Primary angiosarcoma of the breast

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ABSTRACT

Primary angiosarcoma (AS) of the breast is a rare neoplasm that is not related to radiation exposure. It represents less than 0.05% of all malignant breast tumors. This lesion is characterized by aggressive patterns and poor prognosis and by the absence of typical features at radiologic examination.

Currently there are not evidence-based guidelines regarding surgical and adjuvant treatment for this tumor even though wide surgical resection followed by chemo-radiotherapy appears to improve both disease free survival and overall survival.

The aim of this study was to analyze the available series of AS patients suggesting the most reliable treatment options for this rare neoplasia.

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1. Introduction

Primary breast sarcomas are rare conditions that present an histological heterogeneity. They are mostly represented by fibrosarcomas, angiosarcomas, myxoid/round cell liposarcomas, phylloides tumors and malignant fibrous histiocytomas [1].

Angiosarcoma (AS) of the breast represents 1% of all soft tissue breast tumors. It arises from the connective breast tissues and may extend into the overlying skin [2].

AS can arise de novo with a median age at onset of 40 years or can be secondary to radiation treatment of an epithelial breast cancer with a median onset age of 70 years (median of 10.5 years after radiotherapy) [3–5].

The overall incidence rate of primary angiosarcomas is less than 0.05% of all malignant breast tumors. Borrmann in 1907 described the first documented case of breast angiosarcoma [6].

Three main histopathological patterns have been described: type I, characterized by vascular channels invading the breast tissue with scarce endothelial proliferation; type II, presenting patterns of papillary endothelial components and type III, with evidence of endothelial components, necrosis and hemorrhage [7].

Available literature reports many papers focusing on post-radiation angiosarcomas but only small series of patients affected by primary angiosarcoma are presented.

The aim of our review is to verify if there is a correlation between histopathological–clinical features and patient outcomes.

We selected articles from the PubMed database using search terms “primary”, “angiosarcoma” and “breast”. We found 297 English language papers. We reviewed all abstracts and reviewed the available evidence.

2. Presentation and diagnosis

Primary AS usually presents as a poor defined mass in breast parenchyma characterized by a rapid growth. Large tumors can lead to thrombocytopenia and hemorrhagic manifestations (Kasabach–Merritt syndrome) [8].

The typical patient with primary breast angiosarcoma is a young woman with a dense breast parenchyma.

Imaging of angiosarcoma is not specific. It is of note that mammogram or ultrasound study do not present proper pathological
pattern. AS could be diagnosed as a benign lesion in particular in youngest patients.

The most supportive imaging exam is considered the magnetic resonance imaging (MRI) that can show typical malignant signs (hyperintensity on T2 images and a rapid initial intense phase followed by washout) [9,10].

Fine-needle aspiration or core needle biopsy are necessary to obtain a definitive diagnosis [10].

In addition immunohistochemistry can be used to identify the CD31 endothelial, indicator of vascular proliferation. Other specific markers for this kind of lesions are Factor VIII, and FLI1 [11–13].

3. Surgical treatment

The gold-standard treatment in patients affected by primary angiosarcoma of the breast is surgery consisting in modified radical mastectomy combined, when necessary, with axillary node dissection.

Patients with smaller tumors may benefit of breast-conserving surgery.

We analyzed surgical indication in series presenting more than 20 breast sarcoma cases selecting in this way 7 studies [1,9,10,14–18].

In our review we analyzed data on surgical treatment of 251 patients with primary angiosarcoma of the breast: 75% of the patients underwent mastectomy and 25% underwent breast conserving treatment.

Even if it is unlikely that this kind of tumors metastasize to regional lymph nodes, axillary node dissection was performed in 42% of all patients.

Rosen et al. presented a series of 63 patients with primary angiosarcoma of the breast from the Sloan Kettering Cancer Center; 35 patients underwent axillary node dissection and only one presented metastatic lesions [9].

Bousquet et al., Cofraveux et al. and Blanchard et al. presented their interesting works describing nodal involvement in less than 10% of cases [10,14,15].

4. Chemotherapy

In the available literature there is not an international consensus about chemotherapy regimens to be used in patients with angiosarcoma.

In the article analyzed in this review the use of chemotherapy varied largely: 36% of patients affected by primary angiosarcoma received chemotherapy as adjuvant or neoadjuvant therapy.

Soft tissue sarcomas are known to be very aggressive tumors: the probability of the onset of a systemic recurrence is about 50%, even in case of localized disease [19].

