

## Primary breast angiosarcoma: Prognostic and therapeutic approach

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**Abstract: Background:** Primary breast angiosarcoma is a rare disease with an aggressive pattern and poor prognosis.

**Methods:** We retrospectively reviewed clinical, pathological and therapeutic data of 10 cases of primary breast angiosarcoma diagnosed pathologically in Salah Azaïez National Institute of Cancerology between 1977 and 2007.

**Results:** Median age was 40 years (ranged 20-54 years). The average tumor size was 5.5 cm (ranged 0.5-14 cm). Immunohistochemical staining on paraffin sections was performed in all cases to confirm the diagnosis. Radical mastectomy was performed in 70% of cases and 30% of patients underwent conservative surgery. Axillary lymph node dissection was performed in four cases. Follow-up ranged from 4 months to 13 years. One patient has been lost of view since the diagnosis. Four patients had no evolutive disease (NED) after 42, 60, 108 and 156 months. Two patients developed bone metastases (lumbar rachis) after 30 months and 60 months of evolution managed by chemotherapy and radiotherapy. Lung metastases were observed in two cases after 9 and 15 months of remission.

**Conclusion:** Due to the rarity of this entity there is no standard therapeutic approach and surgery remains the only curative treatment. The prognosis of the primary breast AS is related to the tumor grade and complete resection.

**Key words:** angiosarcoma, breast cancer, therapy

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### I. Introduction

Breast angiosarcoma (AS) is a rare conjunctive tumor accounting for less than 0.05% of primary breast cancers(1). These tumors are divided into two entities: primary breast AS and cutaneous angiosarcoma or secondary breast AS occurring after radiation therapy. Primary breast AS is a high malignant tumor that affects electively young woman. The diagnosis is based on histological exam of biopsies or resections. It poses a serious differential diagnosis problem with benign angioma especially for low grade angiosarcoma. Because of the rarity of this tumor, therapeutic recommendations are difficult to establish currently. Basically, surgery is the core of treatment for curative intent. Both radiotherapy and chemotherapy have been used, but treatment indications have not been clearly defined.

### II. Methods and Materials

We analyzed the clinical and pathological features of 10 cases of primary angiosarcoma diagnosed pathologically in Salah Azaïez National Institute of Cancerology between 1977 and 2007. Histological diagnosis was made by core needle biopsy (CTNB) or excisional biopsy. Primary angiosarcoma was defined as de novo angiosarcoma without risk factors. We retrospectively reviewed clinical and pathological data: age, gender, tumor grade according WHO classification and size, type of surgery, surgical margin, adjuvant therapy and evolution. Disease-free survival (DFS) was defined from the date of diagnosis of angiosarcoma as any local, regional distant relapse or death from breast cancer. Overall survival times (OS) were measured in months from the date of initial diagnosis to death or last available follow-up

### III. Results

The average age was 40 years (ranged 20-54 years). There was no history of previous surgery, radiation, any hormone or drug. The main reason of consultation was a mammary node. Two patients presented a rapidly growing tumor with cutaneous ulcerations (fig(1)). The average consultation delay was 3 months and half.

The average tumor size was 5.5 cm (ranged 0.5-14 cm). Axillary lymph node was noted in only one patient. The mammography has been achieved in 7 patients showing a well limited opacity in 5 cases and an irregular opacity in two cases fig(2). Staging of breast AS revealed a bone metastasis in a patient.

Frozen sections concluded to an angiosarcoma in four cases and to a vascular tumor in two other cases. In the other four cases, the frozen section showed a carcinoma, an undifferentiated carcinoma, a sarcoma and one benign tumor.

In final histopathological examination, the diagnosis of low grade angiosarcoma was established in five cases. Four patients had an intermediate grade angiosarcoma with one case of subcutaneous AS of thoracic wall. Two lesions of angiosarcoma were associated in another case which was initially diagnosed with a multifocal tumor. One patient had a high grade AS. Immunohistochemical staining on paraffin sections was performed in all cases to confirm the diagnosis. CD34, CD31, Factor VIII, Pancytokeratin (AE1/AE3) and EMA was performed in all cases. Tumor cells were positive for CD34, CD31, factor VIII and negative for EMA, CK, indicating an endothelial origin Fig 3-4-5.

All the patients underwent surgical management with negative margin status. Breast conservative surgery was performed in three cases (30%): One case with a small lesion measuring 1.5cm followed by radiotherapy, in another case of 4 cm tumor while the patient refused radical surgery and in one case of patient with bone metastatic disease.

A total of seven patients underwent radical mastectomy (70% of our patients) which was followed by radiotherapy in two cases and both of radiotherapy and chemotherapy in one other case. Radical surgery was associated to axillary lymph node dissection in 4 cases without histological lymph node metastasis.

