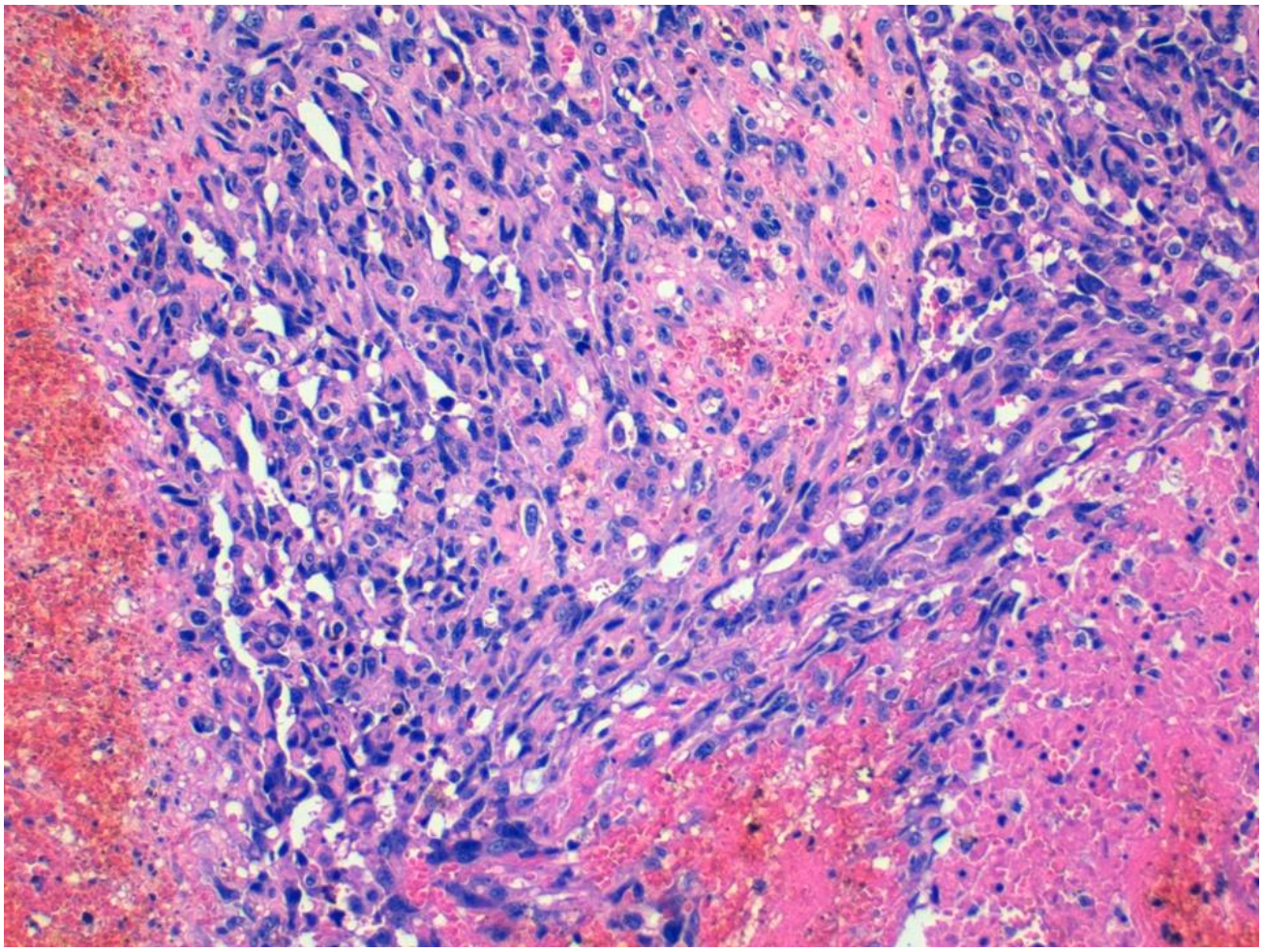

Figure 1. Angiosarcoma with low-grade irregular anastomosing vascular channels and solid areas (high grade) consisting of fusiform or atypical epithelioid cells with hyperchromatic nuclei (Hematoxylin-Eosine H&E staining, magnification 20x2).

1.2 cm, 1.3 cm and 1.5 cm. An NCB was performed and the histological findings were tumour necrosis and a positive immunohistochemical staining with markers CD34, CD31, FLI1 (figures 2 and 3) and ERG. An angiosarcoma with a high rate of proliferation (high levels of Ki-67) was the diagnosis.

