Atypical Presentation of Radiation-Associated Breast Angiosarcoma: A Case Report and Review of Literature

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Conflict of interest: None declared

Patient: Female, 67
Final Diagnosis: Breast angiosarcoma
Symptoms: Skin lesion
Medication: —
Clinical Procedure: Surgery
Specialty: Oncology

Objective: Unusual clinical course
Background: Radiation-associated breast angiosarcoma is a rare clinical entity that is thought to be increasing in incidence. Here we present the case of a 67-year-old female with a history of left breast invasive ductal carcinoma who received breast conserving surgery and radiation therapy eight years ago. She then presented with a painless mild skin discoloration of the left breast that had been present for over one year. Mammograms and ultrasounds were normal. A punch biopsy and a subsequent excisional biopsy revealed the diagnosis of angiosarcoma. The patient was treated with mastectomy and had no subsequent recurrences.

Conclusions: The long-term clinical surveillance for all patients who receive breast conservation surgery is recommended and a high degree of suspicion should be exercised in view of potential atypical presentations of this disease.

MeSH Keywords: Breast Neoplasms • Heavy Ion Radiotherapy • Hemangiosarcoma • Mastectomy

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Background

Angiosarcoma is a rare vascular malignancy originating from endothelial cells (endoderm tumor) and can arise spontaneously or in association with factors like chronic lymphedema and radiation therapy. Most angiosarcomas develop in the skin or superficial soft tissue, while only 20% are in the deep soft tissues. Typical immunohistochemical expression profiles for angiosarcomas include upregulation of certain vascular-specific tyrosin kinase receptors, including, TIE1-2 and VEGFR1(FLT1), VEGFR2 (KDR), and downregulation of VEGFR ligand expression [1,2]. Interestingly, recent studies have shown that de novo angiosarcomas have distinct genetic profile compared to radiation-induced or lymphedema-associated angiosarcomas. As an example, a high level of amplification of MYC on 8q24.21 is found in most radiation-induced angiosarcomas while it is extremely rare in de novo angiosarcomas [3]. Prognosis has been historically poor especially for radiation-induced and large deep soft tissue angiosarcomas with a median survival of less than years [4]. Surgical resection is rarely curative, and there is only a modest sensitivity of angiosarcoma to taxanes or anthracycline-based chemotherapy [5,6]. However early detection and radical surgical treatment is potentially curative [7] hence the importance of increased awareness and knowledge about presenting symptoms.

Case Report

A 67-year-old Hispanic female with a past medical history of left breast invasive ductal carcinoma treated with lumpectomy, axillary lymph node dissection, and standard radiation therapy to the breast eight years ago, presented with a well circumscribed red skin discoloration with no additional skin changes or nodules in the left breast. Examination of the left breast revealed a flat 1 cm area of mild skin redness in the left lower quadrant of the breast without any palpable mass, warmth, or tenderness. The lesion was not associated with any edema, lesions, or blisters. Subsequent mammogram and ultrasound were negative for malignancy (BI-RADS-2). A punch biopsy demonstrated a vascular neoplasm with malignant cytological and histologic features (including nuclear pleomorphism, irregular nuclear contours, and invasion). Confirmatory immunohistochemistry stains were positive for endothelial marker (CD31, CD34, factor VIII), negative for pancytokeratin, ER, PR, HER2 and HHV8. A c-MYC immunohistochemical stain was equivocally positive, but was verified with a positive FISH study for MYC amplification (MYC/CEP8 ratio of 3.3). The patient was referred to surgery and underwent a left excisional biopsy in September 2016. The lesion from the excision was suspicious for angiosarcoma, positive for immunohistochemical endothelial markers CD31 (Figure 1) and CD34 (Figure 2) as well a positive c-MYC (Figure 3), however, with low Ki-67 at 5%. To further confirm the diagnosis, this case was sent to an outside consulting institution, and a consensus diagnosis of angiosarcoma of the breast involving the superficial dermis was established (Figures 4, 5). As margins of the biopsy were focally positive for angiosarcoma, the excisional biopsy was considered inadequate for treatment purposes and the patient underwent a left mastectomy in February 2017 with immediate reconstruction with tissue expanders and latissimus dorsi musculocutaneous flap. Pathology following this final surgery confirmed the absence of residual angiosarcoma. The patient was discharged home after surgery and currently is disease free and continues with routinely visits at our University Breast Clinic.
The association between radiation and angiosarcoma of the breast has been reported in the literature in various cohort studies [17]. Breast angiosarcoma is typically seen affecting the dermis within the radiation field making these angiosarcomas cutaneous in origin [7–12]. Cases of angiosarcoma developing in the breast parenchyma, arising from parenchymal vascular endothelial cells, have also been reported [8–11]. Radiation-associated angiosarcomas have distinct biological features. A study comparing the histopathology of sporadic angiosarcoma and radiation-associated angiosarcoma showed that radiation-associated angiosarcoma does not have overexpression of p53 and does not have a mutation in ATM [12]. High Ki-67, a marker associated with increased rates of metastasis, was found in 44% of radiation-associated angiosarcomas and hTERT expression was found in both radiation-associated and sporadic angiosarcomas [12]. Another study found MYC gene amplification in 90% of angiosarcomas cases associated with radiation for breast cancer [18,19]. Proposed mechanisms for the development of radiation-induced angiosarcoma link lymphedema as a causative factor, as chronic lymphedema may result in an increase of vascular growth factors and thus, enable the transformation to malignant tumors, or impair the repair of genetic mutations [17]. Radiation therapy itself may be a cause as it results in similar genetic damage.

