Secondary breast angiosarcoma: A multicentre retrospective survey by the national Italian association of Breast Surgeons (ANISC)


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A B S T R A C T

Background: Breast angiosarcoma is a malignant mesenchymal neoplasm, which accounts for approximately 2% of all soft tissue sarcomas. Secondary breast angiosarcoma (SBA) may be related to chronic lymphedema after a mastectomy with lymph node dissection (Stewart Treves syndrome) and previous radiotherapy for complications from breast radiation treatment. It is a very rare condition; therefore, diagnosis and management are still a challenge.

Methods: The ANISC collected SBA data by means of a survey sent to all Italian breast centres in the ANISC. The clinicopathological characteristics and the management of this disease were analysed.

Results: Twenty-four centres participated in this survey in which 112 cases of SBA were analysed. The median age of the women with SBA was 68.9 years and it appeared approximately 90 months after the first irradiation for breast cancer. In 92% of cases, a mastectomy was performed without axillary dissection for those patients having a high grade of SBA (74.2%). The prognosis was worse in the high-grade cases (overall survival-OS: 36 months) as compared with the low-grade cases (OS: 48 months). After a follow-up of 5 years, 50.5% of the patients were still alive.

Disease-free survival (DFS) was 35 months, and there were no differences between the groups of patients with either high- or low-grade histology.

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Introduction

Breast angiosarcoma is a rare and malignant mesenchymal neoplasm accounting for approximately 2% of all soft tissue sarcomas having an incidence of 6.8 per 100,000 people per year [1]. Although rare, the incidence of SBA appears to have increased by approximately 0.9 per 1000 cases over a 15-year period [2], perhaps reflecting the long latency period for the development of these tumours following the widespread adoption of adjuvant radiotherapy for breast cancer. The malignancy of this type of tumour is due to the endothelial cells lining the blood vessels [3]. There are two categories of breast angiosarcoma: primary breast angiosarcoma (de novo development) and secondary breast angiosarcoma (SBA). The latter type of angiosarcoma is cutaneous in origin, arising from the dermis and subcutis of the irradiated field, and may or may not actually involve the underlying breast tissue. Secondary angiosarcoma is associated with two aetiologic factors: chronic lymphedema after mastectomy with lymph node dissection (Stewart Treves syndrome) and previous radiotherapy for breast conserving surgery [4-5].

Secondary breast angiosarcoma is usually found in older women (60/70 years of age) after a median latency period between radiation for breast cancer and a subsequent diagnosis 6/7 years later [6]. The tumour will often form in the cutaneous tissue and might secondarily invade the breast parenchyma, accompanied by a bluish/reddish discoloration of the skin. Its aggressiveness is a peculiarity of this disease, with a propensity for local recurrence and distant metastasis. A mastectomy is the primary surgical option, even if the prognosis is poor: 5-year survival rates vary from 28 to 54% [7,8].

Due to the rarity of this pathology, there are few studies concerning SBA in the literature, and the best management alternatives have not yet been clarified. The aim of the present study was to analyse the clinicopathological characteristics, and the management and follow-up of a patient population with SBA by means of the experience of the ANISC centres.

Methods

The Italian Association of Breast Surgeons (ANISC) is dedicated to the study of breast pathology. Data from patients with SBA treated in all Italian breast centres affiliated with the ANISC were retrieved from 24 institutional databases. Data for this study of SBA were obtained by means of a survey requesting data. Data regarding patient characteristics, time of radiation therapy for breast cancer and interval of the development of angiosarcoma, type of surgical treatment, tumour grade and follow-up (Fig. 1) were retrieved and analysed. Metastatic disease at presentation, sarcomatoid carcinoma, dermatofibrosarcoma of the breast, and benign, borderline and malignant phyllodes tumours were excluded from the analysis owing to their different behaviours in terms of clinical management and prognosis. All diagnoses were reached using core needle biopsy or excision biopsy, and were confirmed with a final histological examination. The histological type of tumour was defined according to the World Health Organization’s (WHO) classification system [10,11]; tumour grade was defined as low- or high-grade. In the follow-up, disease-free survival (DFS) was defined as the period from the date of the pathological diagnosis of angiosarcoma to any local or regional distant relapse or death from breast cancer or to the last visit date in the cases in which no events were reported. Overall survival (OS) time was measured in months from the date of initial diagnosis to death or the last available follow-up with a maximum follow-up of five years. The follow-up also evaluated tumour grade. Statistical analysis was carried out using SPSS v.18.0 (IBM Corp., Armonk, NY, USA).