Following the third cycle of chemotherapy with paclitaxel, the axillary mass measured approximately 2 cm. The patient was suffering from headaches. A neurological examination was performed and the findings were normal. A cranial CT with contrast revealed no evidence of metastatic disease. It was decided to continue with three more cycles of paclitaxel. A decreased axillary lymphadenopathy measuring 1.5x0.8x1.7 cm was identified in a right axillary ultrasound. A smaller lymphadenopathy with a measurement of 1.5x0.6x0.7 cm, similar to that in the previous study was also diagnosed. A thoracic-abdominal-pelvic CT with contrast was requested for reassessment. It revealed a hypervascular nodule in the 4th left hepatic lobe segment, remaining stable with a decreased axillary adenopathy. On the fourth cycle of chemotherapy a clinical progression of the axillary lymph node measuring 4cm was diagnosed. Results of thoracic-abdominal-pelvic CT with contrast was similar to the previous one, except for an increase from 1.0 cm to 1.8 cm in the size of the right axillary adenopathy in the short axis in the axial plane. The patient was referred to the Breast Cancer Unit.

Examination in the Breast Cancer Unit revealed a 4 cm right axillary nodule attached the pectoralis major muscle. A necrotic hypoechoic adenopathy with irregular and lobulated contours was identified in a right axillary ultrasound; it was smaller than in the previous study, measuring 1.5x0.8x1.7 cm in its transverse, craniocaudal and anteroposterior

