Radio-induced breast angiosarcoma: features of diagnostics and treatment (a clinical case and literature review)

I.V. Kolyadina[1, 2], V.V. Kometova[2], Yu.V. Bikeev[2], S.V. Khokhlova[2], V.V. Rodionov[2]
[1]Russian Medical Academy of Postgraduate Education, Ministry of Health of Russia; 2/1 Barrikadnaya St., Moscow 125993, Russia;
[2]V.I. Kulakov National Medical Research Center of Obstetrics, Gynecology, and Perinatology, Ministry of Health of Russia; 4, Akademika Oparina St., Moscow 117198, Russia

Contacts: *Irina Vladimirovna Kolyadina irinakolyadina@yandex.com*

Breast angiosarcoma (BAS) is an extremely rare and poorly studied neoplasm, the etiology of primary BAS remains controversial, and secondary BAS is most often radio-induced. Radio-induced breast tumors usually appear 10–20 years after the initial treatment; however, for BAS this period is much shorter and is about 4–7 years. This review presents literature data on the features of the clinic, diagnosis and treatment of BAS, as well as own clinical case observation of radio-induced sarcoma of the left breast, that developed 4 years after the primary breast cancer treatment

Key words: *breast angiosarcoma, radio-induced tumors, surgical treatment*

DOI: 10.17650/1994-4098-2020-16-2-38-43

Breast angiosarcoma (BAS) is an extremely rare and poorly studied neoplasm new growth proceeding from endothelial cells of blood vessels, the proportion of which is about 0.05–0.3 % of all malignant breast tumors [1]. The etiology of primary angiosarcomas remains controversial, and secondary BAS is most often radio-induced [1]. According to the SEER population register with 195.000 patients who have undergone treatment for breast cancer (BC), postoperative radiation therapy is the leading pathogenetic factor in the development of BAS, increasing the risk of its occurrence 26 times higher compared with the patients without radiation treatment [1]. It should be noted that the first case of radio-induced sarcoma was described in 1920 [2]; however, even today, the issues of diagnosis and treatment of this tumor remain relevant.

Radio-induced breast tumors usually appear 10–20 years after the initial treatment of BC; however, for angiosarcomas this period may be shorter [3–5]. Such tumors are more often localized on the skin of the surgical scar, although the area of the tumor lesion can be very extensive. At the initial manifestations, the diagnosis of BAS is extremely difficult, since the clinical manifestations are very poor – thickening and discoloration of the skin area and the absence of any specific radiological signs, which are very similar to postoperative and post-radiation changes in the breast. With the growth of the tumor, the first characteristic signs appear – thickening and infiltration of the skin, as well as a change in its color (red, burgundy and even bluish tint). However, even after the onset of characteristic visual skin symptoms, mammography results can remain negative, which contributes to the erroneous decision about follow-up of the patient. The only reliable method for diagnosing BAS is performing a tumor biopsy with histological and immunohistochemical studies [3–6].

Morphologically there are 3 degrees of malignancy of angiosarcomas:

1) highly differentiated tumors, consisting of pathological vessels that surround the ducts of the mammary gland and involve adipose tissue in the tumor process; blood vessels are lined with single-layer endothelial cells with hyperchromic nuclei and a small number of mitoses;
2) moderately differentiated angiosarcomas have small foci of spindle-shaped cells;
3) poorly differentiated angiosarcomas are characterized by solid growth of spindle-shaped cells with high proliferation and severe atypia, often with areas of necrosis and hemorrhage [7].

The main type of treatment for the localized form of BAS is a radical surgery with clear margins. However, the risk of developing local relapses remains extremely high (50–68 %) even after clear radical surgery; therefore, many authors recommend an indentation from the tumor margins not less than 2–4 cm [8, 9]. The preferred choice operation for BAS is mastectomy without axillary lymph node dissection, since regional metastasis is not typical for this type of tumor [9, 10].