Results

The survey was presented to all breast centres in the ANISC. Twenty-four centres received the survey and 18 provided data. Data from 112 cases of SBA occurring from 1997 to 2016 were collected. All the cases selected underwent initial conservative surgery for breast cancer following adjuvant radiotherapy. The diagnosis was reached after a baseline biopsy of a reddish area associated with a lump in the breast which had undergone previous surgery for breast cancer; axillary lymphadenopathy was the first presentation of disease in only two patients. All the patients were female, with a mean age of 68.9 years (range 34–93 years) at diagnosis (media 68.9; dev. Standart 11.974). The SBAs developed approximately 90 months after the first radiation for breast cancer and, in the majority of cases, the total radiation dose delivered to the breast was 50 Gy (range 40–60Gy).

In 92% of the cases (104 patients), a mastectomy was the first surgical option; only 7% (8 patients) underwent conservative surgery. Eight patients who underwent a mastectomy also underwent axillary dissection/sampling. In four cases, the final lymph node examination was negative for the presence of metastasis; however, in two cases more than one metastatic lymph node was found and, in one case, the data was lost.

Two cases involving a mastectomy also had a contralateral axillary dissection since it was the first manifestation of the angiosarcoma.

Histological examinations of the tumour showed aggressive tumours, with 74.3% being high grade (78 cases) and 25.7% (27 cases) being moderate or low grade; final histology was missing in 7 patients (Table 1).

After surgery for SBA, 46 patients underwent adjuvant therapy and 44 received no additional treatment after surgery; for 22 patients, the data were missing (Table 2). In particular, 36 patients received adjuvant chemotherapy with anthracyclines and taxane-containing regimens. Radiotherapy was performed in 9 patients (two patients received both adjuvant treatments) (Table 3). In the adjuvant chemotherapy group (34 patients), 79% (27 patients) had a high-grade tumour and their mean survival was 36 months; instead, 20% (7 patients) had a low-grade tumour and their mean survival was 39 months (Table 4). In the group which did not undergo adjuvant therapy (44 patients), 68% (30 patients) had a high-grade tumour and their mean survival was 38 months (p = 0.65);
instead, in the 30% (13 patients) with a low-grade tumour not undergoing adjuvant therapy, the mean survival was 50 months (Table 5).

After a 5-year follow-up, approximately 50.5% (49 patients) of

Table 1
Histology grade of SBA.

<table>
<thead>
<tr>
<th>HISTOLOGY</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>High grade</td>
<td>78</td>
<td>65%</td>
</tr>
<tr>
<td>Low grade</td>
<td>27</td>
<td>28%</td>
</tr>
<tr>
<td>Tot.</td>
<td>105</td>
<td>94%</td>
</tr>
<tr>
<td>Missing</td>
<td>7</td>
<td>6.3%</td>
</tr>
<tr>
<td>Tot.</td>
<td>112</td>
<td>100%</td>
</tr>
</tbody>
</table>
the patients were still alive of whom 31 patients (72%) were disease free, 12 patients had a recurrence and, for 6 patients, the data were missing (Table 6). In the 12 patients with a recurrence, 8 patients (66%) had local recurrence and only 4 patients had a distant metastasis, the majority of which were in the lung.

Comparing clinical outcome in relation to histological grade, it was observed that the prognosis was worse in patients with a high-grade angiosarcoma, although there were no statistically significant differences between OS of the high-grade tumours as compared to the low-grade tumours (high-grade OS C.I. 31–41 months vs. low-grade OS C.I. 40–57 months, Log-Rank p = 0.74). A higher mortality risk was noted in the high-grade group in the first months after diagnosis (Breslow-Wilcoxon p = 0–042). The global OS was 39 months (C.I. 35–44) and the global DFS was 38 months (C.I. 31–45); there were no differences in recurrence rate regarding the histological or the type of adjuvant therapy (when performed).