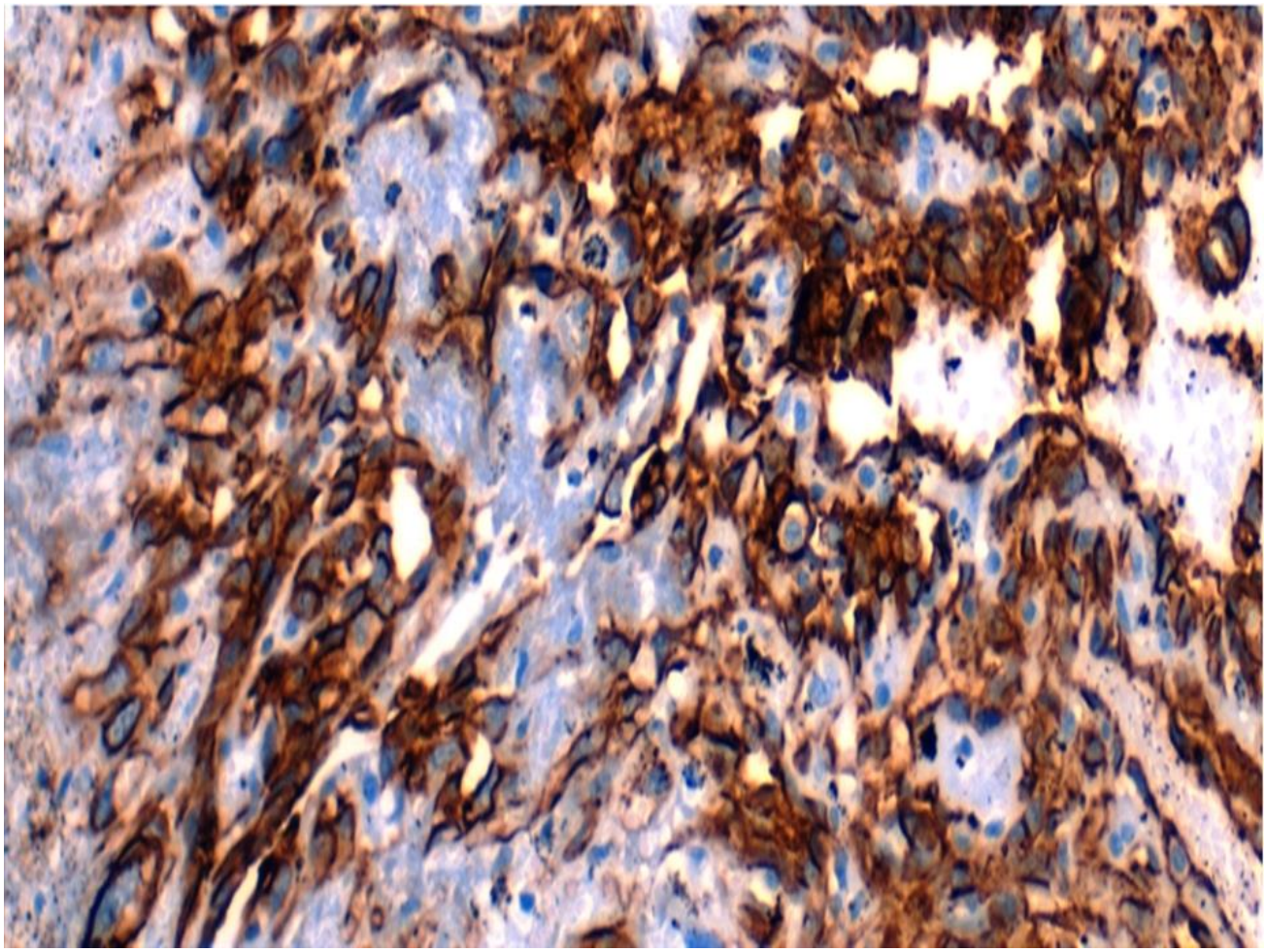

Figure 2. Immunohistochemical staining with endothelial marker CD31. This technique stains the cytoplasm and membrane of endothelial cells supporting the diagnosis of angiosarcoma (CD31 staining, magnification 20x).

axes. These findings were suggestive of tumour recurrence. A further lower adenopathy, located next to the side edge of the breast prosthesis, was identified; it was of similar appearance to that in the previous study, with a size of 1.5x0.6x1.3 cm. An MRN was requested to assess infiltration of the pectoral region. It revealed intracapsular rupture of the right breast, a retropectoral prosthesis in the upper outer quadrant and a large right axillary adenopathic mass of 6x3 cm.

Due to these findings an axillary clearance and breast prosthesis replacement were performed. The histopathology of axillary dissection identified metastatic angiosarcoma with several tumour nodules, the largest measuring 3 cm; some tumours were found very close to the resection margins.

The case was presented to the Breast Cancer Committee. Here it was decided not to extend surgery, in accordance with the evaluation of the Sarcomas Committee of the referral hospital. Currently the patient is being monitored by the Medical Oncology Department and has an appointment for a CT and reassessment.

Discussion

PBAS is a rare tumour derived from endothelial cells. It is usually seen in young women of child bearing age who have no previous cancer history or other known risk factors.

It is usually diagnosed as a painless smooth deep mass greater than 4 cm, with a rapid growth. In this case the tumour measured 10cm at diagnosis. Large masses have previously been reported as leading to platelet sequestration and disseminated

