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Primary angiosarcoma of the breast—series of 11 consecutive cases—a single-centre experience

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ABSTRACT

Angiosarcomas of the breast are rare parenchymal malignancies of the chest wall. Surgery is the main treatment modality with chemotherapy and radiotherapy used in case of recurrence. With generally unfavourable prognosis and lack of clear treatment guidelines due to its rarity and scarcity of available data, angiosarcoma of the breast is a challenging clinical situation for both oncologist and patient. We present here the results of a series of 11 consecutive primary angiosarcoma cases treated at our institute between 2000 and 2015.

Key Words Breast cancer, soft tissue sarcoma, sarcoma of the chest wall, angiosarcoma, treatment

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INTRODUCTION

Angiosarcomas are exceedingly rare and highly aggressive breast tumours that occur in less than 0.05% of patients with malignant tumour within this organ[1]. We can distinguish two main types of angiosarcomas affecting the breast: the primary angiosarcoma (PAS) developing *de novo* and secondary angiosarcoma (AS) developing as a consequence of previous breast cancer treatment (e.g., prior postoperative radiotherapy and/or long-lasting lymphedema after treatment for breast cancer known as Stewart-Treves syndrome). In contrast to secondary AS, the natural history of primary AS is only partially understood. It is thought that PAS arises within breast parenchyma and then infiltrates skin and subcutaneous tissue overlying nearby[2]. Moreover, amongst adult patients diagnosed with soft tissue sarcoma, primary breast angiosarcoma accounts for approximately 2% of cases[3]. It is most commonly seen in younger patients, women in their thirties and forties[4]. Clinically, women with PAS usually present with swelling, a sensation of fullness, and exponential growth within the breast[5,6]. The prognosis for PAS is generally poor, and the diagnosis may be delayed because of possible unusual clinical presentation and its rarity. Surgery (either mastectomy or wide excision) remain the cornerstones of the treatment. Due to the highly aggressive course of the disease and its tendency to have local recurrence and distant metastasis, other treatment methods such as chemotherapy or radiotherapy should be used, under the supervision of a multidisciplinary team.

Unfortunately, recommendations for treatment of AS based on strong medical evidence are lacking. In addition, within medical databases, most available papers concern post-radiation angiosarcoma (SAS), and there are only a few small case reports focusing on SAS. Therefore, we present and analyze the correlation between clinical and histopathological features, treatment provided, and patient outcomes in our clinic.

MATERIALS AND METHODS

We retrospectively analyzed 11 consecutive patients with PAS treated at the Department of Breast Cancer and Reconstructive Surgery, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw, Poland, between 2000 and 2016. The basic criterion for inclusion in the study was the presence of histopathologically confirmed primary angiosarcoma of the breast; graded into low (G1, G2) and high (G3) grades in the classification proposed by Donnell *et al.*[7]. Specific data such as age at diagnosis, sex, symptoms at presentation, as well as clinical history—tumour size, side, clinical condition, prior radiotherapy, rendered treatment, presence of local recurrence and distant metastasis, and patient survival—were evaluated based on the available medical records and then finally analyzed.

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RESULTS

During the period of 16 years, a total of 11 patients diagnosed with primary breast angiosarcomas were seen and treated at the Department of Breast Cancer and Reconstructive Surgery, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology (Table I). All the patients were female with no previous history of radiotherapy, one patient had been previously treated for luminal cancer in the contralateral breast with mastectomy followed by adjuvant hormonotherapy with tamoxifen. The median age of the patients at diagnosis was 53.5 years (range 24 to 83 years). In 64% of the patients, the size of the tumour at diagnosis was larger than 50 mm (median tumour size was 6.7 cm ranging from 2.0 to 20 cm) and in 63,7% of histopathological results, the tumour necrosis exceeded 30%. Furthermore, the majority (45.4%) of the tumours were high grade (G3), while the remaining (54.6%) were low grade (G1) and intermediate grade (G2). Most of the patients sought medical care because of a swelling within the breast. None of the 11 women had a distant metastasis at time of diagnosis.

