Vascular Lesions of the Breast

UCSF 32nd Annual
Current Issues in Anatomic Pathology and Cytology

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For Pathologists

- The most important goal when encountering a mammary vascular lesion is to identify (or exclude) ANGIOSARCOMA.
- Two most difficult diagnostic challenges:
  - Identify low grade primary angiosarcoma in core needle biopsy material.
  - Distinguish atypical vascular lesion from post radiation angiosarcoma in skin punch biopsy material.

Angiosarcoma

**Primary:** Breast +/- cutaneous involvement

**Secondary:** Mammary skin +/- subadjacent breast

1. Radiation-induced (↑)
2. Lymphedema-associated (Stewart-Treves) (↓)
   - Arm, may extend to chest wall

Primary angiosarcoma

- Rare (<0.05% breast malignancies).
- Constitutes about 10-25% of all mammary sarcomas.
- No known risk factors.
- Younger patients (20s-50s) than those with breast carcinoma or radiation-induced angiosarcomas.
- Presents with a breast mass.
- Mastectomy.
- Aggressive clinical behavior with high propensity to metastasize and high risk of dying from disease.
Grading of primary angiosarcomas

- Rosen’s three tiered grading system
  - Grade I (low grade)
  - Grade II (intermediate grade)
  - Grade III (high grade)
- Individual tumors can exhibit the full spectrum of grades
- Grading should be done only on the excised tumor specimen

Low grade angiosarcoma

- Complex anastomosing vascular channels
- Minimal endothelial nuclear atypia
- No cellular stratification
- Low mitotic rate
- No necrosis
- Dissects into adipose tissue and breast elements
Intermediate grade angiosarcoma

- More cellular than low grade
- Moderate cytologic atypia
- Multilayering of lesional endothelial cells
- Papillary structures can be seen but not solid areas
- Moderate mitotic rate
High grade angiosarcoma

- Solid areas with poorly formed vascular channels; spindled tumor cells
- Blood lakes (hemorrhage)
- Necrosis
- Marked cytologic atypia including hyperchromasia
- Brisk mitotic rate

Grading and prognosis

- Rosen et al reported a similar estimated survival probability for angiosarcomas grades I, II and III at year 1 but much worse outcome at 5 and 10 years as well as worse recurrence-free survival for grade III
- Study limitations: small cohort, short follow-up
- More recently, the prognostic value of histologic grading in primary angiosarcomas has been challenged
Nascimento AF, et al. AJSP 2008

- Similar tumor sizes and numbers of cases for each histologic grade (n=49)
- No statistically significant correlation between
  - tumor size and likelihood of local recurrence or dying of disease
  - histologic grade and the rate of local recurrence or distant mets
  - tumor grade and death owing to disease

DIAGNOSTIC CHALLENGE #1

- Know the differential diagnosis
- Correlate with clinical and radiologic findings
- Know the diagnostic pitfalls
- Know when/how ancillary studies can help

Differential Diagnosis

- Hemangioma
- Papillary endothelial hyperplasia
- Angiolipoma (if lesion is involving the subcutaneous fat)
Clinical and radiologic correlation

- Angiosarcoma
- Hemangioma, papillary endothelial hyperplasia, angiolipoma
- >2 cm or radiographically occult
- <2 cm; nodule/MRI enhancement/ rarely calcs; well circumscribed

DIAGNOSTIC CHALLENGE #1

- Hemangioma
- Papillary endothelial hyperplasia
- Angiolipoma (if lesion is involving the subcutaneous fat)

Hemangioma

Various morphologies
- capillary
- cavernous
- venous

Location
- parenchymal vs non-parenchymal (adipose tissue)
- if parenchymal, extralobular vs perilobular
Circumscribed

Lobulated

No mitoses

Capillary vessels, minimal atypia

Low grade angiosarcoma
Hemangioma – focal infiltrative borders

Extralobular hemangioma
Hemangiomas and Angiosarcomas of the Breast
Diagnostic Utility of Cell Cycle Markers With Emphasis on Ki-67

Sandeck J. Shin, MD; Martin Lesser, PhD; Paul Peter Rosen, MD

Context.—Vascular tumors comprise a minor subgroup of tumors arising in the breast and represent variants of hemangiomas and angiosarcomas. Diagnostic challenges may arise when differentiating hemangiomas from types I and II angiosarcomas. Ki-67 expression has been used as an adjunct to distinguish between benign and malignant lesions exhibiting histologic overlap at various anatomic sites.

Objective.—To investigate the utility of Ki-67 and other cell cycle regulatory proteins (S-phase kinase-associated protein 2 [Skp2], p27, and cyclin D1) in the differential diagnosis of mesenchymal vascular lesions.

Design.—Thirty-four vascular tumors (21 hemangiomas and 13 angiosarcomas) of the breast were studied. The Ki-67 index and immunoreactivity for Skp2, p27, and cyclin D1 were determined in each case. Appropriate statistical methods were used.

Results.—The mean value of Ki-67 index was statistically different when comparing hemangiomas and angiosarcomas (p < .001). Angiosarcomas were typically positive for Skp2, whereas hemangiomas were negative (p < .001). Sensitivity and specificity cutoffs for Ki-67 index to distinguish hemangiomas from angiosarcomas showed a candidate cutoff point of 1.75. The mean values of Ki-67 of low-grade angiosarcomas were significantly different from all hemangiomas (p < .001) and also different from the subset of atypical hemangiomas (p < .05). Sensitivity and specificity cutoffs for Ki-67 index to distinguish all hemangiomas from low-grade angiosarcomas showed a candidate cutoff point between 150 and 175. Among angiosarcomas, positivity for Ki-67 was inversely related to that of p27 but not to Skp2 or cyclin D1. This was also true among hemangiomas.

