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Educational Case: Radiation-Associated Angiosarcoma in Patients With Breast Cancer

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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/10.1177/2374289517715040.[1]

Keywords
pathology competencies, disease mechanism, neoplasia, DNA damage repair, radiation exposure, radiation-associated angiosarcoma, MYC amplification

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Primary Objective

Objective N2.2: Mechanism 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 N: Neoplasia; Learning Goal 2: Environmental Influences on Neoplasia.

Patient Presentation

A 70-year-old woman presents with skin changes over her left breast for 1 month (Figure 1). No pain, fever, or other associated symptoms were present. Her past medical history is significant for left breast invasive ductal carcinoma, treated with lumpectomy and radiation therapy 7 years ago.

Diagnostic Findings

A punch biopsy of the skin lesion is performed to establish a definitive diagnosis. The patient subsequently underwent mastectomy to completely excise the tumor.

Questions/Discussion Points

What Is Your Clinical Differential Diagnosis Based on the Exam Findings?

The image (Figure 1) is showing skin with dark red and violaceous discoloration and ulceration. Clinical diagnostic considerations include neoplastic processes such as recurrent breast carcinoma, melanoma, and vascular tumors. Infections (mastitis) can also cause erythema of the breast but are often associated with pain and/or fever.

Describe the Gross and Histologic Findings Seen in Figures 2 to 6

Gross examination of the mastectomy specimen shows a hemorrhagic mass immediately underlying the skin measuring

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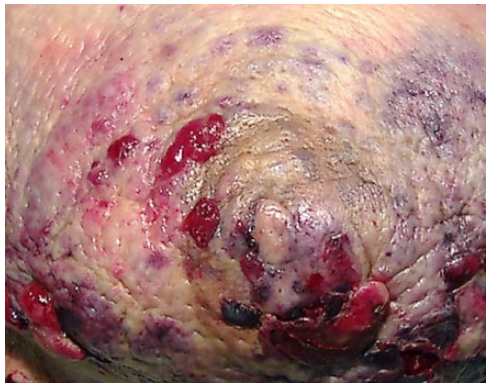

Figure 1. Clinical image of the breast skin lesion characterized by irregular borders with dark red and violaceous discoloration and ulceration.

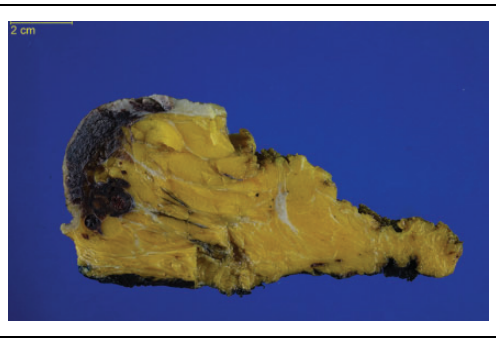

Figure 2. Gross image from a cross section of the mastectomy specimen demonstrating a dark red-brown mass with irregular borders underlying the skin. The tissue posterior to the mass consists of grossly unremarkable fatty breast tissue.

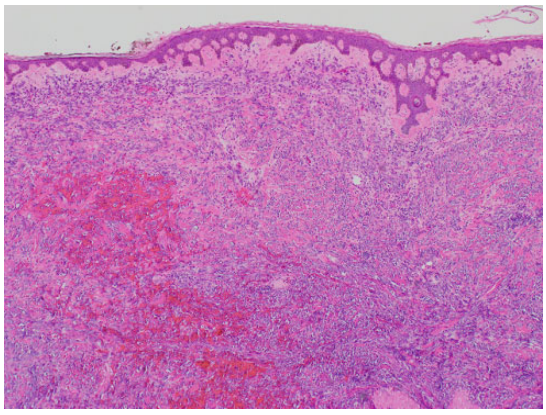

Figure 3. The mass is widely infiltrative and extensively involves the dermis (H&E, hematoxylin and eosin; ×2).

4.5 × 3.7 × 2.0 cm (Figure 2). Microscopically, the mass infiltrates extensively through the dermis (Figure 3). On higher magnification, the mass is composed of irregular, anastomosing channels, some of which contain red blood cells (Figure 4).

