Vascular Lesions in the Breast

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Outline

- Benign vascular lesions
  - Hemangiomas
  - Angiomatosis
  - Angiolipoma
- Atypical vascular lesions
- Angiosarcoma
  - Primary
  - Secondary
- Differential Diagnoses

Benign vascular lesions

- Diagnostic challenge in core needle biopsies
  - Angiosarcomas can show areas that are very well differentiated and resemble benign lesions
  - Benign lesions can occasionally show atypical cytologic or architectural features (occasional hyperchromasia, anastomosing channels, etc)
- Some recommend excision of all benign appearing vascular lesions to fully exclude an angiosarcoma
- Others advocate for conservative management of patients whenever there is pathologic-radiologic concordance.

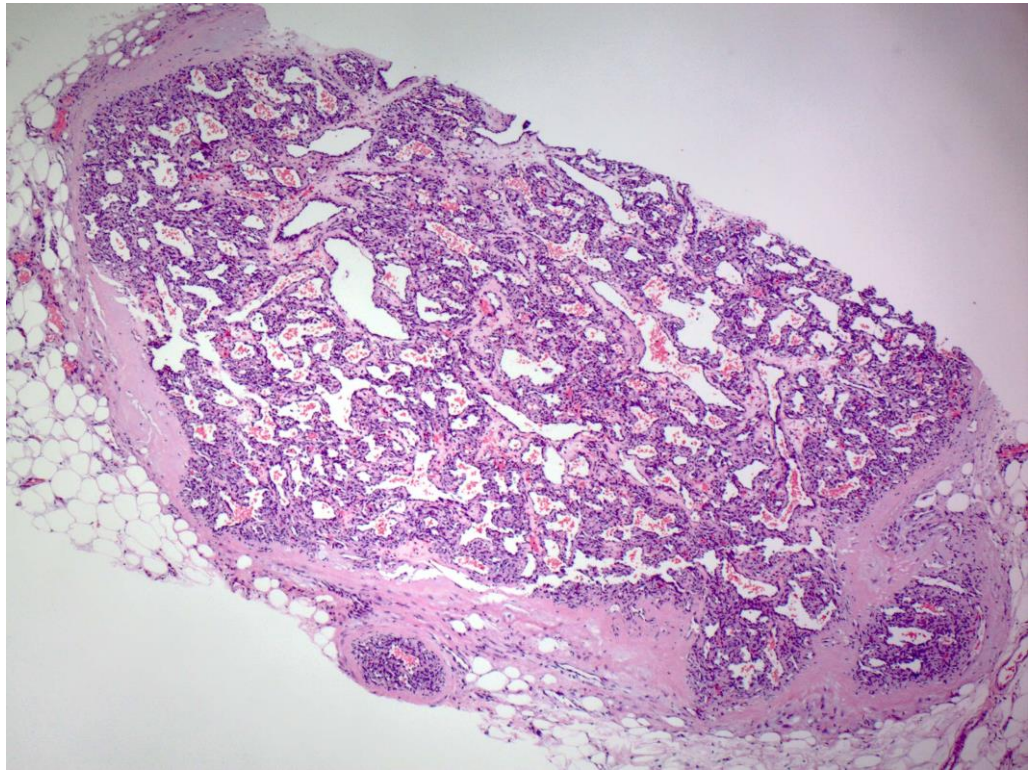
Hemangioma

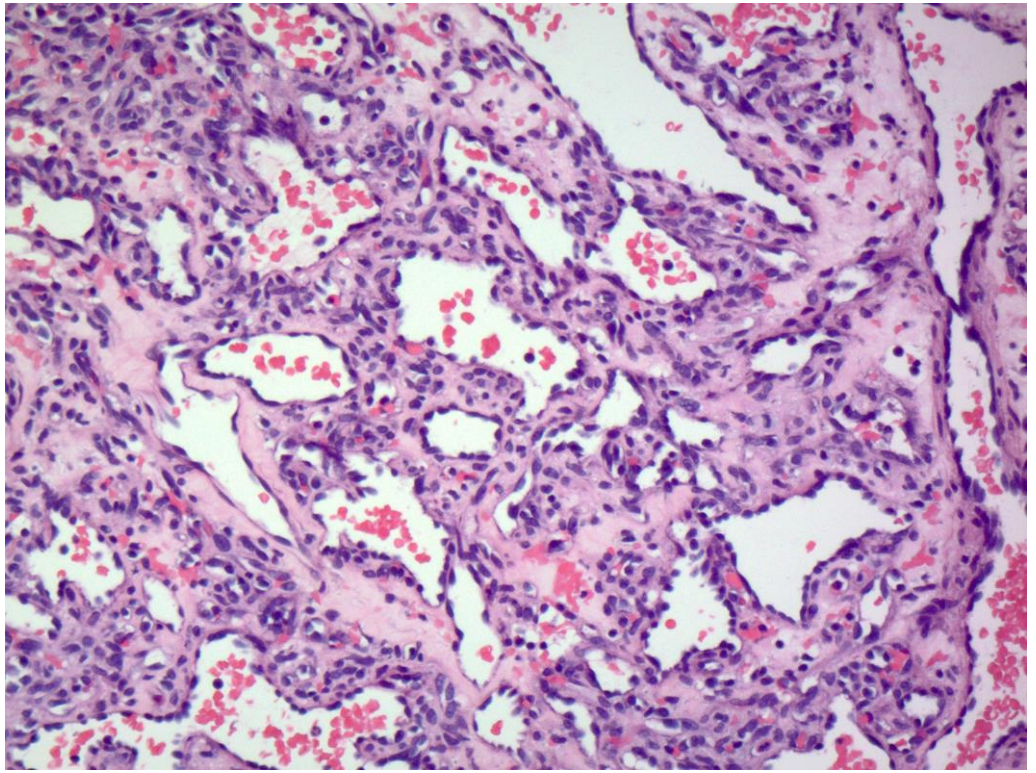
- Benign vascular lesion, likely non-neoplastic vascular malformations
- Located in skin or breast parenchyma
- Mammography: Lobulated mass, mass with microlobulated margins, rarely calcifications.
- Most are <2.0 cm (range 0.3-6.0 cm)
- 0.4% of all breast tumors.
- Found in approximately 1.2% of mastectomy specimens and 11% of autopsies.

Hemangioma

- Most commonly incidentally detected on imaging or excision for unrelated pathology, rarely palpable.
- Histopathology: Non-anastomosing vascular spaces of varying size. Bland nuclei, no increased mitoses. Well circumscribed. Thrombosis with secondary endothelial hyperplasia can occur. Larger feeding vessel can be seen in proximity.
  - Perilobular: Most common subtype. Present within intralobular stroma.
  - Other types: Cavernous, venous, capillary, complex (mixture of small and cavernous vessels)

Hemangioma





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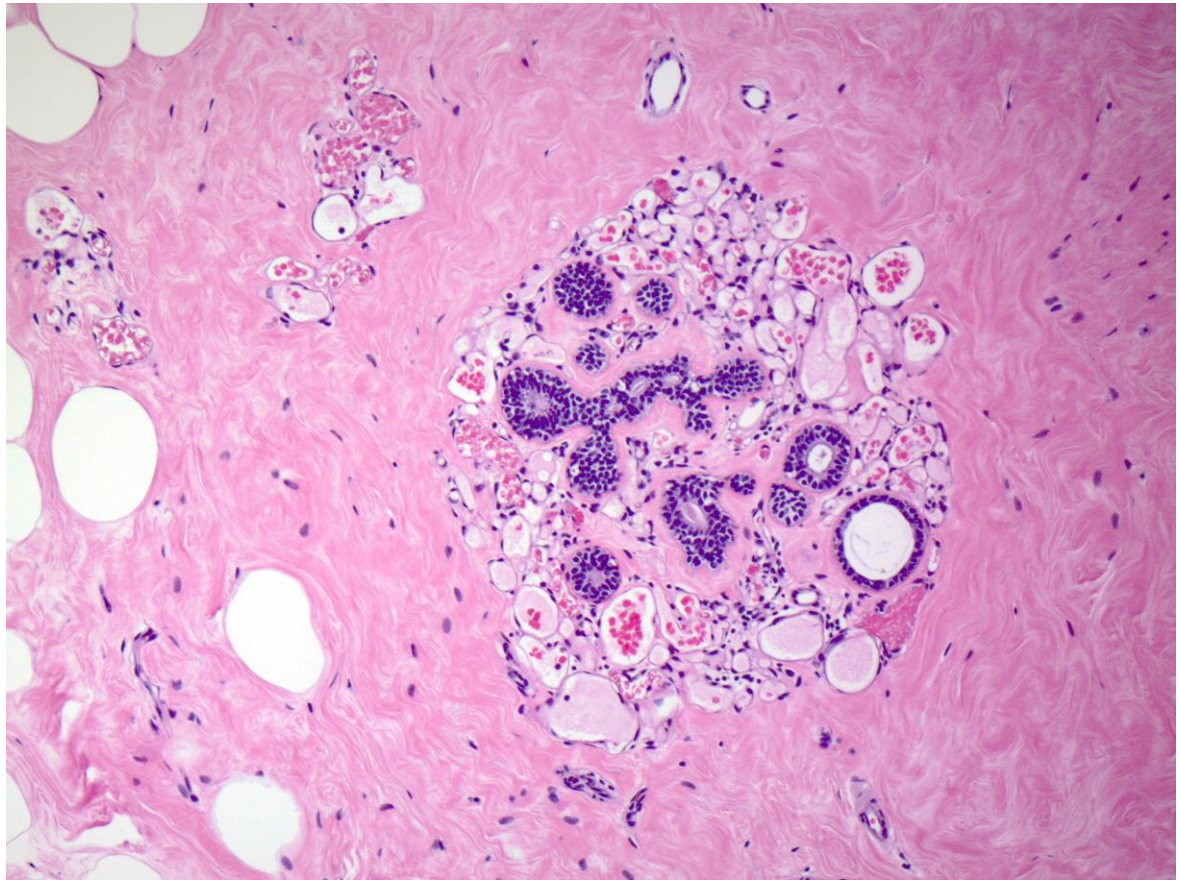
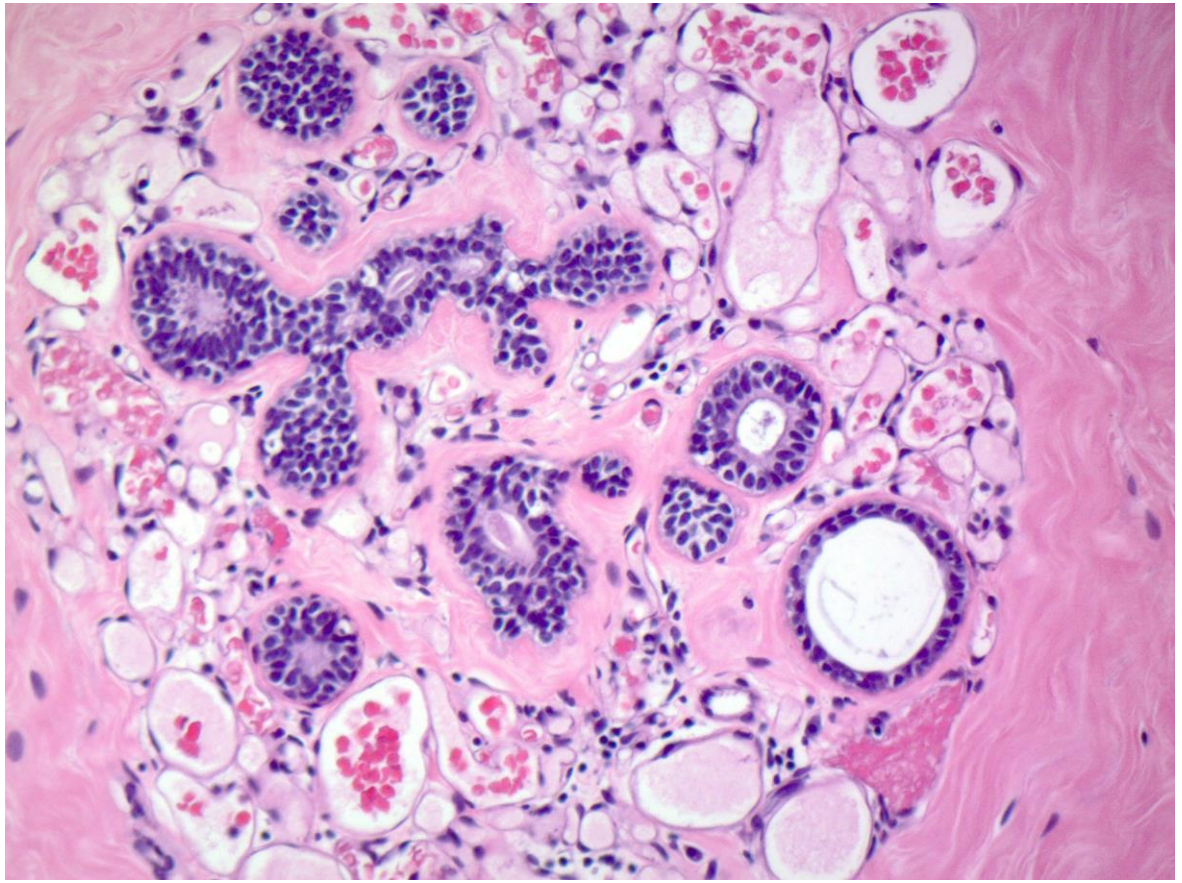
Perilobular hemangioma





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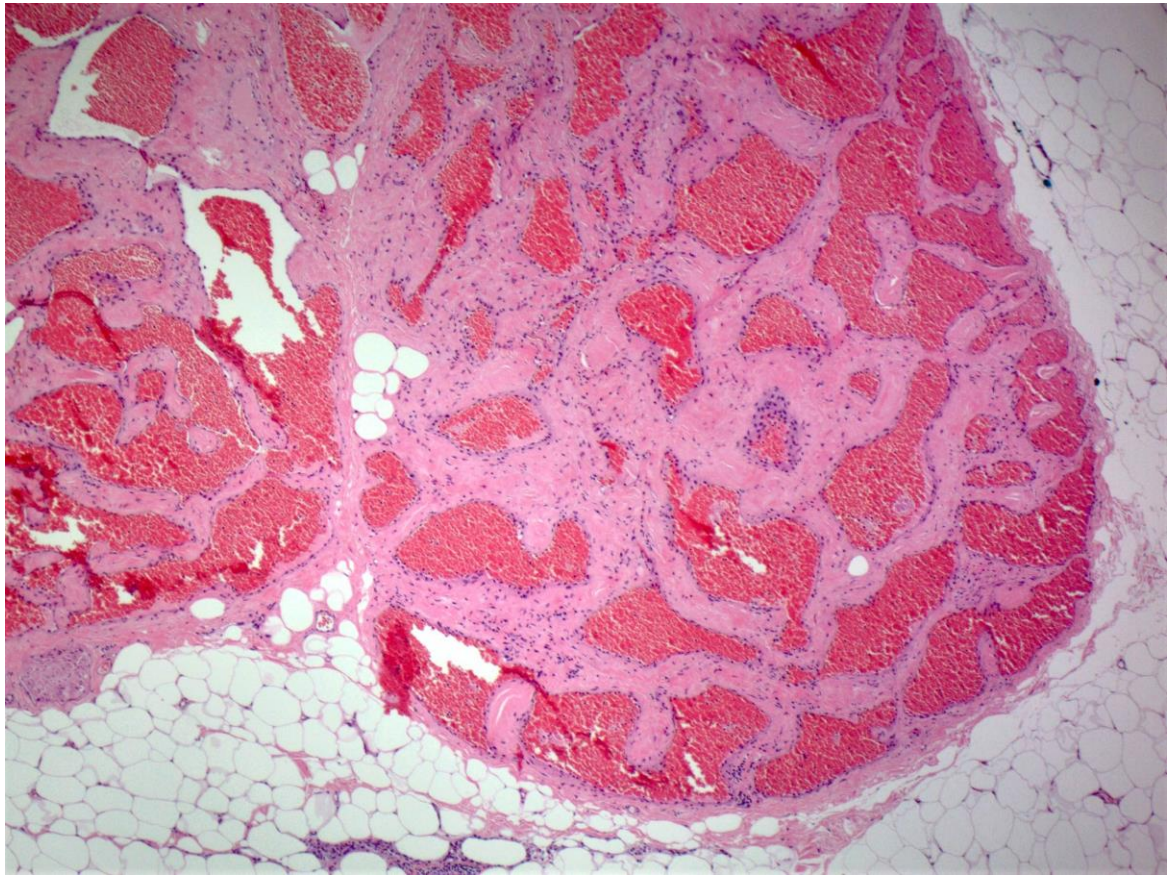
Cavernous hemangioma



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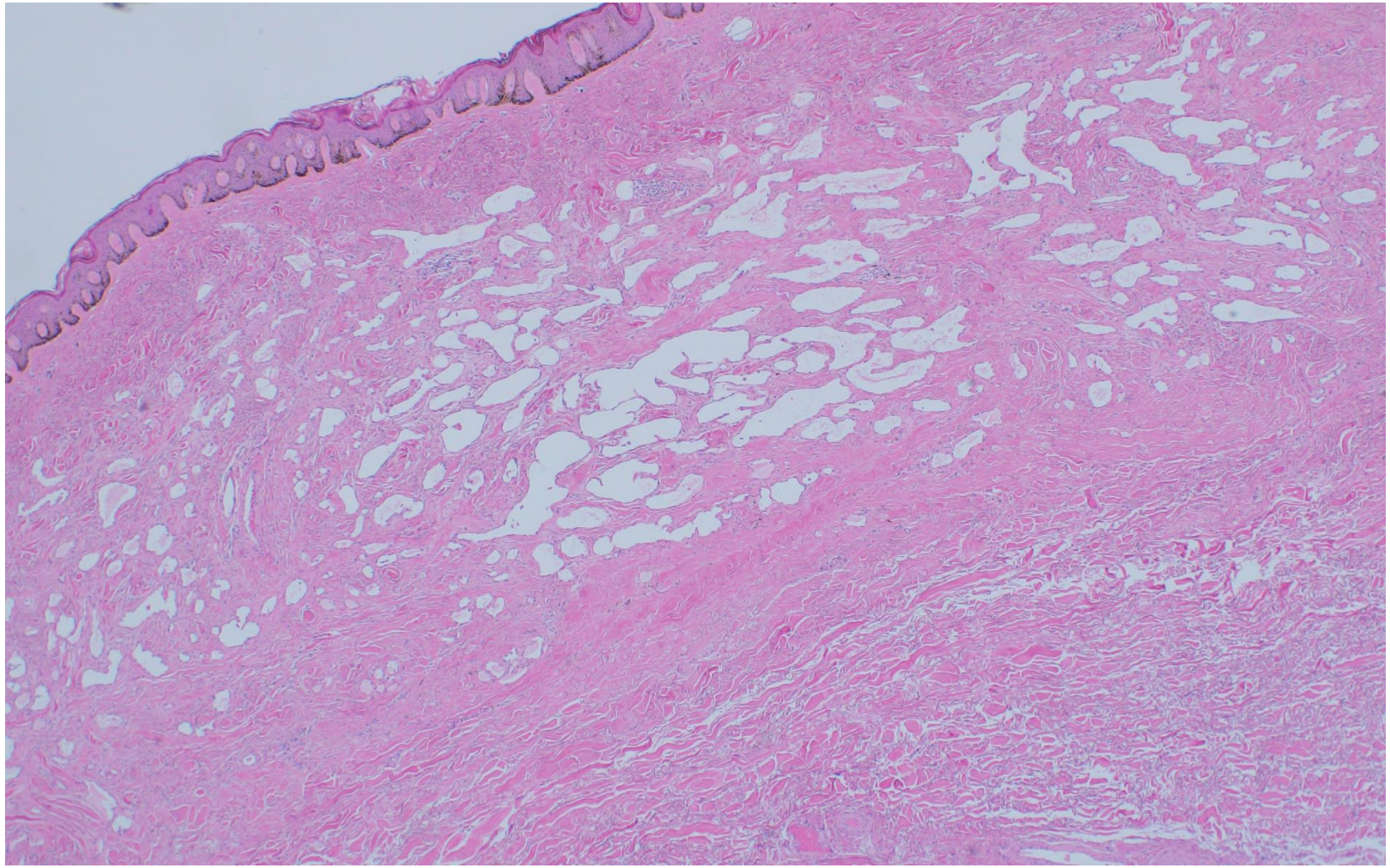
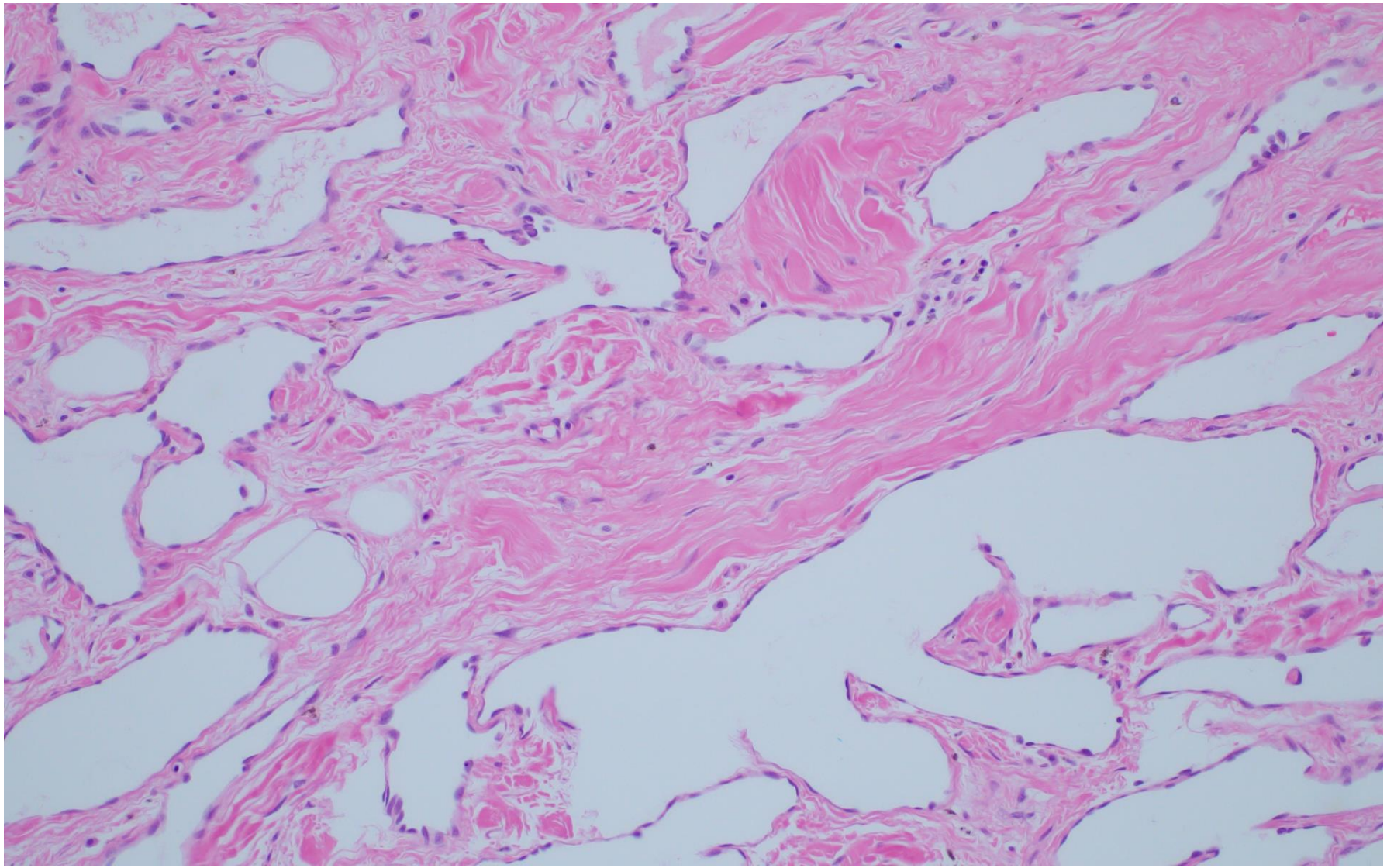
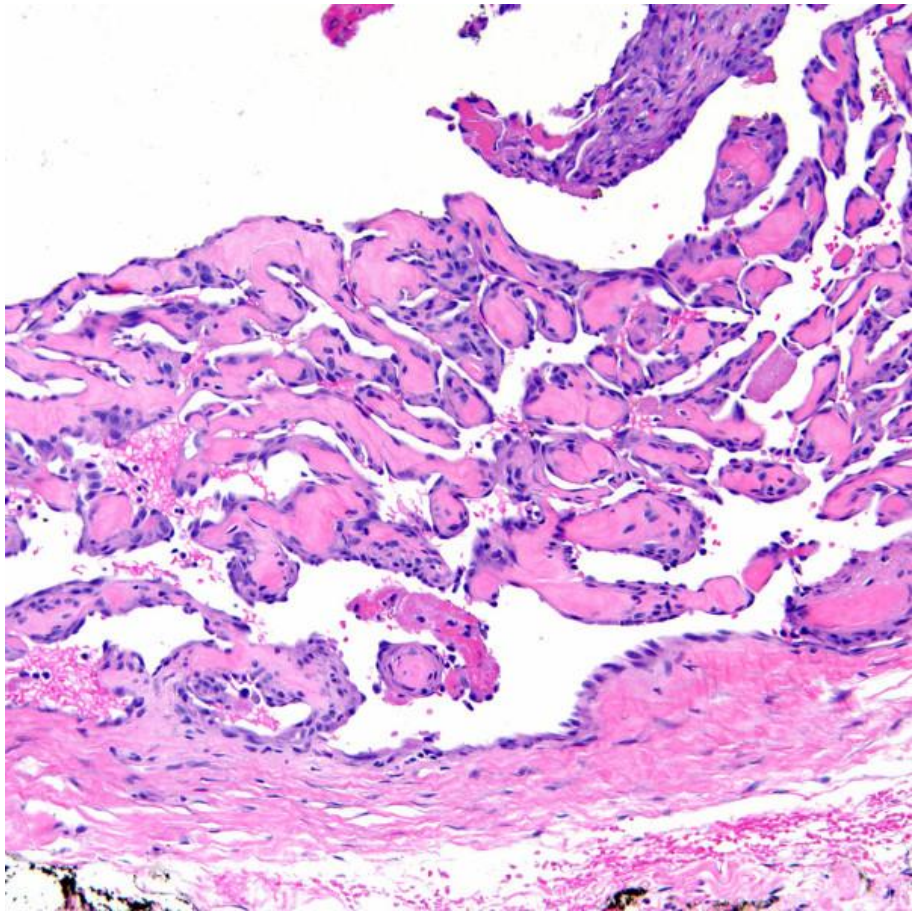
Hemangioma



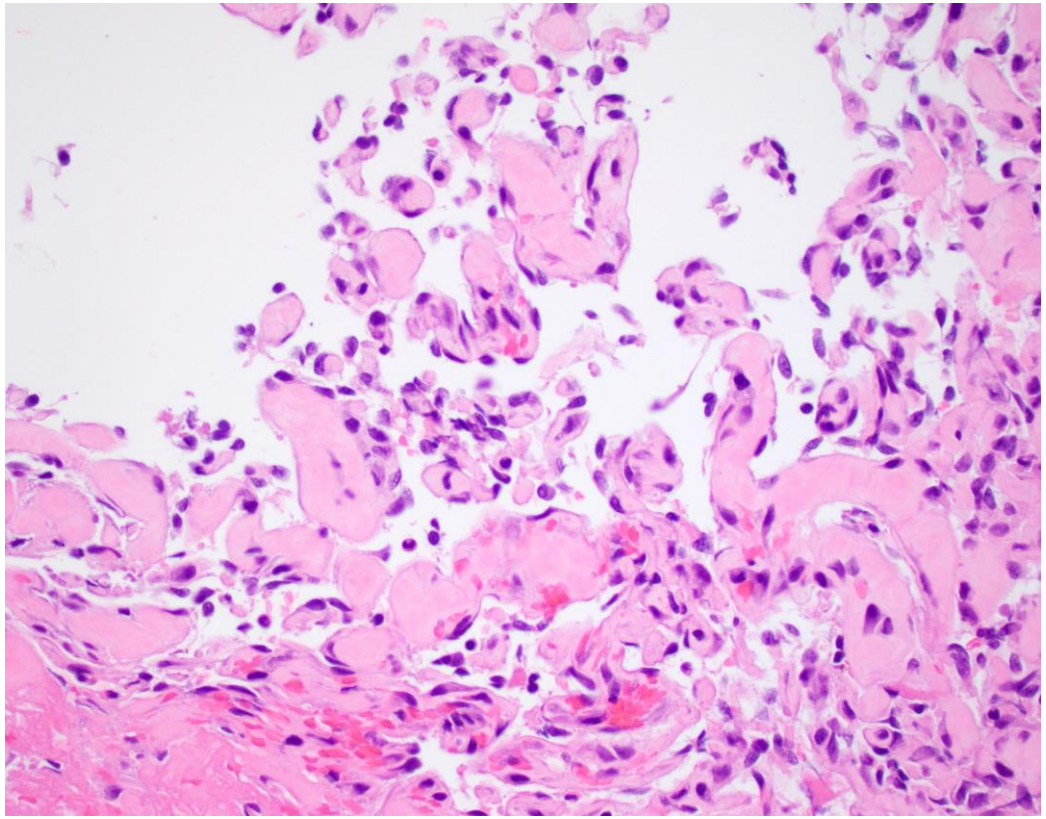
Hemangioma



Papillary endothelial hyperplasia



Credit: Liron Pantanowitz



Credit: Laura Warmke, MD

Hemangioma

- Endothelial cells show expression of ERG, CD31, D2-40, fVIII.
- AR expression in the stroma of benign and malignant vascular lesions has been described.
- In the past, excision was mandatory to exclude a low grade angiosarcoma.
- Now, if there is radiologic-pathologic correlation, excision following CNB is not mandatory.