All the patients underwent surgery as primary treatment. The most common surgical procedure was total mastectomy without axillary lymph node dissection (82%); axillary dissection was done in the case of two patients, due to the presence of cN+ without fine-needle aspiration biopsy (FNAB) (Table II). In six patients (54.5%) out of 11 who underwent mastectomy, good surgical margin resection was achieved (R0). The rest of the patients underwent a non-radical surgical margin—with micro residual tumour (R1: 4 cases) or macroscopic residual tumour (R2: 1 case with debulking rescue mastectomy). Five patients were characterized by a high grade (G3) with necrosis. Five patients (45%) were treated with radiation therapy after the surgical procedure. Furthermore, one person received neoadjuvant chemotherapy (AC regimen), and two other patients received adjuvant chemotherapy (AC and Taxotere regimen).

Overall, 10 patients (91%) relapsed with local or distant recurrence. The average time from surgery to the onset of local or distant recurrence was 27.5 months. Moreover, distant recurrence was most frequent in the lungs (Table III). After relapse, 30% of patients were treated with chemotherapy, 30% received combination therapy: chemotherapy + radiotherapy + excision, and 20% received chemotherapy and radiotherapy. Eight out of 11 patients treated for PAS at our department received systemic chemotherapy mainly consisting of—in six cases—doxorubicin and ifosfamide. One patient presenting with local recurrence did not agree to further medical treatment. In our study, we observed a correlation between higher tumour grade combined with the greater extent of tumour necrosis in the histopathological results with shorter time to disease progression. The average time from recurrence or development of metastasis to death was 7.5 months. At the time of analysis, one patient is still alive—following up treatment at the time of identification (June 2015).

TABLE I Clinicopathological profile of patients with primary angiosarcoma of the breast

Total number of patients	11
Age	
Median (years)	53.5
Range (years)	24–83
>50 years	7 (63.7%)
<50 years	4 (36.4%)
Patients who underwent radiotherapy for other reasons	0
Patients with previous medical history including invasive breast cancer	1[a]
Frequency of particular symptoms	
Swelling	8 (72.8%)
Hemorrhage from tumour	2 (18.2%)
Pain	2 (18.2%)
Without symptoms	1 (9.1%)
Size of the primary tumour	
>50 mm	7 (63.7%)
≤50 mm	4 (36.4%)
Grading	
Low/intermediate (G1–G2)	6 (54.6%)
High grade (G3)	5 (45.4%)
Necrosis	
>30%	7 (63.7%)
<30%	4 (36.4%)
Immunohistochemical data	
CD31	11 (100%)
Factor VIII	5 (45.4%)
Histopathological subtype	
I	4 (36.4%)
II	1 (9.1%)
III	4 (36.4%)
n/a	2 (18.2%)

[a] Ductal cancer of the second breast at the same time: Luminal A subtype—simple mastectomy and tamoxifen in adjuvant hormonotherapy.

TABLE II Treatment methods used in PAS-diagnosed patients (*n*=11)

Method of treatment	Number of patients
Surgery	
Mastectomy	0
Breast-conserving surgery type of resection margin	
R0	6
R1	4
R2	1
Chemotherapy	
Preoperative	1
Adjuvant	2
Radiotherapy	
Preoperative	0
Adjuvant	5

PAS = primary angiosarcoma.

TABLE III Characteristics of patients diagnosed with local or distant recurrence

Total number of patients		11
Local recurrence		5 (as a first symptom: 4)
Distant metastasis		
Lung		5
Subcutaneous tissues		2
Liver		2
Bones		2
CNS		1
Lymph nodes		1
Second breast		1
First location of distant metastasis		
Lung		4
Bones		2
Median period of time from surgery to disease progression		27.5 months
Treatment options after diagnosis of local/distant recurrence		
Palliative chemotherapy (p-CHTH)		8
Palliative radiotherapy (p-RTH)		6
Surgical excision of recurrence		4
No treatment		1
Types of introduced treatment		
p-CHTH		3
p-CHTH + p-RTH + surgical excision		3
p-CHTH + p-RTH		2
p-RTH + surgical excision		1
Median period of time from disease progression to patients' death		
7.5 months	Death	10
		1[a]

CNS = central nervous system.
[a] 1 patient after radical surgery in June 2015, last control in April 2017, without any signs of disease.