The medical treatment plays a fundamental role in these patients as demonstrated by Tierney et al. in their study published in 1995. An anthraclycine-based chemotherapy lead to a significant improvement of disease free survival and overall survival [20].

Pervaiz et al. demonstrated the importance of adjuvant doxorubicin-based chemotherapy in delaying local and distant recurrence and improving the overall recurrence-free survival [21].

The series presented by Frustaci et al. showed the improvement in both disease free survival and overall survival using an adjuvant regimen based on epirubicin plus ifosfamide [22].

In a report published by Sher et al., adjuvant chemotherapy using combinations of anthracycline–ifosfamide or gemcitabine–taxane was administered in more than 60% of patients with AS of the breast without any improvement in disease-free survival [16].

In a more recent work on 41 cases of metastatic angiosarcoma treated with taxane regimens, Hirata et al. showed an improvement in overall survival rate [23].

5. Radiation treatment

The role of radiation treatment (RT) is limited to the residual microscopic disease after surgery of the primary tumor.

The potential impact of RT on local control and survival of patients with soft tissue sarcomas of other sites has been well documented.

Adjuvant radiotherapy after surgery may have a beneficial effect for breast sarcomas, particularly for patients with microscopically positive margins.

In the analyzed series, 35% percent of the patients have been treated with adjuvant radiotherapy according to the tumor features [9,10,14,15].

Rosen et al. used adjuvant radiotherapy in combination with chemotherapy in 17% of their patients and only radiation in 6% of their patients without improving disease free survival and overall survival [9].

In the study by Sher et al., 68% of patients received radiotherapy with a documented recurrence-free survival of 47% and 44% at 5 and 10 years. This rate shows an improvement in recurrence free survival compared with patients who did not receive radiotherapy (33% and 25% at 5 and 10 years respectively) [16].

Even though these results are encouraging, there is not a statistically significant correlation between adjuvant radiotherapy and improved survival due to the small number of included patients.

6. Prognostic factors

The prognosis of the angiosarcoma of the breast, like each histotype of sarcoma, is related to the tumor size, the tumor grade and the resection margin status [13].

Wide excision is mandatory to obtain free margins but even in this way, it is not easy to join a radical surgery. Most papers show how an incomplete exeresis is strictly connected with both local relapse and worst survival [1,10,26–33].

Literature presents different opinions regarding the correlation between tumor size and prognosis. Most of the authors like Rosen et al., Bousquet et al., Blanchard et al. and Sher et al. found no correlation between the size of the primary tumor and the risk of recurrence or death [9,10,15,16].

On the contrary, other authors, like Adem et al. and Zelek et al., underlined in their series of primary sarcoma of the breast the association between tumor size and disease free survival [1,32].

Another fundamental parameter that has to be analyzed is the mitotic index defining the tumor grade.

Therefore high-grade sarcomas of the breast present a higher risk of mortality [24–29].

Bousquet et al., Rosen et al. and Luini et al. in their series proved that grade I and II lesions were associated with better disease free survival [9,10,30] while Nascimento et al., in his group of 49 patients with primary angiosarcoma of the breast, demonstrated no correlation between tumor grade and overall survival [17].

7. Conclusions

Primary angiosarcoma of the breast is a malignant vascular neoplasm arising within breast parenchyma with or without extension into the skin. It should be considered a different neoplasia from radiation-related AS.

The incidence of primary breast angiosarcoma is approximately 17 new cases per million women [31–33].
This neoplasia does not present any pathognomonic sign on mammogram or ultrasound examination and can show specific radiological characteristics only at MRI.

There are few available series analyzing the best option for surgical and adjuvant treatment for primary angiosarcoma of the breast. An aggressive surgical approach seems to be accepted by most of the authors [1,9,10,15], however breast conserving surgery can be proposed in selected cases.

Auxiliary clearance is not necessary in all the patients, in fact the tumor do not follow a lymphatic way of dissemination; however bulky masses invading the axilla, necessitate an axillary node dissection in order to achieve free margins.

Even though some series present an increase in disease free survival and in the overall survival, standard medical regimens in patients suffering from breast angiosarcoma remain unclear [16]. Adjuvant chemotherapy with Taxan agents showed good outcomes but more investigations are needed.

Radiotherapy also does not present a clear consensus and should be considered as adjuvant treatment in selected cases.