Angiomatosis

- Benign vascular proliferation affecting a large area of the breast, sparing the intralobular stroma.
- Rare lesion, can occur in any age but most cases described in young women. Can be congenital or acquired.
- Clinical findings: Breast enlargement or palpable mass. Significant growth can occur in pregnancy. +/- discoloration or hyperpigmentation of overlying skin. Can be transilluminated.
- Imaging can show a vascular or a multicystic septated mass.
    - Moderate blood flow with color Doppler

Angiomatosis - Pathology

- Macroscopic: Multicystic, spongy appearing mass.
- Microscopic:
  - Poorly defined borders
  - Vascular spaces of varying caliber, can anastomose
  - Even distribution over a large area of the breast
  - Does not involve intralobular stroma
  - Lined by bland endothelial cells
  - Can extend to skin or pectoralis muscle
  - Capillary subtype: Nodular arrangement of small vessels with a central larger vessel (less common)

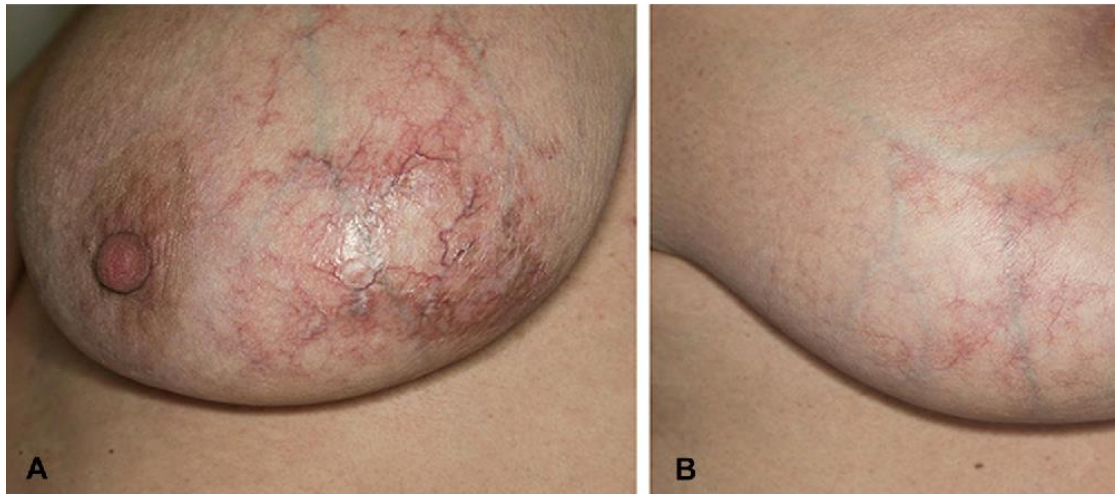
Angiomatosis

- Main critical DD is angiosarcoma:
  - Angiomatosis shows uniform distribution of vessels
  - Bland nuclei
  - No endothelial tufting, papillae, necrosis or blood lakes.
  - Spares the TDLUs
  - Ki-67 usually low (<2%)
- Prognosis: Incompletely excised lesions are at high risk for local recurrence. Can be locally aggressive but metastases or malignant transformation have not been documented.

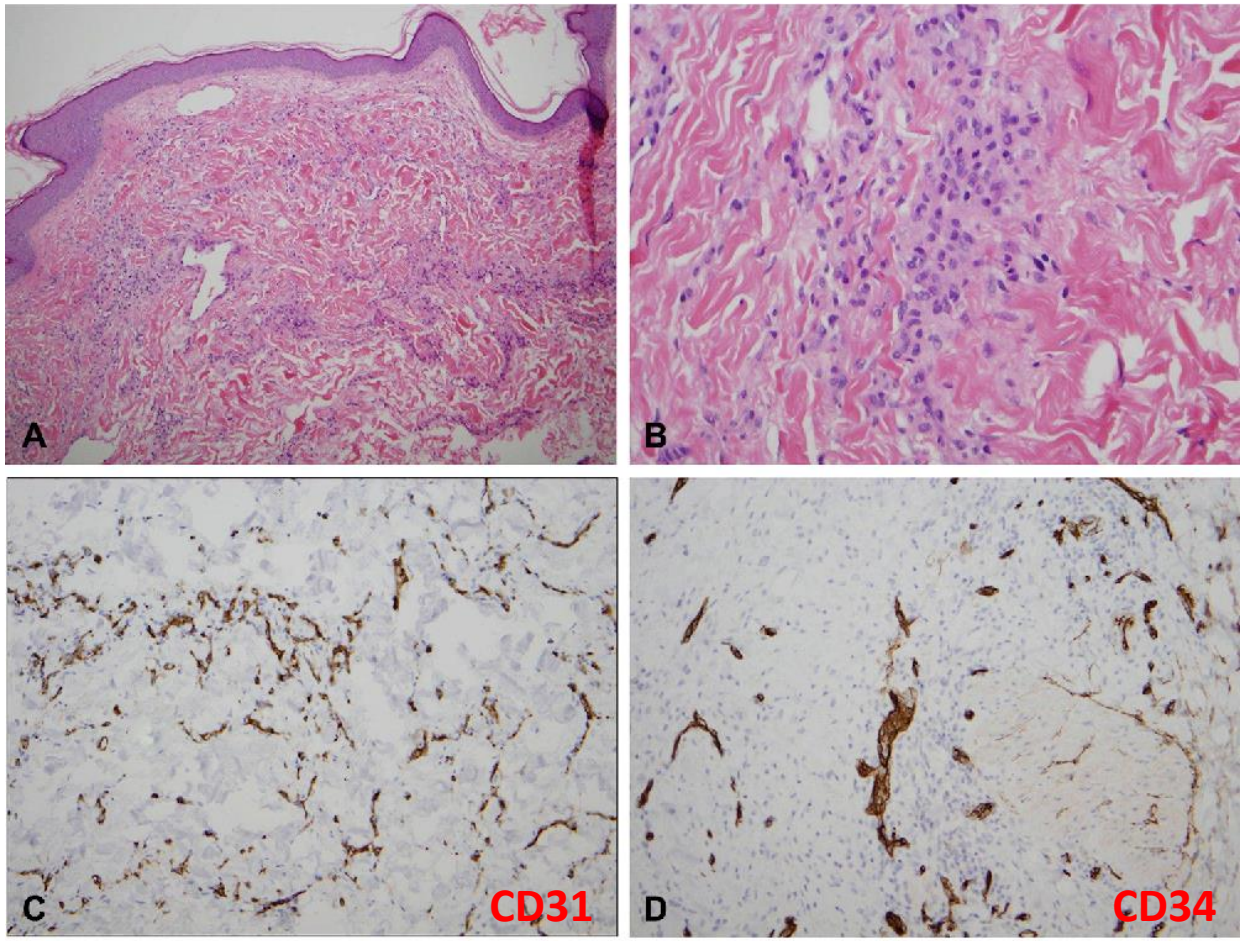
Diffuse Dermal Angiomatosis

- Distinct rare variant of reactive angioendotheliomatosis associated with smoking, hypercoagulable states, trauma, underlying veno-occlusion, pendulous macromastia
- Clinical presentation: Painful cutaneous erythematous to violaceous plaques and papules that tend to ulcerate. Surrounding tissue necrosis.
- Lesions tend to grow over time
- Treatment: Lifestyle modifications for atherosclerosis, revascularization, reduction mammoplasty or excision of lesions

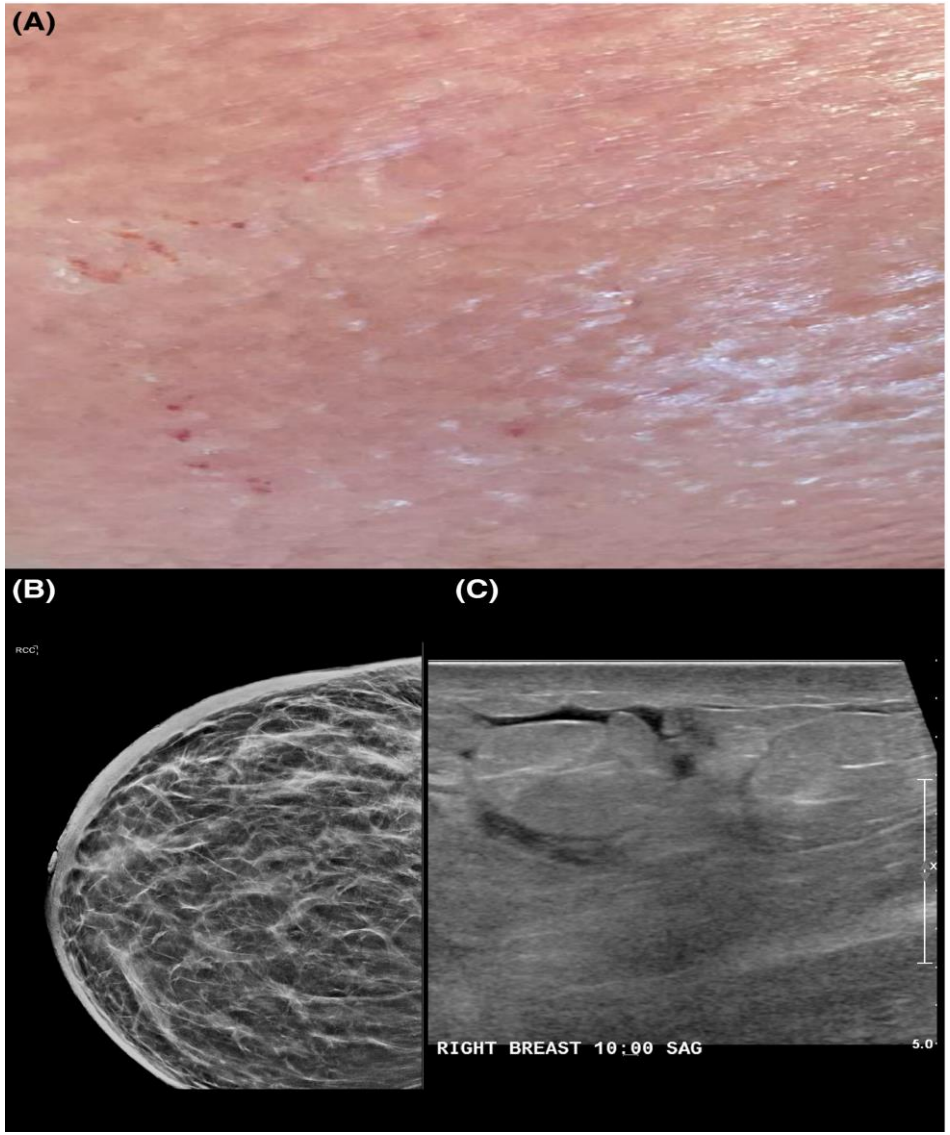
Diffuse dermal angiomatosis



Tollefson M et al Diffuse dermal angiomatosis of the breast: clinicopathologic study of 5 patients. Journal of American Academy of Dermatology; 2014



Diffuse dermal angiomatosis mimicking inflammatory breast carcinoma



The Breast Journal, Volume: 24, Issue: 2, Pages: 196-198, First published: 26 July 2017, DOI: (10.1111/tbj.12866)

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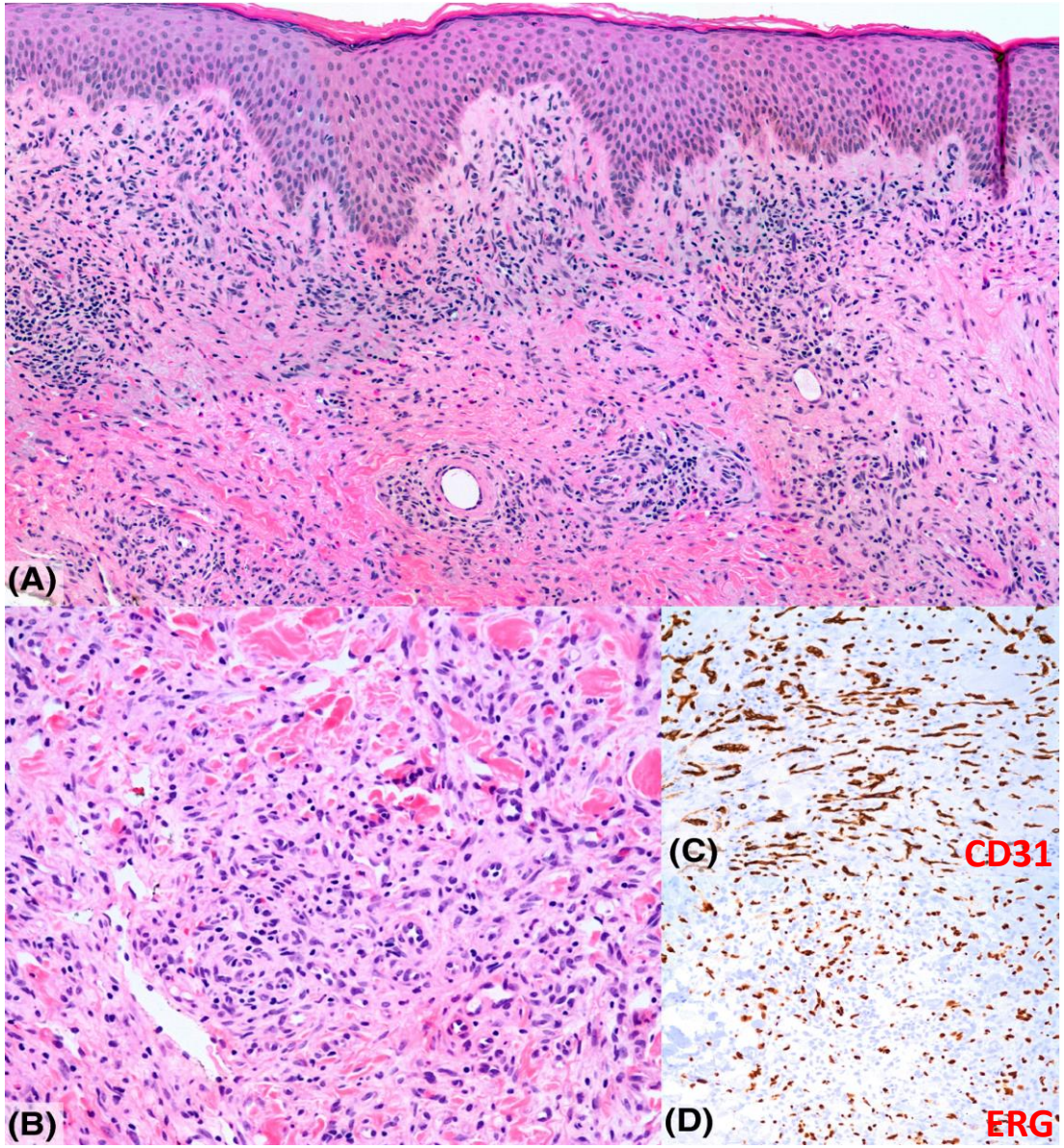

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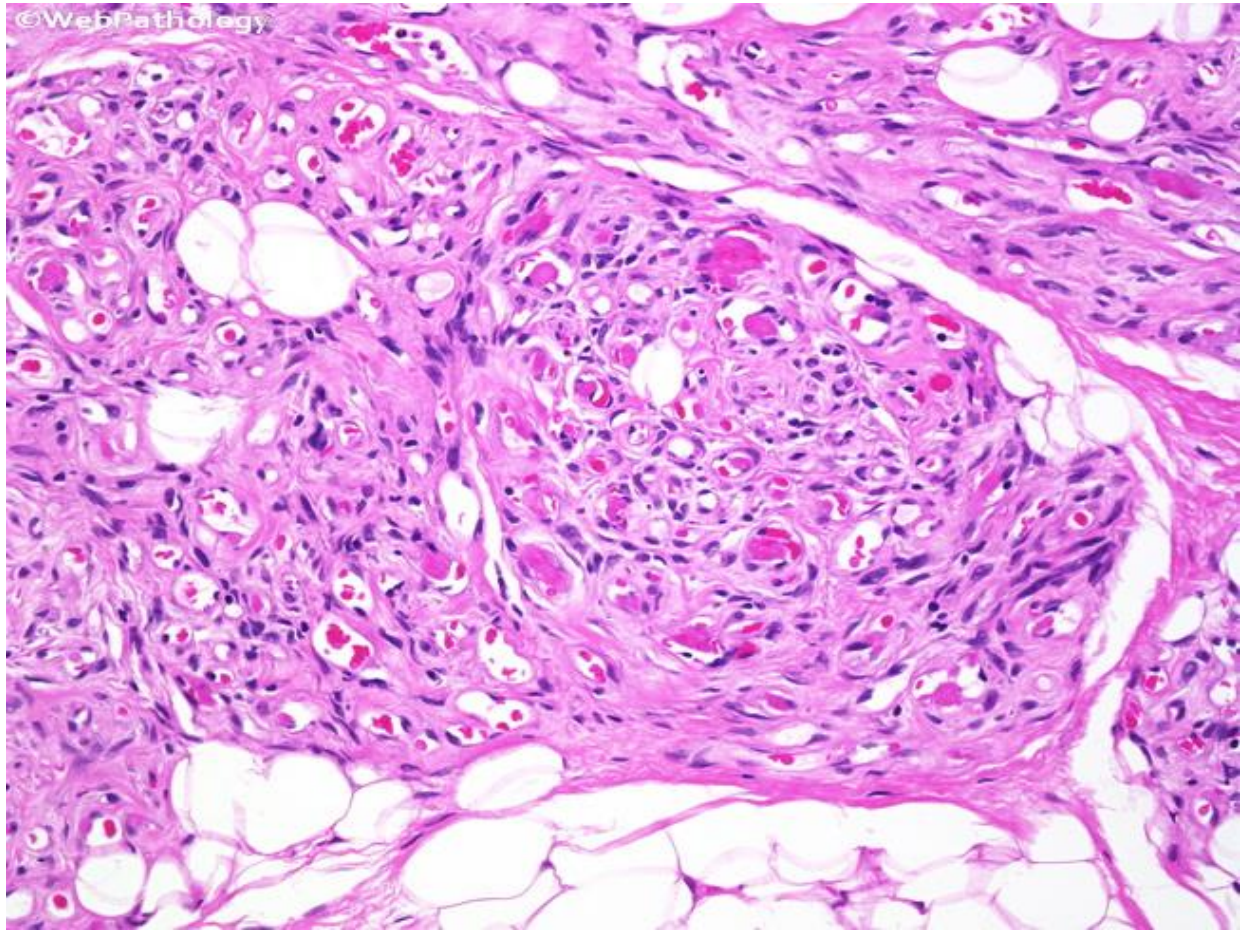
Angiolipoma

- Benign lesion with variable proportion of adipose tissue and vascular elements
- More frequent in subcutaneous tissue than in breast parenchyma
- Palpable mass or incidental finding on imaging studies
- Microscopic: Capillary sized vessels often containing thrombi admixed with adipose tissue. Vessels are unevenly distributed and tend to be clustered in the periphery.
  - Cellular variant: Vascular elements represent >50% of lesion

Angiolipoma



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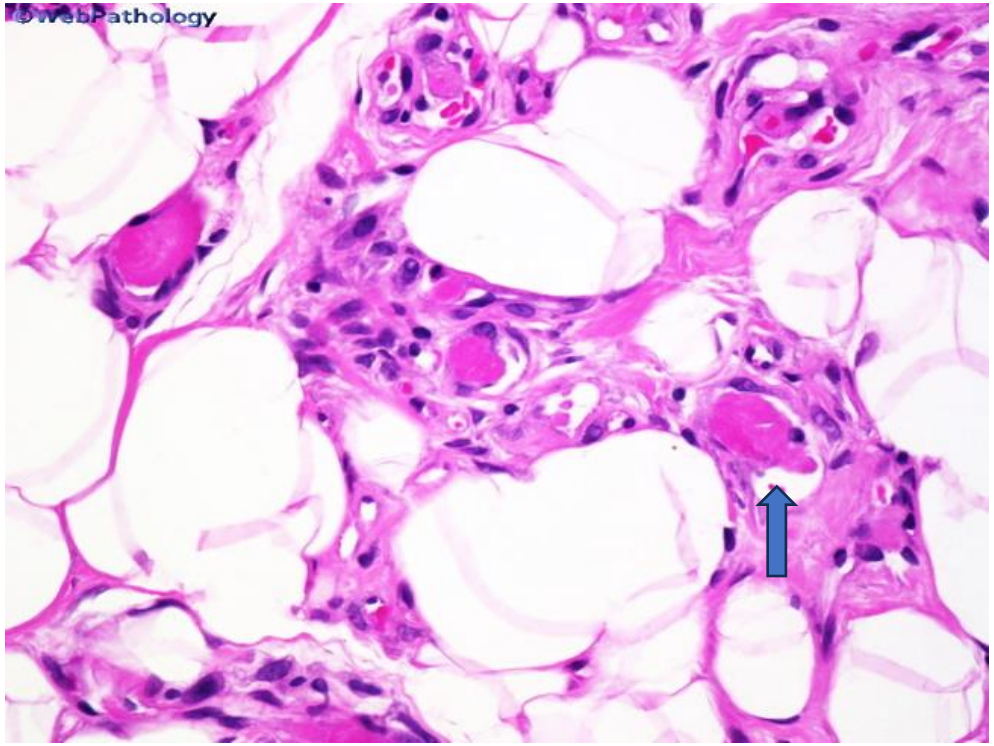

