DOI: 10.4149/BLL_2014_062

Bratisl Lek Listy 2014; 115 (5)
307 – 310

CASE REPORT

Analysis of radiation-induced angiosarcoma of the breast

Zemanova M[1,2], Rauova K[3], Boljesikova E[2], Machalekova K[4], Krajcovicova I[1], Lehotska V[1,3], Mikulova M[5], Svec J[1]

1st Oncological Clinic, Faculty of Medicine, Comenius University, Bratislava, Slovakia.
mata.zemanova@gmai.com

Abstract: Breast angiosarcoma may occur de novo, or as a complication of radiation therapy, or chronic lymphedema secondary to axillary lymph node dissection for mammary carcinoma. Both primary and secondary angiosarcomas may present with bruise like skin discoloration, which may delay the diagnosis. Imaging findings are nonspecific. In case of high-grade tumours, MRI may be used effectively to determine lesion extent by showing rapid enhancement, nevertheless earliest possible diagnostics is crucial therefore any symptoms of angiosarcoma have to be carefully analysed.
The case analysed here reports on results of 44-year old premenopausal woman who was treated for a T1N1M0 invasive ductal carcinoma. After a biopsy diagnosis of carcinoma, the patient underwent quadrantectomy with axillary lymph node dissection. She received partial 4 cycles of chemotherapy with adriamycin and cyclophosphamide, followed by radiation treatment. Thereafter, a standard postoperative radiotherapy was applied at our institution four months after chemotherapy (TD 46Gy in 23 fractions followed by a 10Gy electron boost to the tumour bed). Adjuvant chemotherapy was finished six months after operation, followed by tamoxifen. Follow up: no further complications were detected during regular check-ups. However, 12-years later, patient reported significant changes at breast region which was exposed to radiation during treatment of original tumour.
In this article, we describe the clinical presentation, imaging and pathological findings of secondary angiosarcoma of the breast after radiotherapy *(Fig. 2, Ref. 26)*. Text in PDF *www.elis.sk.*
Key words: angiosarcoma, secondary malignancy, radiotherapy, treatment outcomes.

Angiosarcomas may occur in any organ of the body. They can originate in the liver, breast, spleen, bone or heart, but they arise most frequently in the skin and soft tissue, and approximately 1 % of all soft tissue sarcomas are angiosarcomas (1). Angiosarcomas can be primary or secondary. Primary angiosarcomas are rare and account for 0.04 % of all malignant breast tumours (2) and primary angiosarcoma represents only 1 in 1700–2000 primary breast cancers (3). They occur sporadically in young women, usually during the third and fourth decades, and usually present as palpable mass, that may by growing rapidly. Secondary angiosarcomas usually are found in older women who have undergone breast conservation therapy. The median latency of secondary angiosarcomas after radiation treatment is 5–8 years (4). The inclusion criteria used for secondary angiosarocoma were the ones proposed by Cahan and modified by Arlen as follows : a sarcoma arising within the field of previous radiotherapy, differing histology between the sarcoma and primary tumor and 3–year latency period between radiation therapy end development of the sarcoma (5).

[1]1st Oncological Clinic, Faculty of Medicine, Comenius University, Bratislava, Slovakia, [2]Department of Radiation Oncology, St. Elizabeth Cancer Institute, Bratislava, Slovakia, [3]Department of Radiodiagnostics, St. Elizabeth Cancer Institute, Bratislava, Slovakia, [4]Department of Pathology of Slovak Medical University and St. Elizabeth Cancer Institute, Bratislava, Slovakia, and [5]Department of Clinical Oncology, St. Elizabeth Cancer Institute, Bratislava, Slovakia

Address for correspondence: M. Zemanova, MD, 1st Oncological Clinic, Faculty of Medicine, Comenius University, Heydukova 10, SK-825 10 Bratislava, Slovakia.
Phone: +421.2.59249147

Angiosarcoma, first described by Schmidt in 1887 (6) and subsequently by Borrmann in 1907, is a highly lethal and a rather rare neoplasm accounting for less than 0.05% of primary mammary cancer.

