

Educational Case: Radiation-Induced Angiosarcoma of the Breast

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/23742895211060529>.¹

Keywords

pathology competencies, disease mechanisms, neoplasia, environmental influences, DNA damage, radiation therapy, breast carcinoma, angiosarcoma

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Primary Learning Objective

Objective N2.2: Mechanisms of DNA Damage Repair. Describe the mechanisms by which exposure to radiation, tobacco, alcohol, or other environmental chemical agents can produce cancer.

Competency 1: Disease Mechanisms and Processes; Topic: Neoplasia (N); Learning Goal 2: Environmental Influences on Neoplasia

Patient Presentation

A 73-year-old woman presents to her oncologist concerned about multiple evolving, nontender, violaceous patches on her right breast. The atraumatic lesions have become darker and increased in size over the past 2 to 3 months. The patient has a history of ductal carcinoma in situ (DCIS) of the right breast diagnosed 12 years ago and was treated with a partial mastectomy. Pathologic examination of the partial mastectomy specimen demonstrated a single 1.1 cm focus of intermediate grade DCIS (pTis, pNX, pMX) with negative margins. Surgical excision was followed by adjuvant radiation therapy and chemotherapy (tamoxifen) without complications. Since that time, her mammograms, with the most recent imaging performed 6 months prior, have been unremarkable. Her medications include hydrochlorothiazide,

for hypertension, and occasionally aspirin, for headaches. The patient is otherwise healthy and has no other relevant past medical history.

Diagnostic Findings, Part I

On physical examination, the patient is afebrile and normotensive. Inspection of the right breast reveals a well-healed excisional scar in the upper outer quadrant. Multifocal erythematous to violaceous patches are observed on the skin along the medial and lateral aspects of the right breast (Figure 1) but do not involve the excisional scar. Palpation of the largest lesion along the medial aspect demonstrates no areas of induration, fluctuance, or drainage. The lesion is nontender and measures approximately 7 cm in greatest dimension. The smaller patches measure approximately 3 cm and likewise appear to

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Figure 1. Along the medial aspect of the patient's right breast, there is a large, polygonal, erythematous to violaceous patch.

involve the skin only, without deep soft tissue involvement. The nipple is erect and the skin lesions do not involve the areola. No palpable lymph nodes are found in the right axilla. The remaining physical examination, including the left breast and left axilla, are also unremarkable.

Questions/Discussion Points, Part 1

What Is the Differential Diagnosis Based on the Clinical Presentation?

The patient is presenting with multifocal, nontender, erythematous to violaceous patches, in a previously irradiated field of skin. Clinically the differential diagnosis would include ecchymoses, cellulitis, chronic radiation dermatitis, atypical vascular lesion, radiation-induced angiosarcoma, and recurrent breast carcinoma. Ecchymoses are common in elderly patients and can be seen in the setting of trauma, an underlying coagulopathy, or secondary to a medication effect (eg, blood thinners). This patient states she has no history of trauma, has no other medical problems, and only occasionally takes an aspirin for headaches, making this unlikely. Cellulitis is a bacterial infection of the skin and soft tissue and would be accompanied by warmth, pain, edema, and occasionally systemic symptoms. These plaques are relatively asymptomatic and she reports no fever or chills, helping to exclude an infectious etiology. Chronic radiation dermatitis can develop months to decades following radiotherapy. The clinical presentation can range from normal to atrophic skin with variable

pigmentation and telangiectasias. Although the patient has a history of radiation, the history of rapidly enlarging, violaceous patches would be unusual for this. Multifocal atypical vascular lesions can develop following radiotherapy but typically present as small erythematous macules and papules rather than large violaceous patches. For definitive diagnosis of an atypical vascular lesion, a biopsy would be necessary. Given the large size of the lesions and the rapid evolution of the lesions, radiation-induced angiosarcoma is the leading differential. Lastly, with a prior history of breast cancer, recurrent breast carcinoma is a possibility, however a negative mammogram 6 months earlier makes this diagnosis less likely.