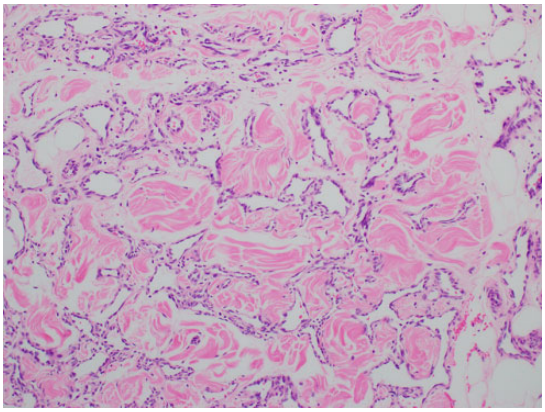

Figure 4. The tumor shows well-differentiated areas with irregular, anastomosing vascular channels lined by atypical endothelial cells. Red blood cells are present in some of the spaces (H&E, hematoxylin and eosin; ×10).

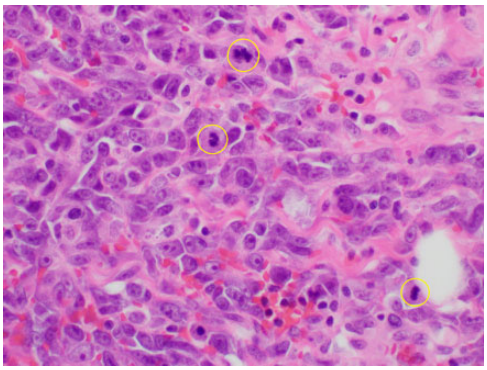

Figure 5. The tumor also shows poorly differentiated areas with solid sheets of markedly atypical cells with frequent mitoses (circled; H&E, hematoxylin and eosin; ×40).

There are also areas with a more solid growth pattern and markedly atypical cells with frequent mitoses (Figure 5).

What Is Your Histopathologic Differential Diagnosis?

Tumors can arise from different cell types, which impart different morphologic characteristics that are diagnostically useful. When well differentiated, they more closely approximate the normal histology of their origin. Given her history, recurrent breast carcinoma is an important consideration. Carcinomas are malignant neoplasms that arise from epithelial cells, which in the breast are the glandular elements (ducts and lobules) so the tumors are gland forming. However, the breast also contains different mesenchymal tissues, such as fat and blood vessels. These tissues can give rise to a different category of malignant neoplasms: sarcomas.

Microscopically, there are red blood cells within slit-like spaces making a vascular tumor the primary diagnostic consideration in this case. Hemangiomas are benign vascular neoplasms that are well circumscribed and lack cytologic atypia