Although it is most commonly known as an angiosarcoma, it has also been referred to as hemangiosarcoma, haemangioendothelioma (7, 8), haemangioblastoma (9), angioblastoma (10), and benign metastasizing haemangioma (11). There are two types: lymphedema – associated cutaneous angiosarcoma and postirradiation angiosarcoma. Lymphedema-associated cutaneous angiosarcoma was first described in 1948 by Stewart and Treves, it develops on lymphedematous limb and chest wall after mastectomy and auxiliary lymph node dissection. Increased use of breast conservation therapy and sentinel lymph node salping has lowered the incidence of treatment-related lymphedema (12). Secondary angiosarcoma of the breast is distinguished from primary angiosarcoma by its association with a number of presumed etiological factors, most commonly radiation and long standing lymphedema. Postradiation angiosarcoma is seen either in the skin of the chest wall or in residual breast tissue, with most tumors being cutaneous. The latency period, or interval between radiation and diagnosis of angiosarcoma, ranges from 3 to 12 years, with most tumors occurring within 6 years after radiation therapy (13).

Theoretical background

The first reported case of breast angiosarcoma postradiation and breast-conserving therapy following radiation to the breast was reported in 1987 (14). The incidence may be increasing due to

the increase in the number of women receiving radiation therapy following breast conserving surgery. A retrospective cohort study of 194.798 women with breast cancer concluded that patients who had received adjuvant radiotherapy were at a significantly higher risk of developing angiosarcoma (15) with an estimated incidence of around 1 %.

Since angiosarcoma is a rare disease there is only limited number of papers on this specific subject. However, in recent years, post-treatment angiosarcomas of the breast are described more often. There are several scientific papers on the increase of the risk of developing a soft tissue sarcoma in breast region of patients after Breast-Conserving Therapy (BCT). Few of them deal with therapeutic options but some also report on relatively bad prognosis. It is clear that the prognosis is determined by early diagnosis which is often very difficult. Today, only radical surgery seems to be accurate curative treatment, therefore very prompt and appropriate diagnostics must be applied in a timely manner in order to avoid any delays related to determination of such disease (16). When the clinical picture is present, even though imaging techniques do not provide further information, an incisional biopsy provides the fastest way to early diagnosis and treatment. Angiosarcoma characteristically presents as a painless mass in the breast often accompanied by blueish, reddish, purple or even black skin discolouration. This may be confused with mastitis carcinomatosa in an irradiated breast or with post radiotherapy sequellae. Unfortunately, MMG, USG and MRl have a low diagnostic sensitivity and even fine needle aspiration cytology is not verifiable diagnostic tool in this case. Therefore, incisional biopsy, including discoloured skin and underlying tumour is the most accurate way to diagnosis.

It is important to emphasise that treatment of angiosarcoma should be planned by a multidisciplinary team. The primary treatment for localised disease is surgery. Mastectomy is generally performed for more sizeable tumors, but lumpectomy obtains equivalent oncologic result, if technically feasible. Obtaining negative surgical margins is more important than the type of surgery (17). Adjuvant or neo-adjuvant chemotherapy should be considered in high-risk cases. For locally advanced inoperable or metastatic disease, chemotherapy is the pillar of the treatment. Angiosarcomas are particularly sensitive to taxanes and liposomal doxorubicin (18). This appears to be true also for breast angiosarcomas given that some reports have confirmed responses to these agents (19). As a result, weekly paclitaxel or liposomal doxorubicin may be considered as valid alternative to standard ifosfamid /anthracycline treatment for this particular histology in view also of their manageable adverse effect profile and ease of administration (20).The limited data on the use of chemotherapy in the management of AS makes it difficult to asses the bona fide effect of this treatment modality (21). In a phase II trial, paclitaxel has shown encouraging results in unresectable angiosarcomas (22) The tyrosine-kinase inhibitor, imatinib, which inhibits c-KIT, also has been proposed in the treatment of radiation-induced sarcomas (23). Vascular endothelial growth factor is a mitogen known to promote angiogenesis in vivo and hence may have an important role in the development and progression of angiosarcomas (24). Vascular endothelial growth factors have been shown to be present in angiosarcomas (25) and trials involving antibodies directed against their receptor (bevacizumab) are in progress. Disease response or prolonged disease stabilization is obtained in a significant minority. Most clinicians are reluctant to include radiation treatment in the therapy plan because of surrounding healthy tissue radiation limits even years after initial radiotherapy. Nevertheless, a small retrospective series of 13 patients with radiation-induced AS, who received hyper-fractionated accelerated radiotherapy, showed that this mode of treatment is well tolerated and provides local control in nearly 60 % of patients (26). Patients in these series received a median of 60 Gy total with three fractions of 1 Gy per day at least 4 hours apart, and had surgery before or after radiation. Their 5-year overall survival was 86 %.