Follow-up ranged from 4 months to 13 years. One patient has been lost of view since the diagnosis. Four patients had no evolutive disease (NED) after 42, 60, 108 and 156 months. Two patients developed bone metastases (lumbar rachis) after 30 months and 60 months of evolution managed by chemotherapy and radiotherapy. Lung metastases were observed in two cases after 9 and 15 months of remission. The patient diagnosed with synchronic bone metastasis died within 4 months.

#### **IV. Discussion**

AS generally concerns young women in genital activity period(2). Most often, primary AS of the breast presents as a poorly defined mass characterized by a rapid growth with associated skin discoloration(3). Lymph nodes extension is exceptional.

There are no typical imaging features of breast angiosarcoma and AS could be diagnosed as a benign lesion particularly in youngest patients. Mammography shows a rounded or multilobular homogeneous opacity with regular limits. Ultrasound exam is rarely reported in literature and it shows either a mass, or, less often, diffuse mixed hypoechoic and hyperechoic areas in the breast (4). In our study the mammography was falsely reassuring in 4 of 6 cases showing a dense, rounded and well limited opacity. However, magnetic resonance imaging (MRI) is able to identify patterns of malignancy in AS showing a typical hyperintensity on T2 images and a rapid initial intense phase followed by washout(5). The diagnosis is often made by fine-needle aspiration or core needle biopsy. Immunohistochemistry is useful to identify the endothelial marker CD31, the indicator of vascular proliferation as well as other specific markers such as Factor VIII and FLI1(6).

There is no consensual treatment of primary breast AS and recommendations are extrapolated from soft tissue sarcoma studies (7). Surgery represents the only potential curative therapy and the extent remains controversial. Radical mastectomy is recommended by most authors, in order to reduce risk of recurrence(8). Some authors propose a large tumor resection for less than 3 cm well differentiated tumors, achieving negative margins of more than 1 cm(9). In our study we indicated radical treatment in six patients and four patients underwent breast conservative surgery. Nodal metastasis is not common in AS and the necessity for axillary nodal dissection (ALND) remains unclear except for axillary bulky tumors. Some studies undergoing lymph node dissection reported nodal involvement in less than 10% of patients(10). In our study ALND was performed in three cases and nodes were free from involvement.

For adjuvant treatment, some authors indicated adjuvant radiations to improve local control particularly for patients with microscopically positive margins. Sher et al. reported an improvement in recurrence free survival of patients receiving adjuvant radiation therapy compared with patients who did not receive radiotherapy(33% and 25% at 5 and 10 years respectively)(11). However Ming Ying and al, showed that there was no significant survival difference between surgery with radiation therapy and surgery alone (7). Even if some studies reported an improvement in DFS and in OS, standard medical regimens remain unclear because of the rarity of these tumors (11).

The median OS of primary breast AS is about 93 months with 5-year survival rates of 44.5% (7). The prognosis of the primary breast AS is related to the tumor grade defined by the mitotic index, the tumor size, and the resection margin status (6). Some authors proved that incomplete resection and high grade angiosarcoma are associated with both local relapses and mortality(12). The 5-year overall survival for grade 1 is 75% and 15%

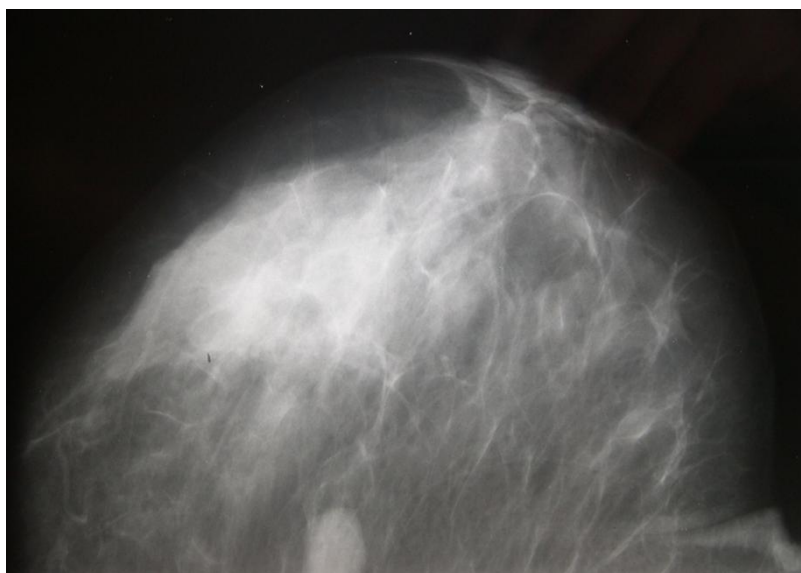
for grade 3 tumors(13). However, the correlation between the tumor size and survival remains debated. In our study the average of survival was 22 months.