Examining the data regarding disease free survival and overall survival, we would like to mention Blanchard study in which the author compared the outcome for patients with different histological types of breast sarcoma presenting a median disease free survival (DFS) of 25 months [4].

Rosen et al. presented a 5-year disease-free survival ranging from 15% for patients with high-grade tumors to 76% for those with low-grade tumors [9].

The series of Bousquet et al. presented a 5 and 10-year DFS of 27% and 12% respectively [10], while the group from Mayo Clinic presented a mean survival of 48 months [1].

In conclusion we underline the heterogeneity of surgical and adjuvant therapy proposed for primary AS. Largest series of patients are requested to reach a shared consensus on the treatment of primary angiosarcoma of the breast. We recommend a multidisciplinary approach in which the collaboration of radiologist, oncologist, breast surgeon, radiotherapist and plastic surgeon could lead to an evident benefit for patient’s health and quality of life.

Conflict of interest

The authors declare to have no conflict of interest.

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Ethical approval

Ethical approval was not necessary, being the study design a literature review.

Author contribution

Daniele Bordoni: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Elisa Bolletta: Participated substantially in the drafting and editing of the manuscript.

Giuseppe Falco: Participated substantially in conception and design of the study.

Pierfrancesco Cadenelli: Participated substantially in the drafting and editing of the manuscript.

Nicola Rocco: Participated substantially in conception and design of the study.

Ariel Tessone: Participated substantially in design of the study.

Stefania Guarino: Participated substantially in collecting data.

Antonello Accurso: Participated substantially in design of the study.

Bruno Amato: Participated substantially in design of the study.

Cesare Magalotti: Participated substantially in conception and design of the study.