Materials and methods

This paper reports the case of a patient with indicated angiosarcoma after BCT with postoperative radiotherapy. The description of primary breast cancer and secondary malignancy including the overview of diagnostic methods and therapy is summarized. A 44-year old premenopausal woman was treated for a T1N1M0 (stage IIA) invasive ductal carcinoma (grade 2, l.sin) with quadrantectomy and node biopsy (level I,II) and the surgery was completed on January 27, 1998. The size of the tumour was 20 mm and there was negative surgical margin. One out of eleven nodes was detected with metastasis. All investigated oncological markers were negative, specifically CEA (1.36), CA 15-3 (14.98), CA 125 (16.39), CA 19-9 (31.6). The chemotherapy was administrated before (4xAC) and after (2xAC) radiotherapy. Postoperative adjuvant radiotherapy with TD 46 Gy in 23 fractions followed (Co-60) by a 10-Gy electron boost to the tumour bed was completed on July 25, 1998. Thereafter, TMX was prescribed for next 5 years. Only limited post radiation dermatitis (stage I) was observed and there was no history of breast or arm oedema or visible radiation effect as a teleangiectasia or fibrosis.

During the next 12-years no objective problems were observed and the patient did not report any complications related to the original disease. The last regular check -up was completed on July 7, 2010 with no indication of recurrence. Standard diagnostics by MMG and USG was applied and there was no sign for locoregional relapse. All investigated oncological markers were also negative. However, two weeks later, the patient claimed intensive pain in the left axilla and arm. Although, the pain was declining in this area during next days, further complications occurred, specifically an inflammation of mammilla and areola. She was treated for this inflammation by standard antibiotics (amoxicillin). The pain occurred again and she first noted a persistent “red-ring” decoration of areola. A few days later, the patient reported further induration of central quadrant directly behind areola. Based on anamnesis, there was an indication for initial phase of suspected mastitis.

In July 2010, an investigation by the percutaneous aspiration biopsy (PAB) was done. Its result gave an indication for local recurrence. Thereafter, local skin excision was done in order to identity the origin of induration, however the finding was negative. Due to observed flat infiltration (34 x 22 mm) MRI was done on August 16, 2010. The MRI described some indication for a new