Typically, a patient with angiosarcoma of the breast will present with a painless cutaneous lesion and blue-red skin discoloration resembling a hematoma [1,17]. It may be multifocal, typically involves a significant part of the breast, and is often associated with swelling, skin dimpling and thickening. The tumor size may vary and has been reported to range between 0.4 and 20 cm, with a mean tumor size of 7.5 cm [8]. In this case report, the clinical presentation was somewhat atypical as the tumor was small, not associated with edema or purple skin discoloration and showed low proliferation. However, despite being a low grade tumor, the characteristic MYC gene amplification was detected in this patient’s tumor.

The diagnostic work-up for radiation-induced angiosarcoma includes imaging and biopsy. Imaging modalities include mammogram and ultrasound, but lesions can be occult on mammography, as was the case in this patient. MRIs are useful in defining disease extent but have low diagnostic sensitivities [10,11]. Incisional biopsy of the discolored skin and underlying mass is the most accurate and fastest way to obtain a diagnosis [10]. The hallmark findings of angiosarcoma microscopically are abnormal, pleomorphic, malignant endothelial cells. There may be well-differentiated areas, in which the endothelial cells form functioning vascular sinusoids that have areas of monocyte infiltration. In poorly differentiated areas, malignant endothelial cells form sheets of cells and have areas of hemorrhage and necrosis [20]. MYC amplification can be used as a prognostic indicator, as it was found to be associated
with an adverse prognosis. However, it is a highly specific but poorly sensitive marker for angiosarcoma, and a negative result would not exclude the diagnosis [21].

The treatment for angiosarcomas is surgical resection with mastectomy aiming at obtaining negative margins. Obtaining negative surgical margins is more important than the type of surgery, and the standard surgical procedure is mastectomy with negative margins [22]. However, studies following patients treated with radical surgery have noted that extensive recurrences can occur as soon as two months of surgery, and might occur in the chest wall flap [14].

The role of chemotherapy has not been clearly established. Most data came from retrospective case series studies or even case reports suggesting that angiosarcomas are relatively sensitive to taxanes and anthracyclines with initial overall response rate from 20% to 60% [23–26]. However, the relapse rate is high and overall survival is between 5 and 48 months [6,25]. A small study using hyperfractionated accelerated re-irradiation (HART) found that 79% of patients achieved disease control beyond the typical intervals to recurrence, suggesting that this treatment method may be more favorable than chemotherapy, however, it would be best to avoided in radiation-induced angiosarcomas [15].

Conclusions

In conclusion, this case illustrates an atypical presentation of radiation-associated secondary angiosarcoma, presenting with a small flat skin discoloration in the radiation field, not associated with a mass, edema, or other skin changes. Also, the tumor was low grade and was not detected on mammogram. A high level of suspicion should be exercised when patients who receive breast conservation surgery and radiation present with any skin discoloration. Continuous long-term surveillance and increasing both patient and physician awareness is also indicated.

Conflicts of interest

None.