Given the Clinical Differential Diagnosis, What Diagnostic Studies Would Be Most Appropriate to Help Narrow the Differential Diagnosis?

In conjunction with the physical findings, an unremarkable complete blood count and coagulation studies would provide additional evidence against an underlying infectious process or coagulopathy, respectively. A biopsy of the skin lesions would be essential in differentiating between chronic radiation dermatitis, atypical vascular lesion, radiation-induced angiosarcoma, and recurrent breast carcinoma.

Diagnostic Findings, Part 2

A punch biopsy is performed of a patch on the patient's right medial breast.

Questions/Discussion Points, Part 2

Describe the Histologic Findings From the Patient's Punch Biopsy.

The punch biopsy at low magnification (Figure 2) shows an unremarkable epidermis with a subtle vascular proliferation within the superficial dermis. At high magnification (Figure 3), several irregular vascular spaces are seen, lined by a single layer of enlarged and hyperchromatic endothelial cells. The endothelial cells show irregular nuclear contours without prominent nucleoli.

Which Histologic Findings Would Help Differentiate Between an Atypical Vascular Lesion, Radiation-Induced Angiosarcoma, and Chronic Radiation Dermatitis?

In the setting of radiotherapy to the skin, the histologic differential includes an atypical vascular lesion, radiation-induced angiosarcoma, and chronic radiation dermatitis. Atypical vascular lesions are small, well circumscribed vascular proliferations most often limited to the superficial dermis. Histologically, they consist of thin-walled blood vessels with a single cell layer of nonatypical endothelial cells. Although