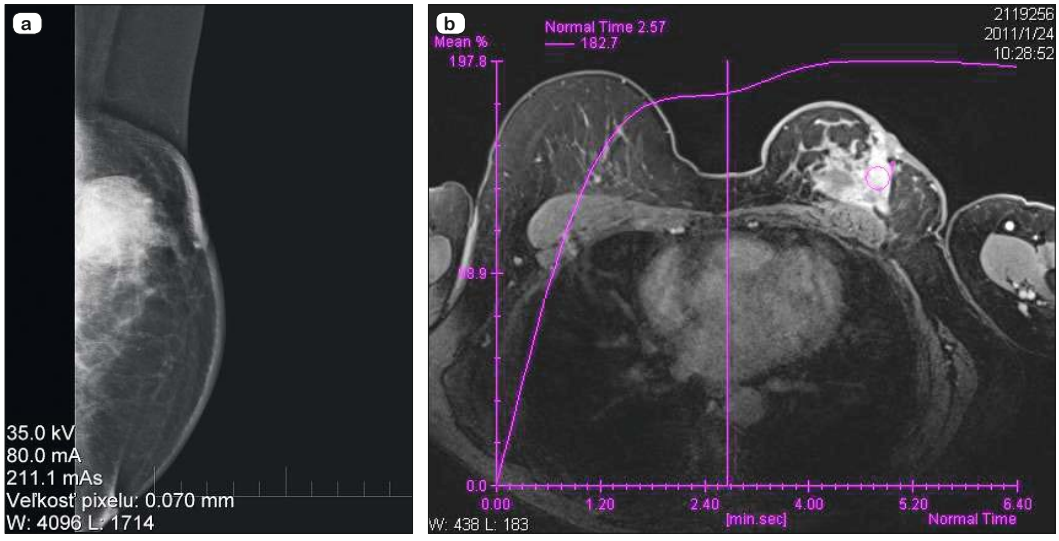

Fig. 1. (a) Mammography of the left breast – MLO projection – increased density of fibroglandular tissue with focal appearance in the upper quadrant of the left breast, (b) MRI of the breast-dynamic contrast enhanced study – markedly enhanced infiltration with retractive changes and middle to high proliferating activity.

proliferated infiltration between central and lower median quadrant with further induration of skin, deformation of affected breast and retraction of its mammilla. Core-cut biopsy performed after MRI examination did not determine any neoplastic changes, however on the edge of specimen inflammatory mesenchymal cellulization was increased. Recommended histologisation of the supraclavicular lymphnode and PET examination were not performed, because the patient decided to undergo antibiotic treatment recommended by her family doctor. This treatment was without any therapeutical effect. Due to pending complications with no improvement after conventional treatment in January 2011, the patient came to oncological centre for further investigation. Immediately mammography (Fig. 1a) and ultrasound examinations were performed. The outcomes of these modalities excluded inflammatory mastitis and indicated possible tumorous changes of mastitis carcinomatosa. Very significant progress in skin induration was confirmed by MRI (Fig.1b). Infiltrated region almost doubled its size (60 x 40 mm) from previous control. Finally, high grade angiosarcoma was confirmed based on additional core-cut biopsy.

Results and discussion

It is specified as inter-anastomosing vascular channels which are intermingled with solid endothelial or spindle cell areas that show necrotic foci and numerous mitoses. Grade III (poorly differentiated) angiosarcoma was diagnosed. In this particular case, more than 50 % of the total neoplastic area is composed of solid and spindle cell components without evident vascular channels (Fig. 2). From January to March, the patient received neoadjuvant chemotherapy (3 cycles of combination Docetaxel 150 mg and Gemcitabin 2000 mg). After chemotheraphy a simple left mastectomy was performed. Pathological examination of a mastectomy specimen revealed satisfactory post therapeutic response, only a minimal residual angiosarcoma population was present. Regres-