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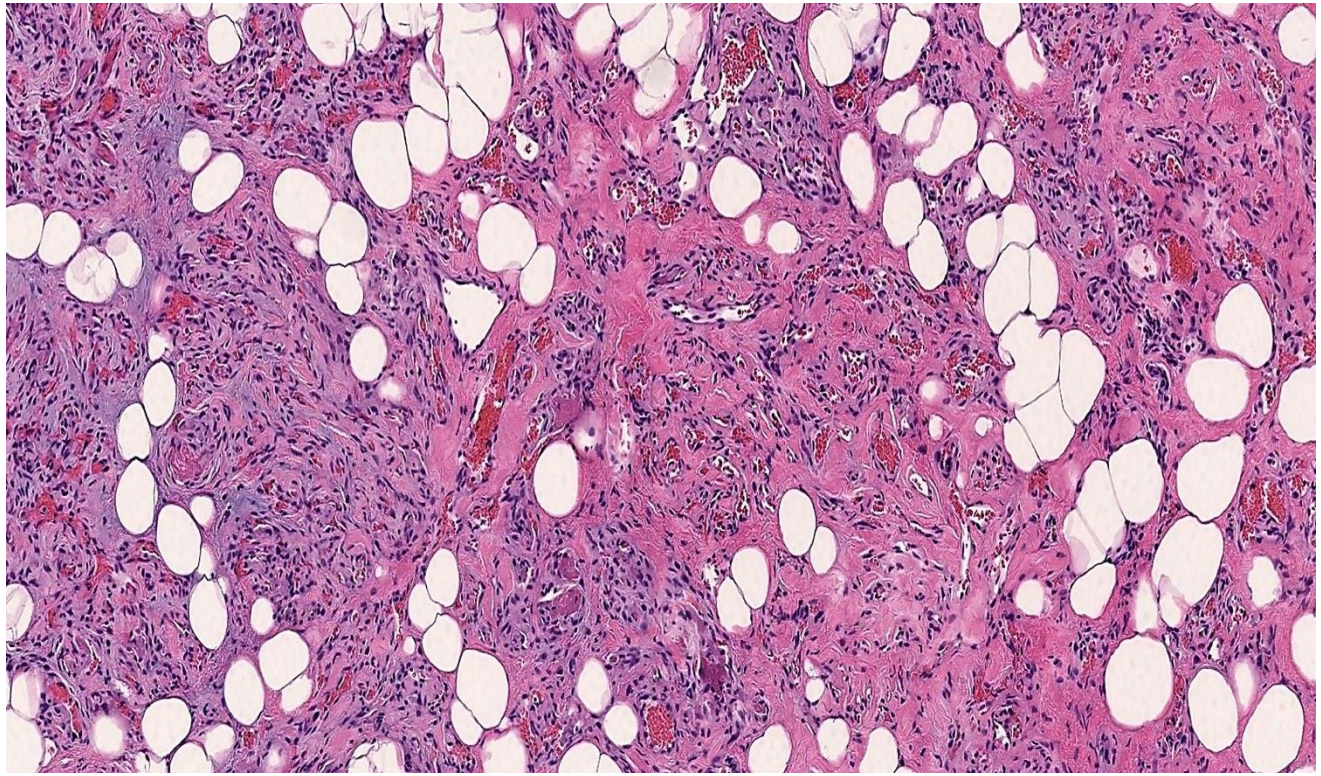
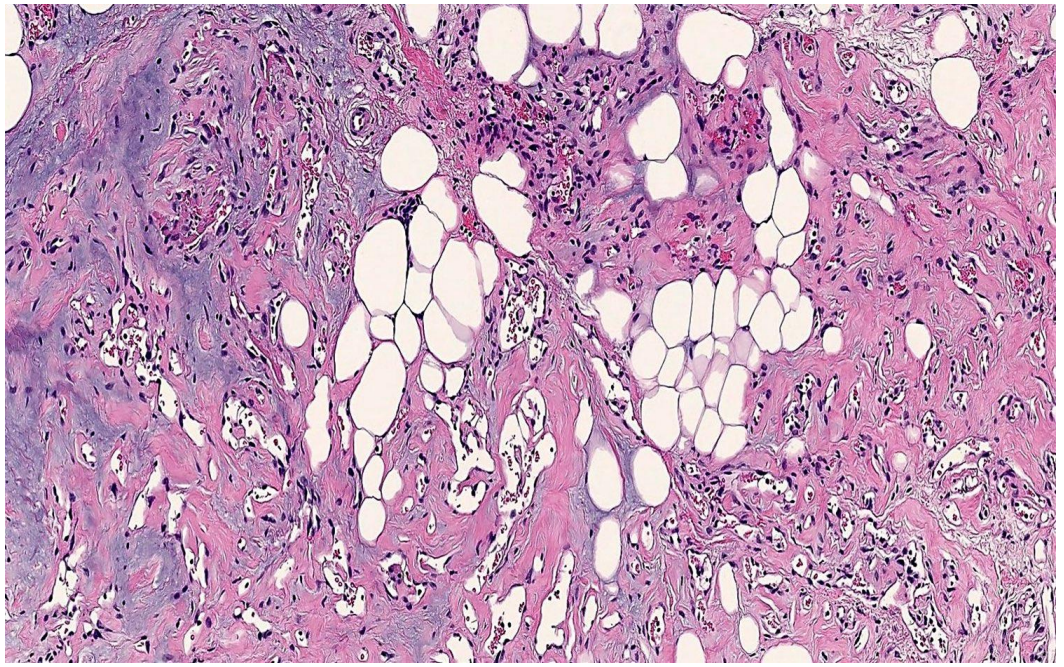
Cellular Angiolipoma





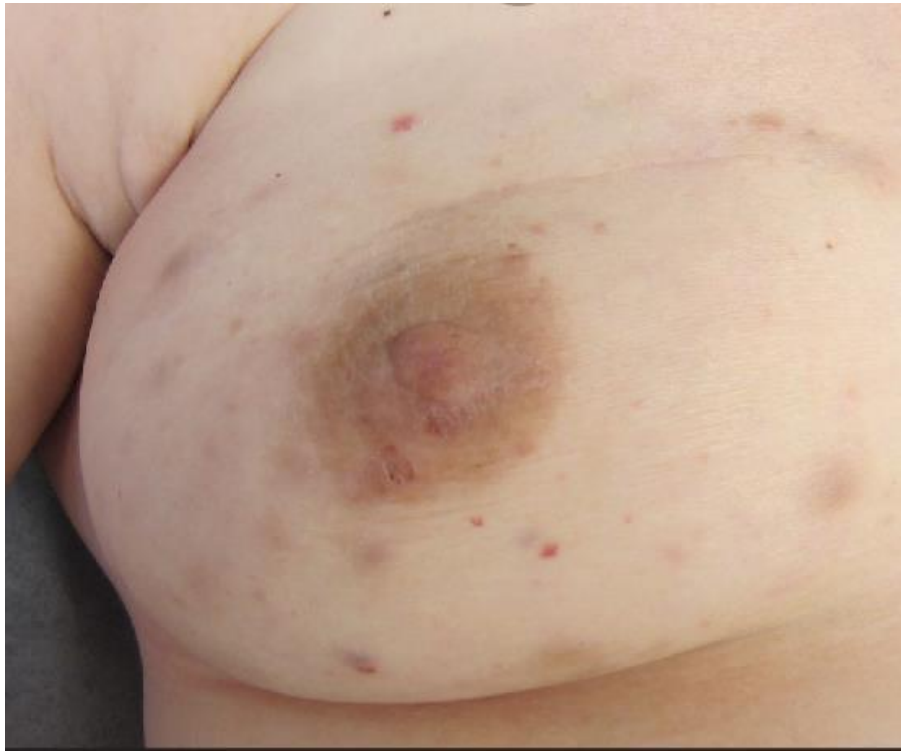
https://www.pathologyoutlines.com – Contributed by Jeanne Meis, MD

Conservative vs Surgical Management in Benign vascular lesions

- A study by Zhang et al (*The Breast Journal*, 2019) in 117 patients (106 with diagnosis of hemangioma and 17 with diagnosis of atypical hemangioma)
  - All of the atypical cases were surgically excised
    - 7 reclassified to benign diagnosis
    - 4 remained atypical hemangioma
    - One case recurred 3 years after excision with no evidence of disease at 87 months
  - 16.9% of benign hemangiomas were excised with no upgrades
  - At 87 months, 5 patients died from unrelated caused and the rest were alive with no evidence of vascular lesions.

Atypical Vascular Lesions (AVL)

- Described in 1994 by Fineberg and Rosen
- Vascular lesions in irradiated skin, often small and multiple
- Most common in 6^{th}-7^{th} decade
- Total median radiation dose is 50 Gy.
- Clinical findings: Affects breast skin or anterior chest wall. Multiple erythematous to brown papules, rarely plaques. Usually appear 3-4 years post radiation, but latency period can be as short as 1 year.

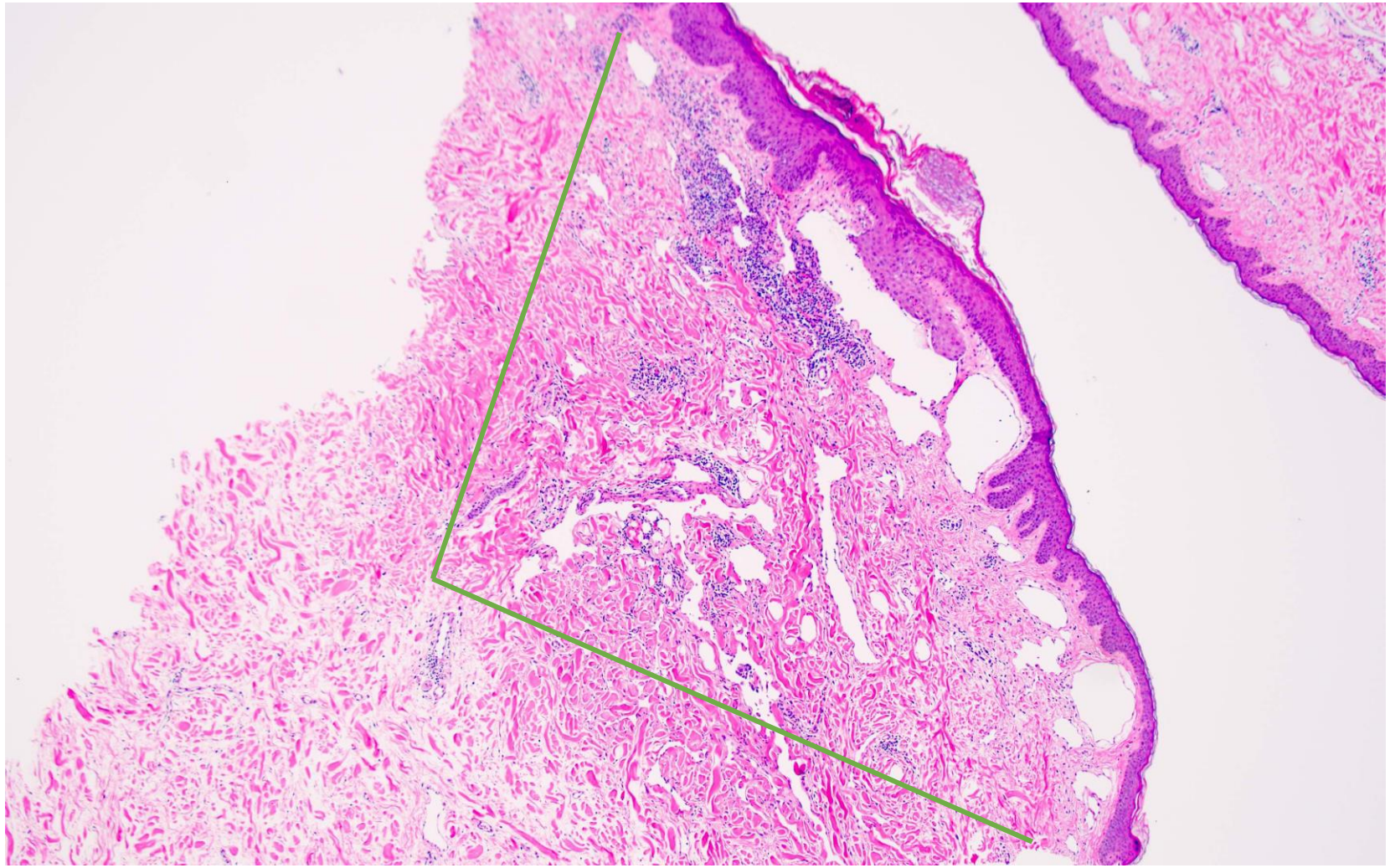


Berrebi, K et al Multiple atypical vascular lesions following breast-conserving surgery and radiation. *Cutis*; 2019

Atypical vascular lesions - Pathology

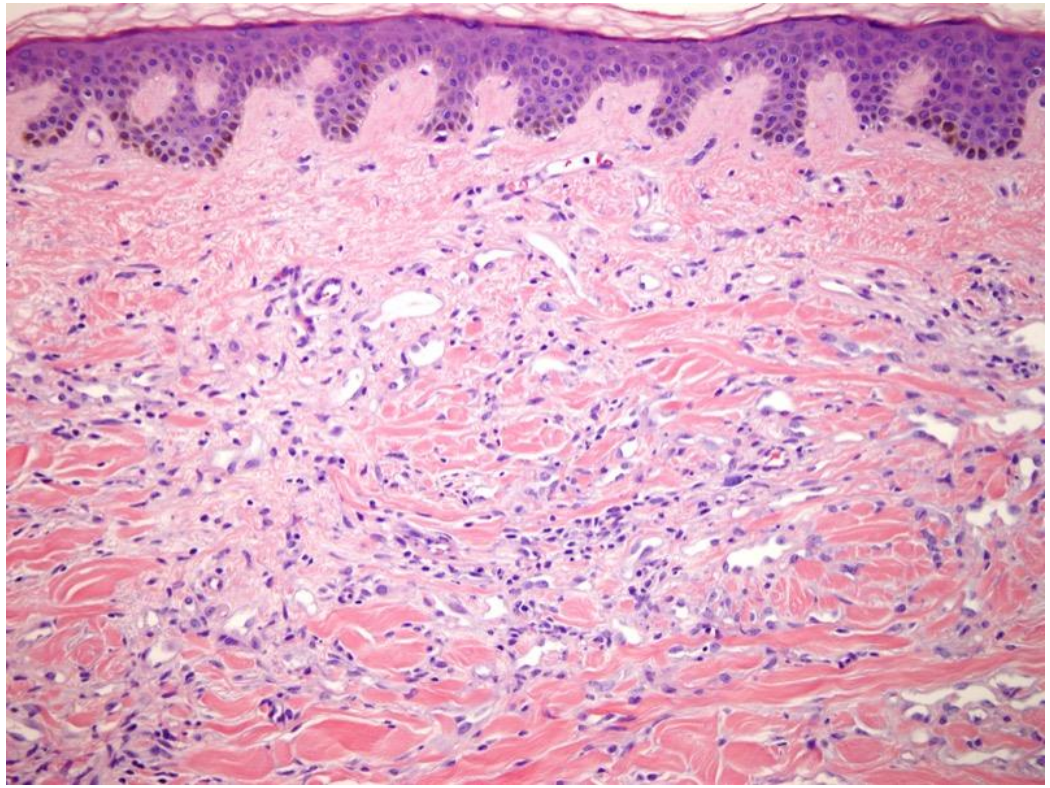
- Thought to arise as a result of lymphatic obstruction
- Microscopy: Well circumscribed, usually wedge shaped and located in superficial to mid dermis.
  - Lymphatic subtype: Most common. Irregular, thin walled vessels that can show branching and anastomoses. Valve-like structures can be seen. Lining endothelium can show hobnailing or hyperchromasia. Surrounding lymphoid infiltrate. Expresses CD31, CD34 (variable), and D2-40
  - Vascular subtype: Resembles microvenular or hobnail hemangioma. Lacks D2-40 expression. Vessels are surrounded by pericytes (highlighted with smooth muscle markers).
- Negative for *MYC* amplification or overexpression

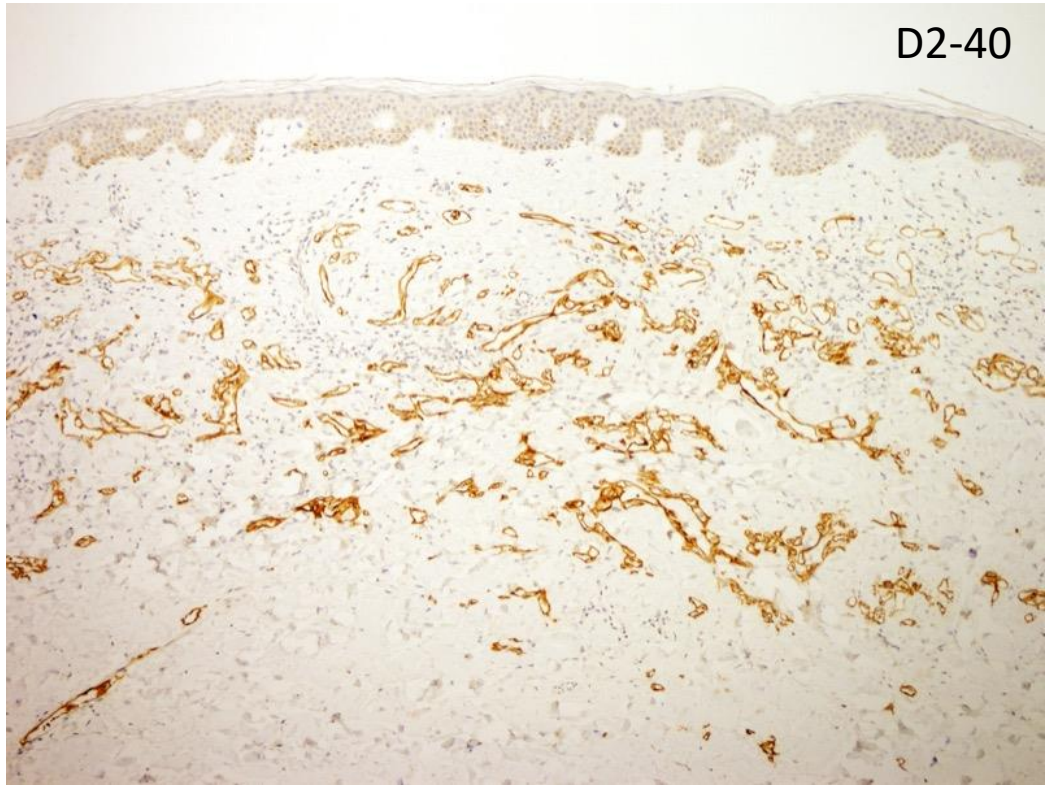
Atypical vascular lesions



https://www.pathologyoutlines.com – Contributed by Indu Agarwal, MD and Sarlene See, MD

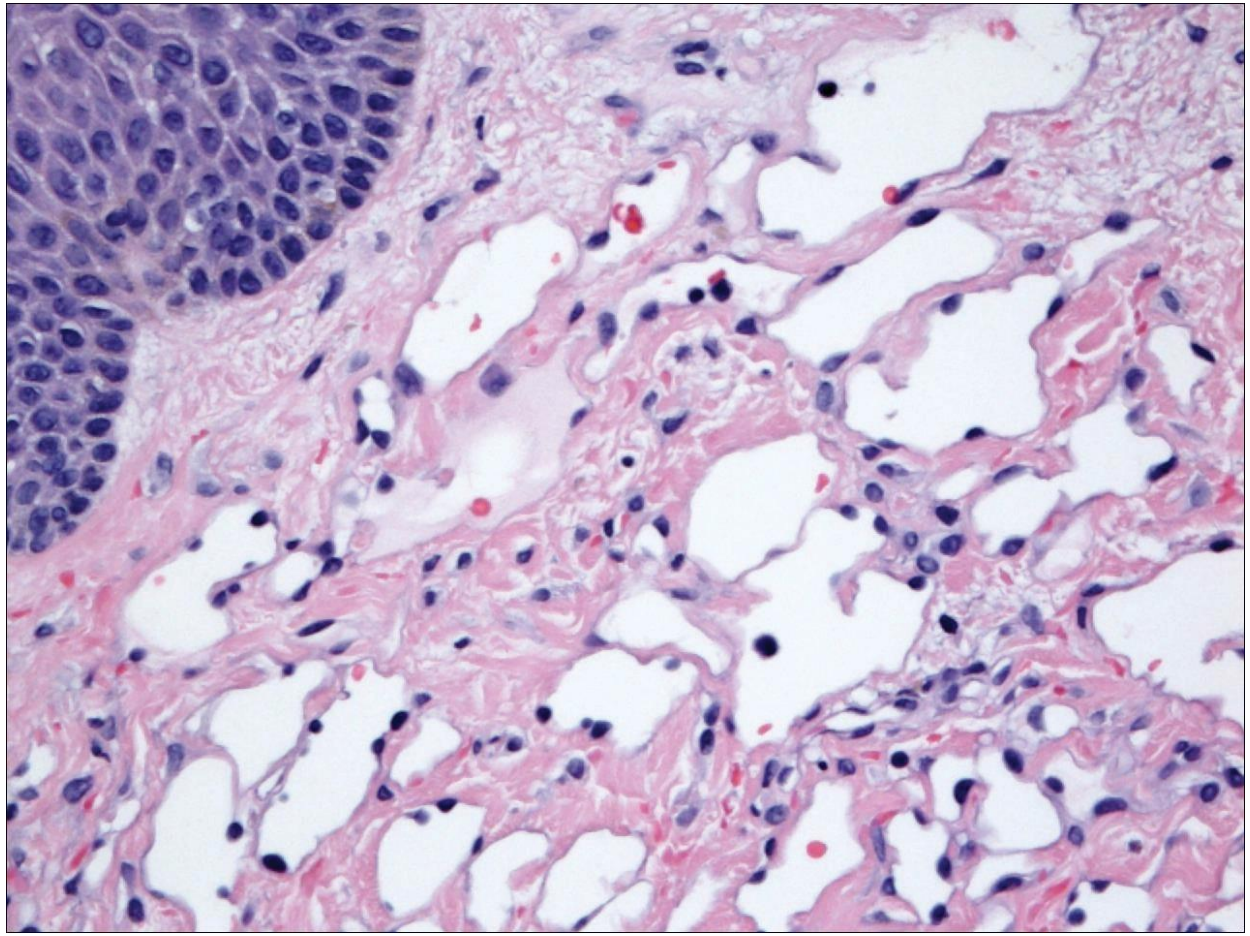
Atypical vascular lesions



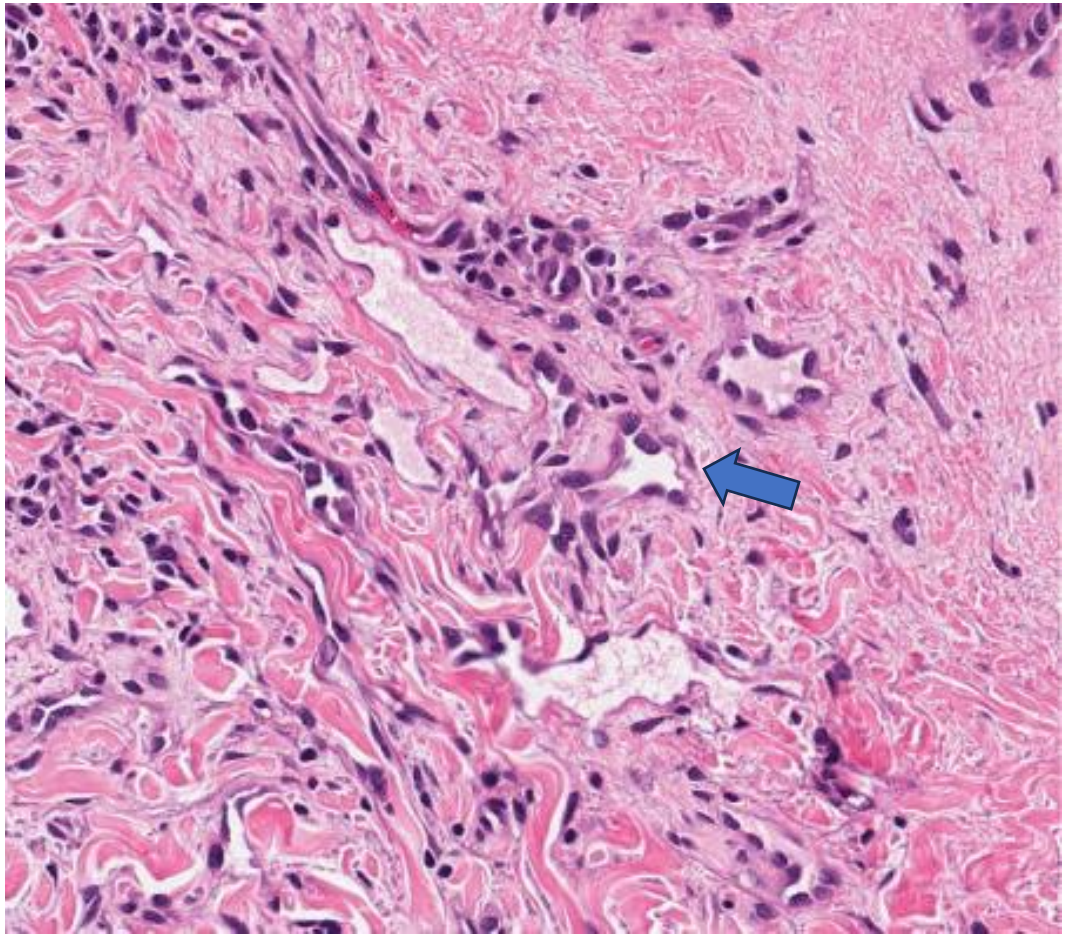


https://dermpath.weill.cornell.edu

Atypical vascular lesions

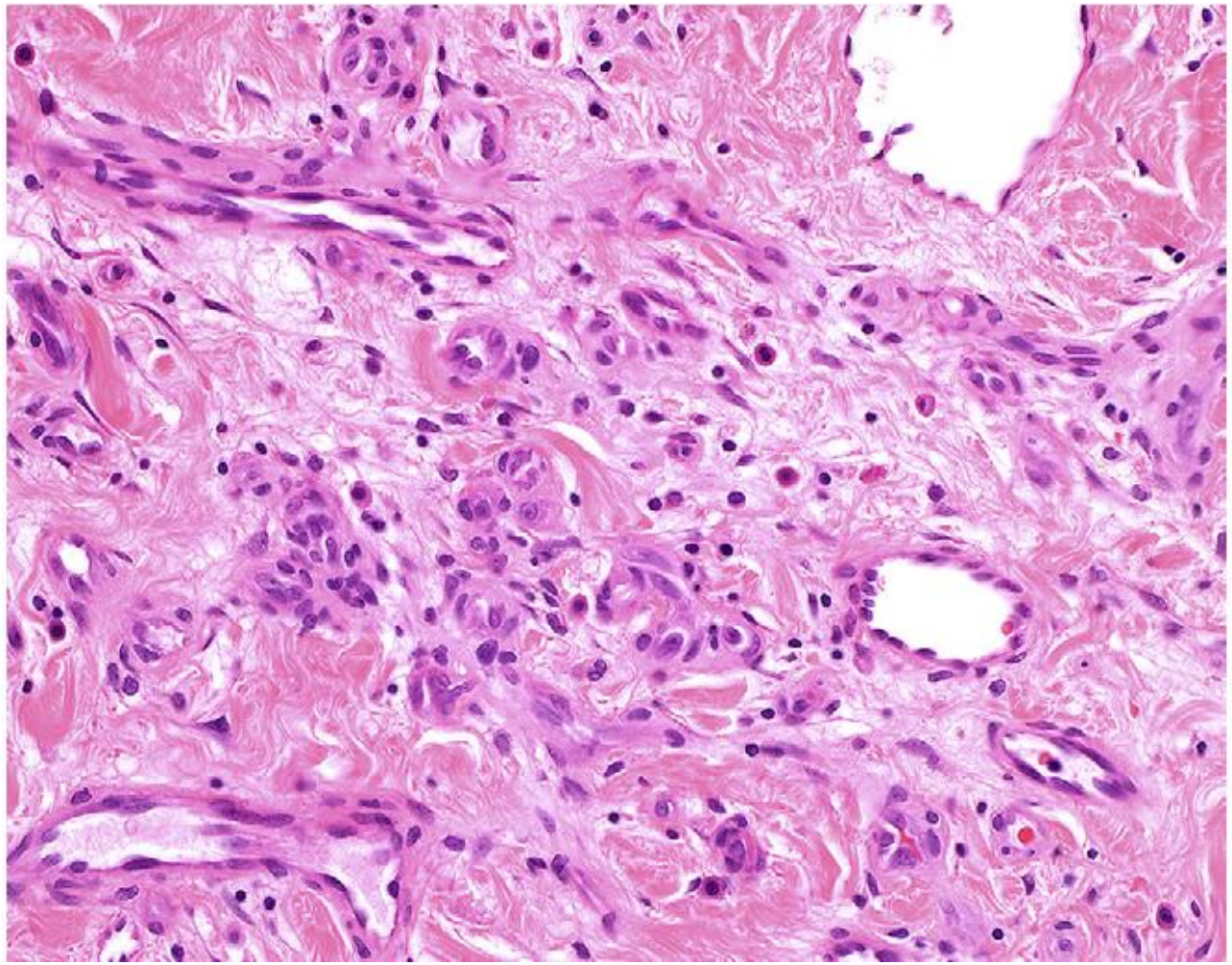


Mandrell, J et al Multiple Primary Atypical Vascular Lesions Occurring in the Same Breast *Cutis*; 2017