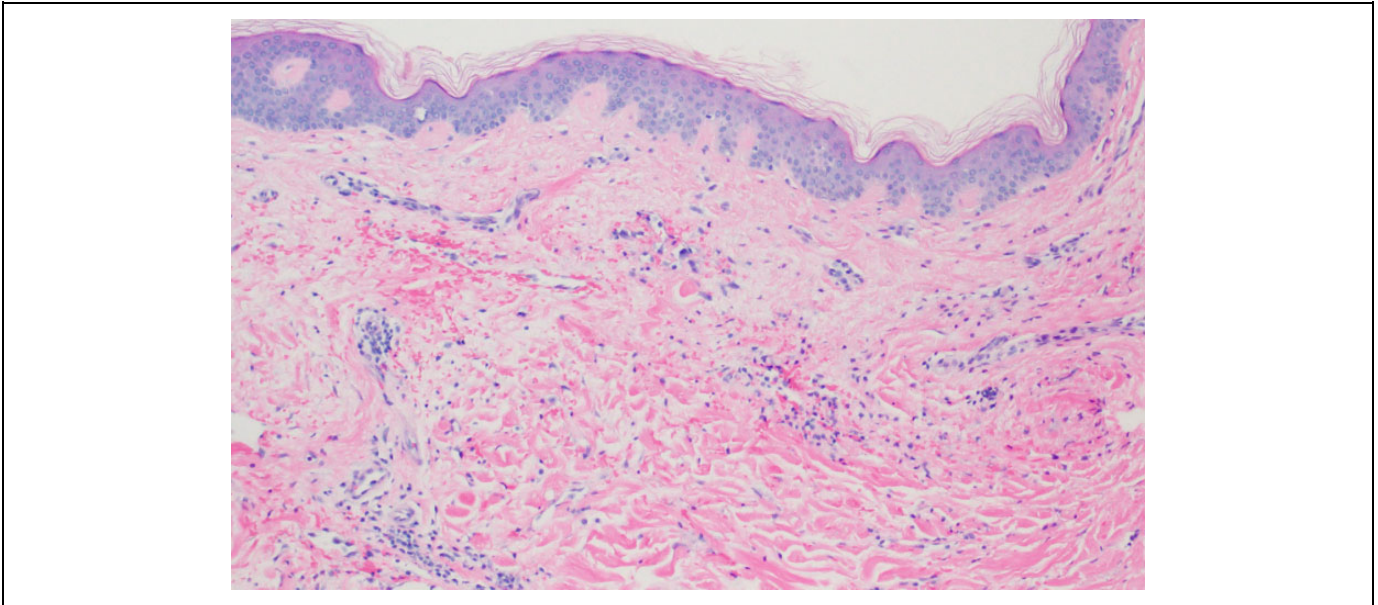


Figure 2. The patient's punch biopsy from the medial aspect of the right breast. The epidermis is unremarkable. Within the dermis, there is subtle vascular proliferation and red blood cell extravasation (hematoxylin and eosin, $\times 10$).

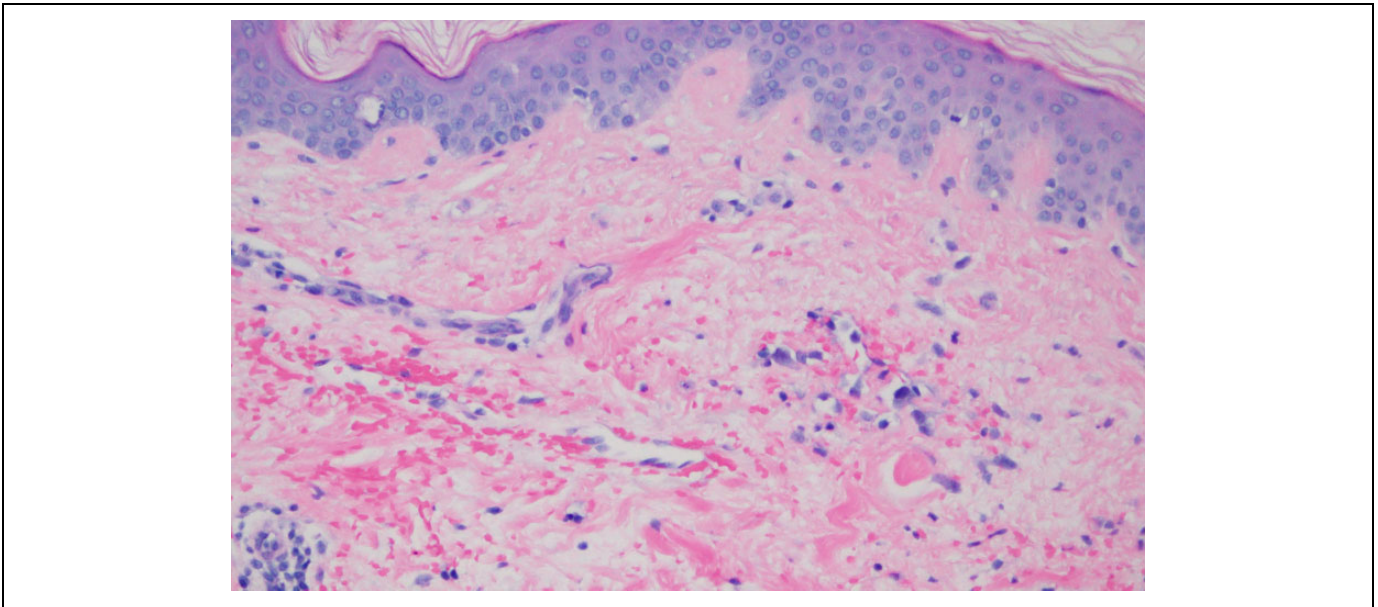


Figure 3. The patient's punch biopsy from the medial aspect of the right breast. Within the dermis, there are irregular vascular spaces lined by endothelial cells with nuclear enlargement and hyperchromasia (hematoxylin and eosin, $\times 20$).

these lesions are considered benign, many authors consider them to be precursors of angiosarcomas and are therefore closely followed or completely excised.² On the contrary, angiosarcomas are much larger, infiltrative, and typically involve the deep dermis and subcutaneous tissues. The anastomotic vascular channels are lined by cytologically atypical endothelial cells with a high N:C ratio, nuclear hyperchromasia, and irregular nuclear contours.