#### **V. Conclusion**

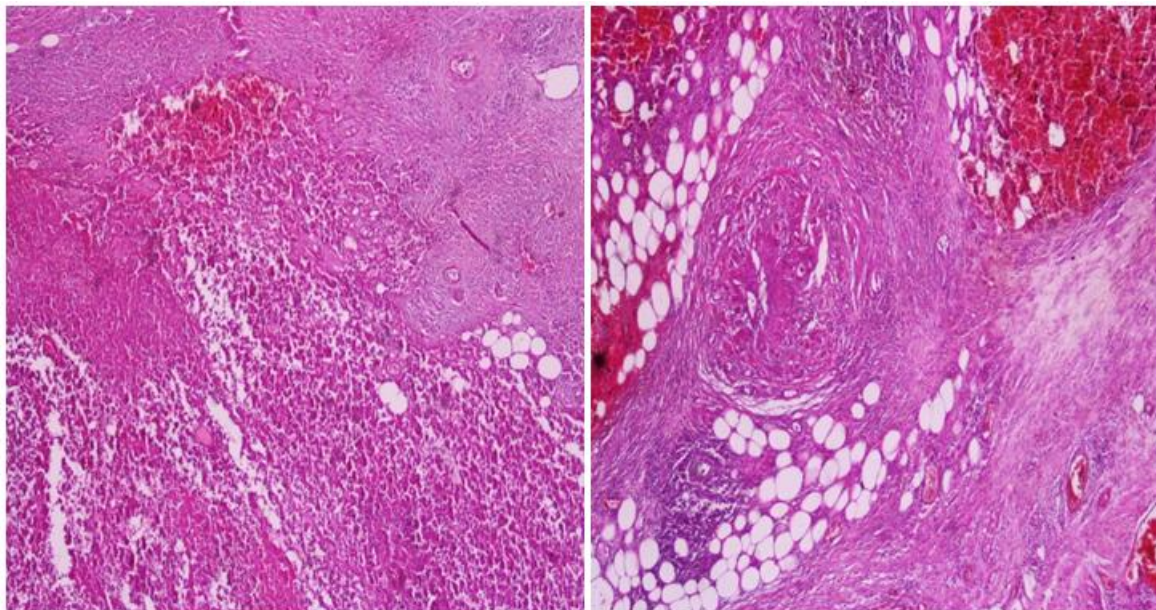
Primary breast angiosarcoma is a rare aggressive tumor. Due to the rarity of this entity there is no standard therapeutic approach and surgery remain the only curative treatment. Indication of radiation therapy and chemotherapy are debated. The prognosis of the primary breast AS is related to the tumor grade and complete resection.



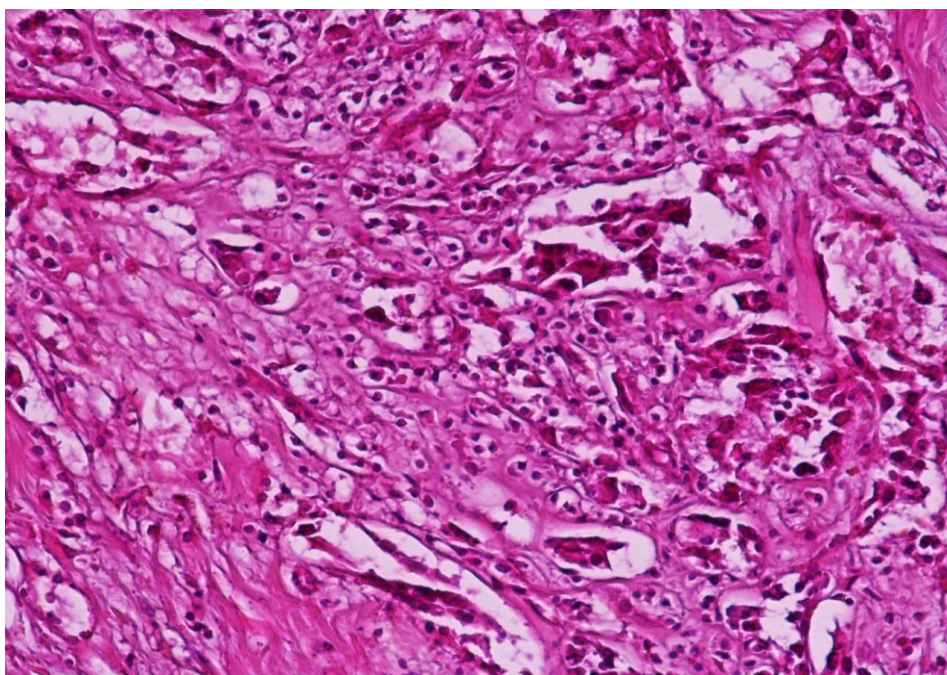
**Fig1.** Rapidly growing tumor with cutaneous ulcerations and area of skin purplish discoloration