Kaley, J et al Dropping the MYC: A review of post-radiation atypical vascular lesions and angiosarcoma of the breast. *Global Dermatology*; 2016

Atypical vascular lesions



Fisher, C. Unusual myoid, perivascular, and postradiation lesions, with emphasis on atypical vascular lesion, postradiation cutaneous angiosarcoma, myoepithelial tumors, myopericytoma, and perivascular epithelioid cell tumor. Seminars in Diagnostic Pathology; 2014

Atypical vascular lesions

- Molecular characteristics not very well known
- Low numbers of *HRAS* and *TERT* promoter mutations
- Very rare mutations involving *TP53* or *MYC* amplification
- A study by Corradini et al (*Histopathology*; 2020)
  - 8 AVLs and 62 angiosarcomas
  - 1 AVL case was positive for MYC by IHC but negative for rearrangement by FISH
  - 10/17 secondary angiosarcomas positive for MYC
  - 2/4 AVLs showed *hTERT* mutations

Atypical Vascular Lesions

- Prognosis:
  - Usually benign clinical course. No deaths or metastases have been reported.
  - Can recur (16-46%) or patients can develop new lesions
  - Progression to angiosarcoma is rare
  - Relationship to angiosarcoma still under debate
    - Radiation dermatitis pattern of angiosarcoma has been proposed as an intermediate lesion between AVL and angiosarcoma
- Avoid diagnosing in CNB
  - “Atypical vascular proliferation”
- Excision with negative margins is recommended
- Close clinical follow up

Atypical vascular lesions

- Main DD is with angiosarcoma
  - “Tip of the iceberg” phenomenon
    - In one series of 11 cases diagnosed as AVL on biopsy, 5 were upgraded to angiosarcoma on excision (Mattoch et al, 2007)
  - No strict histologic parameters
  - AVLs are typically well demarcated; oftentimes wedge-shaped
    - Extension into subcutis can rarely happen in AVLs
  - AVLs are diverse lesions, but the architectural complexity of angiosarcomas is not seen
  - Nuclear hyperchromasia and hobnailing should be distinguished from the more prominent atypia in angiosarcoma.
  - Necrosis, increased mitotic activity and blood lakes are not seen.
  - MYC expression/rearrangement useful in distinguishing AVL from secondary angiosarcoma

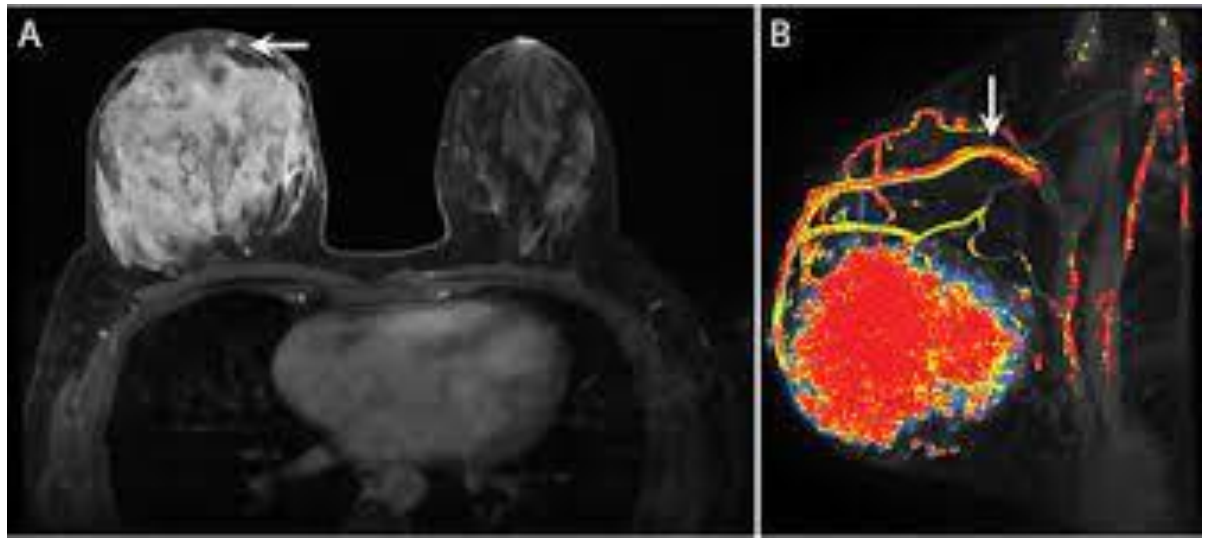
Other terminologies encountered

- Benign lymphangiomatous papule (BLAP)
  - Benign lesion resulting from radiation
  - Flesh colored to hyperpigmented papules
  - Similar histology to AVLs but without infiltration
  - Believed to be another manifestation of AVL
- Atypical hemangioma
  - Benign vascular lesions with atypical features (anastomoses, papillary endothelial hyperplasia, ill appearing borders, mitoses, nuclear atypia)
  - No prior history of radiation

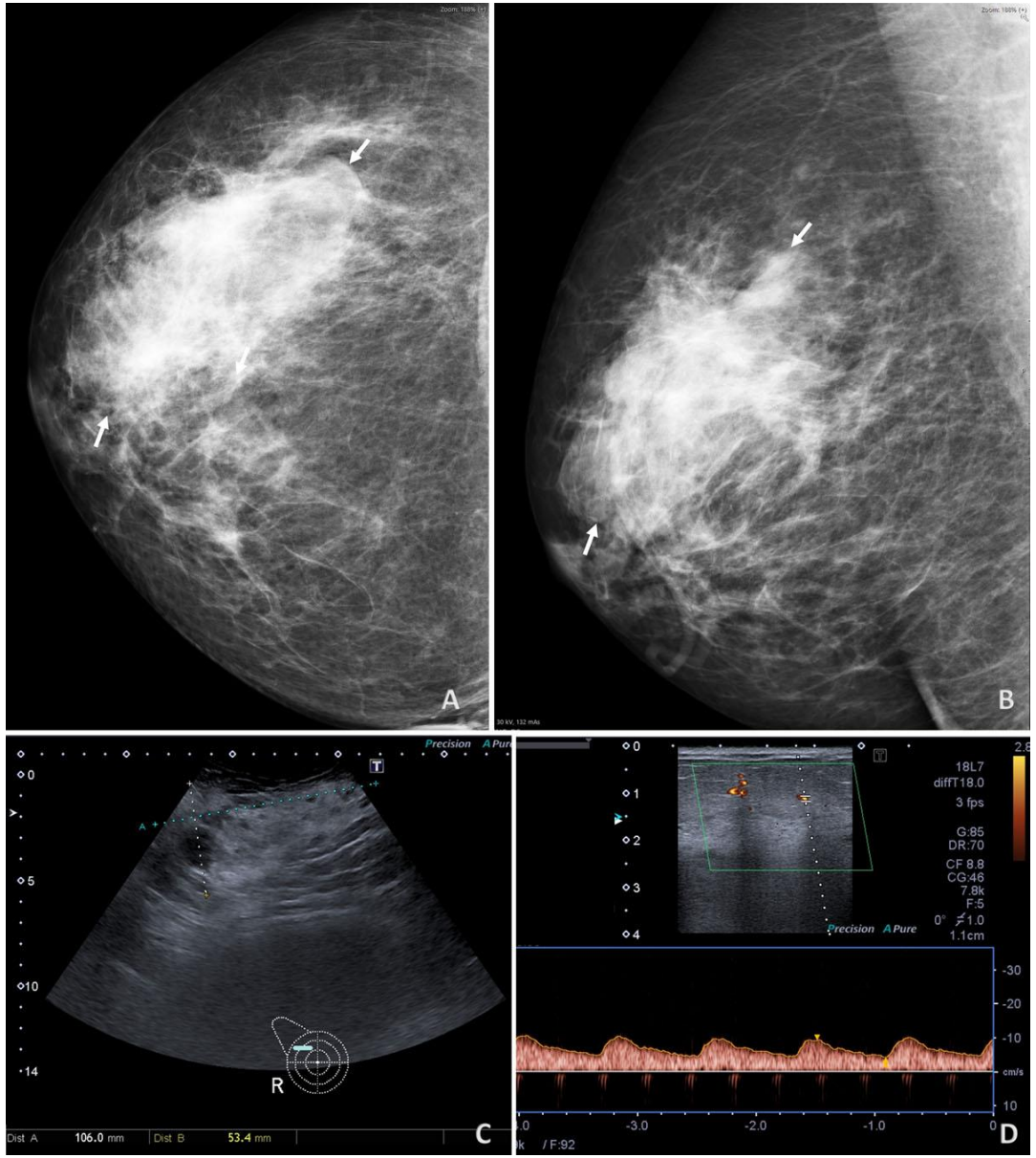
Primary Angiosarcoma

- Rare (<0.05% of malignant breast tumors)
- Malignant primary vascular neoplasm involving breast parenchyma, not associated with prior radiation
- Clinical Features:
  - Median age is 40 years (compared to 70y for secondary angiosarcoma)
  - Most patients present with painless mass, swelling or asymmetry
  - 2/3 of tumors measure > 5 cm
  - Ultrasound: Hyperechoic or mixed hypo and hyperechoic mass or architectural distortion
  - MRI shows malignant enhancement characteristics
  - 20% present with regional disease at diagnosis

Primary angiosarcoma



Brown A and Wahab R MRI of Primary Angiosarcoma of the Breast. *Radiology*; 2020



Costa et al Imaging Tips to Recognize Primary Breast Angiosarcoma *Journal of the Belgian Society of Radiology* 2022

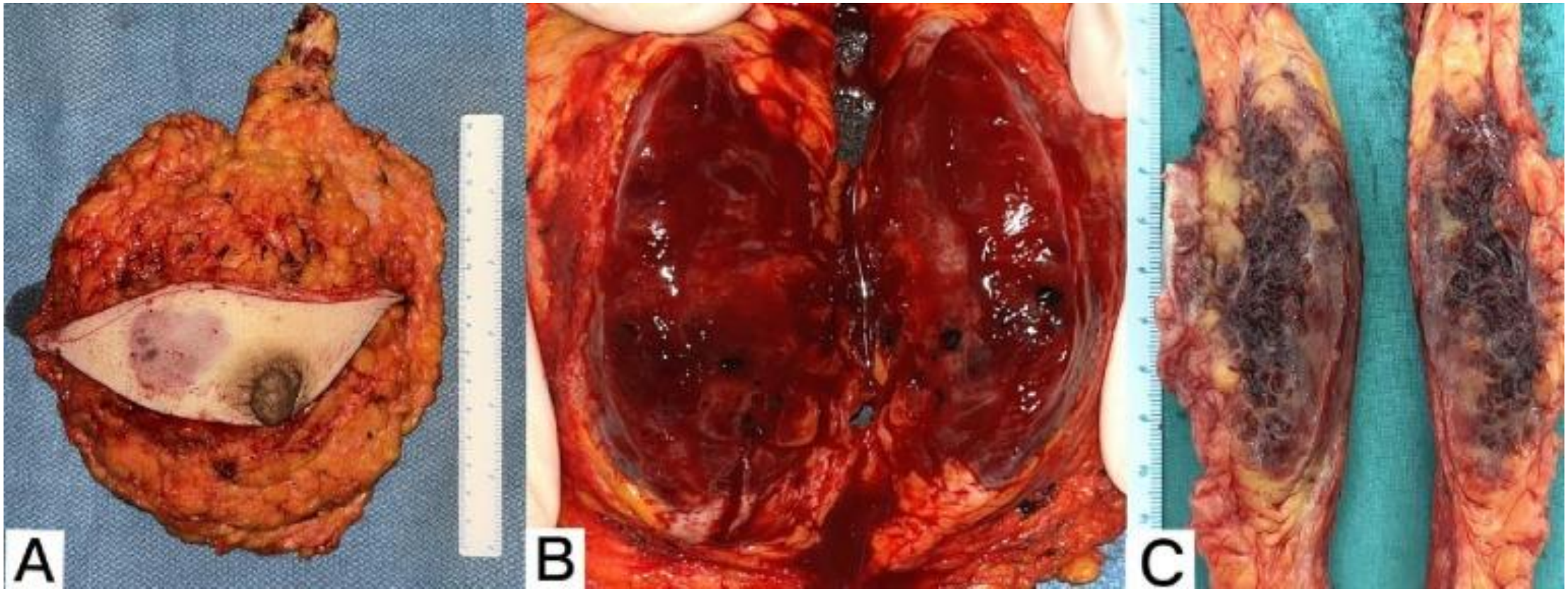
Primary Angiosarcoma

- Pathogenesis
  - Higher frequency of *KDR* and *PIK3CA* mutations compared to angiosarcomas in other body sites
  - A subset shows mutations in *PLCG1*
  - Rare cases show *MYC* gene amplification

Primary Angiosarcoma - Pathology

- Macroscopic:
  - Mean size is 6.7 cm (range 0.7-25 cm)
  - Better differentiated tumors tend to be hemorrhagic and spongy, while more poorly differentiated ones have a more fleshy to solid appearance
  - Well or poorly circumscribed
  - Most are centered in the breast parenchyma and can extend into subcutis or skin

Primary Angiosarcoma - Pathology

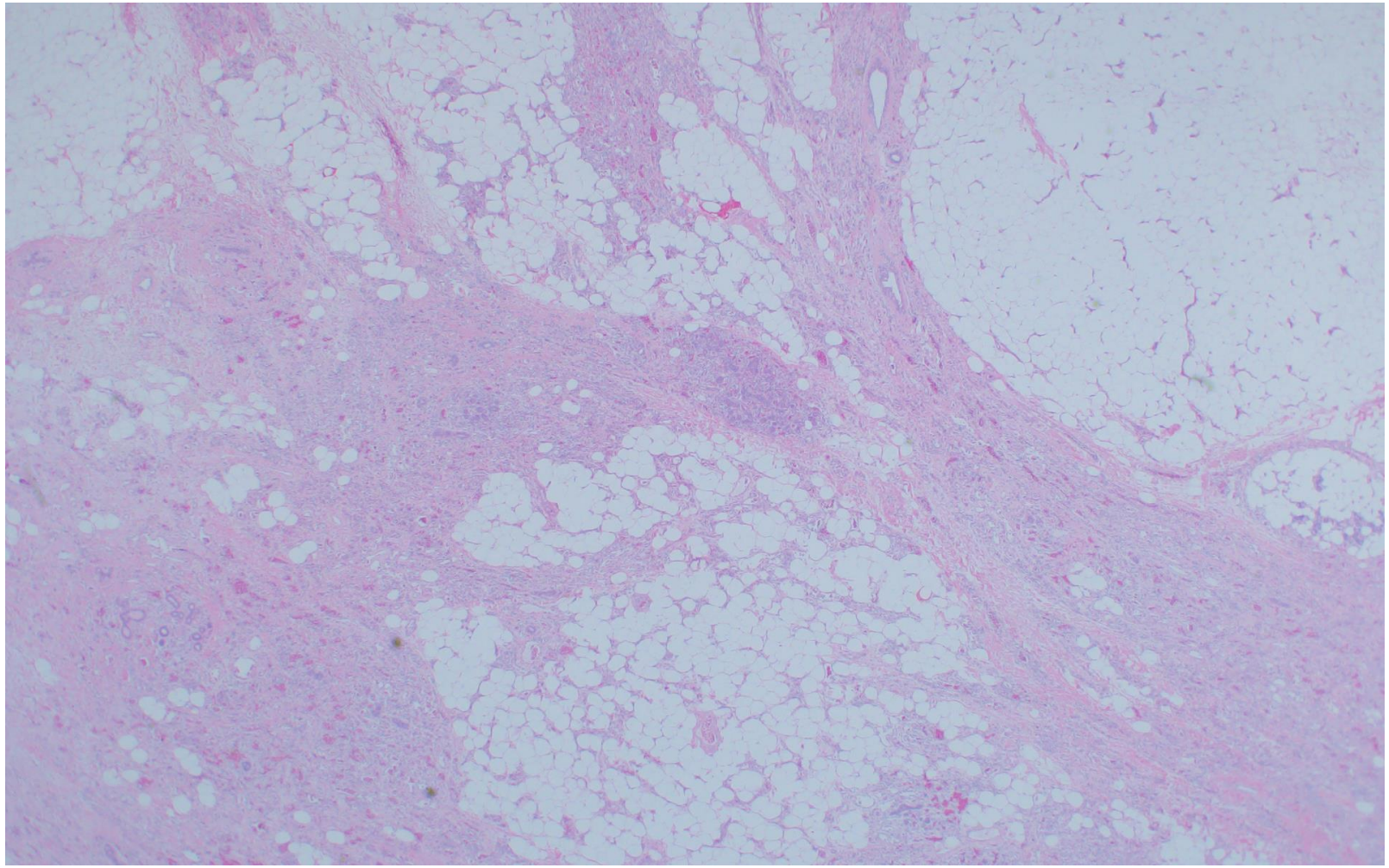


Min L. et al Primary angiosarcoma of breast: A case report and literature review *International Journal of Surgery Case Reports*; 2023

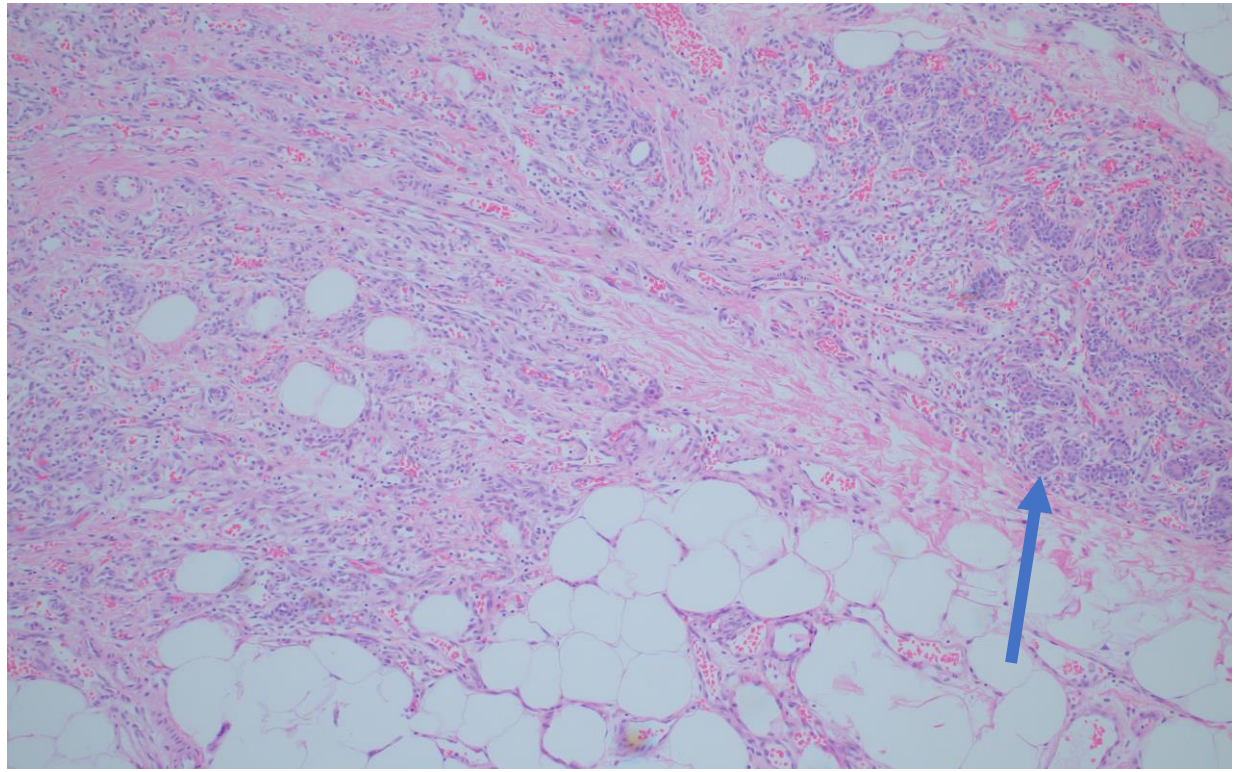
Primary Angiosarcoma - Pathology

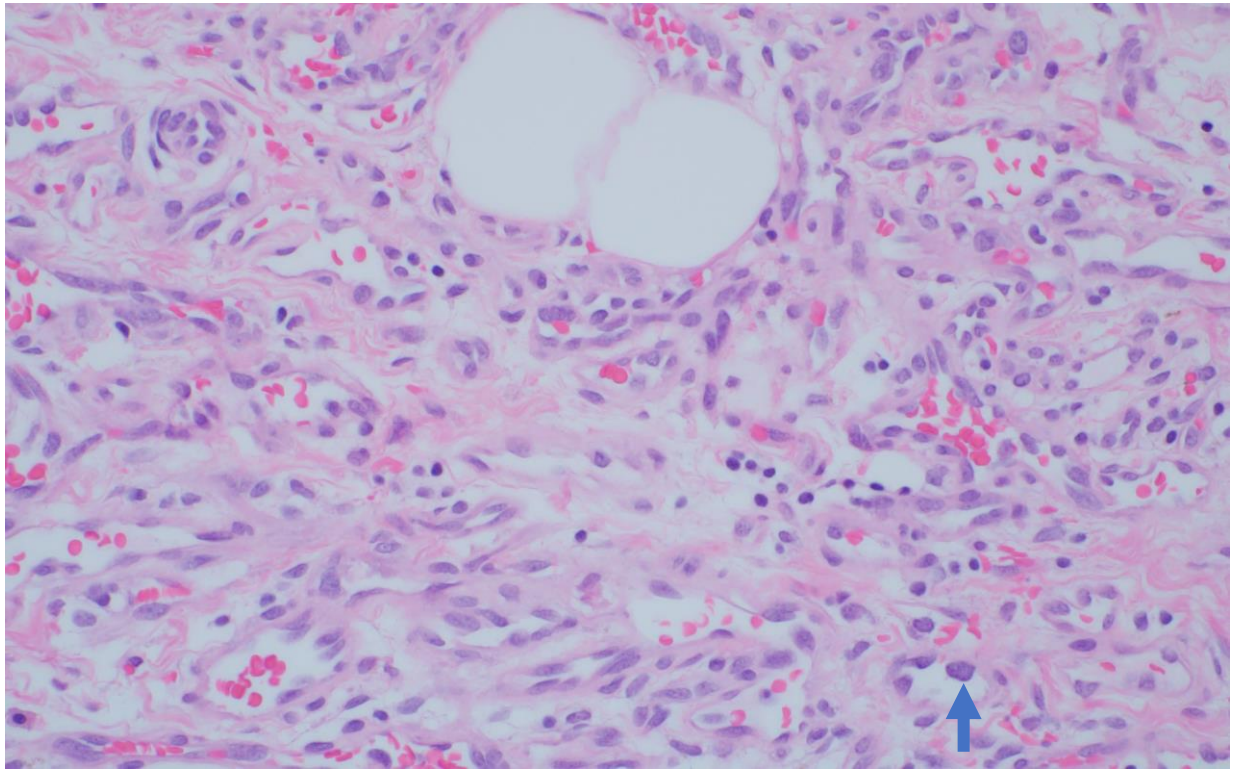
- Infiltrative borders
- Diverse morphologic spectrum
- Well differentiated: Well formed vascular channels that can be angulated, dilated or compressed and dissect through adipose tissue and lobular units. Variable degree of nuclear atypia and mitoses
- Intermediate cases show more prominent hobnailing, endothelial multilayering, or papillary formations
- Poorly differentiated cases have a more predominant solid growth pattern composed of spindled to epithelioid cells with variably admixed well differentiated areas.
- IHC: Positive for endothelial markers (CD31, CD34, ERG, FLI1), Most lack MYC overexpression.
    - Pitfall: Epithelioid angiosarcoma can express epithelial markers