There is anastomosing of the vessels, and an infiltrative growth pattern is seen. Angiosarcomas are malignant. Chronic

radiation dermatitis is a benign entity and histologically shows epidermal atrophy, hyalinization of the dermal collagen, and superficially located telangiectasias with endothelial cell swelling. Bizarre fibroblasts can also be found in the stroma.

What Additional Workup Should Be Pursued to Narrow the Histologic Differential Diagnosis?

The biopsy sample demonstrated a limited number of vascular spaces with focal endothelial cell atypia. In the setting of prior

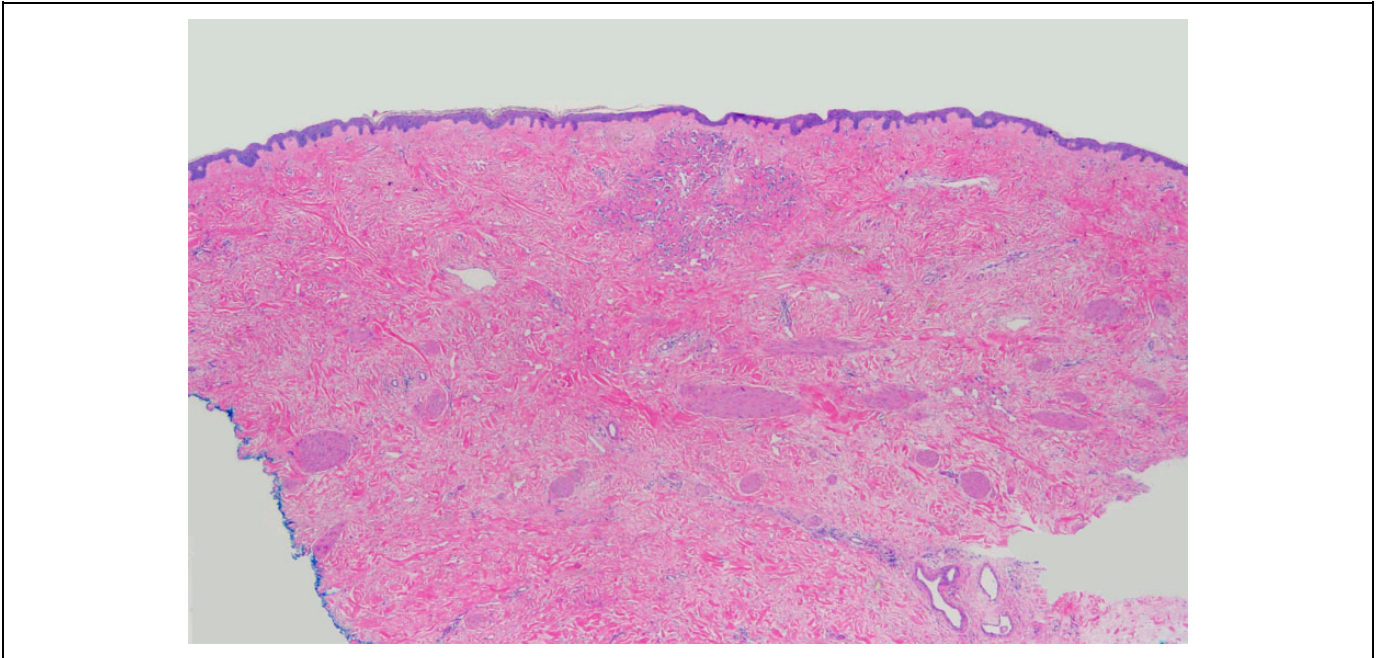


Figure 4. The patient's excisional biopsy from the medial aspect of the right breast. Within the dermis, there is fairly well circumscribed, nodular vascular proliferation (hematoxylin and eosin, $\times 2$).