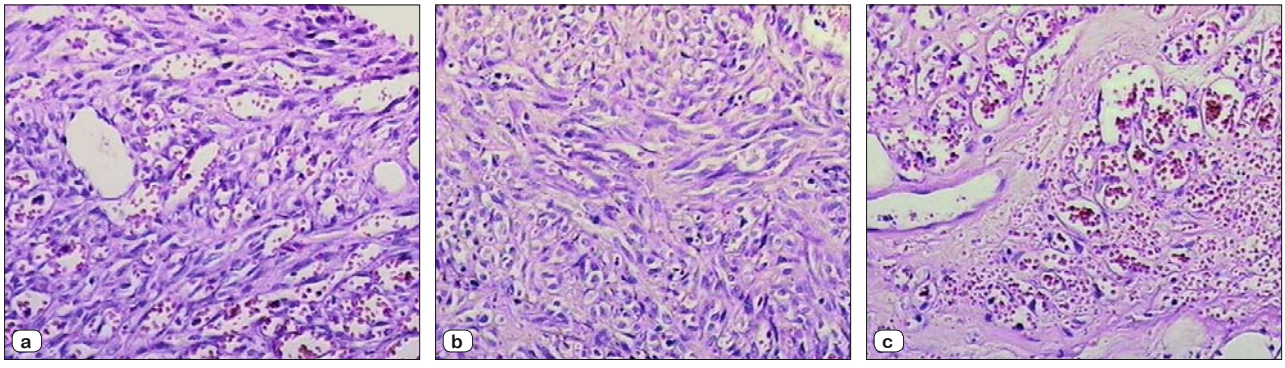

Fig. 2. (a) Core-cut biopsy: high-grade angiosarcoma, composed of neoplastic spindle cell population arranged in cohesive clusters (distinct vascular spaces are formed and covered by hobnail cells), (b) Core-cut biopsy: hypercellulary part of the angiosarcoma, comprising of spindle and epitheloid cells with whorl formations and tiny capillaries, (c) Breast amputation: Residual vascular spaces filled with erythrocytes and covered by atypical endothelial cells, placed in a hyalinne stoma- this represents the sole residual neoplastic formations of the previously diagnosed angiosarcoma (all pictures hematoxylin-eosin stain, original magnification x200).

sive and reparative changes prevailed. Chemotheraphy of further 3 cycles in previous combination was applied. Further control mammography, ultrasound, MRI of the breast, CT of brain, chest and abdomen were with negative results in terms of distant metastases. As of April 1, 2012, 14 months after assessment of this diagnosis and 11 months after treatment the patient was doing well, without evidence of recurrent disease.

Conclusions

Both primary and secondary angiosarcomas are rare. The prognosis for angiosarcoma of the breast whether it develops as "de novo" tumour or arising in a background of lymphedema or radiation therapy, is generally poor. The median survival period is 14.5–34 months with a 5-year survival rate of approximately 15 %. A better survival rate has been correlated with low grade lesions with negative surgical margin. Death is usually due to metastases to lung, skin and bone, however some patients present with massive bleeding metastatic lesions. Association of BCT with angiosarcoma tumour needs further investigation and analysis since only a limited number of clinical cases are available. The multimodal therapeutic approach to this aggressive disease and comparison of clinical experiences from other cancer institutes will be essential for further improvement of early stage diagnostics and treatment approaches.

In the reported case we would like to share our clinical experience with the treatment of secondary angiosarcoma after conservative breast treatment. However, radiotherapy in the treatment of breast cancer is associated with an increased risk of subsequent sarcoma, but the magnitude of this risk is rather small. Adjuvant radiotherapy has become the standard of care in the conservative management of breast carcinoma and because of the number of patients has significantly increased over the past decade it is probable that radiation-induced breast sarcoma incidence will increase in near future. As of today, less than 300 cases are reported in English written papers. Due to lack of clinical data there is no standard treatment procedure for this type of secondary cancer. Further sharing of clinical experience would help to establish the treatment protocols for this secondary malignance. It is clear that angiosarcoma is more prevalent in cases treated with radiotherapy, occurring especially in or adjacent to the radiation field. Nevertheless, the small difference in risk of subsequent sarcoma for breast cancer patients receiving radiotherapy does not supersede the benefit of radiotherapy.

References

1. Folpe AL and Gowen AM. Malignant vascular tumours. In: Weiss SW and Goldblum JR, editors. Enyinger and Weiss Soft Tissue Tumors; St Lois: Mosby, 2001, 917–954.

2. Yang WT, Hennessy BT, Dryden MJ, Valero V.Hunt KK, Krishnamurthy S. Mammary angiosarcomas: imaging findings in 24 patients, Radiology. 2007; 242 (3):725–734.

3. Enzinger FM, Weiss SW, Malignant vascular tumors. En Soft Tissue Tumors (3rd ed.). Mosby, St. Louis, 1995: 641–677.

4. Hodgson NC, Bowen-Wells C, Moffatt F, Franceschi D, Avisar E. Angiosarcoma of the breast. A review of 70 cases. Am J Clin Oncol 2007; 30 (6): 570–357.

5. Brenn T, Fletcher CD. Radiation associated cutaneous atypical vascular lesions and angiosarcoma: clinicopathologic analysis of 42 cases. Am J Surg Pathol 2005; 29 (8): 983–996.