Primary Angiosarcoma - Pathology

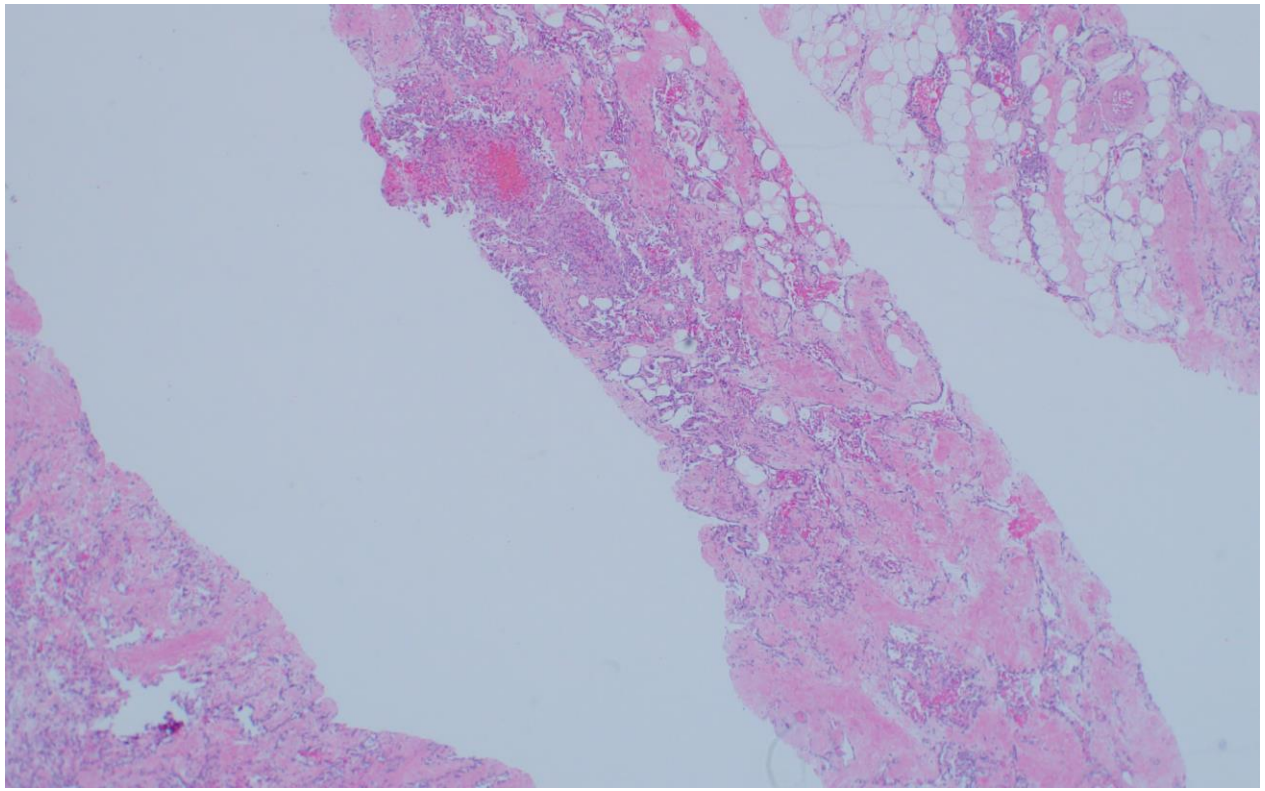


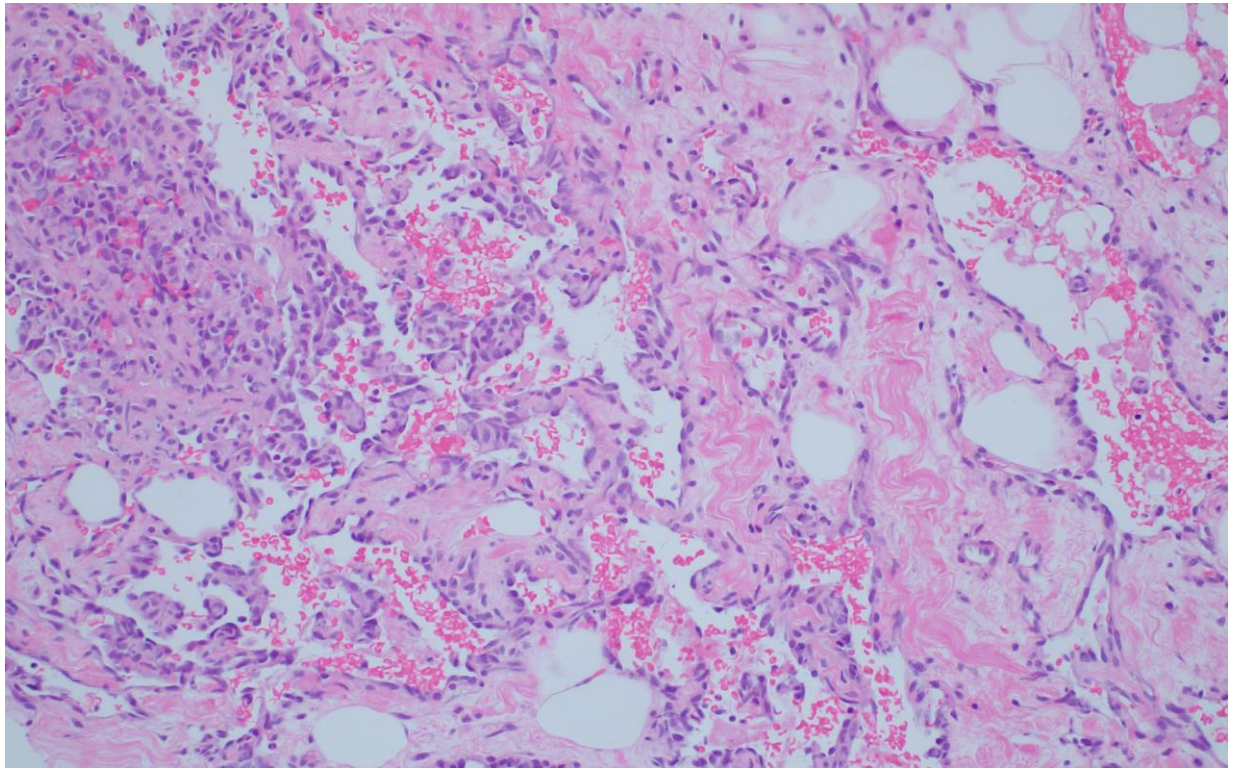
Primary Angiosarcoma - Pathology



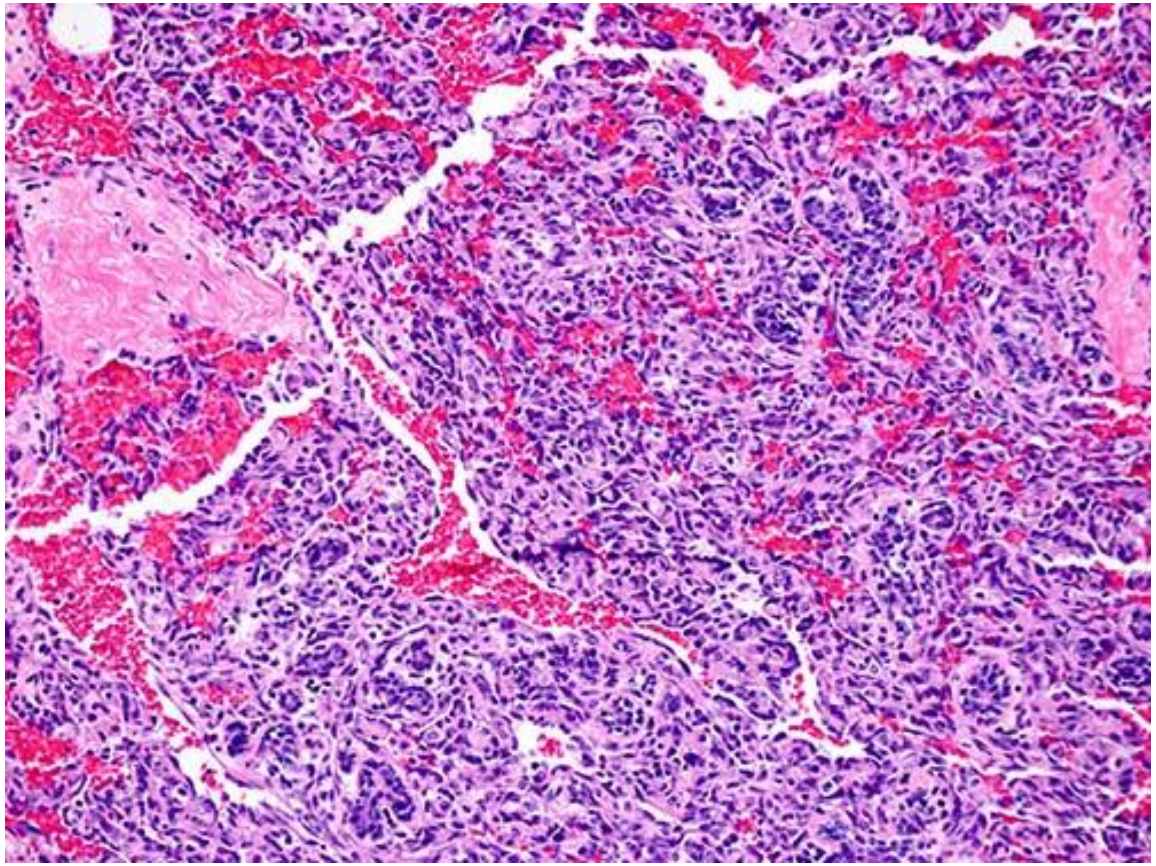


Primary Angiosarcoma - Pathology

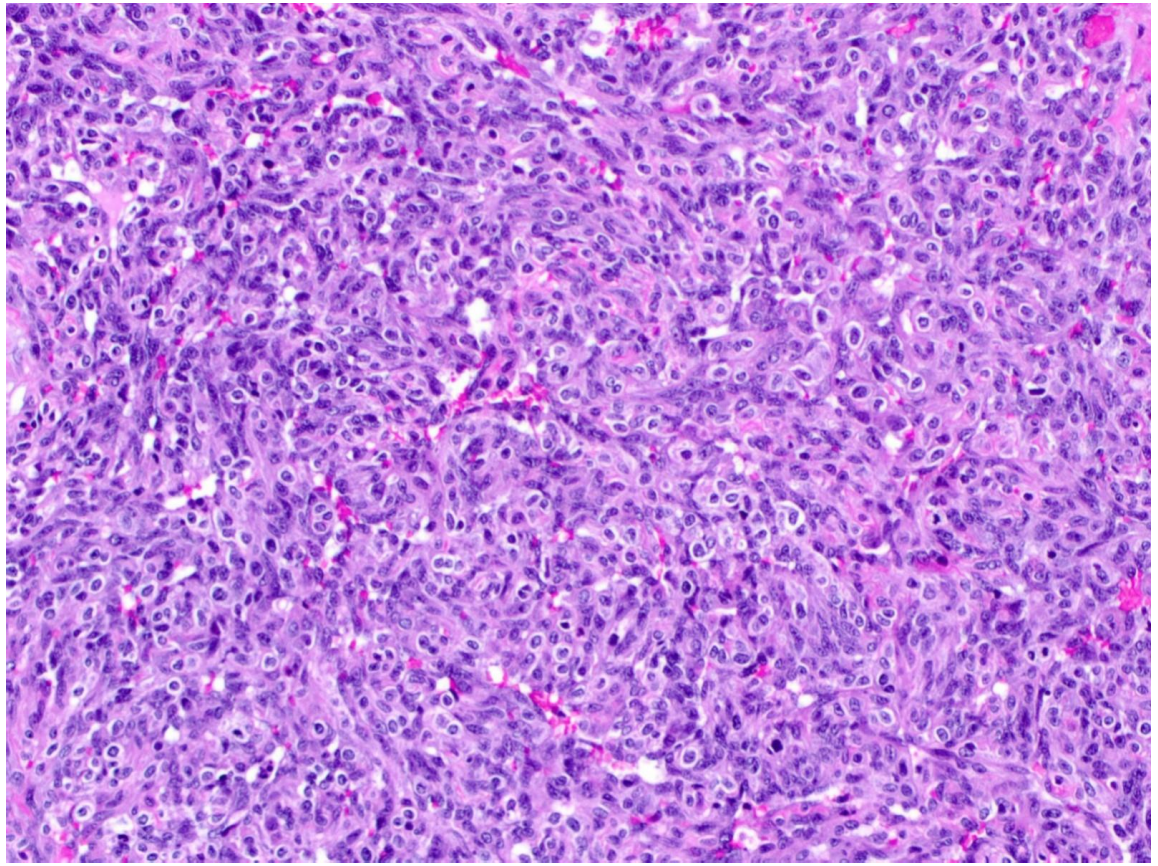




Primary Angiosarcoma - Pathology



Charnoff-Katz et al. A Case of Primary Breast Angiosarcoma. *Radiology Case Reports;* 2013



https://www.pathologyoutlines.com – Contributed by Melinda Lerwill, MD

Primary Angiosarcoma - Grading

Histologic features	Low grade	Intermediate grade	High grade
Lesions involving breast parenchyma	+	+	+
Anastomosing vascular channels	+	+	+
Hyperchromatic endothelial cells	+	+	+
Endothelial tufting	minimal	+	++
Papillary formation	-	Focally +	+
Solid and spindle cell foci	-	-/minimal	+
Mitoses	Rare/-	+ in papillary areas	++ even in low-grade areas
„Blood lakes”	-	-	+
Necrosis	-	-	+

Primary Angiosarcoma - Grading

- Nascimento et al (*Am J Surg Pathol;* 2008)
  - 49 primary angiosarcoma cases
  - Tumors were graded using the 3 tier Rosen system
    - 17 (35.4%) low grade
    - 17 (35.4%) intermediate grade
    - 14 (29.2%) high grade
  - Follow up available for 41 patients for a median duration of 29 months
  - 10 showed local recurrence at a median of 36 months (11-60 mo)
  - 24 patients (58.5%) had metastatic disease
  - 18 patients (44%) died of disease
  - No correlation between tumor grade and local recurrence, metastasis, and death.

Primary Angiosarcoma – Grading

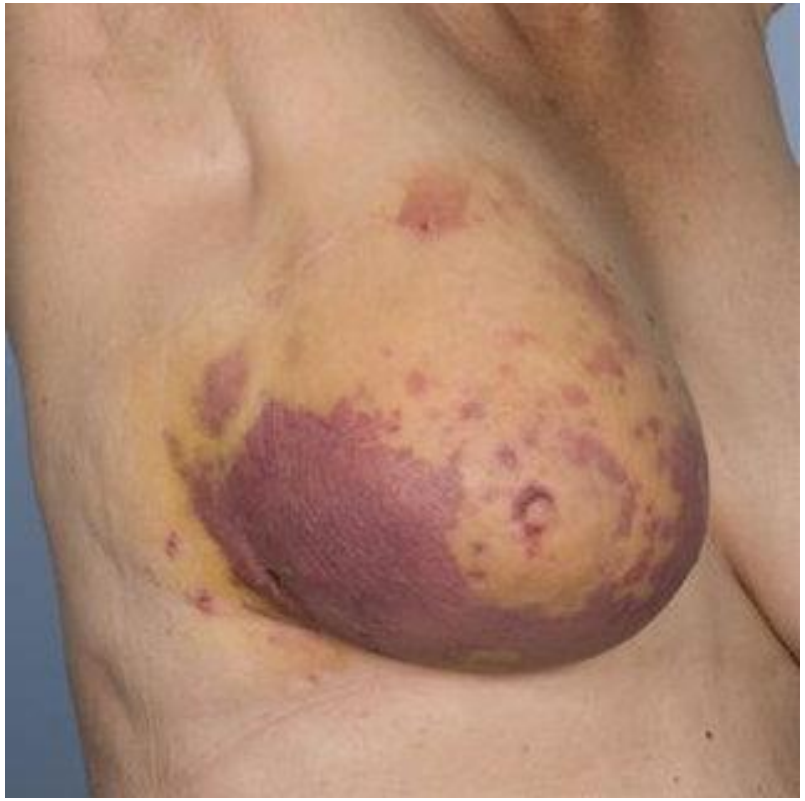
- Kuba et al (*Am J Surg Pathol*; 2023)
  - 49 primary breast angiosarcomas
  - Median follow up time was 33 months
  - Graded according to mitotic count, necrosis, and extent of solid component (modified Rosen system).
    - 29% low grade
    - 20% intermediate grade
    - 51% high grade
  - 22% showed locoregional recurrence
  - 63% developed metastatic disease
  - 47% died of disease
  - Two and three tier grading systems showed strong impact on survival
  - The 2 tier system was found to be independent predictor of disease specific and overall survival
    - 5 year overall survival: 38% for high grade vs 74% for low grade
  - Targeted DNA NGS in 11 cases showed *KDR* mutations in 78% and *PIK3CA* mutations in 44% of high grade lesions
    - *PIK3CA* mutations associated with worse outcome

Primary Angiosarcoma

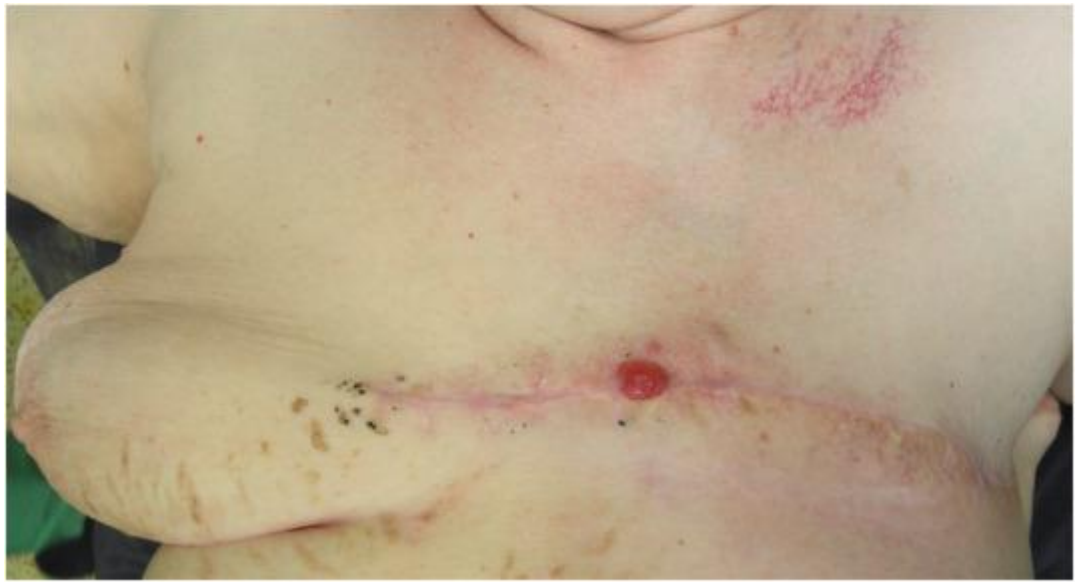
- Mastectomy with or without radiation is standard of care
- No randomized clinical trials comparing lumpectomy vs mastectomy
  - Lumpectomy could be considered with small tumors
- Rate of lymph node metastasis is relatively low, therefore axillary dissection is not routinely performed in patients with clinically negative lymph nodes
- Anthracycline and taxane-based regimens have been the frontline chemotherapy
  - Patients with locally advanced or metastatic disease have had a 25% complete or partial response rate

Secondary Angiosarcoma (radiation-associated)

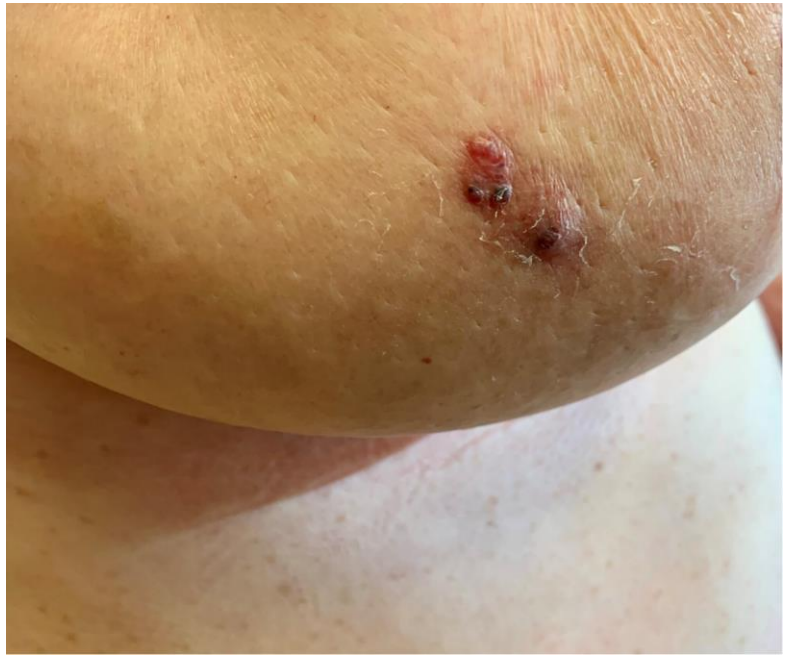
- It is the most common radiation-induced sarcoma of the breast
- Lesions arise in skin of chest wall or in prior lumpectomy scar, in the irradiated field.
- Stewart-Treves syndrome: Angiosarcoma arising in setting of chronic lymphedema (less common today due to less aggressive axillary surgeries)
- Median age 70y (in contrast to 40y for primary angiosarcoma)
- Mean latency period is 5-6 years, rare cases can have a much shorter (1-2y) or longer (30-40y) latency periods
- Clinical findings: Single or multiple skin plaques, nodules, or papules, erythematous to violaceous. Rarely it can present as a focal thickening of the skin.
- More common in the setting of lumpectomy followed by radiation than in cases of mastectomy followed by adjuvant radiation



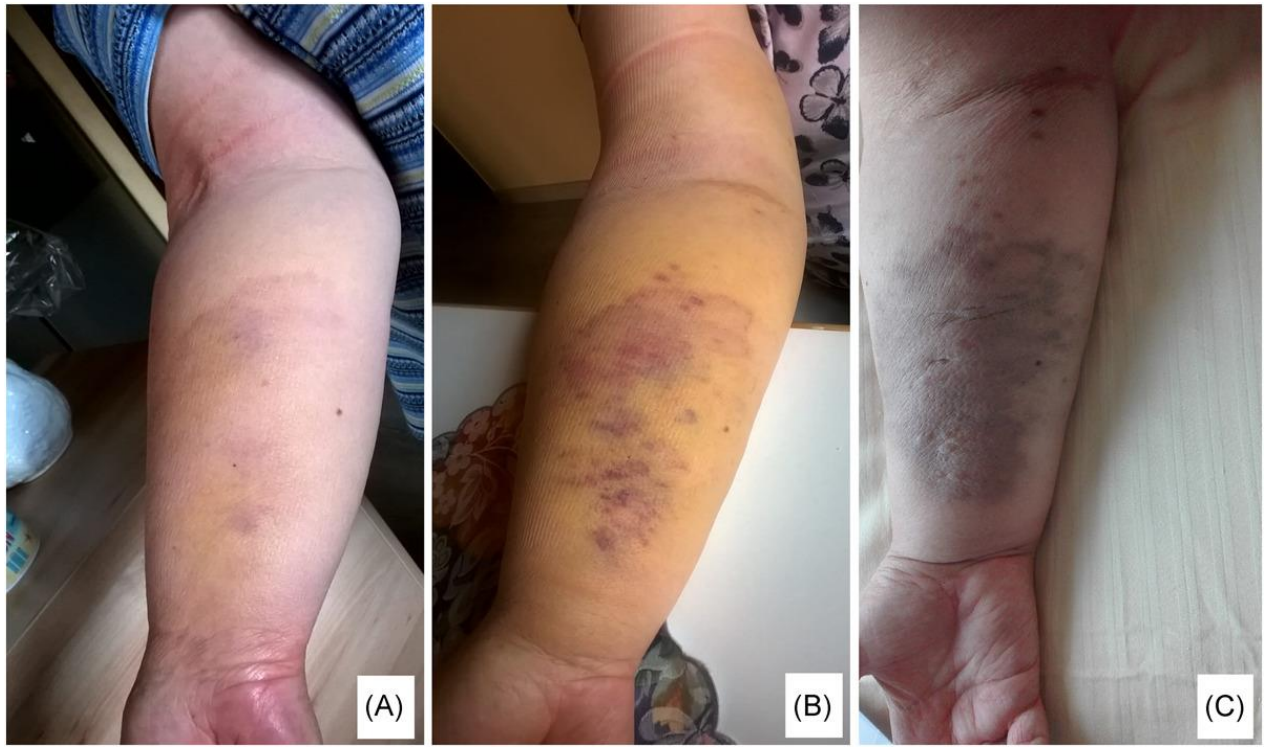
Cohen-Hallaleh et al Radiation induced angiosarcoma of the breast: outcomes from a retrospective case series. *Clinical Sarcoma Research;* 2017



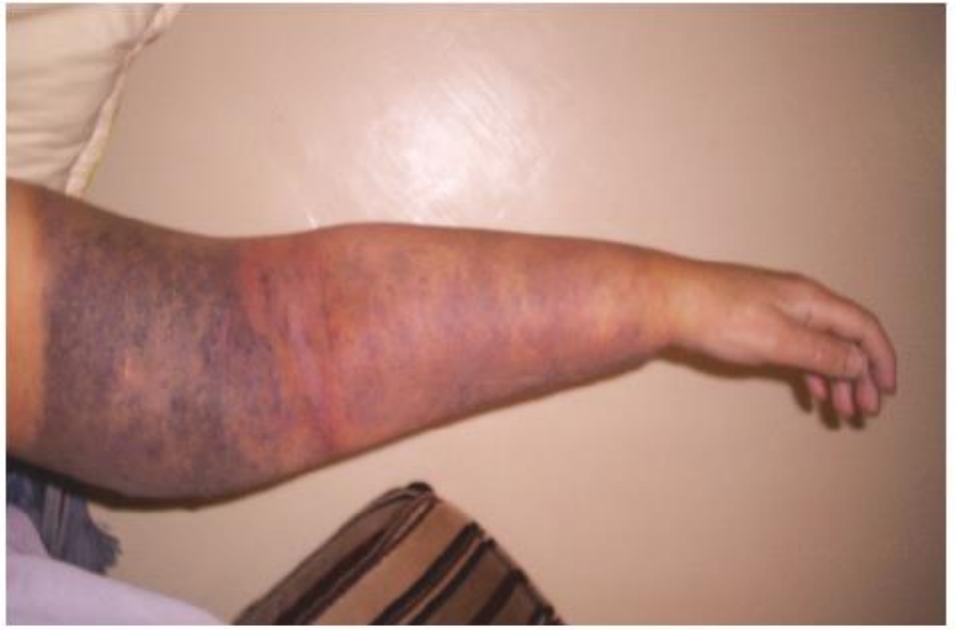
Mergancova et al Radiation-associated angiosarcoma of the breast: An international multicenter analysis. *Surgical Oncology;* 2022



Rose and Owuscu-Brackett Loss of TSC1 in secondary angiosarcoma of the breast. *Clinical Case Reports;* 2023