Discussion

Secondary breast angiosarcoma is a rare and malignant disease which mostly affects women who had undergone previous chest radiotherapy for breast cancer. The cumulative incidence of SBA in 1 per 1000 patients with breast cancer as reported in literature in smaller series of 0.9 to 1.1 per 1000 patients [4]. The malignancy of this disease relates to the aggressiveness of the tumour of the vascular endothelium, characterised by rapidly proliferating and extensively infiltrating growth. This specific feature of the disease correlates with a short survival outcome [13].
The widespread adoption of conservative breast surgery and adjuvant radiotherapy in the management of primary breast cancer has been accompanied by a steady increase in the incidence of SBA. Secondary breast angiosarcoma is typically a late complication of adjuvant radiotherapy and, in the present study, it developed approximately 90 months after the first radiation for breast cancer. These findings are consistent with those reported in the literature and, due to the substantial variability in the latency of this disease, a high index of suspicion is warranted for any patient undergoing adjuvant radiotherapy, but importantly, angiosarcoma did not occur in any of the patients who did not receive radiotherapy.

An early diagnosis and the surgical approach are crucial for the outcome of the disease.

A surgical biopsy must be able to reach a diagnosis of certainty and then choose the appropriate surgical approach. Unfortunately, due to the low incidence of the disease, the diagnosis is not reached early enough. In fact, the clinical signs which occur are not always easily recognisable; therefore, a histological diagnosis by surgical biopsy is reached only when other causes have been excluded, sometimes in an already advanced stage of the disease.

However, nowadays with the advent of specialisation which is dedicated exclusively to breast disease, this disease is more frequently recognised, and the diagnosis is promptly reached on the basis of both clinical signs and the patient’s clinical history.

The best surgical approach is definitely a mastectomy without axillary dissection in order to achieve radical local control of the disease. In these cases, breast reconstruction should be considered\[8,9]\.

Although conservative surgery is still used in cases of SBA, no sufficient data exist to recommend this treatment due to the high risk of recurrence.

A definitive histological examination is also important in defining the prognosis of this disease. In fact, a higher grade of tumour is related to a higher risk of death in the first three years after diagnosis; this risk is no longer higher in the late course of the disease since, after the third year, it become equivalent for both histological grades.

Aggressiveness is a peculiarity of this disease with a propensity for local recurrence and distant metastasis. There was no proven benefit of either overall or disease-free survival in patients who underwent adjuvant therapy as compared to patients who underwent only surgical treatment but there were not sufficient data to recommend one strategy over the other. As reported in a recent published study whose data derive from databases from the nationwide Netherlands Cancer Registry, the SBA must be treated with surgery and in particular with mastectomy: radiotherapy after surgery does not seem to bring a real benefit on survival\[12].

A limitation of the present study includes the long period of data collection and the difficulty regarding the collection of the follow-up data of the patients. There is no strict recommendation as to whether chemotherapy should be performed or not in SBAs; therefore, the choice to administer chemotherapy to patients was made by the oncologists of the different breast centres.

Conclusions

An SBA is not very frequent and it is often not easy to diagnose and treat; this is reflected by the authors to carry out a survey aimed at all Italian Breast Units in order to understand the progression of this disease on a national scale. The collection of these data has served to analyse the presentation characteristics of SBA and, above all, the most correct method of diagnosing and treating it.

The result of the present study showed that mastectomy probably represented the best surgical approach. Vice versa, axillary dissection should not be mandatory since sarcoma does not usually spread to the axillary lymph nodes. Furthermore, the final historical report has become more accurate in predicting the prognosis. According to the existing literature, a high degree of malignancy appears to be related to a worse prognosis and to the overall survival rate in these patient categories. However, no clear benefit was seen as regards the use of adjuvant therapy for this disease. All these data were gathered by means of a careful follow-up. In patients with SBA, it is advisable to carry out a clinical follow-up at least every six months for the first 3 years from the development of the disease and, thereafter, every year.

The data collected did not deviate from the existing literature; therefore, it can be concluded that this disease, although not frequent, should be diagnosed promptly and treated using a multidisciplinary approach.

References