References

[1] C. Adem, C. Reynolds, J.N. Ingle, A.G. Nascimento, Primary breast sarcoma: clinicopathologic series from the Mayo Clinic and review of the literature, Br. J. Cancer 91 (2004) 237–241.
[2] L. Liberman, D.D. Dershaw, R.J. Kaufman, P.P. Rosen, Angiosarcoma of the breast, Radiology 183 (1992) e649–e654.
[3] J.L. Lagrange, A. Ramaiol, M.C. Chateau, et al., Sarcoma after radiation therapy, Radiology 216 (2000) 197–205.
[4] D.K. Blanchard, C. Reynolds, C.S. Grant, D.R. Farley, J.H. Donohue, Radiation-induced breast sarcoma, Am. J. Surg. 184 (2002) 356–358.
[5] J. Huang, W.J. Mackillop, Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma, Cancer 92 (2001) 172–180.
[6] R. Borrman, Metastasenbildung bei histologisch gutartigen geschwulsten: fall von metastasierendem Angiom, Beitr. Pathol. Anat. 40 (1907) 372–393.
[7] R.M. Donnell, P.P. Rosen, P.H. Liberman, R.J. Kaufman, S. Kay, D.W. Braun Jr., et al., Angiosarcoma and other vascular tumors of the breast. Pathologic analysis as a guide to prognosis, Am. J. Surg. Pathol. 5 (1981) 629–642.
[8] M. Bernathova, W. Jaschke, C. Pechlhauner, et al., Primary angiosarcoma of the breast associated Kasabach–Merritt syndrome during pregnancy, Breast 15 (2006) 255–258.
[9] P.P. Rosen, M. Kimel, D. Ernsberger, Mammary angiosarcoma. The prognostic significance of tumor differentiation, Cancer 62 (1988) 2145–2151.
[10] G. Bousquet, C. Confavreux, N. Magne, C.T. de Lara, P. Poortmans, E. Senkus, et al., Outcome and prognostic factors in breast sarcoma: a multicenter study from the rare cancer network, Radiother. Oncol. 85 (2007) 355–361.
[11] J. Hart, S. Mandavilli, Epithelioid angiosarcoma: a brief diagnostic review and differential diagnosis, Arch. Pathol. Lab. Med. 135 (2011) 268–272.
[12] A.L. Folpe, E.M. Chang, J.R. Goldblum, et al., Expression of Rb-1, a nuclear transcription factor, distinguishes vascular neoplasms from potential mimics, Am. J. Surg. Pathol. 25 (2001) 1061–1066.
[13] A. Bemanni, L. Chahini, M. Lammahab, et al., Primary angiosarcoma of the breast: a case report, Diagn. Pathol. 8 (2013) 66.
[14] C. Confavreux, A. Lurkin, N. Mitton, R. Blondet, C. Saba, D. Ranchère, et al., Sarcomas and malignant phylloides tumors of the breast—a retrospective study, Eur. J. Cancer 42 (2006) 2715–2721.
[15] D.K. Blanchard, C.A. Reynolds, C.S. Grant, J.H. Donohue, Primary nonphylloides breast sarcomas, Am. J. Surg. 186 (2003) 359–361.
[16] T. Sher, B.T. Hennessy, V. Valero, K. Broglio, W.A. Woodward, J. Trent, et al., Primary angiosarcomas of the breast, Cancer 110 (2007) 173–178.
[17] A.F. Nascimento, C.C. Raut, C.D.M. Fletcher, Primary angiosarcoma of the breast. Clinicopathologic analysis of 49 cases suggesting that grade in not prognostic, Am. J. Surg. Pathol. 32 (2008) 1896–1904.
[18] J.J. Mazeron, H.D. Suit, Lymph nodes as sites of metastasis from sarcomas of soft tissue, Cancer 60 (1987) 1800–1808.
[19] T.F. Delaney, J.C. Yang, E. Glatstein, Adjuvant therapy for adult patients with soft tissue sarcomas, Oncol. (Williston Park) 5 (1991) 105–118.
[20] J.F. Tierney, V. Mossere, L.A. Stewart, R.L. Souhami, M.K. Parmar, Adjuvant chemotherapy for soft-tissue sarcoma: review and metaanalysis of the published results of randomized clinical trials, Br. J. Cancer 72 (1995) 469–475.
[21] N. Perviazi, N. Colterjohn, F. Farrokhkyar, R. Tozer, A. Figueredo, M. Ghert, A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft tissue sarcoma, Cancer 113 (2008) 573–581.
[22] S. Frustaci, F. Chirinzoni, A. De Paoli, M. Bonetti, A. Azzarelli, A. Comandone, et al., Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the italian randomized cooperative trial, J. Clin. Oncol. 19 (2001) 1238–1247.
[23] T. Hirata, K. Yonemori, M. Ando, et al., Efficacy of taxane regimens in patients with metastatic angiosarcoma, Eur. J. Dermatol. 21 (2011) 539–545.
[24] T.S. McGowan, B.J. Cummings, B. O’sullivan, C.N. Catton, N. Miller, T. Panzarella, An analysis of 78 breast sarcoma patients without distant metastases at presentation, Int. J. Radiat. Oncol. Biol. Phys. 46 (2000) 383–390.
[25] B. Amato, C. Rispoli, L. Iannone, et al., Surgical margins of resection for breast cancer: current evidence, Minerva Chir. 67 (5) (2012) 445–452.
[26] N. Rocco, C. Rispoti, G. Pagano, et al., Undertreatment of breast cancer in the elderly, BMC Surg. 13 (Suppl. 2) (2013) S26.
[27] C. Rispoti, N. Rocco, L. Iannone, et al., Breast reconstruction in older women: a growing request, BMC Geriatr. 9 (Suppl. 1) (2009) A66.
[28] B. Amato, M. Domini, N. Rocco, et al., Breast cancer surgical treatment in elderly patients, Chirurgia (Turin) 26 (4) (2013) 291–294.
[29] P.W. Pisters, D.H. Leung, W. Shi, J. Woodruff, M.F. Brennan, Analysis of prognostic factors in 401 patients with localized soft tissue sarcomas of the extremities, J. Clin. Oncol. 14 (1996) 1679–1689.
[30] A. Luini, G. Gatti, J. Diaz, et al., Angiosarcoma of the breast: the experience of the European Institute of Oncology and a review of the literature, Breast Cancer Res. Treat. 105 (2007) 81–85.

[31] B.J. Barrow, N.A. Janjan, H. Gutman, et al., Role of radiotherapy in sarcoma of the breast—a retrospective review of the M.D. Anderson experience, Radiother. Oncol. 52 (1999) 173–178.

[32] L. Zelek, A. Llombart-Cussac, P. Terrier, et al., Prognostic factors in primary breast sarcomas: a series of patients with long-term follow-up, J. Clin. Oncol. 21 (2003) 2583–2588.

[33] C. Desbiens, J.C. Hogue, Y. Levesque, Primary breast angiosarcoma: avoiding a common trap, Case Rep. Oncol. Med. 2011 (2011), http://dx.doi.org/10.1155/2011/517047, 517047.

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