radiotherapy, the focal findings raise the possibility of an atypical vascular lesion. However, the biopsy is only a small portion of a larger lesion and therefore may not be representative of the lesion as a whole. Angiosarcoma remains in the differential diagnosis. For more definitive classification, evaluation by an excisional biopsy should be performed. The histologic findings on the excisional biopsy, in conjunction with immunohistochemical staining pattern of *MYC*, can further delineate between an atypical vascular lesion and radiation-induced angiosarcoma.

Diagnostic Findings, Part 3

An excisional biopsy of a patch on the patient's right medial breast is performed.

Questions/Discussion Points, Part 3

Describe the Histologic Findings From the Patient's Excisional Biopsy

At low magnification (Figure 4), within the dermis, there is a vaguely circumscribed nodule of proliferative blood vessels. At high magnification (Figure 5), the nodule is comprised of dilated, anastomosing blood vessels, lined by a single layer of plump endothelial cells with a high N: C ratio, nuclear hyperchromasia, and irregular nuclear contours. The *MYC* immunohistochemical stain (Figure 6) shows positive nuclear staining within the atypical endothelial cells.

What Is Your Diagnosis Based on the Clinical Information and Microscopic Findings on the Excisional Biopsy?

The patient has a remote history of breast cancer treated surgically with adjuvant radiation therapy. Within the irradiated skin field, she developed rapidly enlarging, nontender, violaceous patches over the course of a few months. Histologically, variably sized nodules were present throughout the dermis and consisted of anastomosing vascular channels lined by markedly atypical endothelial cells with *MYC* overexpression by immunohistochemistry. The histologic findings, in the clinical context, are supportive of a diagnosis of radiation-induced angiosarcoma.

What Are the Associated Risk Factors for Angiosarcoma?

Angiosarcomas are rare, aggressive malignant neoplasms of endothelial or lymphatic cell origin that account for 2% of all sarcomas. Although angiosarcomas may arise in various organs, they most frequently arise in the skin and deep soft tissues but may also present in the breast, spleen, and liver. The etiology is largely unknown with the vast majority of cases arising spontaneously, however associated risk factors include chronic lymphedema, radiotherapy, and several environmental carcinogens.³

Lymphedema-associated angiosarcomas most often arise in the breast due to chronic lymphedema (Stewart-Treves syndrome) following a radical mastectomy and axillary dissection. The pathogenesis of how chronic lymphedema causes angiosarcomas is unclear. However, it is postulated that blockage of the lymphatic channels may compromise the adaptive immune