Despite the high frequency of diagnosis of localized forms of BAS, the course of the disease is extremely aggressive: rapid progression and resistance to the main cytostatic agents lead to poor survival (5-year relapses-free survival – 35 % and 5-year overall survival (OS) – 48 %) [8–12]. On average, the median survival for patients with BAS is only 23 months; the most important prognostic factors are the tumor sizes and the number of tumor lesions. So, if tumor sizes less than 2.0 cm, the median OS reaches 80 months, while with tumors more than 5.0 cm – only 20 months. The number of tumor lesions is also a significant

factor – with single lesions, the 2-year survival rate is 50 %, while with multiple skin lesions – 0 % [13, 14].

The effectiveness of chemotherapy for BAS remains controversial due to the rarity of the tumors and the lack of an evidence base for studies [9]. The benefit of adjuvant therapy has not been proven, and the experience of using neoadjuvant cytostatic regimens for inoperable BAS is presented in the individual clinical cases only. Thus, in the literature there are isolated reports of the successful use of a combination with doxorubicin, cisplatin and paclitaxel, and a combination of epirubicin with ifosfamide in the neoadjuvant regimen [9, 15, 16]. Patients with metastatic BAS receive chemotherapy in accordance with the recommendations for the treatment of soft tissue sarcomas, however, the results remain very unsatisfactory – response rates are only 25 %, and the median life expectancy is 54 weeks [9, 16, 17].

Most of the publications describe of clinical cases of BAS or small single-center retrospective analyzes. In 2017, the largest analysis of British oncologists from Royal Marsden Hospital was presented, which analyzed the experience of treating 49 patients with radio-induced BAS from 2000 to 2014 [5]. Patients in this study were women of the older age group (from 51 to 93 years, the median age was 72 years), the median time from the end of radiation therapy for BC to the development of radio-induced BAS was 7.5 years (from 1 up to 26 years), the tumor size was from 1.5 to 19 cm. It should be noted that none of patients had signs of BC progression at the time of diagnosis of radio-induced angiosarcoma. The authors note that in 96 % of patients the angiosarcoma was localized, which made it possible to perform surgical treatment at the first stage in 74.5 % of cases, with the achievement of the R0-status of the resection margins in 91.4 % of patients. In patients with an inoperable tumor status, chemotherapy was prescribed (in 5 patients with doxorubicin and in 2 – with weekly paclitaxel), after which, in 3 cases, it was possible to perform mastectomy. Despite the performed surgical treatment with clear margins, local relapses were observed in 18 out of 35 patients after surgery (51.4 % of cases); the 2-year survival rate without local recurrence was 51.2 %, the 2-year survival rate without distant metastases was 67.3 %, and the 2-year OS was 71.1 %. The survival rates in patients with inoperable sarcoma were significantly lower: the 2-year survival rate without distant metastases was 57.3 %, and OS was only 33.3 %. As a result, the median life expectancy with and without surgery was significant different – 37 vs. 18 months, p <0.001. This study confirms BAS tumor size over 5.0 cm was an unfavorable prognostic factor for the risk of recurrence and death [5].

We present our clinical case of a patient with radio-induced BAS in patient 62 years old after radical BC treatment.

Clinical case

Patient 62 years old, in menopause. In 2015, she received radical treatment for left BC pT1N1M0, stage IIA (luminal HER2-negative subtype); breast-conserving surgery, adjuvant chemotherapy (4 cycles of doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2), adjuvant radiation therapy on the left breast (50 Gy, 2D planning), from 2015 to 2020 used anastrozole 1 mg daily.

In February 2020, the patient found thickening and discoloration of the skin in the area of the postoperative scar of the left breast. When contacting the oncologist, mammography and ultrasound were performed, in which there were no signs of tumor lesions in the breast, only post-radiation fibrosis. In clinical examination within a month a tumor node about 1.5 cm became visible around the postoperative scar in the left breast. Tumor node was purple color, towering above the skin surface, inactive, painless (fig. 1a). The skin and breast tissue around the formation were some infiltrated, regional lymph nodes were not involved (fig. 1b).