6. Madox JC, Evans HL. Angiosarcoma of skin and soft tissue a study of forty four cases. Cancer 1981; 48 (8): 1907–1921.

7. Neugut AI, Weinberg MD, Ahsan H et al. Carcinogenetic effects of radiotherapy for breast cancer. Oncology 1999 (Huntingt), 1245–1256, discussion 1257, 1261–1245.

8. Boice JD, Harvey EB, Blettner M et al. Cancer in the contralater breast after radiotherapy for breast cancer. N Engl J Med 1992; 326 (12): 781–785.

9. Gao X, Fisher SG, Emamyi B. Risk of second primary cancer in the contralateral breast in women treated for early stage breast cancer: a population based study. Int J Radiat Oncol Biol Phys 2003; 56 (4): 1038–1045.

10. Abdalla I, Thisted RA, Heimann R. The impact of contralateral breast cancer in the outcome of breast cancer patients treated by mastectomy. Cancer J 2000; 6 (4): 266–272.

11. Inskip PD, Stovall M, Flannery JT. Lung cancer risk and radiation dose among women treated for breast cancer. J Nat Cancer Inst 1994; 86 (13): 983–988.

12. Brenn T, Fletcher CD. Postradiation vascular proliferations: an increasing problem. Histopathology 2006; 48 (1): 106–114.

13. Hodgson NC, Bowen-Wells C, Moffat F et al. Angiosarcoma of the breast: A review of 70 cases. Am J Clin Oncol 2007; 30 (6): 570–573.

14. Body G, Sauvanet E, Calais G, Fignon A, Fetissof F, Lansac J. Cutaneous angiosarcoma of the breast following surgery and irradiation of breast adenocarcinoma. J Gynecol Obstet Biol Reprod (Paris) 1987; 16 (4): 479–483.

15. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. Cancer 2001; 92 (1): 172–180.

16. West JG, Oureshi A, West JE et al. Risk of angiosarcoma following breast conservation : a clinical alert. Breast J 2005; 11 (2): 115–123.

17. Al-Benna S, Poggemann K, Steinau H-U, Steinstraesser L. Diagnosis and management of primary breast sarcoma. Breast Cancer Res Treat 2010; 122 (3): 619–626.

18. Mano MS, Fraser G, Gray M, Evans V, Kazmi A et al. Radiation-induced angiosarcoma of breast shows major response to docetaxel after failure of anthracycline-based chemotherapy. Breast 2006; 15 (1): 117–118.

19. Perez-Ruiz E, Ribelles N, Sanches-Munoz A, Roman A,Marquez A. Response to paclitaxel in a radiotherapy-induced breast angiosarcoma. Acta Oncol 2009; 48 (7): 1078–1079.

20. Voutsadakis IA et al. Breast sarcomas: Current and future perspectives. Breast 2011; 20 (3): 199–204.

21. Jallali N et al. Breast angiosarcoma after BCT. Amer J Surg 2012; 203 (2): 156–161.

22. Penel N, Bui NB, Bay JO et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX study. J Clin Oncol 2008; 26 (32): 5269–5274.

23. Komdeur R, Hoekstra HJ, Molenaar WM et al. Clinopathologic assessment of postradiation sarcomas: KIT as a potential treatment target. Clin Cancer Res 2003; 9 (8): 2926–2932.

24. Itakura E, Yamamoto H, Oda Y et al. Detection and characterization of vascular endothelial growth factors and their receptors in a series of angiosarcomas. J Surg Oncol 2008; 97 (1): 74–81.

25. Folpe AL, Veikkola T, Valtola R et al. Vascular endothelial growth factor receptor–3: a marker of vascular tumors with presumed lymphatic differentiation, including Kaposis sarcoma, Kaposi form and Dabska-type hemangioendotheliomas, and a subset of angiosarcomas. Mod Pathol 2000; 13 (2): 180–185.

26. Palta M, Morris CG, Grobmyer SR, Copeland III EM, Mendenhall NP. Angiosarcoma after breast-conserving therapy. Cancer 2010; 116(8): 1872–1878.

Received May 1, 2012.
Accepted February 28, 2014.