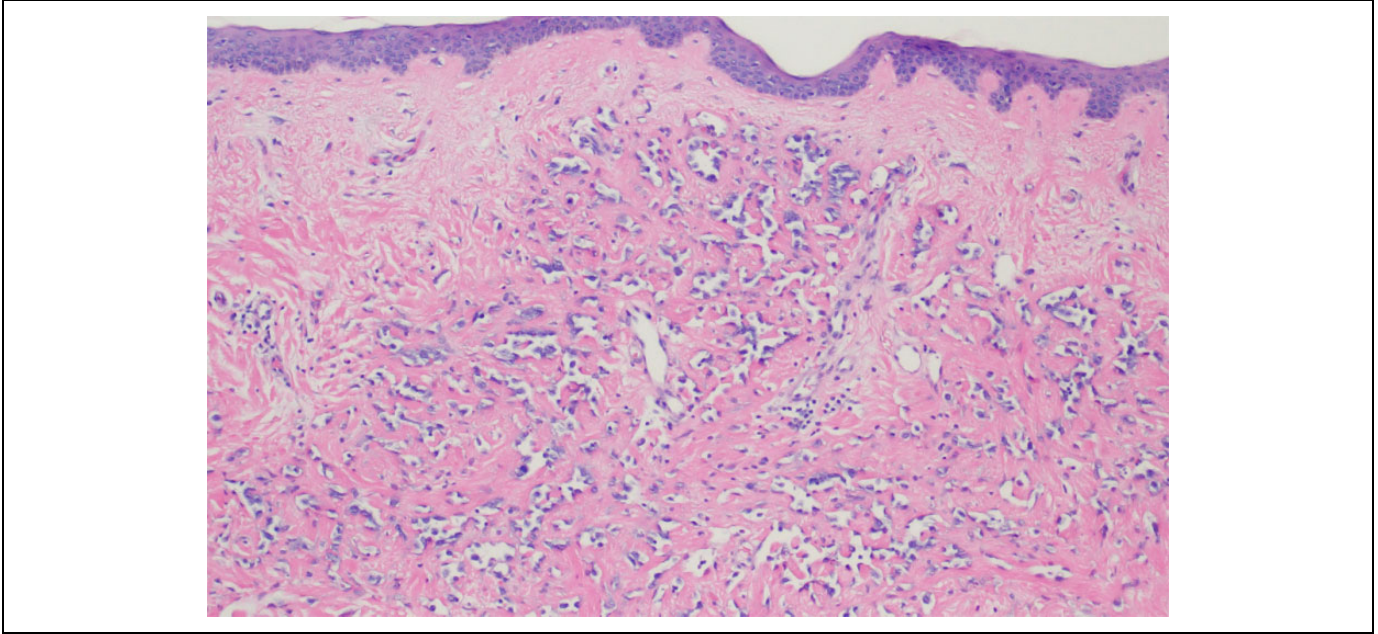


Figure 5. The patient's excisional biopsy from the medial aspect of the right breast. Higher magnification highlights the anastomosing vascular spaces lined by endothelial cells with nuclear enlargement and hyperchromasia (hematoxylin and eosin, $\times 10$).