DISCUSSION

Women aged between 20 and 50 who do not have a previous history of epithelial breast cancer are most commonly affected[6]. In our cohort, the median age at diagnosis was 53.5 years, the age range was 24 to 83 years and older patients overmatched. The age range of our study group differs from that of patients enrolled in the Wang *et al.* study. In this study, the median age was 35.5 (17 to 68 years)[8]. Johnson *et al.* and Nascimento *et al.* indicate higher prevalence of PAS in the right mamma[2,9]. Amongst our patients, it was more common in the left breast (7 out of 11 vs. 4). Fast-growing breast lump with edema, usually not tender during palpation, was the most prominent physical examination feature, which is in line with that reported in the literature[10]. In the majority of patients, the primary tumour was at least 5 cm in size, which is associated with unfavourable prognosis and shorter disease-free survival related to the presence of distant metastases[11]. The most common site of distant metastases reported by Søndenaa *et al.* was the liver[12], and in our group the most common site of metastasis was lungs. Primary angiosarcoma diagnosis is confirmed by core biopsy[13] as fine-needle biopsy leads to approximately 40% of false negative results[14]. Other rare histologies, such as liposarcoma, fibrosarcoma, osteosarcoma, metaplastic carcinoma, and stromal sarcoma, are excluded as part of a differential diagnosis[13]. Presence of CD31 and factor VIII in immunohistochemical assessment are diagnostic features of PAS in the pathological report, related to the vascular origin of the tumour[13]. About one third of angiosarcomas were discovered during routine mammography[15]. In our study group, all the patients underwent mammography and ultrasonography (both breasts), X-ray of the chest wall, and, in the majority of cases, a computed tomography (CT) scan was also done.

Complete excision is the key treatment modality, with preference given to mastectomy[5]. Such a procedure was performed in all of our patients. Risk of recurrence after radical surgery is estimated to be 8% vs. 23% after breast conserving treatment[9]. Local recurrence, unfortunately, affects 45% of patients, which is possibly related to the same rate of non-complete excisions without clean margins (non-R0). Primary angiosarcoma metastases arise via the vascular route, and local lymph-node involvement is extremely rare; therefore, a routine lymphadenectomy should not be performed[16]. Enlarged lymph nodes in the course of PAS are most often reactive only and resulting from local compression of the large tumour.

So far, three main histopathological patterns have been described about angiosarcoma:

- type I—characterized by vascular channels invading the breast tissue with scarce endothelial proliferation,
- type II—presenting papillary endothelial components,
- type III—additionally presenting necrosis and hemorrhage[17].

The histological malignancy grade (GX) in the 11 patients we analyzed had a distinct relation to clinical presentation and overall prognosis. Median local or distant recurrence-free survival in our patients after radical surgery with either G1 or G2 was 32 months and, with Grade 3, only 7.8 months—with increased risk of death. This concurs with findings of Vorburger[18] and Hodgson[1], but Nascimento, in his large 49-patient cohort, did not demonstrate such a trait[2].

Pre-operative radiotherapy for PAS is not recommended[9]. Adjuvant radiotherapy after surgery, according to Johnstone *et al.* allows for better local control[19], but without effect on overall survival as noted by Pandey *et al.*[20]. In our group, 45% of patients were treated with adjuvant radiotherapy—that is a higher ratio than reported in the literature, where cohorts were larger in overall size[21,22]. The role and efficacy of chemotherapy has not been established as the available body of data comes from small size samples, from which definite conclusions cannot be drawn[23,24]. It seems that the majority of available data come from sarcoma populations as a whole, not specifically from PAS populations[21,25]. According to a study published by Sher *et al.*, patients with higher malignancy grade, G3 and with recurrence, benefit most from neo or adjuvant chemotherapy[26].

The toughest problem with PAS treatment is the absence of common standards. Perhaps, the specific solution for this would be clinical research about molecular disorders like p53, PI3K, or mTOR pathways[27]. An interesting direction may be studies about anti-angiogenic agents like bevacizumab administered in conjunction with chemotherapy due to PAS histopathology[28].

In this publication, we presented a relatively large group of PAS patients, not presented earlier in Poland. Analyzing the data retrospectively, we decided to prospectively follow up patients with PAS in the future.

CONCLUSIONS

Primary breast angiosarcomas are exceptionally rare malignant tumours occurring in this location. In contrast to epithelial hyperplasia in the breast, due to their extremely different histological nature, they require separate medical procedures. Actually, it is thought that PAS should be considered as soft-tissue sarcomas and treated according to the accepted medical standards for this group of tumours. Because PAS are extremely rare entities, patients with PAS should be referred to highly specialized medical units. Diagnosis should always be based on core biopsy (CB) and the primary treatment should be a simple mastectomy, without axillary lymph node dissection (ALND). Neoadjuvant or adjuvant chemotherapy and/or radiotherapy[9] should be considered in large G3 tumours.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest and declare that we have none.

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