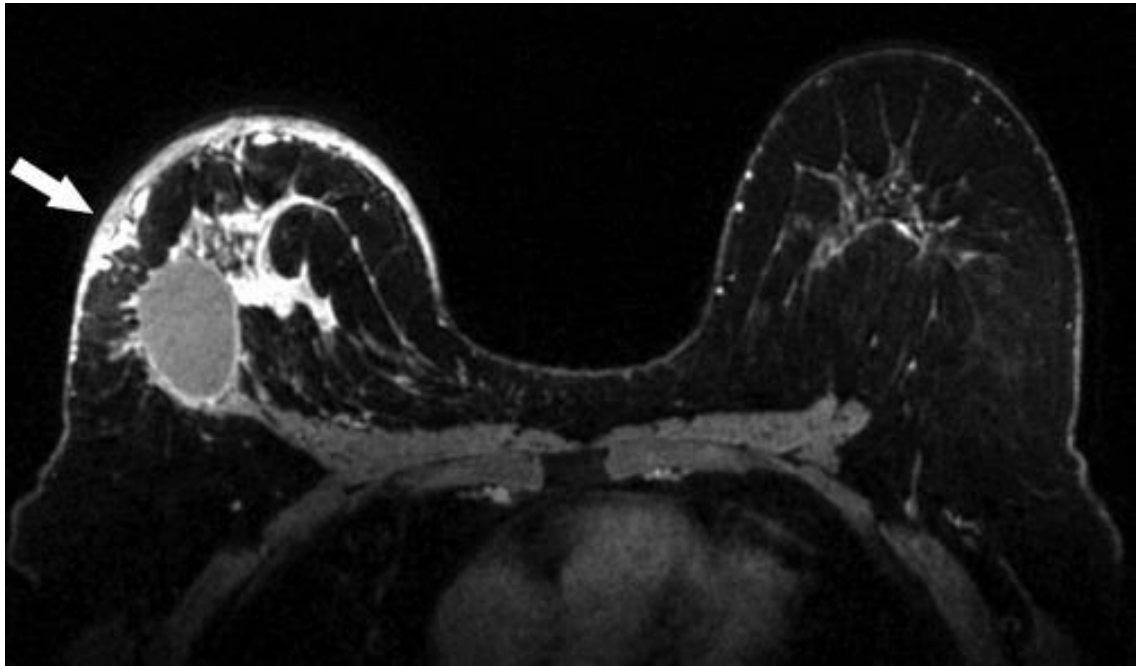


Secondary angiosarcoma: A fatal complication of chronic lymphedema

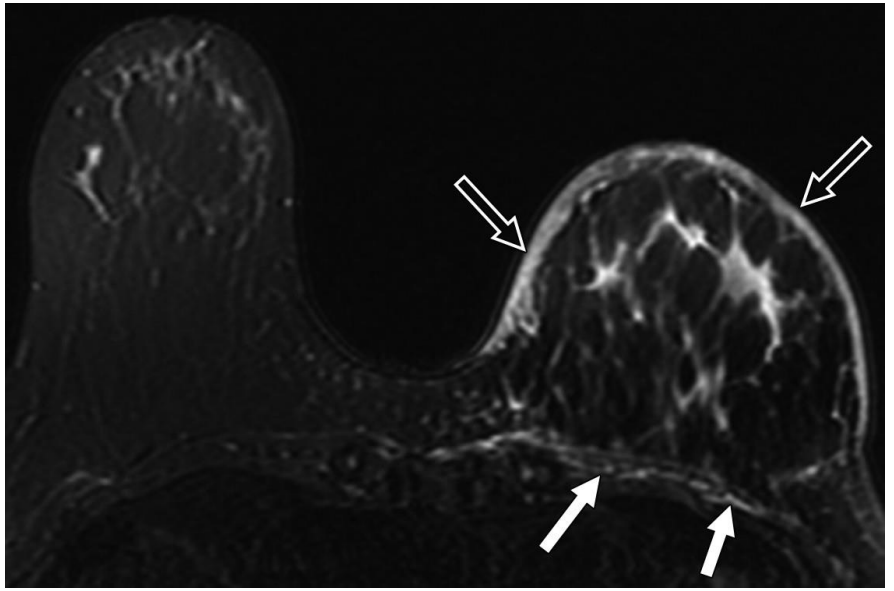


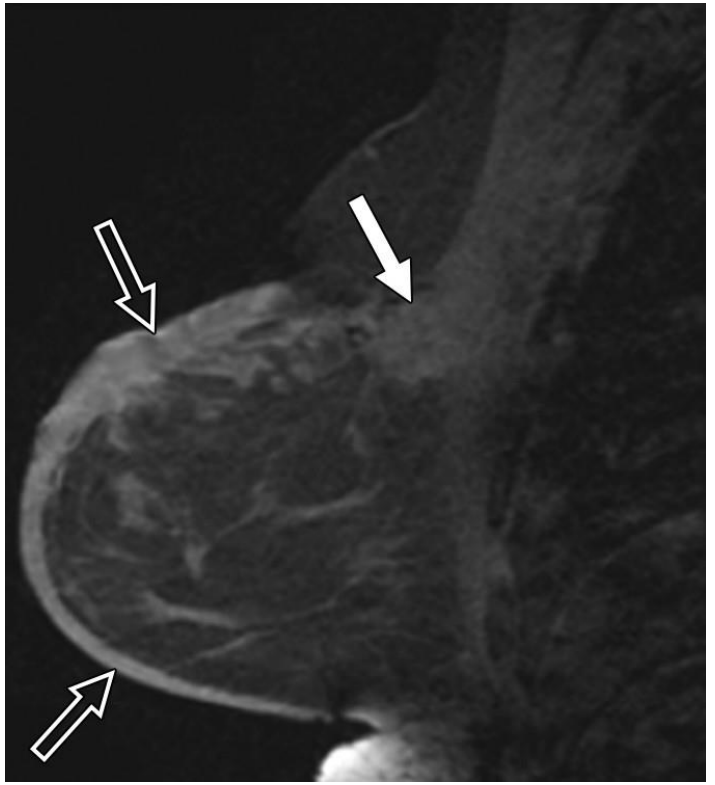
Mesli, S et al Case Report Stewart-Treves Syndrome Involving Chronic Lymphedema after Mastectomy of Breast Cancer. *Medicine*; 2017

Secondary angiosarcoma: A fatal complication of chronic lymphedema
Journal of Surgical Oncology, Volume: 121, Issue: 1, Pages: 85-90, First published: 24 June 2019, DOI: (10.1002/jso.25598)



Disharoon et al Case 242: Radiation-induced Angiosarcoma. *Radiology;* 2017





Chesebro, A et al. Radiation-Associated Angiosarcoma of the Breast: What the Radiologist Needs to Know. *American Journal of Roentgenology;* 2016

Secondary Angiosarcoma - Pathogenesis

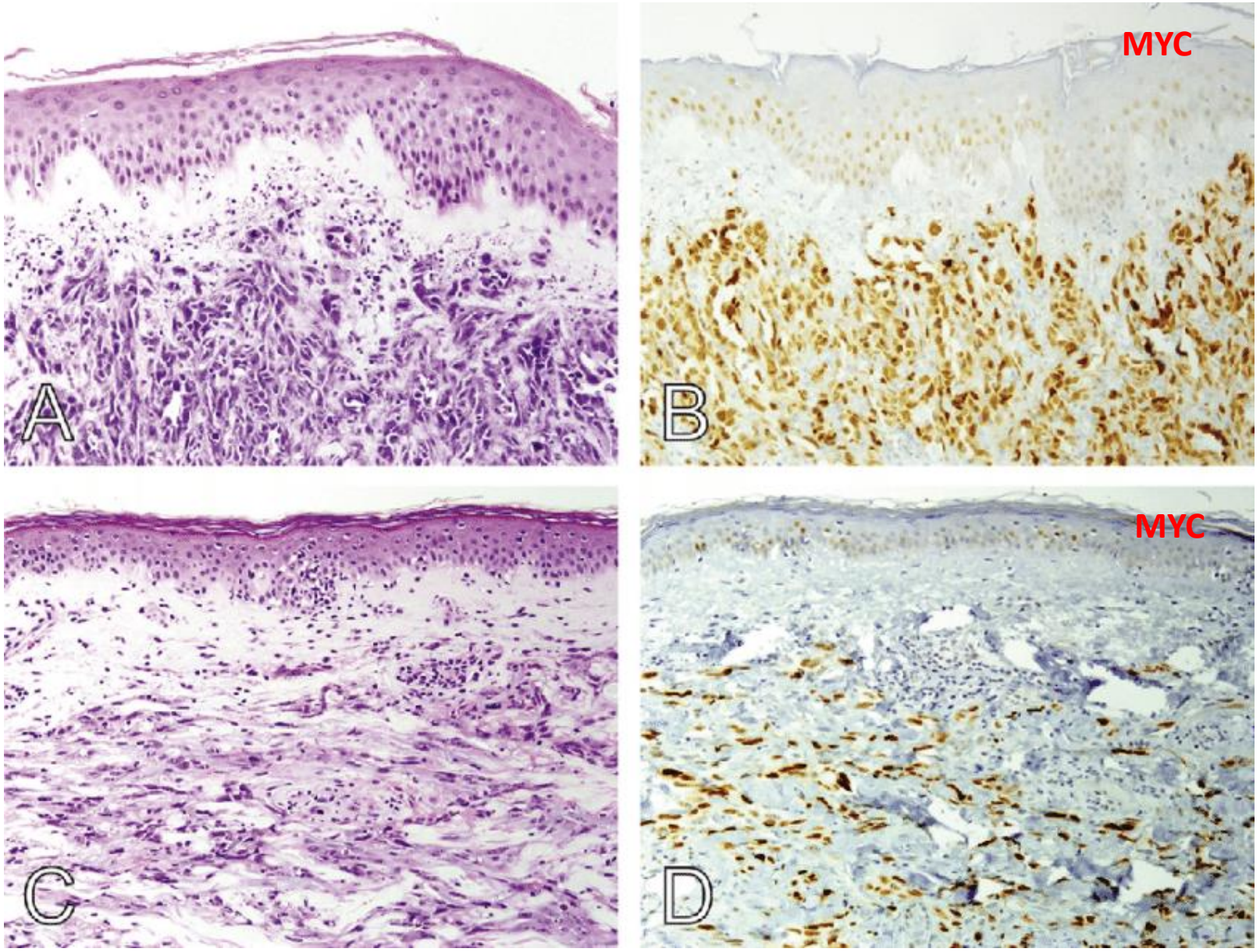
- Upregulation of vascular specific receptor tyrosine kinases such as *TIE1, KDR, TEK, FLT1*
  - Mutations in *KDR, PLCG1, PTPRB*
  - *FLT4* amplification (5% of these are co-amplified with *MYC*)
- *MYC* amplification seen in >90% of secondary angiosarcomas

Secondary Angiosarcoma - Pathology

- Arise in dermis and can extend into subcutis or rarely into breast parenchyma
- Variable morphology
  - Well differentiated: Irregular, dilated, or angulated vessels in sieve-like configuration
  - Intermediate: Papillary formations or endothelial multilayering
  - Poorly differentiated: Solid growth of epithelioid or spindle cells, necrosis, blood lakes
  - Nuclear atypia: Hyperchromasia, prominent nucleoli, increased mitoses
  - Less common patterns: Capillary lobule and radiation dermatitis-like pattern
- Grading not recommended

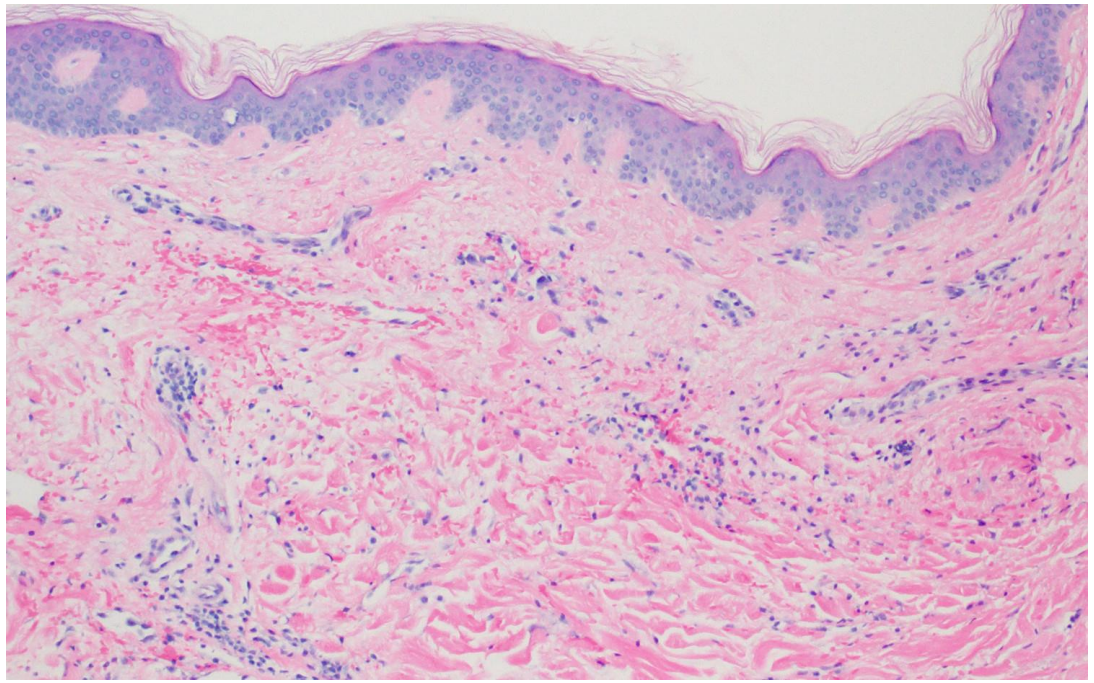
Secondary Angiosarcoma - Pathology

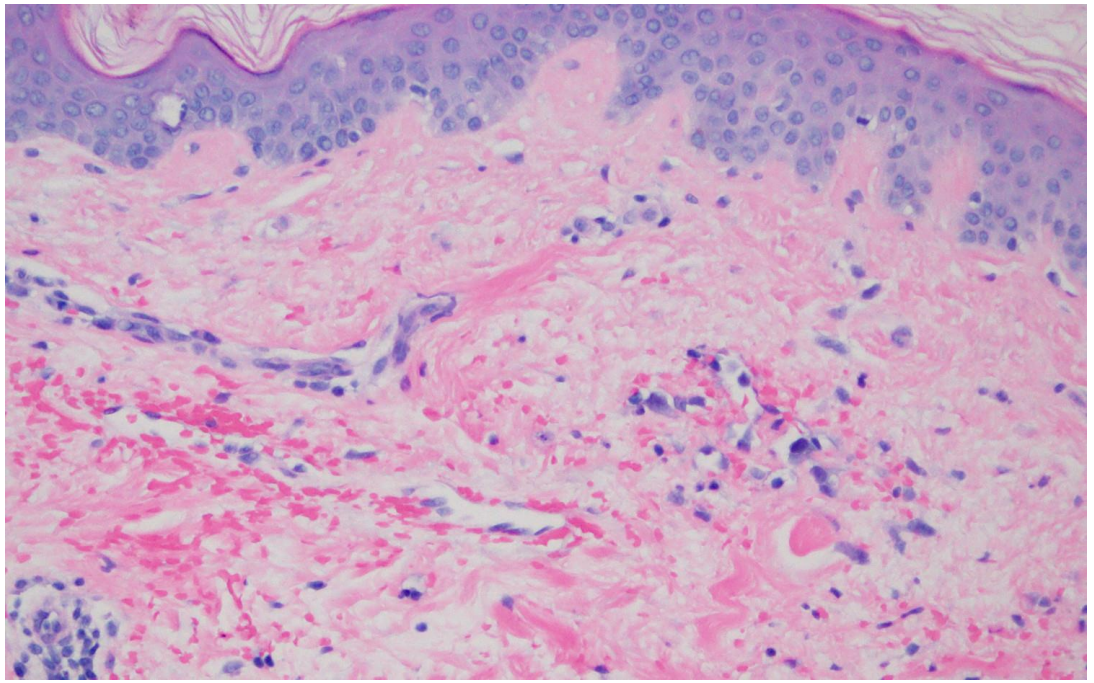
- IHC: Strong expression of CD31 and ERG. Variable expression of CD31, D2-40, and FLI1.
  - Epithelioid subtypes can express EMA or cytokeratin
- MYC nuclear over expression
- Loss of H3K27me3
  - Retained in atypical vascular lesions (AVL) and benign entities
- FISH: High level amplification (>100 copies of *MYC*) in the form of homogenously staining regions or multiple focal amplicons



Udager, A et al MYC immunohistochemistry in angiosarcoma and atypical vascular lesions: practical considerations based on a single institutional experience. *Pathology*; 2016

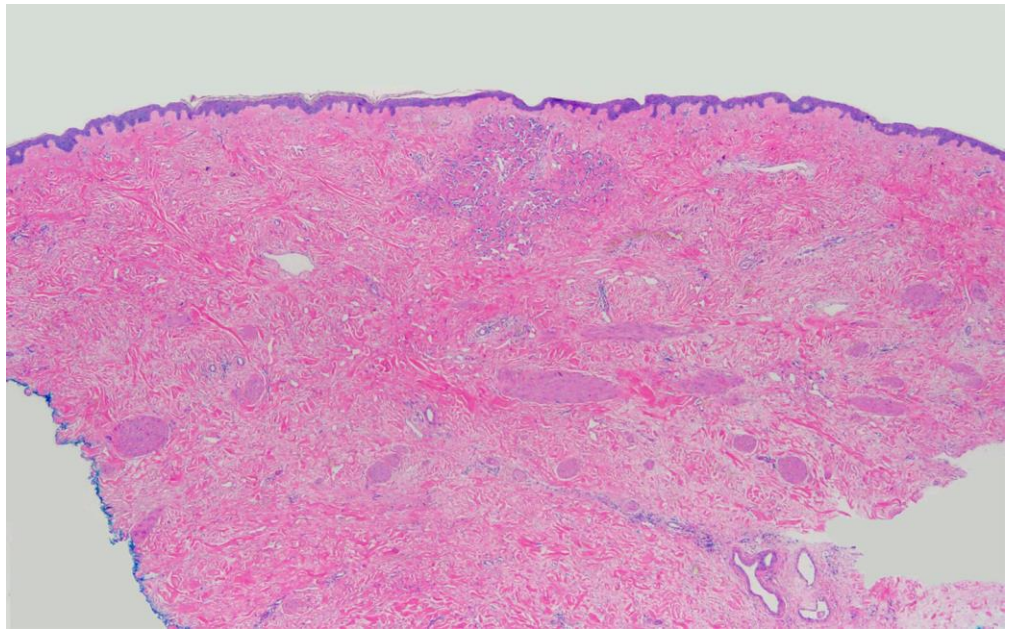
Skin punch biopsy

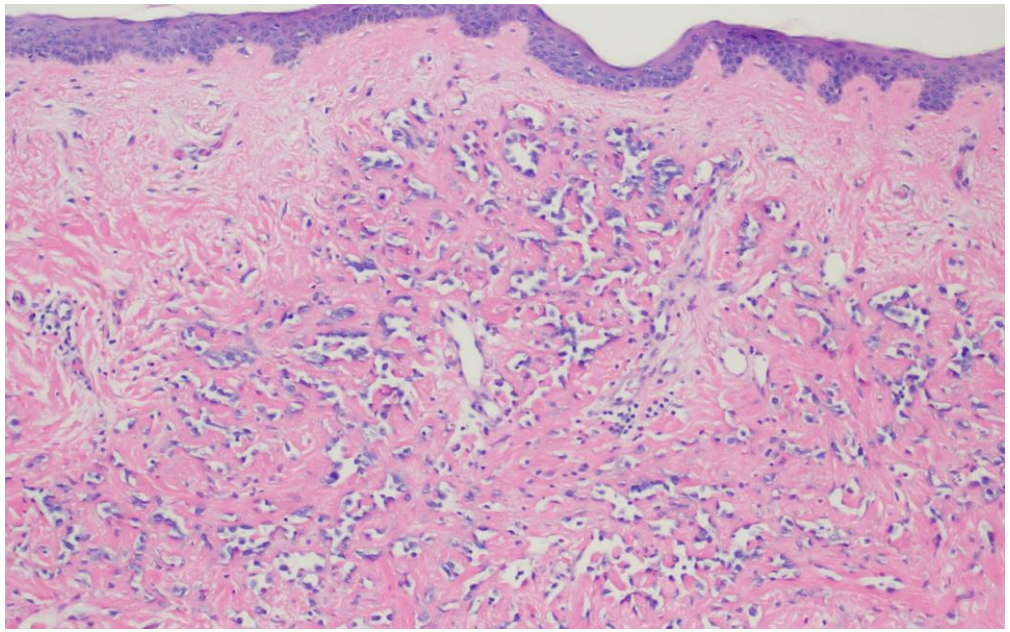


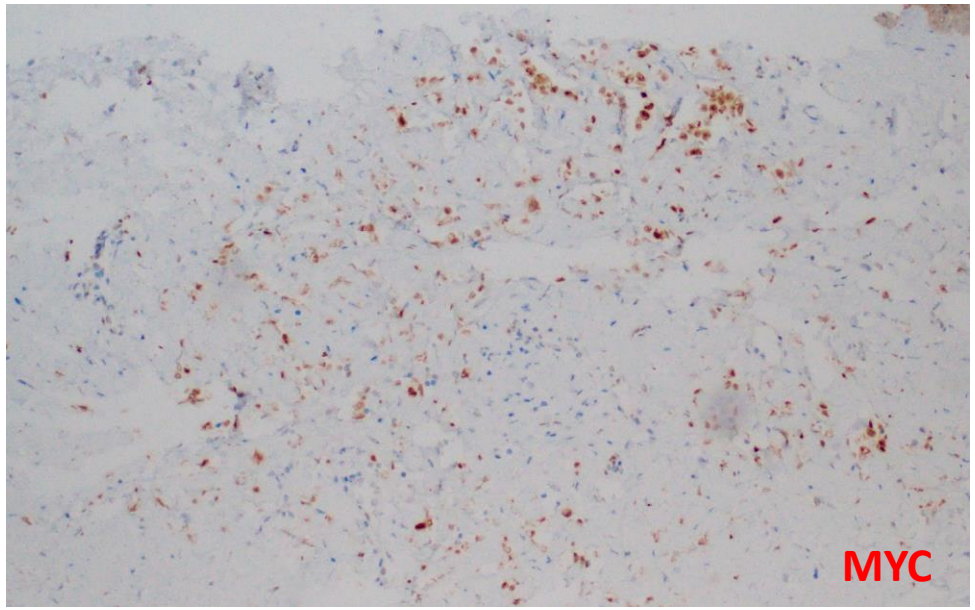


Javed, N and Stowman, A Educational Case: Radiation-Induced Angiosarcoma of the Breast. *Academic Pathology*; 2021