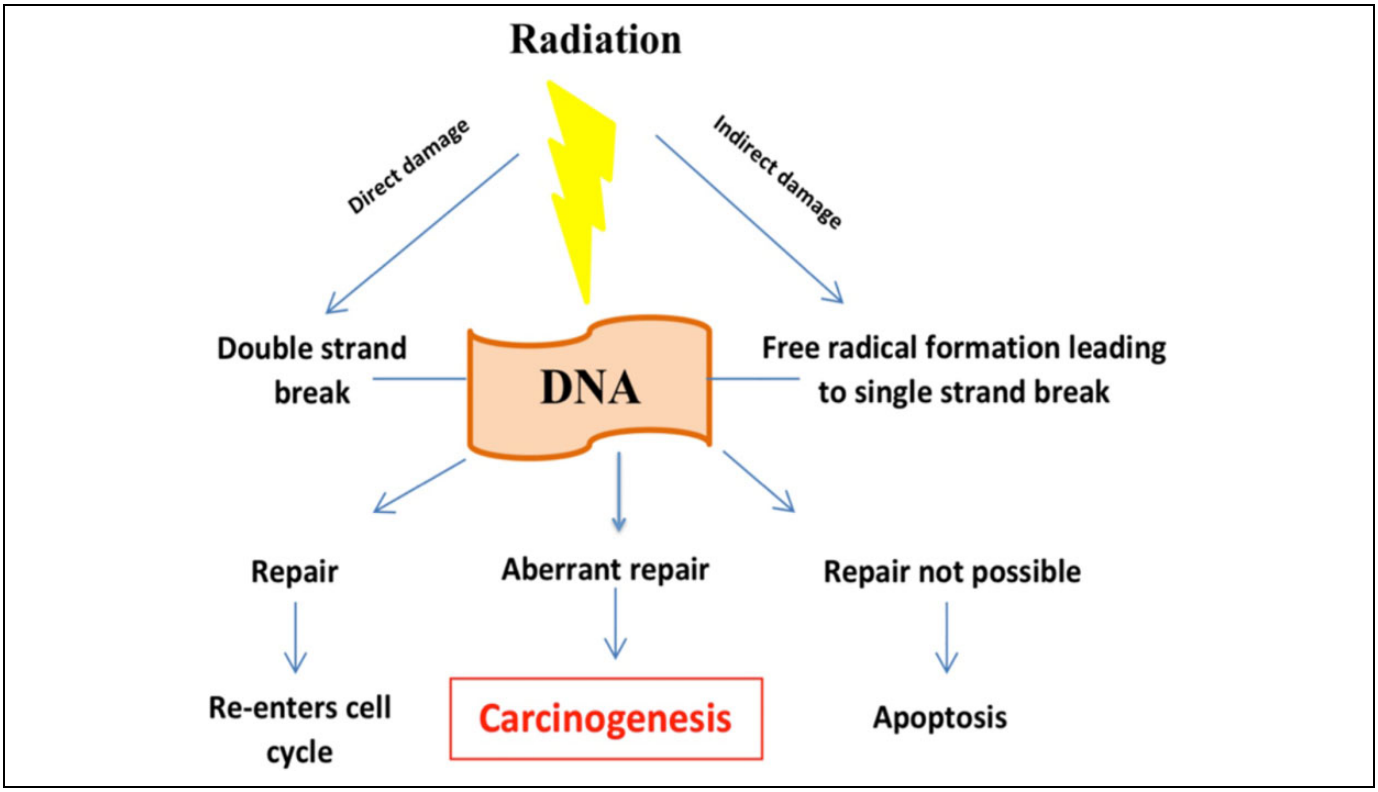

Figure 6. Direct and indirect effect of radiation on DNA and its consequences.

and mitotic figures. The tumor in this case is not circumscribed either clinically (Figure 1) or microscopically, making a benign hemangioma very unlikely. Angiosarcomas are malignant vascular neoplasms that can show a wide range of morphology depending on the degree of differentiation but that are often characterized by infiltrative growth. Well-differentiated angiosarcomas are composed of infiltrative well-formed vascular channels lined by endothelial cells with hyperchromatic nuclei. Anastomosing vessels are often present while mitotic figures and solid growth are generally absent.[2] In contrast, poorly differentiated angiosarcomas have more irregular and complex vascular channels as well as solid growth. The endothelial cells are markedly atypical with large, pleomorphic nuclei and prominent nucleoli. The walls of these vascular channels are weak and this leads to extravasation of the blood, forming blood lakes. Mitotic figures, necrosis, and apoptotic bodies are common. With poorly differentiated malignancies, there may be no resemblance to the cell type of origin and additional studies by immunohistochemistry are utilized to make the diagnosis. Angiosarcomas will express mesenchymal and vascular markers (such as CD34 and CD31), whereas carcinomas will express epithelial markers, such as cytokeratins.

What Are the Clinicopathologic Characteristics of This Tumor?

Angiosarcoma is a malignant mesenchymal neoplasm derived from endothelial cells that can present in many different anatomic locations. In the breast, there are primary and secondary angiosarcomas, which look similar under the microscope but differ in patient demographics and clinical presentation.[3] Primary angiosarcomas arise de novo and present in younger women as a painless breast mass. They typically involve the deeper breast parenchyma but can extend into the overlying skin. By definition, secondary malignancies are caused by external agents that induce genetic damage that cause neoplastic transformation; the most well-known example of a secondary malignancy is smoking-associated lung cancer. Secondary angiosarcomas in the breast arise as a result of prior radiation treatment. Many women with breast cancer are treated by breast-conserving surgery (lumpectomy) followed by radiation. Although radiation therapy is effective in reducing the risk of local recurrence of breast cancer, 0.3% of those treated will develop secondary angiosarcomas. Radiation-associated angiosarcomas arise in the dermis of the exposed area after a latency period of 5 to 6 years.[4] They clinically present as dark red or violaceous skin lesions.

How Does Radiation Contribute to Tumor Development?