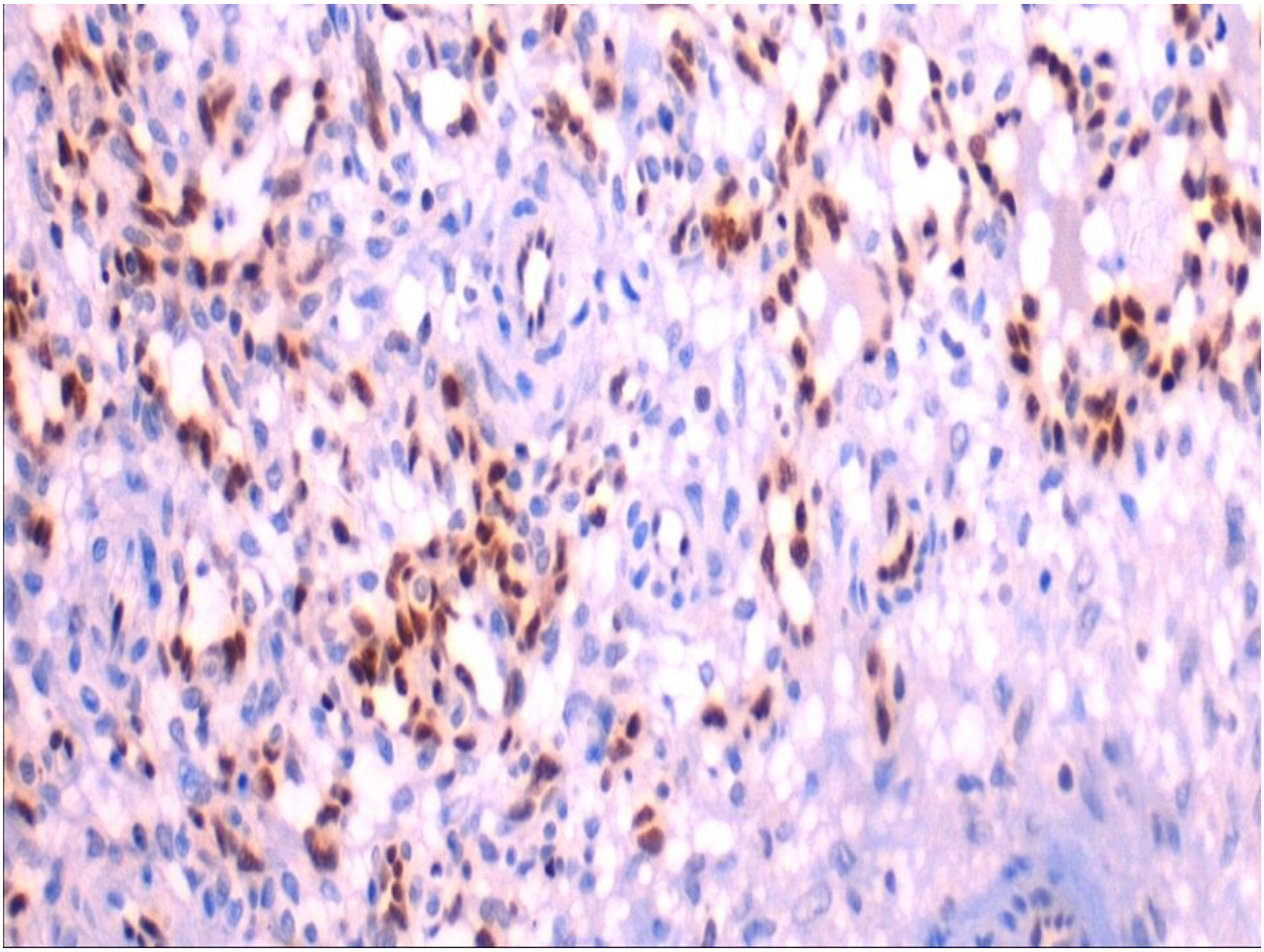

Figure 3. Immunohistochemical nuclear staining FLI1 shows endothelial cell differentiation (FLI1 staining, magnification 20x)

intravascular coagulation and hemorrhagic manifestations of Kasabach Merritt syndrome. Infrequently the patient presents with nipple retraction, discharge or axillary lympadenopathy.

On mammograms, angiosarcoma is identified as a mass without spiculation, microcalcification or lympadenopathies. In a review of radiologic findings with angiosarcomas, Liberman *et al.* (12) established that echotexture of these lesions is highly variable. They conclude that breast X-rays may appear completely normal in about 33% of cases but patients with higher grade lesions have abnormal mammograms with a higher probability (12). Multiple studies have shown the ability of NMR to identify patterns of malignancy in angiosarcoma (low signal intensity on T1-weighted images, hyperintensity on T2 images and a rapid initial intense phase followed by washout MRI) (13).

In histological and immunohistochemical diagnosis, the marker CD31 is considered to be the most sensitive and the most specific indicator of angiogenic proliferation. The lesions will also stain positive for the vascular markers factor VIII, FLI1 and for CD34 (8). The immunohistochemical study in this case was positive for CD31 and CD34, negative for D2-40 and pan CK, with a high Ki67 (> 60%), a proliferation marker. Data indicating levels of WT-1 were unavailable. The presence of progesterone or oestrogen receptors were not confirmed. Many authors have reported primary angiosarcomas to be well differentiated, with histological features sometimes mimicking benign lesions.

Pathologically, these tumours are subdivided into three groups according to the classification proposed by Donnell *et al.* (14). The groups are graded as follows. Grade 1 tumours are well differentiated and contain open anastomosing vascular channels that

proliferate within dermis, subcutaneous or breast tissue. These channels contain a single layer of endothelial cells, which dissect through the stroma, causing distortion but little destruction of the preexisting lobules and ducts. Grade 2 (intermediate grade) angiosarcomas differ from low-grade tumours by containing additional cellular foci. These can form of papillary formations or solid and spindle cell proliferation. The greater part of the tumour, however, is still composed of low-grade histology. Slightly increased mitotic activity is observed. In grade 3 angiosarcoma endothelial tufting and papillary formations are prominent. Conspicuous solid and spindle cell areas, without vascular formations, are also present. Mitoses may be brisk, especially in more cellular areas. Areas of hemorrhage, known as "blood lakes", and necrosis can also be seen.