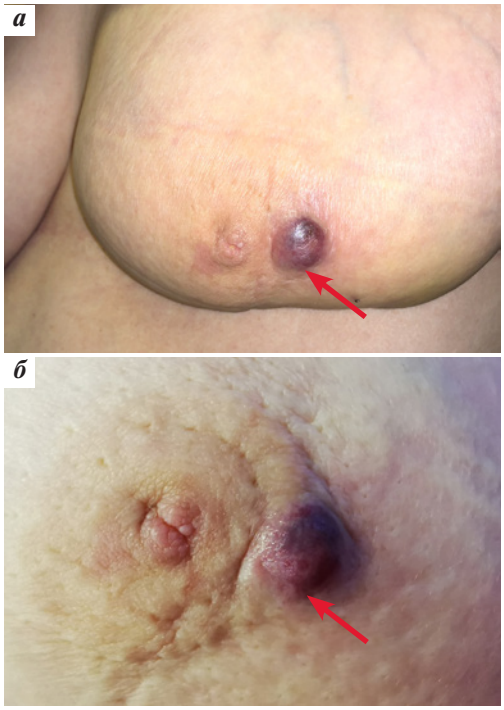

Fig. 1. *Left breast with a tumor node (arrow) in the area of the postoperative scar (a). Infiltration of the skin and tissue from the central part of the breast around the tumor (arrow) (b)*

By ultrasound data, in the paraareolar region of the left breast visualizes a tumor 17 × 9 × 9 mm within the skin and subcutaneous tissue with reduced echogenicity, a heterogeneous structure (less echogenic in the central part) with smooth and fuzzy boundaries, with lateral acoustic shadows (fig. 2a). Blood flow was visualized along the lower edge of the nodular formation, and intranodular blood flow was not pronounced (fig. 2b). With compression elastography, the formation and perinodular tissues were stained blue (incompressible) with single more compressible green areas – 5 elastotype according to Ueno (fig. 2c).

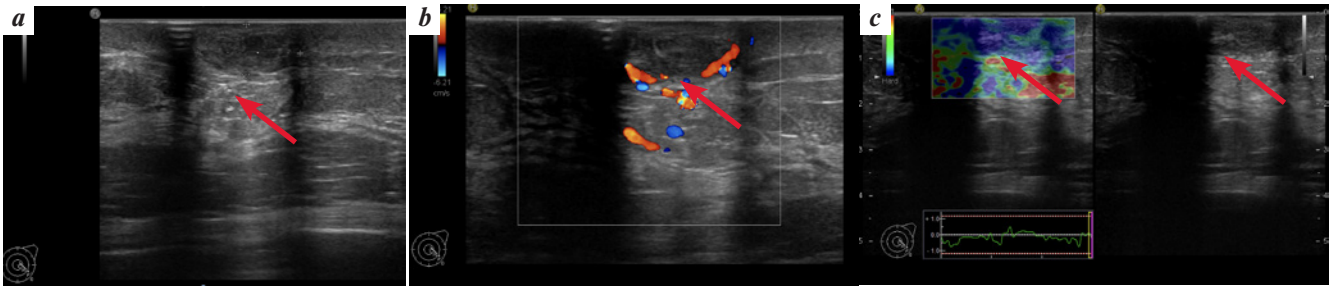

Fig. 2. *Tumor sonography: a hypoechoic heterogeneous formation with a smooth and unclear contour (a); blood flow is detected in the lower edge of the tumor (b). Tumor (arrow) elastography (c)*

The patient underwent a tumor biopsy under ultrasound assistance.

The pathological examination revealed a malignant spindle cell solid tumor with high mitotic activity of tumor cells (fig. 3).