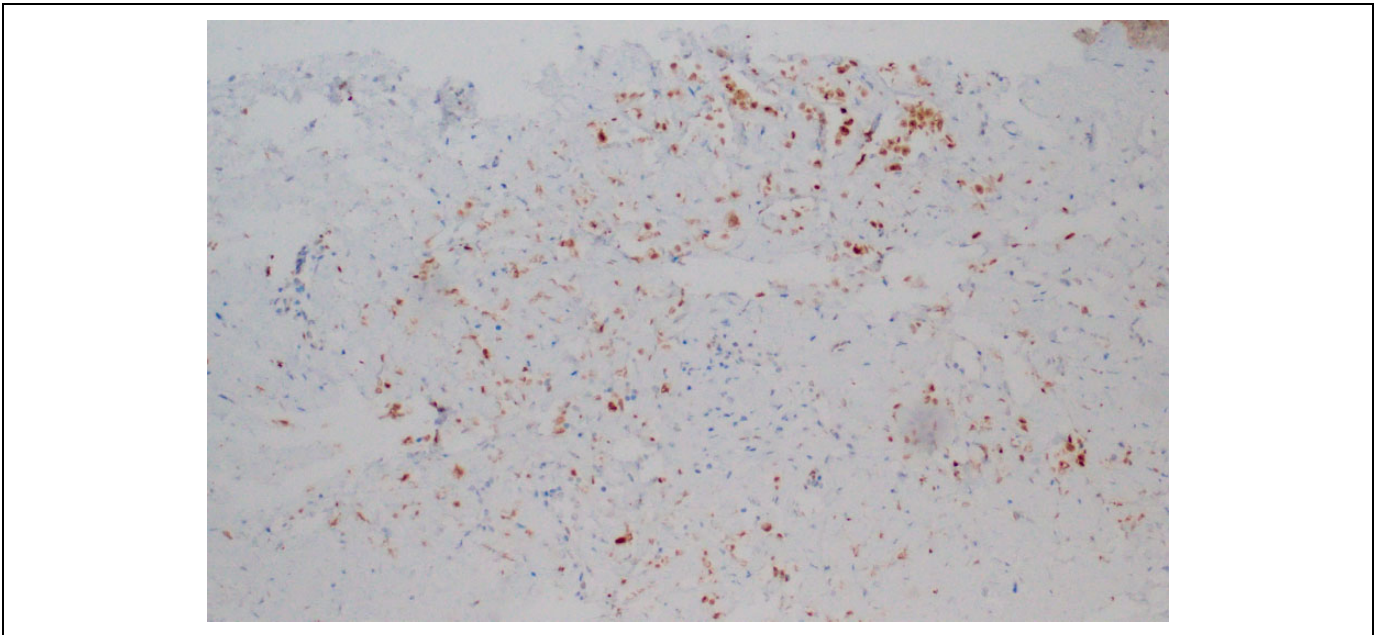


Figure 6. The patient's excisional biopsy from the medial aspect of the right breast. The atypical endothelial cells show nuclear positivity for MYC (MYC, $\times 10$).

system locally due to limited antigen presentation by T-cells and dendritic cells, thereby creating an immunologically privileged site for malignant transformation.⁴ Radiotherapy is thought to be an independent risk factor for radiation-induced angiosarcoma and is most often observed following treatment of breast cancer. Arguably, the subsequent risk may also be heightened due to concurrent lymphedema and potential underlying point mutations in the DNA repair genes, *BRCA1* and

BRCA2. Lymphedema can increase stimulation of angiogenic cytokines (eg, *VEGF*) further propagating vascular proliferation. Although the pathogenesis of *BRCA1* and *BRCA2* genes in the development of radiation-induced angiosarcomas has yet to be fully characterized, it is postulated that prolonged cellular stimulation during repair of ischemic tissues may increase the risk of tumorigenesis. Additionally, angiosarcomas have also been reported following radiotherapy of Hodgkin lymphoma

and several gynecological carcinomas. Various environmental carcinogens may also be associated with the development of angiosarcomas. Dioxin (a by-product of industrial processes) and vinyl chloride (a contaminant of the plastic industry) are frequently associated with hepatic angiosarcomas.³

What Is the Prognosis for Angiosarcomas of the Breast?

The clinical presentation of angiosarcomas of the breast is highly variable and may present as a rash or as a benign vascular lesion. Unfortunately, these tumors have a tendency to grow rapidly and show an infiltrative growth pattern. A delay in diagnosis can lead to widespread metastatic disease and portends a poor prognosis with a 5-year survival of less than 20%.⁵ Therefore, clinicians should maintain a low-threshold for considering angiosarcoma in the differential diagnosis of subtle cutaneous findings of the breast, especially in a patient with a prior history of radiotherapy.

How Does the Clinical Presentation of Primary and Secondary Angiosarcomas of the Breast Differ?

In the breast, angiosarcomas can be primary, arising de novo, or secondary to chronic lymphedema or radiation therapy. Primary angiosarcomas develop in younger women (median age 35 years) and typically present in the breast parenchyma as a rapidly enlarging, painless, palpable mass.⁶

Secondary angiosarcomas arise in older women (median age 70 years) and most often present as a rash or ecchymosis.⁷ Angiosarcomas arising secondary to radiation therapy have an average latency period of 7 years and typically present within the irradiated skin field. Lymphedema-associated angiosarcomas are caused by chronic lymphedema following a radical mastectomy or an axillary dissection and have an average latency period of 10 years. The overall prognosis for both primary and secondary angiosarcomas is poor with a high rate of local recurrence and distant metastasis.⁸⁻⁹

Which Molecular Alterations Can Help to Distinguish Between Primary and Secondary Angiosarcomas?