**Fig 2:** Mammography showing an irregular opacity



**Fig3:** (HEX20) Histological section shows Kaposi like areas showing a hemorrhagic and necrotic area with extravagated red blood cells and fine capillary proliferation in a desmoplastic stroma.



**Fig4:** Sinusoidal capillaries lined by atypical endothelial cells with prominent nuclei

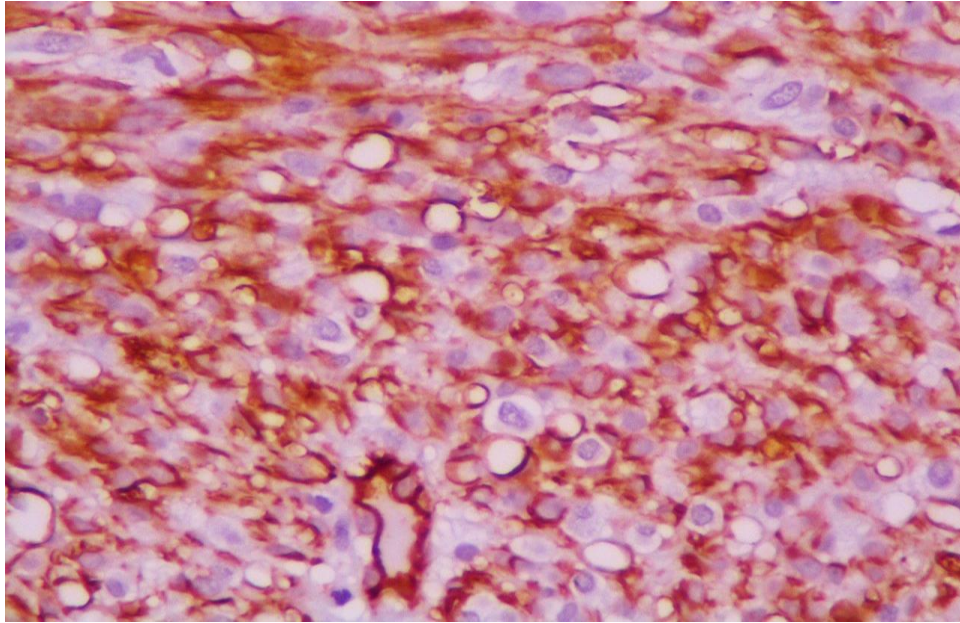


Fig 5: Sinusoidal capillaries showed an expression of the CD 34

Table 1: clinical, therapeutic and prognostic features of patients

Obs	Age (years)	Size (cm)	TNM	Mammography	Treatment	Extempo	Final exam	Evolution
1	32	4	T2N0M0	Well Limited opacity	Tumorectomy + RT	Sarcoma	AS meanly differentiated	108 months NED
2	54	4.5	T2N1M+	Irregular Opacity	Tumorectomy (2 tumors)	Undifferentiated carcinoma/sarcoma	AS meanly differentiated + subcutaneous AS of thoracic wall	Dead at 4 months
3	40	3.5	T2N0M0	Irregular Opacity	Mamnectomy +ALND (N-)	Malignant Vascular tumor	AS meanly differentiated	Dead at 30 months M+ : bone
4	52	13	T4bN0M0	-	Mamnectomy + CT	Carcinoma	Undifferentiated AS	Dead at 9 months M+ lungs
5	22	2 2 13	T2N0M0 T2N0M0 T4bN0M0	- Well limited opacity Well limited opacity	Mamnectomy + CT	AS well differentiated	Angioma Angioma AS well differentiated	Dead at 60 months M+ : bone
6	32	-	NC	Well Limited opacity	Tumorectomy + ALND (N-) + RT	Benign tumor	AS	60 months NED
7	53	1.5	NC	Well Limited opacity	Tumorectomy	Vascular tumor	AS meanly differentiated	42 months NED
8	40	14	NC	-	Mamnectomy	AS	AS well differentiated	Lost of view
9	20	0.5	NC	-	Mamnectomy + ALND + RT	AS	AS	156months NED
10	19	-	NC	Well Limited opacity	Mamnectomy+RT	AS	AS	Dead at 15 months M+ lung

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