Any cell capable of dividing can be injured by ionizing radiation both directly and indirectly. The ions generated by radiation break covalent bonds to directly affect DNA structure, especially by generating double-strand DNA breaks. Reactive oxygen species are also generated which oxidize proteins and lipids, inducing additional changes in DNA such as single-

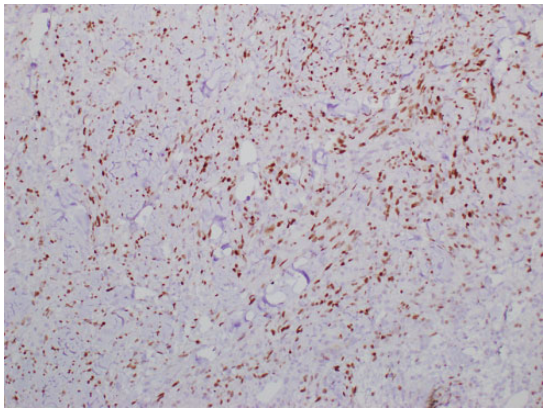

Figure 7. Radiation-associated angiosarcoma with nuclear positivity for *MYC* by immunohistochemistry (×10).

strand breaks. This DNA damage triggers cell cycle arrest so that the cellular repair mechanisms can be activated. If DNA repair is not possible, the damaged cells undergo apoptosis. Rapidly dividing cells such as tumor cells are generally more radiosensitive, and in patients with breast cancer, radiation therapy helps reduce or eliminate residual tumor burden in the breast to reduce the risk of local recurrence. However, healthy cells in the radiation field are also inevitably affected. When DNA damage is not repaired properly, mutations accumulate within the cell; if programmed cell death is not triggered, the mutated cell will continue to divide and lead to tumorgenesis[5] (Figure 6).

What Are the Common Genetic Mutations for Radiation-Associated Angiosarcoma?

Radiation-associated (secondary) angiosarcomas differ from primary angiosarcomas at the molecular level as they show a high level of *MYC* amplification, a proto-oncogene that has a role in cell growth and proliferation. *MYC* amplification is not characteristically seen in primary angiosarcomas and may represent the primary event in radiation-associated angiosarcoma tumorigenesis.[6] This difference can be utilized clinically to aid in the differential diagnosis by looking for MYC overexpression by immunohistochemistry (Figure 7) or MYC amplification by fluoresce in situ hybridization.

What Is the Natural History of This Tumor?

Both primary and secondary angiosarcomas are aggressive malignancies and have high rate of local recurrence, even after surgical excision with wide margins, as well as distant metastases. Similarly, aggressive behavior is seen in both well and poorly differentiated tumors, so histologic grade has no prognostic value. The median overall survival is less than 6 years.[7]

Teaching Points

- Angiosarcomas are often histologically heterogeneous and can range from well differentiated (infiltrative and anastomosing vascular channels lined by atypical cells) to poorly differentiated (highly pleomorphic and mitotically active endothelial cells with areas of solid growth).
- Secondary neoplasms can arise as a result of genetic damage caused by external agents, such as chemicals and radiation.
- Radiation can directly damage DNA by generating double-stranded DNA breaks.
- Radiation-associated angiosarcoma of the breast is a rare and aggressive tumor that presents as dark red skin lesions in women who previously underwent lumpectomy and radiation therapy for breast carcinoma. The latency period is generally 5 to 6 years.
- Radiation-associated angiosarcoma of the breast can be distinguished from primary angiosarcoma as well as other vascular lesions by its characteristic *MYC* amplification, a molecular finding that may also be the primary event in the pathogenesis of this tumor.

Declaration of Conflicting Interests

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References

1. Knollmann-Ritschel BEC, Regula DP, Borowitz MJ, Conran R, Prystowsky MB. Pathology competencies for medical education and educational cases. *Acad Pathol*. 2017:4. doi:10.1177/2374289517715040.
2. Schnitt SJ, Collins LC. *Biopsy Interpretation of the Breast*. Philadelphia, PA: Wolters Kluwer Health; 2018.
3. Brodie C, Provenzano E. Vascular proliferations of the breast. *Histopathology*. 2008;52:30-44.
4. Ronen S, Ivan D, Torres Cabala CA, et al. Post-radiation vascular lesions of the breast. *J Cutan Pathol*. 2019;46:52-58.
5. Kumar V, Abbas AK, Aster JC. *Robbins and Cotran Pathologic Basis of Disease*. Philadelphia, PA: Elsevier/Saunders; 2015.
6. Guo T, Zhang L, Chang NE, Singer S, Maki RG, Antonescu CR. Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions. *Genes Chromosomes Cancer*. 2011;50:25-33.
7. Lakhani SR, Ellis IO. *WHO Classification of Tumours of the Breast*. Lyon, France: IARC; 2012.