References:

1. Abbott R, Palmieri C: Angiosarcoma of the breast following surgery and radiotherapy for breast cancer. Nat Clin Pract Oncol, 2008; 5(12): 727–36
2. Antonescu CR, Yoshida A, Guo T et al: KDR activating mutations human angiosarcoma are sensitive to specific kinase inhibitors. Cancer Res, 2009; 69(18): 7175–79
3. Guo T, Zhang L, Chang NE et al: Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions. Genes Chromosomes Cancer 2011; 50(1): 25–33
4. Gladdy RA, Qin LX, Moraco N et al: Do radiation-associated soft tissue sarcomas have the same prognosis as sporadic soft tissue sarcomas? J Clin Oncol, 2010; 28(12): 2064–69
5. Budd GT: Management of angiosarcoma. Curr Oncol Rep, 2002; 4(6): 515–19
6. Perez-Ruiz E, Ribelles N, Sanchez-Muñoz A et al: Response to paclitaxel in a radiotherapy-induced breast angiosarcoma. Acta Oncol, 2009; 48(7): 1078–79
7. Lehnhardt M, Bohm J, Hirsch T et al: Radiation-induced angiosarcoma of the breast. Handchir Mikrochir Plast Chir, 2017; 49(2): 103–10
8. Glazebrook KN, Magut MJ, Reynolds C: Angiosarcoma of the breast. Am J Roentgenol, 2008; 190(2): 190–92
9. Ito T, Tanaka K, Suzzumura K et al: Angiosarcoma arising in the non-operated, sclerosing breast after primary irradiation, surviving 6 years post-resection: A case report and review of the Japanese literature. Int J Surg Case Rep, 2016; 24: 26–31
10. Zemanova M, Rauova K, Boljeskova E et al: Analysis of radiation-induced angiosarcoma of the breast. Bratil Lek Listy, 2014; 115(5): 307–10
11. Yang WT, Hennessy BTJ, Dryden MJ et al: Mammary angiosarcomas: Imaging findings in 24 patients. Radiology, 2007; 242(3): 725–34
12. Hung J, Hinkler SM, Lucas DR et al: Sporadic versus radiation-associated angiosarcoma: A comparative clinicopathologic and molecular analysis of 48 cases. Sarcoma. 2013; (9): 1–9
13. Mery CM, George S, Bertagnolli MM, Raut CP: Secondary sarcomas after radiotherapy for breast cancer: Sustained risk and poor survival. Cancer, 2009; 15: 4055–63
14. Feigenberg SJ, Price Mendenhall N, Reith JD et al: Angiosarcoma after breast-conserving therapy: Experience with hyperfractionated radiotherapy. Int J Radiat Oncol Biol Phys, 2002; 52(3): 620–26
15. Smith TL, Morris CG, Mendenhall NP: Angiosarcoma after breast-conserving therapy: Long-term disease control and late effects with hyperfractionated accelerated re-irradiation (HART). Acta Oncologica, 2014; 53(2): 235–41
16. Huang J, Mackillop WI: Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. Cancer, 2001, 1(92): 172–80
17. Monroe AT, Feigenberg SJ, Mendenhall NP: Angiosarcoma after breast-conserving therapy. Cancer, 2003; 97(8): 1832–40
18. Huang SC, Zhang L, Sung YS et al: Recurrent CIC gene abnormalities in angiosarcomas: A molecular study of 120 cases with concurrent investigation of PLCG1, KDR, MYC, and FLT4 gene alterations. Am J Surg Pathol, 2016; 40(5): 645–55
19. Manner J, Radwimmer B, Hohenberger P et al: MYC high level gene amplification is a distinctive feature of angiosarcomas after irradiation or chronic lymphedema. Am J Pathol, 2010; 176(1): 34–39
20. Young RJ, Brown NJ, Reed MW et al: Angiosarcoma. Lancet Oncol, 2010; 11(10): 983–91
21. Fraga-Guedes C, André S, Mastroprosas MG et al: Angiosarcoma and atypical vascular lesions of the breast: Diagnostic and prognostic role of MYC gene amplification and protein expression. Breast Cancer Res Treat, 2015; 151(1): 131–40
22. Lindford A, Bohlting T, Vaalavirta L et al: Surgical management of radiation-associated cutaneous breast angiosarcoma. J Plast Reconstr Aesthetic Surg, 2011; 64(8): 1036–42
23. Penel N, Bui BN, Bay JO et al: Phase II trial of weekly paclitaxel for unresectable angiosarcoma: The ANGIOTAX study. J Clin Oncol, 2008; 26(32): 5269–74
24. Mano MS, Fraser G, Kerr J et al: Radiation-induced angiosarcoma of breast shows major response to docetaxel after failure of anthracycline-based chemotherapy. Breast, 2006; 15(1): 117–18
25. Gambini D, Visintin R, Locatelli E et al: Paclitaxel-dependent prolonged and persistent complete remission four years from first recurrence of secondary breast angiosarcoma. Tumori, 2009; 95(6): 828–31
26. Skubitz KM, Haddad PA: Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. Cancer, 2005; 104(2): 361–66

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