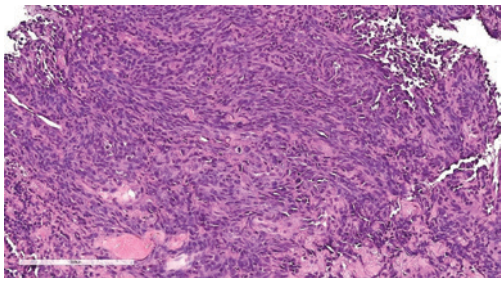

Fig. 3. *Picture of a punch biopsy specimen from the breast tumor. Hematoxylin and eosin staining, ×200*

For differential diagnosis, an immunohistochemical study was performed. The tumor was negative for pan-cytokeratin antibody and S100 (fig. 4a) and had a strong, diffuse, nuclear positive expression for Vimentin (fig. 4b), CD31 (fig. 4c), FLI1 (fig. 4d). The Ki-67 proliferation index of the tumor cells was 90 % (fig. 5).

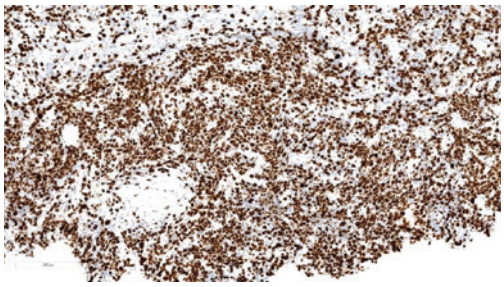

Fig. 5. *Immunohistochemical examination. Ki-67 expression index is 90 % (clone MIB-1)*

In accordance with clinicopathological report and immunohistochemical staining, a diagnosis of radio-induced angiosarcoma with a high degree of malignancy was established. No data were obtained for distant metastases during radiological examination (computed tomography of the chest and abdominal cavity, ultrasound of the pelvis, scanning of bones). The patient underwent surgery – left mastectomy (fig. 6).

The pathological report. Gross description: a rounded violet elevated nodule with ill defined margins 2 cm in diameter localized in the skin under the postoperative scar near the left nipple.

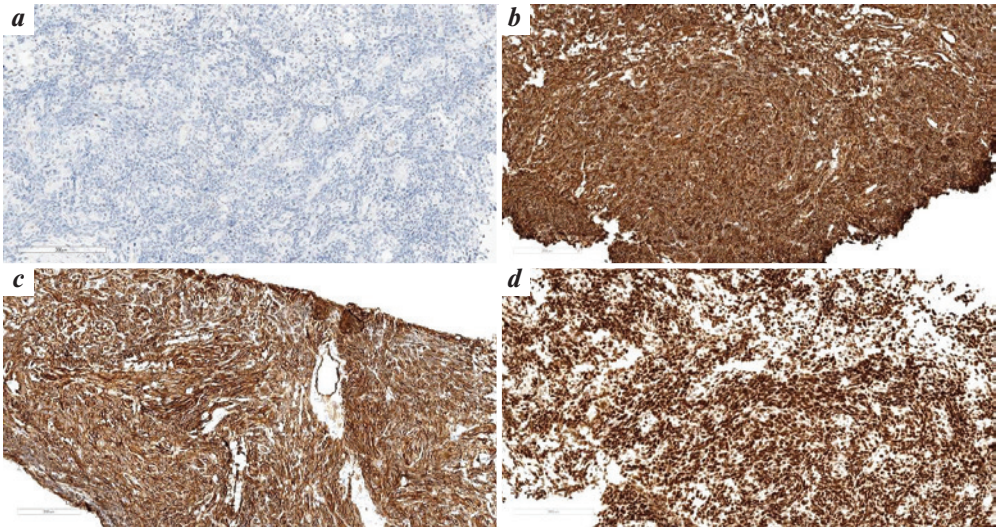

Fig. 4. *Immunohistochemical examination: a – no Keratin PAN expression (clone AE1/AE3/PCK26); b – membrane expression of Vimentin (clone V9); c – membrane expression of CD31 (clone JC70); d – nuclear expression of FLI1 (clone MRQ-1)*