Wide skin excision







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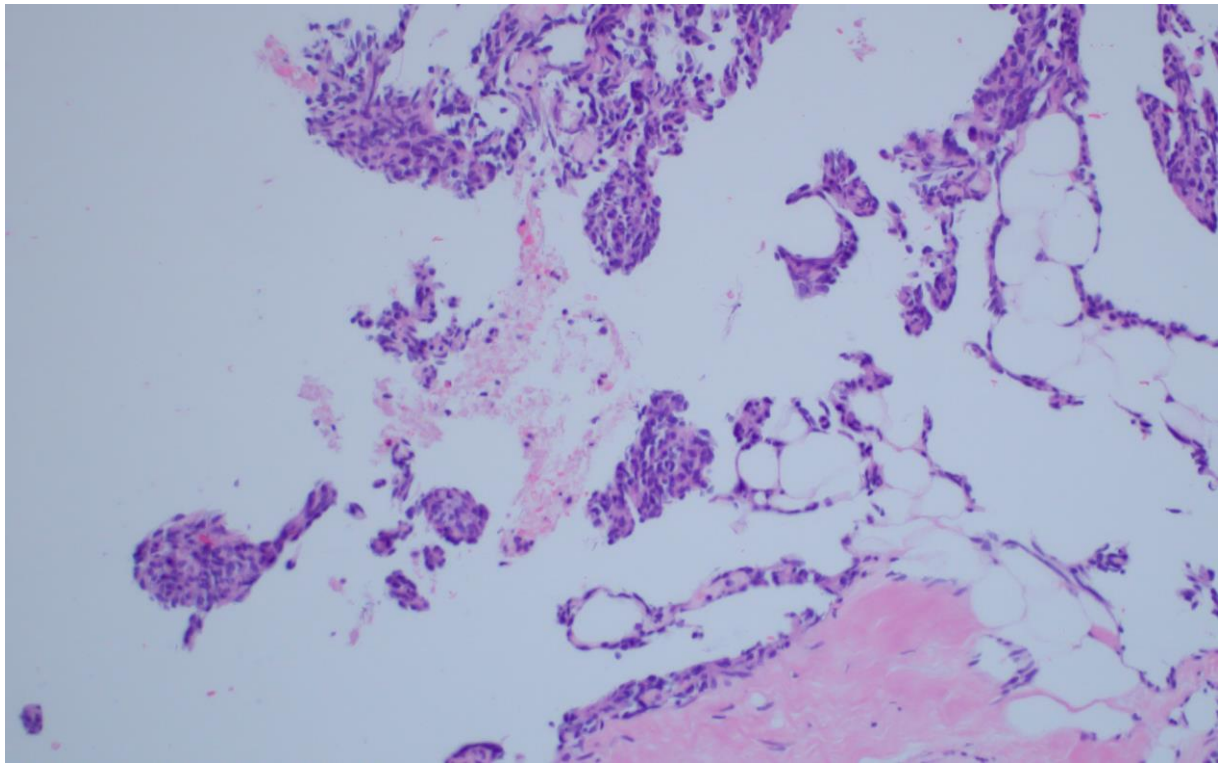
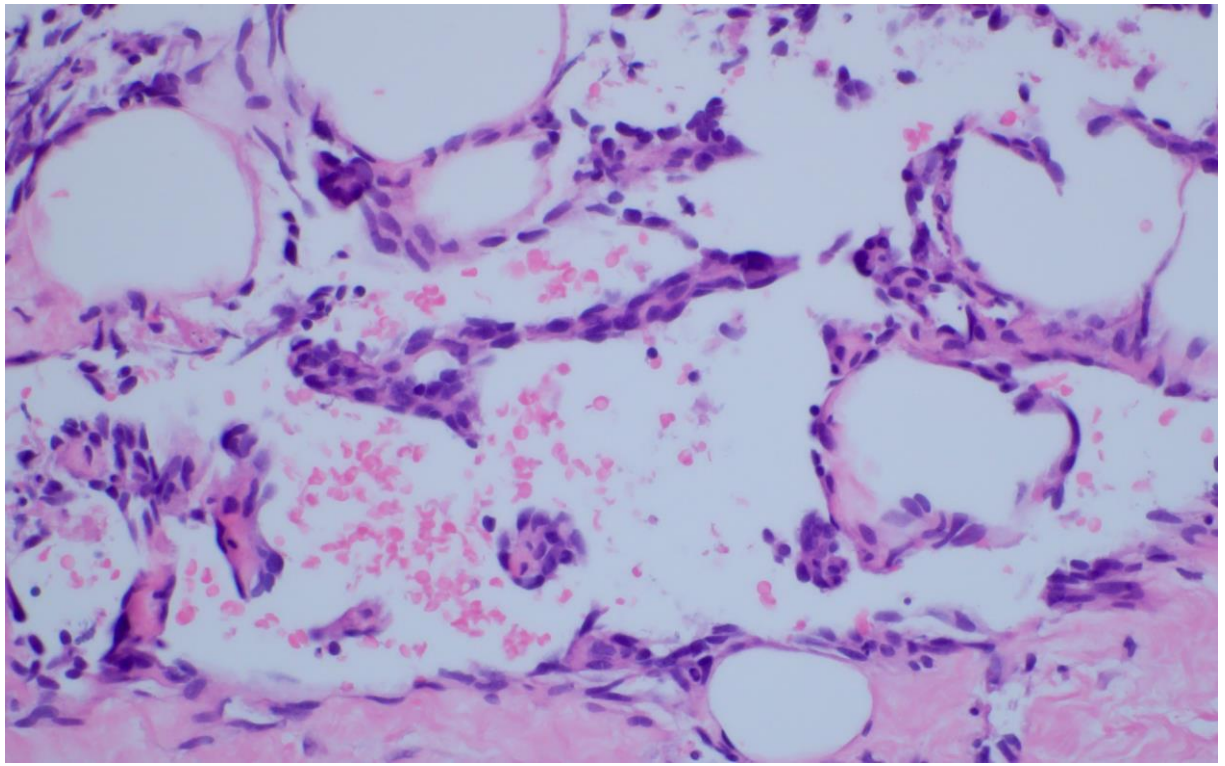
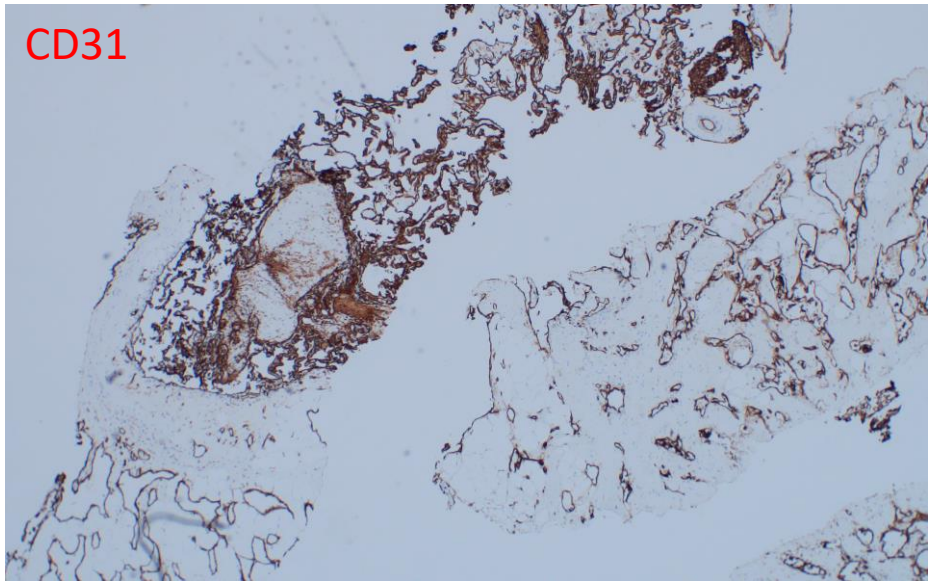
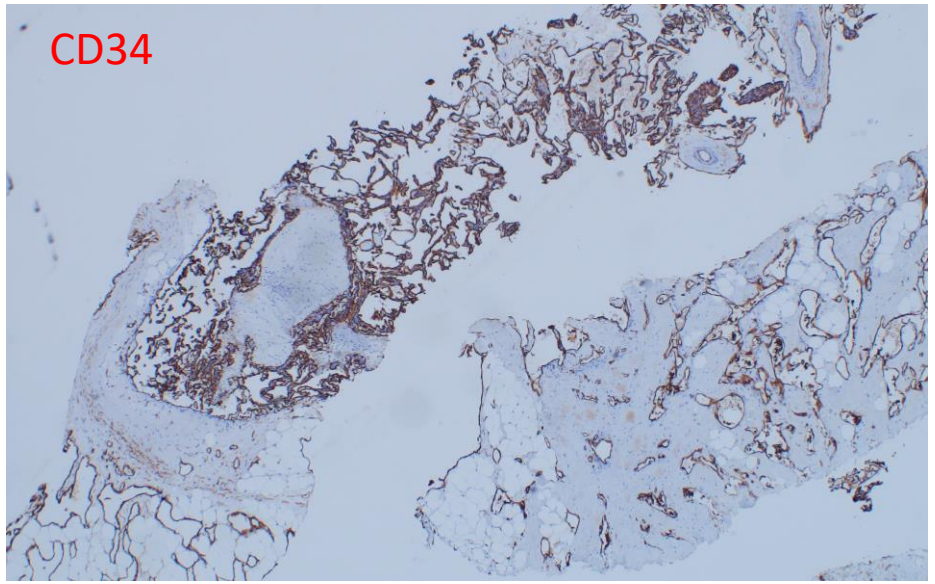
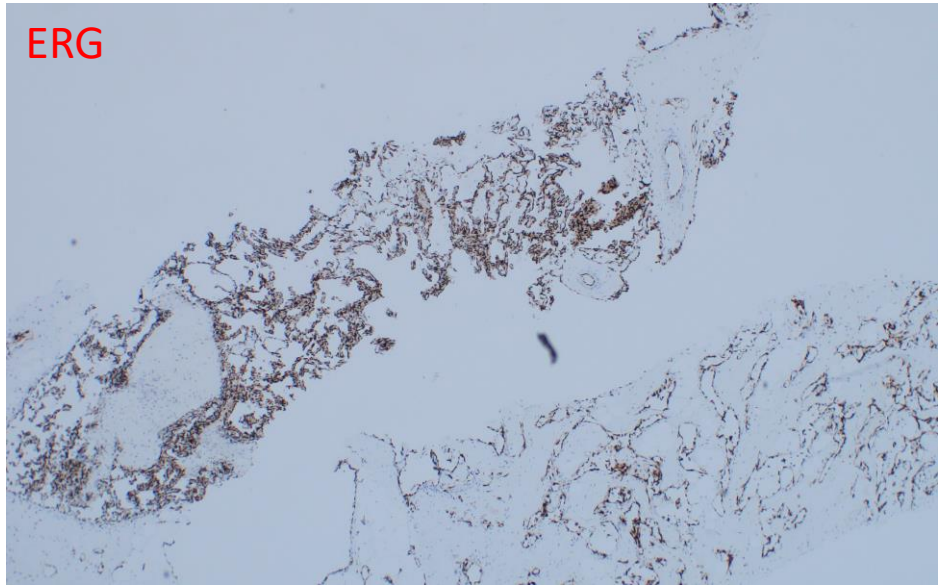
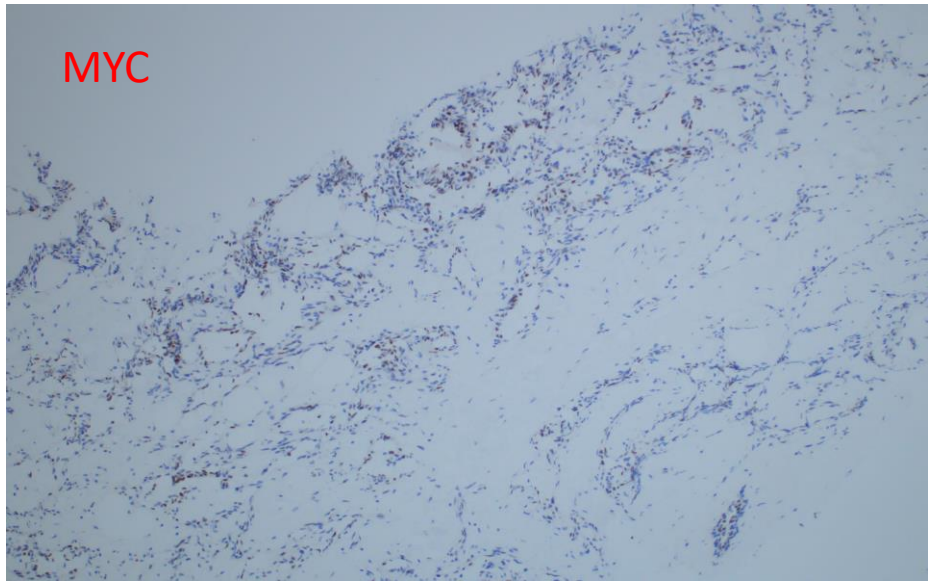


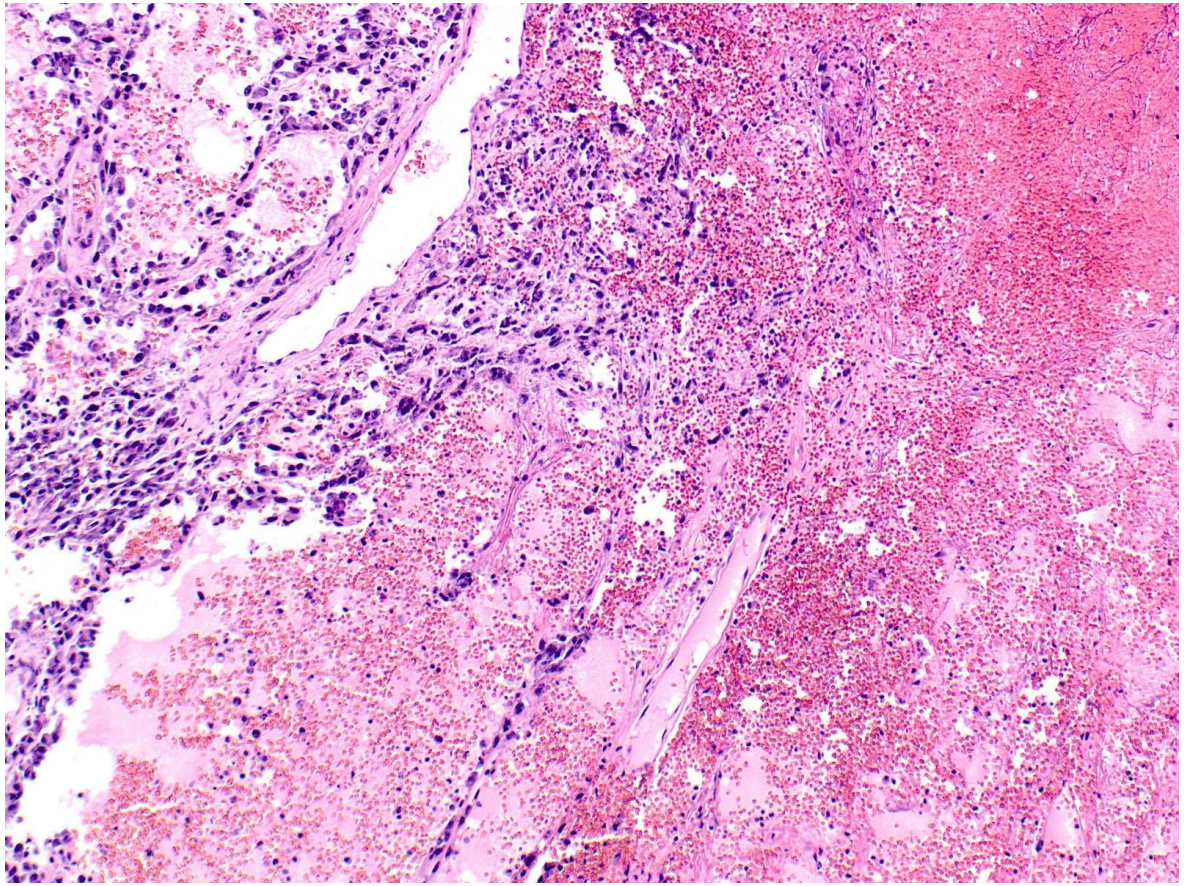


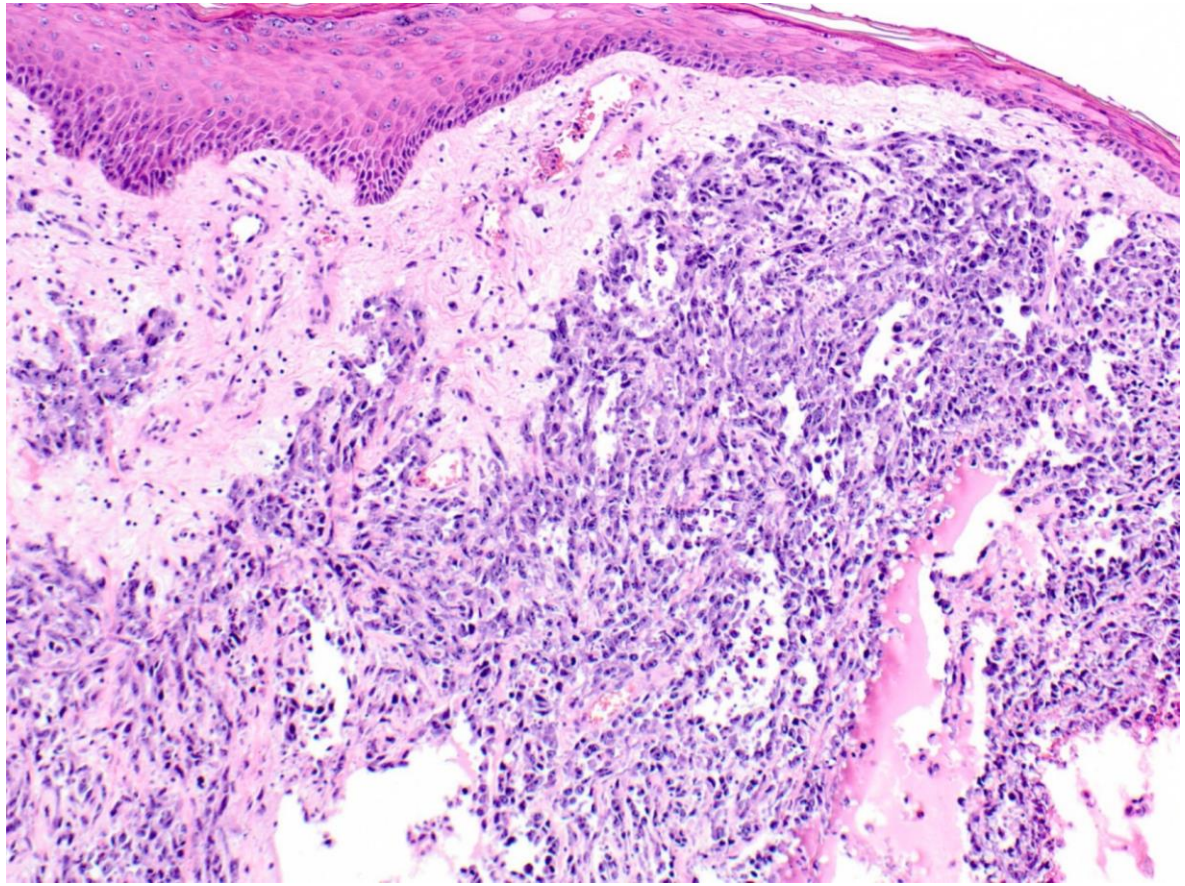






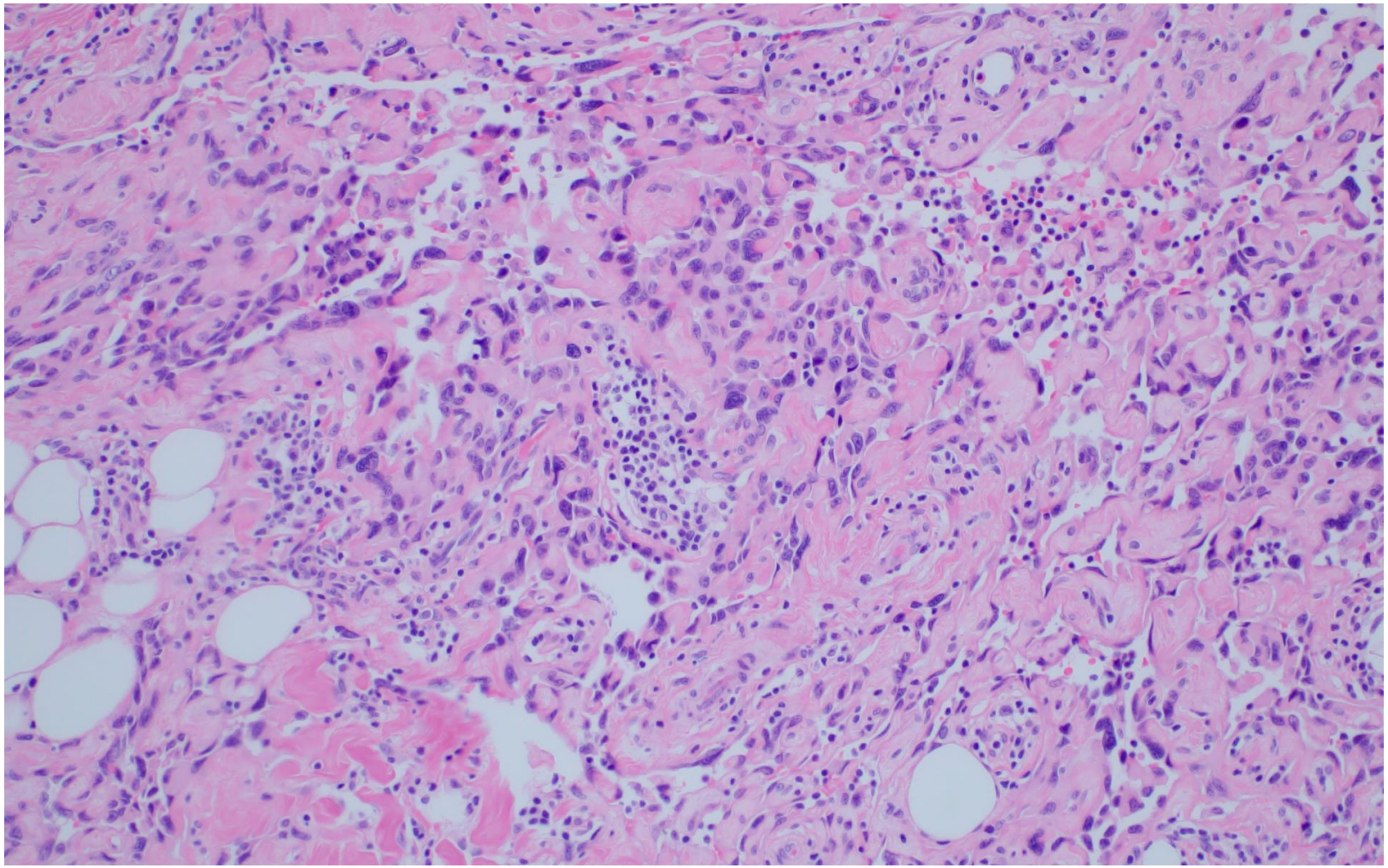




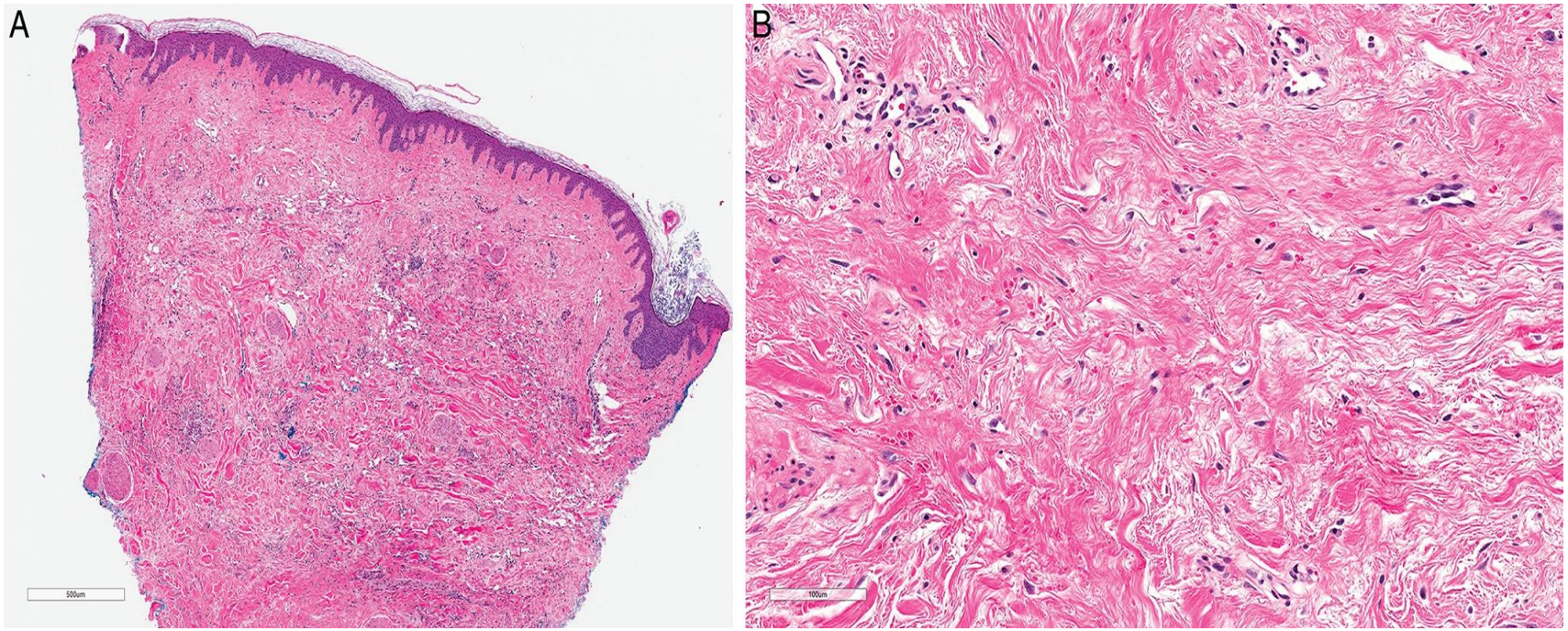


https://www.pathologyoutlines.com – Contributed by Melinda Lerwill, MD

- Epithelioid angiosarcoma

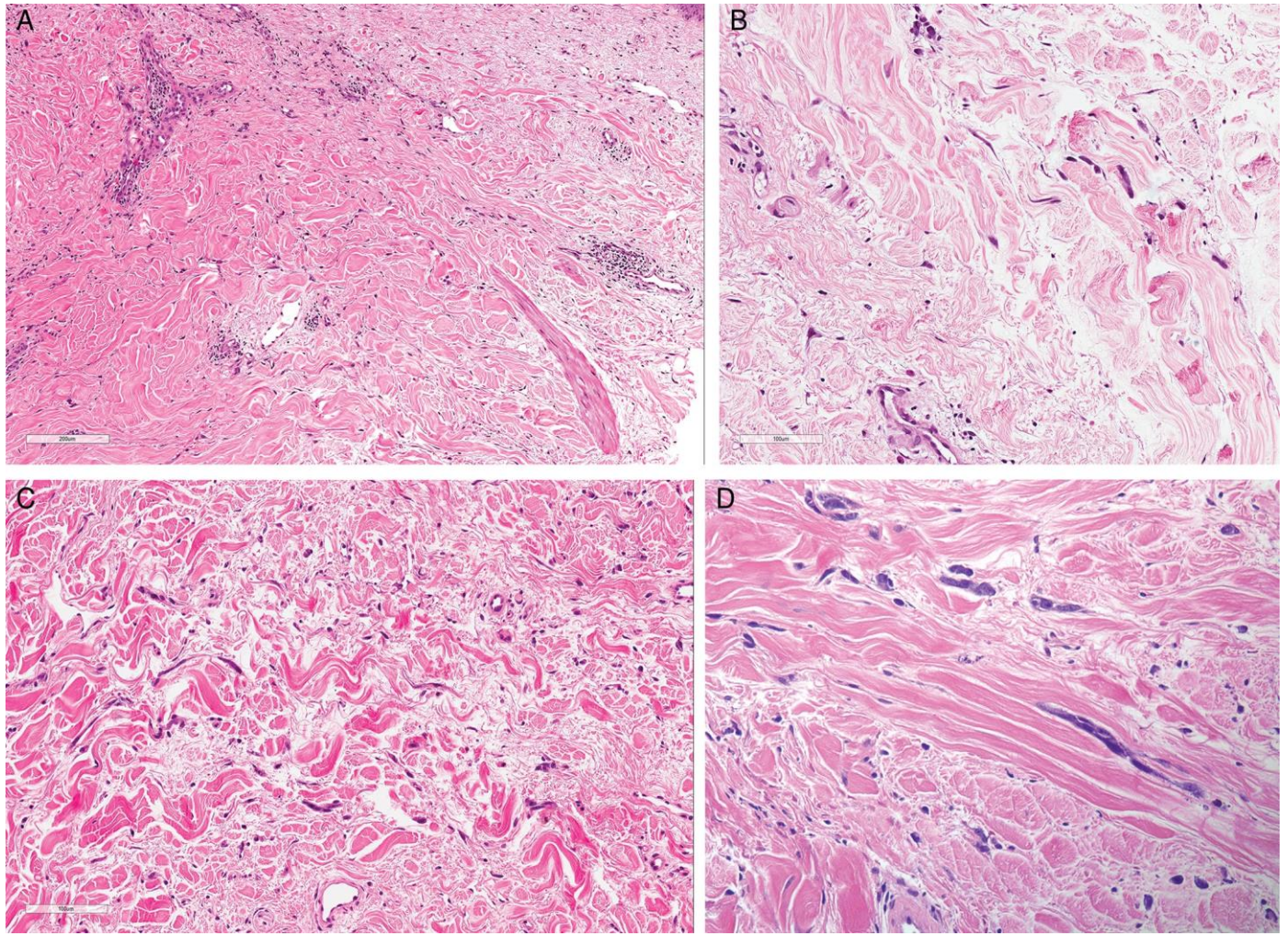


Radiation-associated angiosarcoma in the setting of breast cancer mimicking radiation dermatitis: A diagnostic pitfall



J Cutan Pathol, Volume: 44, Issue: 5, Pages: 456-461, First published: 07 February 2017, DOI: (10.1111/cup.12917)

Radiation-associated angiosarcoma in the setting of breast cancer mimicking radiation dermatitis: A diagnostic pitfall