The correlation between tumour size and prognosis is controversial. Sher *et al* (15), found no correlation between the size of the primary tumour and the risks of recurrence or death. On the contrary, Zelek *et al* (16), Depla *et al* (17) and others underlined an association between tumour size and disease-free survival. Five years after initial treatment the estimated probability of disease-free survival is 76% for patients with Grade 1 tumours; compared to 15% for patients with Grade 3 tumours. There is no precise correlation, however (18). Tumours smaller than 5 cm are usually associated with a better prognosis (15).

In clinical practice, large tumour size (> 5 cm), high histologic grade, vascular invasion and positive margins were generally accepted as factors that predicted high recurrence and poorer survival rates. In this case the tumour was poorly differentiated (Grade 3). It measured more than 5 cm at diagnosis but later metastasized to the ovary and had an axillary recurrence 20 months after the first diagnosis.

Radical surgical en bloc resection with negative margins (R0) is the primary therapy for a potentially curable localised disease (17).

Since hematogenous dissemination is very common, axillary node dissection is not indicated (15). Due to its infrequency, there are no randomised controlled trials comparing breast conserving approaches with mastectomy. Breast conserving therapy has been used but it is only recommended for small lesions of Grade 1 where there is an excellent chance of achieving R0. Radical mastectomy with clear surgical treatment was appropriate in our case because it was a large poorly-differentiated tumour.

Adjuvant therapy is beneficial to patients with a high risk of recurrence. There is still debate in the literature regarding histologic grade as a prognostic factor and therefore for advising adjuvant therapy (14). The role of adjuvant chemotherapy is ill defined, because of the rarity of PBAS and the lack of prospective studies (15). Some studies suggest that treatment with anthracycline-based chemotherapy may improve both disease-free survival and overall survival. In a more recent study of 41 cases of metastatic angiosarcoma treated with taxane regimens, Hirata *et al* showed an improvement in overall survival rates (19). Our patient underwent four cycles of paclitaxel for metastatic angiosarcoma; it was stopped for axillary dissection.

In a report published by Sher *et al* (14), adjuvant chemotherapy using combinations of anthracycline–ifosfamide or gemcitabine–taxane did not reveal any improvement in disease-free survival. However, administration of chemotherapy at the time of recurrence resulted in a response rate of 48% (14). A metaanalysis of patients treated in a randomized controlled trial with doxorubicin, epirubicin and ifosfamide demonstrated longer disease-free survival and overall survival (20). This was the chemotherapy regimen used for PBAS in our case.

In the majority of cases where chemotherapy was used, most authors prescribe cyclophosphamide, anthracycline or an alkylating agent combined with a pyrimidine analogue. Some clinical trials demonstrated that doxorubicin-based regimens and paclitaxel are two of the most active agents (21).

A success rate of 84% was reported when the adjuvant treatment was combined with TNF-α and IFN-α. The results were variable, when using bevacizumab, an anti–vascular endothelial growth factor antibody. Currently two phase II clinical trials are investigating the use of bevacizumab in cases of sarcoma, including angiosarcoma.

Since there is a high likelihood of locoregional recurrence, radiation therapy is proposed after a total mastectomy. It has been suggested that radiation therapy may improve the outcome for patients following surgical resection. Especially for patients with microscopically positive margins (10, 15). Despite surgical margins after a radical mastectomy and adjuvant breast radiotherapy, our patient had an axillary recurrence 20 months later, revealing the malignant potential of this tumour.

Half of angiosarcomas are associated with metastatic disease, either at presentation or at a subsequent point in the disease. Several case series have shown that these tumours most often metastasize to the liver, lungs or bones. Of the verifiable reports of ovarian metastases, all were found at postmortem as widely disseminated.

To our knowledge, there have been only four confirmed previous cases of PBAS metastasizing predominantly to the ovary (22). Inoperable, locally advanced or metastatic angiosarcoma is treated by cytotoxic chemotherapy. Recent investigations have looked at aberrant molecular or gene changes in PBAS. These results may offer hope for a specific target therapy in the future (23, 24).

Conflict of interest

The study has been approved by a research ethics committee and there are no conflicts of interest to declare.

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