Conclusion.—Ki-67 index can be used as a diagnostic tool to distinguish between benign and malignant vascular lesions of the breast. This can be particularly helpful in cases of histologic overlap such as low-grade angiosarcoma and hemangioma.

(Arch Pathol Lab Med. 2007;131:538–544)
Ki-67 and mammary vascular lesions

- Best used in the setting of confirming a lesion with morphologic features highly supportive of the diagnosis (angiosarcoma versus hemangioma)
- Prior biopsy changes in the lesion can lead to a falsely elevated Ki-67 index

DIAGNOSTIC CHALLENGE #1

- Hemangioma
- Papillary endothelial hyperplasia
- Angiolipoma (if lesion is involving the subcutaneous fat)

Papillary endothelial hyperplasia

Mass
Circumscribed
Associated with thrombus, hematoma, hemangioma
DIAGNOSTIC CHALLENGE #1

- Hemangioma
- Papillary endothelial hyperplasia
- Angioplaoma (if lesion is involving the subcutaneous fat)
DIAGNOSTIC CHALLENGE #2

- Know the differential diagnosis
- Correlate with clinical and radiologic findings
- Know the diagnostic pitfalls
- Know when/how ancillary studies can help

Distinguish between AVL and post radiation AS in a skin biopsy

Post radiation angiosarcoma

- First documented case after breast conserving surgery in 1987; >200 cases reported
- Constitutes about 40% of all radiation induced sarcomas
- Older patients than those with primary AS (70s)
- Presents with a rash/bruise +/- ulceration
- Latency after RT is 7-10 years

Post radiation angiosarcoma
Post radiation angiosarcoma

- High or intermediate nuclear grade
- Any growth pattern

Atypical vascular lesion (AVL)
- First described in 1994 by Fineberg and Rosen
- Spectrum of vascular proliferations that develop in previously irradiated skin
- Latency from time of RT is shorter (2-6 years) than for post-radiation angiosarcoma (7+ years)
- Can be multiple
- Benign clinical course
**Atypical vascular lesion (AVL)**

- Localized superficial proliferation composed of well-formed empty vascular spaces lined by plump endothelial cells
- Lack multilayering, significant cytologic atypia, significant infiltrative growth
- Two patterns
  - Dilated vessels resembling lymphangioma (lymphatic-type) – more common
  - Slit-like vascular spaces with hobnail endothelium (vascular-type) – less common but more easily confused with AS

**Atypical vascular lesion (AVL)**

- Overlap with post radiation angiosarcoma
  - Clinically (age at presentation, latency from RT and lesion duration before bx)
  - Histomorphologically (prominent nucleoli, mitotic figures, cytologic atypia, infiltrative growth)
Diagnostic pitfall

Angiosarcomas can exhibit AVL-like areas
May be impossible to distinguish in small biopsy material

Ki-67 proliferation index of AVLs has not been studied
c-MYC is a proto-oncogene located on chromosome 8q24-21 that encodes a transcription factor involved in cell growth, proliferation, apoptosis and other cancer processes such as angiogenesis.

- High level MYC amplification (5-20 fold) limited to post radiation AS and rare primary AS; absent in all reported AVLs and almost all primary AS
- One study found MYC amplified post-radiation AS to have worse prognosis than those without MYC amplification
- Suggests different pathogenetic pathways of
  - primary and secondary (post radiation) AS
  - AVL and secondary (post radiation) AS
**Utility of anti-myc IHC in mammary vascular lesions**

- Used to discriminate between post-radiation AS and AVL
- Highly concordance with MYC gene amplification
- Positive staining is strong and diffuse (>80%) in lesional cells; important in small biopsy samples
- Can also stain lymphocytes
- Benign vessels are negative and should not be mistaken for non-immunoreactive lesional vessels

**FLT4 and mammary vascular lesions**

- *FLT4* gene found on chromosome 5q35.3 which encodes VEGFR-3 and belongs to tyrosine kinase receptor family
- *FLT4* co-amplifies with MYC
- FLT4 protein expression by IHC in benign and malignant neoplasms including up to 80% of AS
- Possible therapeutic target – multi-kinase inhibitors; anti-VEGFR inhibitors
Copy number alterations and gene expression were analyzed in 7 primary AS and 18 post radiation AS

53 gene signature that discriminated post rad AS and primary AS. MYC was not listed confirming that its expression is not a marker of radiation tumorigenesis

- Two distinct transcriptome signatures co-exist in radiation-induced breast AS and both discriminate the tumors as a function of their etiology
- One signature specific to breast AS. The deregulation of marker genes suggests that post rad AS develop from radiation-stimulated lymphatic vessel endothelial cells
- High rate of MYC amplification in post rad AS, likely a consequence of genome instability initiated by ionizing radiation, is NOT a marker of radiation tumorigenesis since it is also observed at a low rate in primary AS
**PTPRB**

- Negative regulator of angiogenesis; Inhibits VEGFR2, VE-cadherin and angiopoietin signalling
- Expressed exclusively in vascular endothelium
- Study showed 14 **PTPRB** mutations in 10/39 (26%) AS
- All PTPRB mutations identified in tumors that were either post-rad AS and/or have MYC amp; 45% in this subgroup (10/22)
- Possible clinical utility as biomarker of radiation associated disease and/or novel therapeutic targets in AS