Many of the molecular pathways associated with primary angiosarcomas are not fully understood. Associations with several genes including *BRCA1* and *BRCA2* expression, *TP53* inactivation, and *MDM2* and *VEGF* overexpression are associated with its pathogenesis.¹⁰

Ionizing radiation causes genomic instability and results in alterations of prominent cancer-related genes. Some of these genes may be used to distinguish between primary and secondary angiosarcomas. In particular, dysregulation of the *MYC* oncogene on chromosome 8p24 is considered to be an important constituent in the pathogenesis of radiation-induced angiosarcomas.¹⁰

MYC is a multifunctional transcriptional factor which helps mediate cell cycle progression and helps regulate apoptosis. In radiation-induced angiosarcomas, *MYC* dysregulation most

often results in gene amplification rather than gene mutation. Gene amplification leads to increased transcriptional activity and helps promote angiogenesis and eventual metastasis. *MYC* amplification is observed in secondary angiosarcomas, including some cases of lymphedema-associated angiosarcomas, but is absent in sporadic forms and, importantly, radiation-induced atypical vascular lesions. Therefore, despite identical morphologic appearances, primary and secondary angiosarcomas are genetically distinct. *MYC* nuclear expression can be demonstrated by immunohistochemistry, and amplification can be detected by fluorescence in situ hybridization analysis.¹⁰

What Are the Management Options for Angiosarcomas of the Breast?

Treatment of angiosarcomas is often managed by a multidisciplinary team. For localized tumors, the standard of care is complete surgical resection with negative margins. Adjuvant radiation therapy may be considered to reduce the risk of local recurrence. For local disease, there is no definitive data to support the use of adjuvant chemotherapy.¹¹

Given the aggressive nature of angiosarcomas, approximately 50% of patients with localized disease will develop metastatic disease. Approximately 30% of patients present with metastatic disease.¹¹ Unfortunately, there are no standardized systemic chemotherapy regimens for metastatic angiosarcomas. Although there are several highly effective cytotoxic and targeted therapies, metastatic angiosarcomas are generally incurable and fatal.¹¹

Following the results of the excisional biopsy, the patient in our case was staged with computed tomography imaging of the chest and abdomen which were both negative for metastatic disease. The patient was surgically managed with a right total mastectomy and sentinel lymph node biopsy. Pathologic evaluation of the mastectomy specimen demonstrated an 11 cm confluent mass (pT3, pN0 [sn]), if appropriate with multiple secondary foci ranging between 0.2 to 8.5 cm. The surgical margins were negative for disease with no evidence of lymphovascular invasion. The sentinel lymph node was negative for metastatic disease. The patient then completed 12 weeks of systemic chemotherapy (Taxol) without complications. At a 6-month follow-up, the patient remained disease free.

Teaching Points

- Angiosarcomas are aggressive malignant neoplasms that most often arise sporadically. Associated risk factors include chronic lymphedema, radiotherapy, and environmental carcinogens such as dioxin and vinyl chloride.
- Ionizing radiation causes genomic instability and thus alterations of cancer-related genes. Amplification of the *MYC* oncogene is thought to cause unregulated angiogenesis leading to rapid growth and eventual metastasis.

- Primary angiosarcomas typically arise in younger patients within the breast parenchyma as an enlarging painless mass.
- Secondary angiosarcomas classically arise as a rash or enlarging vascular lesion on the skin of the breast in older women.
- Angiosarcomas arising secondarily to radiation therapy have a shorter latency period than lymphedema-associated angiosarcomas.
- *MYC* amplification is often present in secondary angiosarcomas but is absent in primary angiosarcomas and radiation-induced atypical vascular lesions.
- Localized disease is treated with complete resection with negative margins with or without radiotherapy. Adjuvant chemotherapy may be used for metastatic disease.
- The overall prognosis of angiosarcoma is poor. Approximately 50% of patients with a localized presentation progress to metastatic disease which has a 5-year survival of less than 20%.

Declaration of Conflicting Interests

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