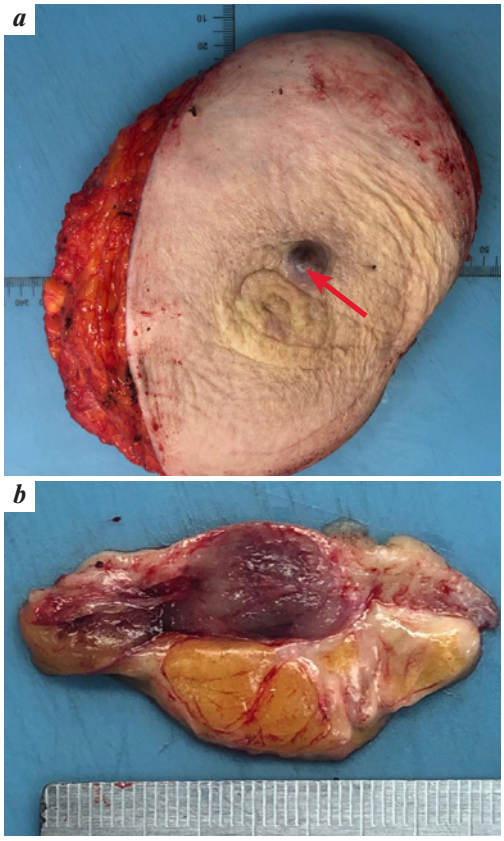

Fig. 6. *Gross specimen: a – removed left breast with a tumor (arrow); b – tumor section*

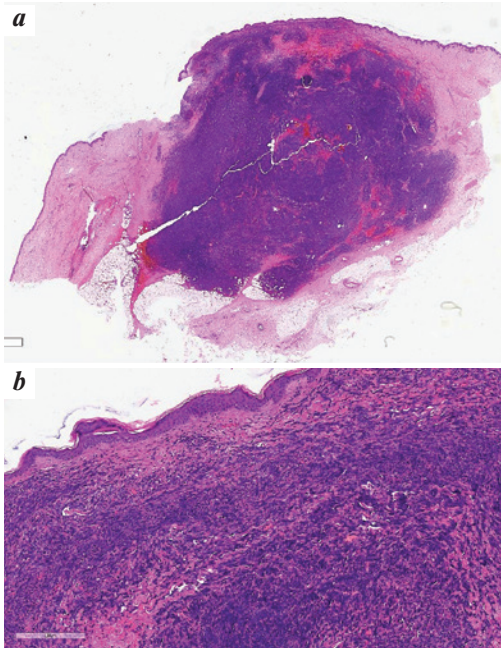

Fig. 7. *Histological examination of the tumor node: a – 4 × magnification; b – 200 × magnification. Hematoxylin and eosin staining*

Microscopic description of the tumor node revealed a histological picture similar to the breast core biopsy (fig. 7). The final pathological diagnosis was radio-induced (post-radiation) BAS.

Angiosarcoma of the mammary gland is an extremely rare and poorly studied tumor for which diagnostic and treatment standards have not been developed. The appearance of the first minimal clinical symptoms, such as thickening and discoloration of the skin, allows one to suspect the onset of the disease, and a biopsy with a qualitative morphological examination allows the correct diagnosis of BAS. The only radical treatment option for this tumor is its surgical removal within the R0 resection margins; however, even in this case, the course of the disease is extremely aggressive. It is necessary to accumulate experience in the diagnosis and treatment of patients with radio-induced BAS.

REFERENCES

1. Huang J., Mackillop W.J. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma.
2. Travis E.L., Kreuther A., Young T. et al. Unusual postirradiation sarcoma of chest wall. Cancer 1976;38:2269–73. DOI: 10.1002/1097-0142(197612)38:6<2269::aid-cncr2820380613>3.0.co;2-7.
3. Fineberg S., Rosen P.P. Cutaneous angiosarcoma and atypical vascular lesions of the skin and breast after radiation therapy for breast carcinoma. Am J Clin Pathol 1994;102(6):757–63. DOI: 10.1093/ajcp/102.6.757.
4. Sessions S.C., Smink R.D. Cutaneous angiosarcoma of the breast after segmental mastectomy and radiation therapy. Arch Surg 1992;127(11):1362–3. DOI: 10.1001/archsurg.1992.01420110114023.
5. Cohen-Hallaleh R.B., Smith H.G., Smith R.C. Radiation induced angiosarcoma of the breast: outcomes from a retrospective case series. Clin Sarcoma Res 2017;7:15. DOI: 10.1186/s13569-017-0081-7.
6. Fant J., Grant M., May S. et al. Angiosarcoma of the breast: Mammographic, clinical, and pathologic correlation. Breast J 2003;9:252–3. DOI: 10.1046/j.1524-4741.2003.09316.x.
7. Ryabchikov D.A., Vorotnikov I.K., Chkhikvadze N.V. et al. Breast sarcomas. Literature review. Tumors of Female Reproductive System 2014;2:12–5. DOI: 10.17650/1994-4098-2014-0-2-12-15.
8. Erel E., Vlachou E., Athanasiadou M. et al. Management of radiation-induced sarcomas in a tertiary referral centre: A review of 25 cases. Breast 2010;19:424–7. DOI: 10.1016/j.breast.2010.04.006.
9. Sheth G.R., Cranmer L.D., Smith B.D. et al. Radiation-induced sarcoma of the breast: a systematic review. Oncologist 2012;17(3):405–18. DOI: 10.1634/theoncologist.2011-0282.
10. Bjerkehagen B., Smeland S., Walberg L. et al. Radiation-induced sarcoma: 25-year experience from the Norwegian Radium Hospital.

Acta Oncol 2008;47:1475–82. DOI: 10.1080/02841860802047387.
11. Strobbe L.J., Peterse H.L., van Tinteren H. et al. Angiosarcoma of the breast after conservation therapy for invasive cancer, the incidence and outcome. An unforseen sequela. Breast Cancer Res Treat 1998;47:101–9. DOI: 10.1023/a:1005997017102.
12. Quadros C.A., Vasconcelos A., Andrade R. et al. Good outcome after neoadjuvant chemotherapy and extended surgical resection for a large radiation-induced high-grade breast sarcoma. Int Semin Surg Oncol 2006;3:18. DOI: 10.1186/1477-7800-3-18.
13. Fodor J., Orosz Z., Szabó E. et al. Angiosarcoma after conservation treatment for breast carcinoma: Our experience and a review of the literature. J Am Acad Dermatol 2006;54:499–504. DOI: 10.1016/j.jaad.2005.10.017.
14. Sheth G.R., Cranmer L.D., Smith B.D. et al. Radiation-induced sarcoma of the breast: a systematic review. Oncologist 2012;17(3): 405–18. DOI: 10.1634/theoncologist. 2011-0282.
15. Alvarado-Miranda A., Bacon-Fonseca L., Ulises Lara-Medina F. et al. Thalidomide combined with neoadjuvant chemotherapy in angiosarcoma of the breast with complete pathologic response: case report and review of literature. Breast Care (Basel) 2013;8(1):74–6. DOI: 10.1159/000346822.
16. Sleijfer S., Ouali M., van Glabbeke M. et al. Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas: an exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG). Eur J Cancer 2010;46(1):72–83. DOI: 10.1016/ j.ejca.2009.09.022.
17. Neuhaus S.J., Pinnock N., Giblin V. et al. Treatment and outcome of radiation-induced soft-tissue sarcomas at a specialist institution. Eur J Surg Oncol 2009;35(6):654–9. DOI: 10.1016/ j.ejso.2008.11.008.

Authors’ contributions
I.V. Kolyadina, V.V. Kometova, Yu.V. Bikeev, S.V. Khokhlova, V.V. Rodionov: concept and design of the study, collection and processing of material, article writing text, article editing.

ORCID of authors
I.V. Kolyadina: https://orcid.org/0000-0002-1124-6802
V.V. Kometova: https://orcid.org/0000-0001-9666-6875
V.V. Rodionov: https://orcid.org/0000-0003-0096-7126

Conflict of interest. The authors declare no conflict of interest.

Financing. The work was performed without external funding.

Article submitted: 29.07.2020. **Accepted for publication:** 03.09.2020.