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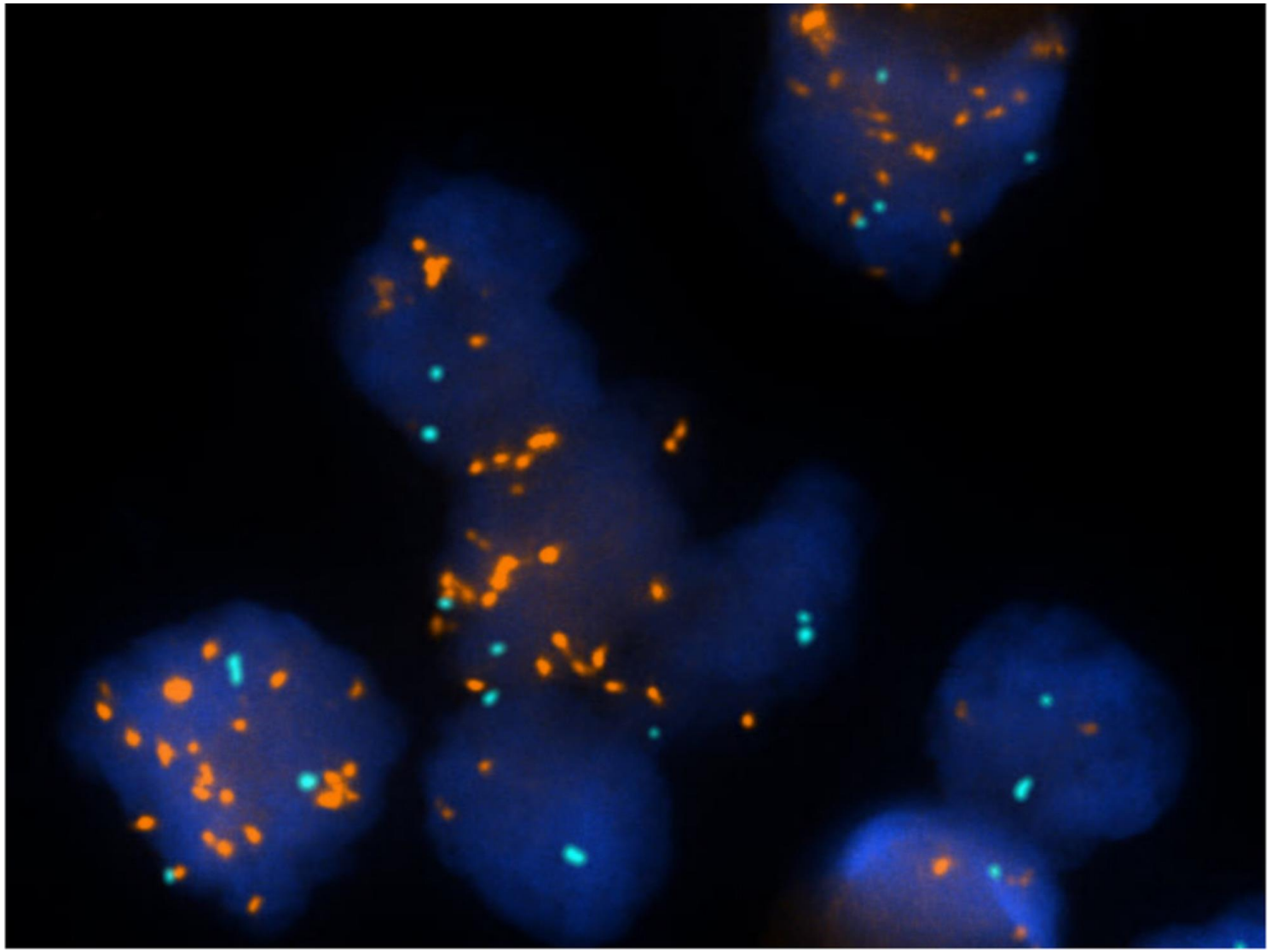


Motaparthi et al MYC gene amplification by fluorescence in situ hybridization and MYC protein expression by immunohistochemistry in the diagnosis of cutaneous angiosarcoma: Systematic review and appropriate use criteria. *Journal of Cutaneous Pathology;* 2020

Secondary Angiosarcoma – Prognosis and Treatment

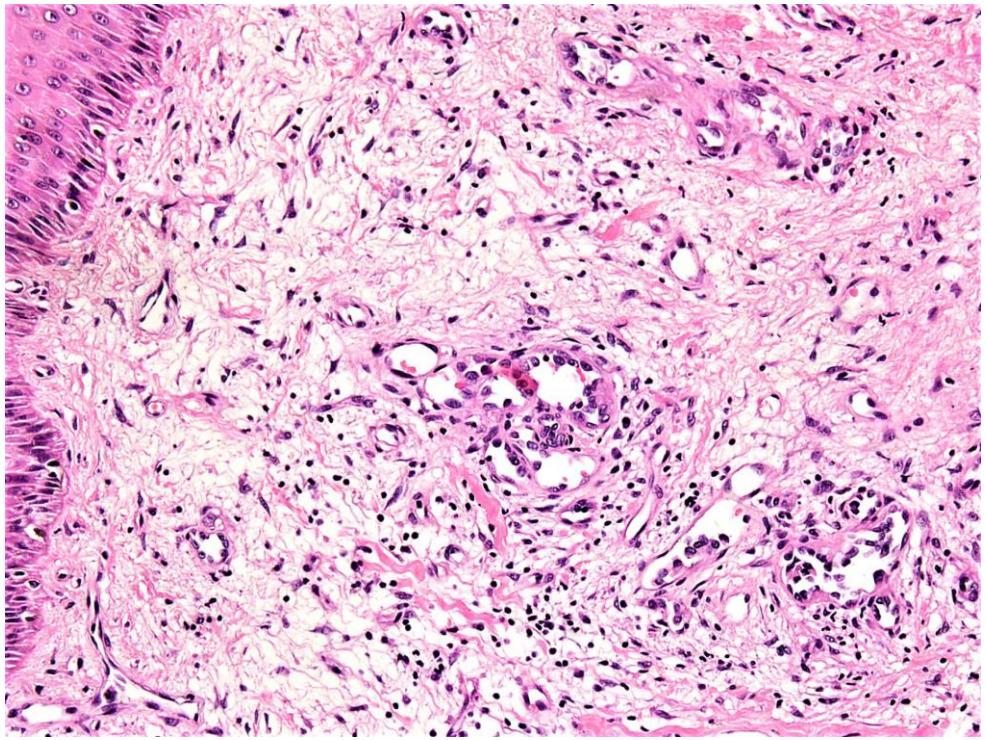
- Surgical excision with negative margins
- Postoperative radiotherapy is used to reduce the risk of local recurrences and improve overall survival
- Recent investigations have demonstrated benefit with high doses of radiation (>70 Gy) as definite therapy without surgery
- Metastatic setting
  - Cytotoxic chemotherapy with taxanes and anthracyclines
    - Initial response rates can be 20-60%
  - Targeted agents
    - VEGF inhibitors (bevacizumab) have benefit in locally advanced and metastatic settings
    - TKI (pazopanib, regorafenib) in patients with metastatic disease
    - Immune checkpoint inhibitors
- Chemotherapy has also shown benefit in the adjuvant setting for patients with locally advanced disease and it has been increasingly used in the neoadjuvant setting

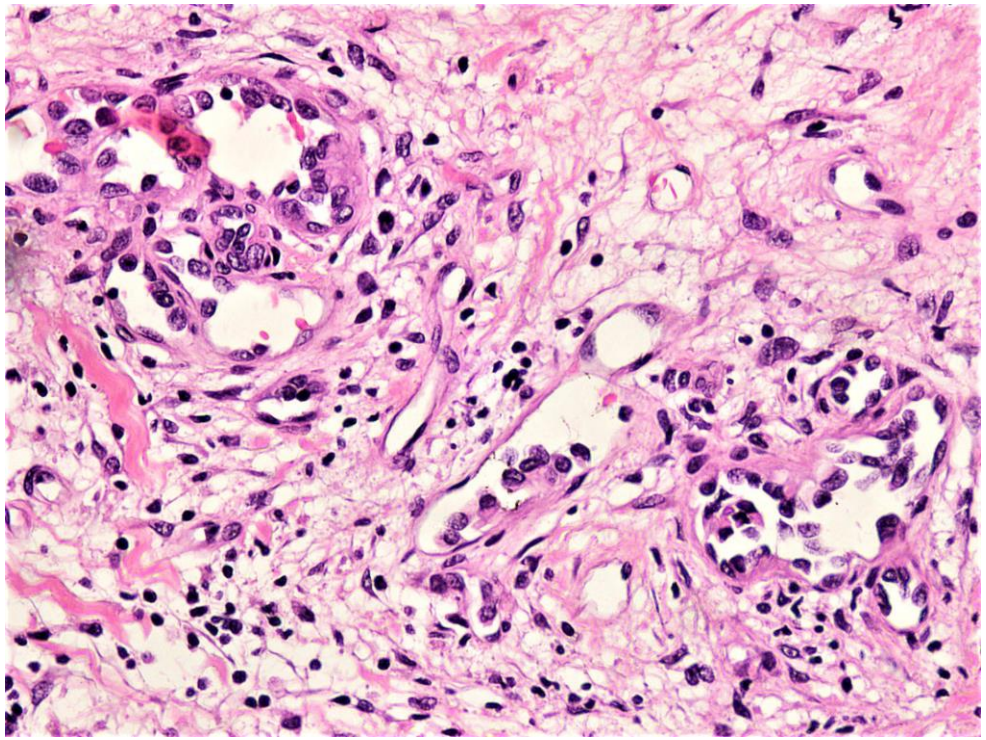
Secondary Angiosarcoma – Prognosis and Treatment

- Recurrences are common (≥50% of cases) even after surgery with negative margins
- Common metastatic sites include lungs, liver, bone, and the contralateral breast.
- Axillary lymph node metastases are rare
- Median recurrence-free survival is <3y and median OS is <5y

Vascular Differential Diagnoses

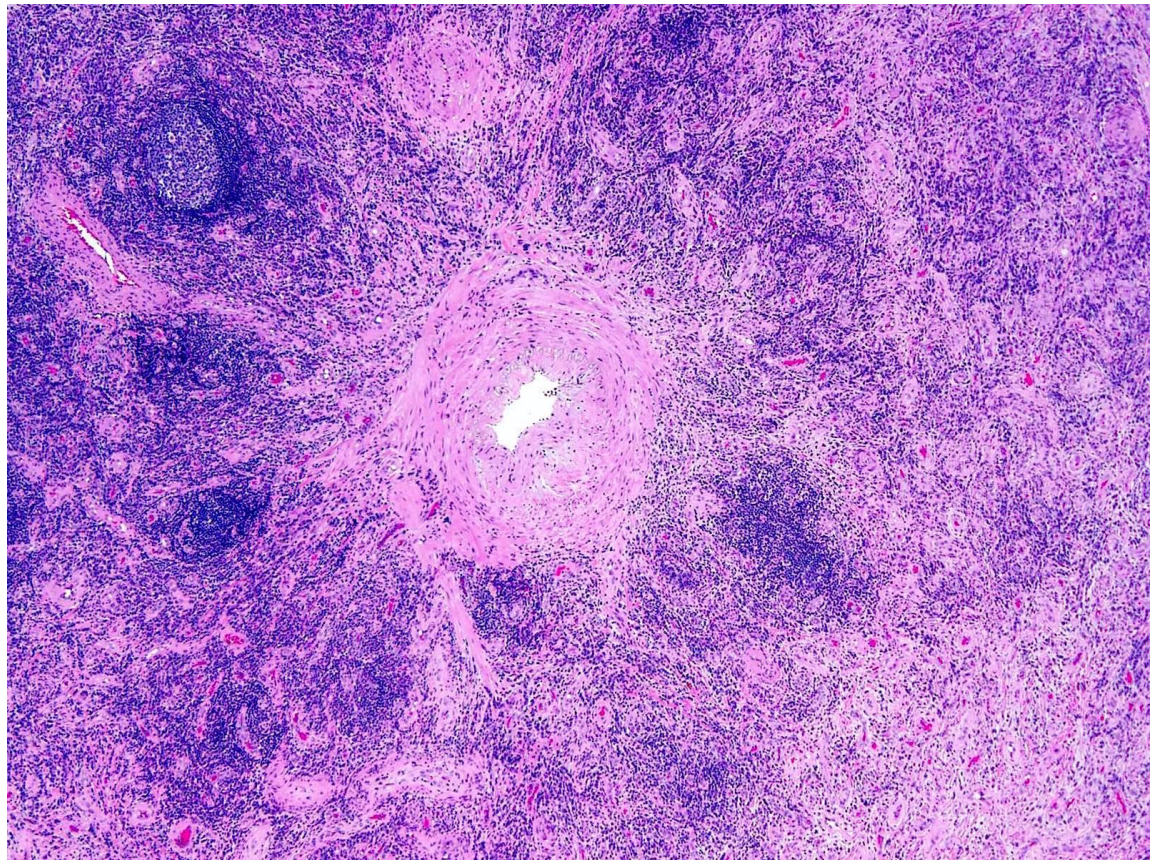
- Hobnail hemangioma

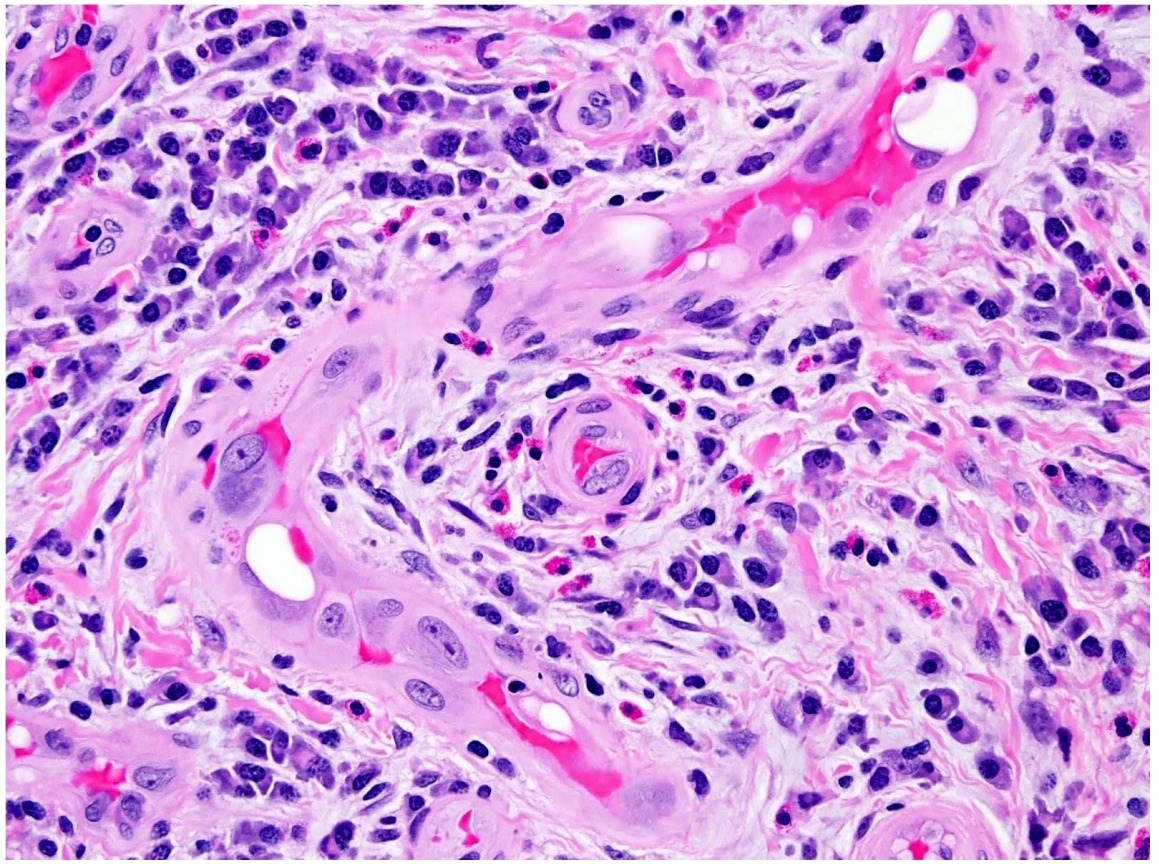




https://www.pathologyoutlines.com

- Epithelioid hemangioma



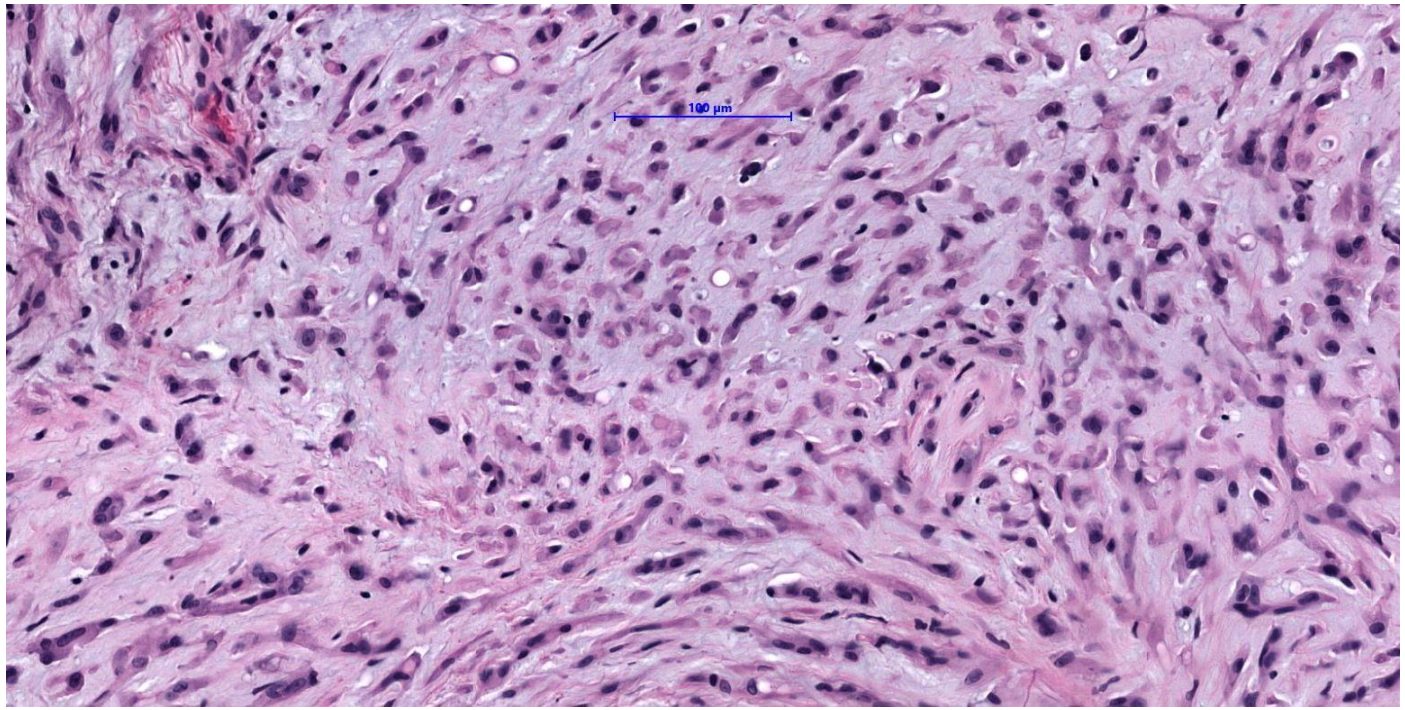


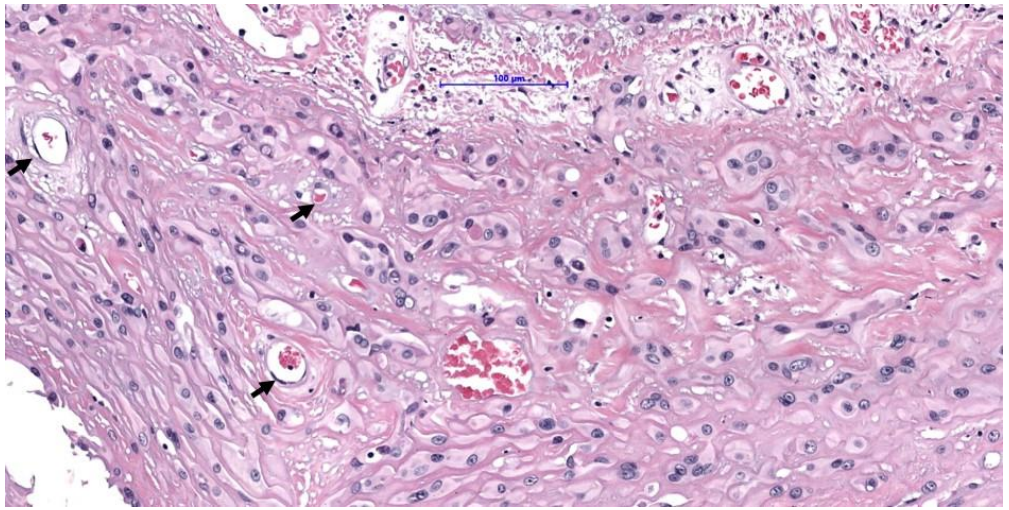
https://www.pathologyoutlines.com – Contributed by Borislav Alexiev, MD

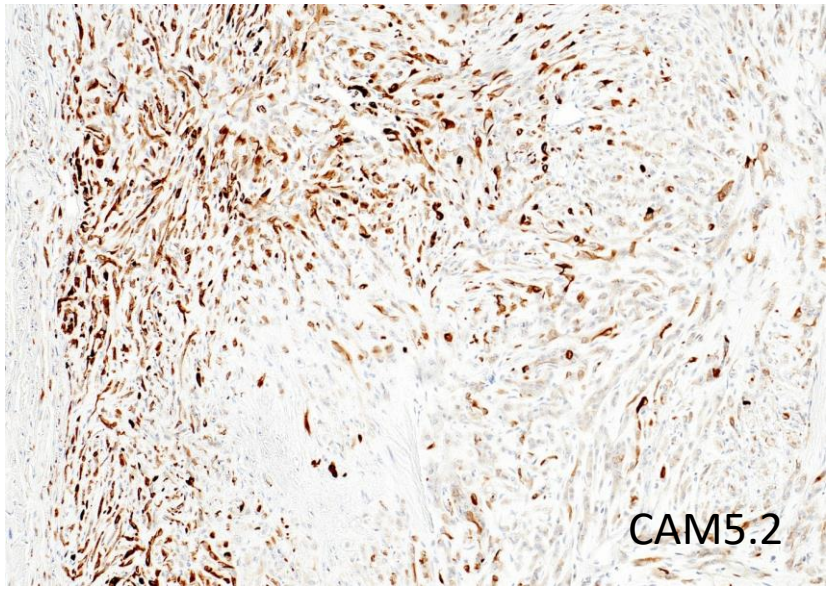
FOSB IHC positive

FOS or *FOSB* gene rearrangements

- Epithelioid hemangioendothelioma



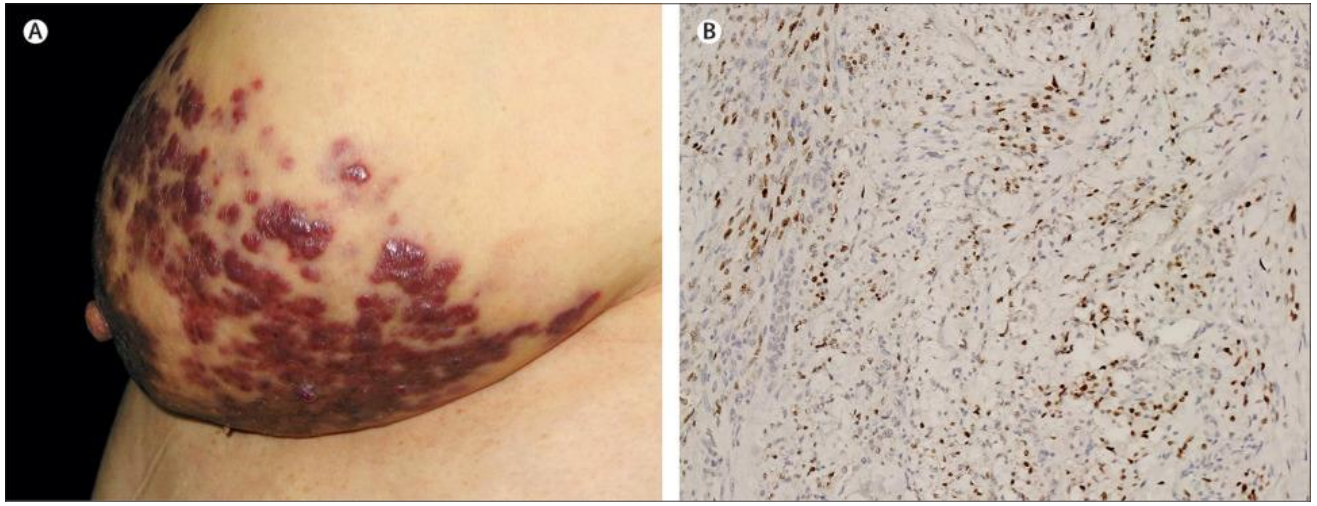




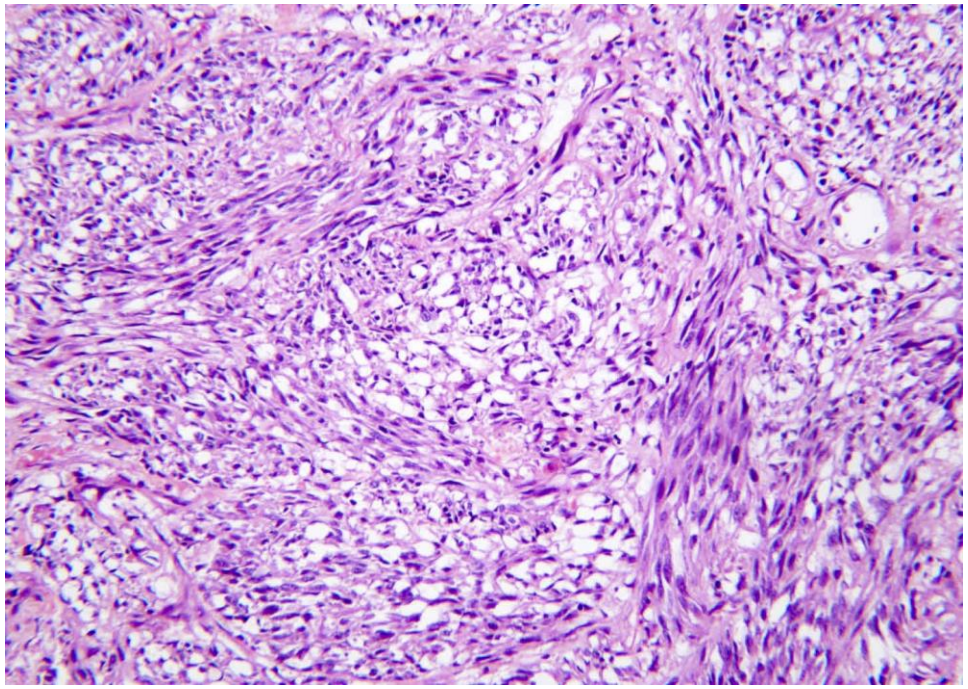
Pathology Outlines - Epithelioid hemangioendothelioma Contributed by Iva Brčić, M.D., Ph.D. and Bernadette Liegl-Atzwanger, M.D

WWTR1:CAMTA1 (classic type)
YAP-TFE3: alveolar type

- Kaposi sarcoma



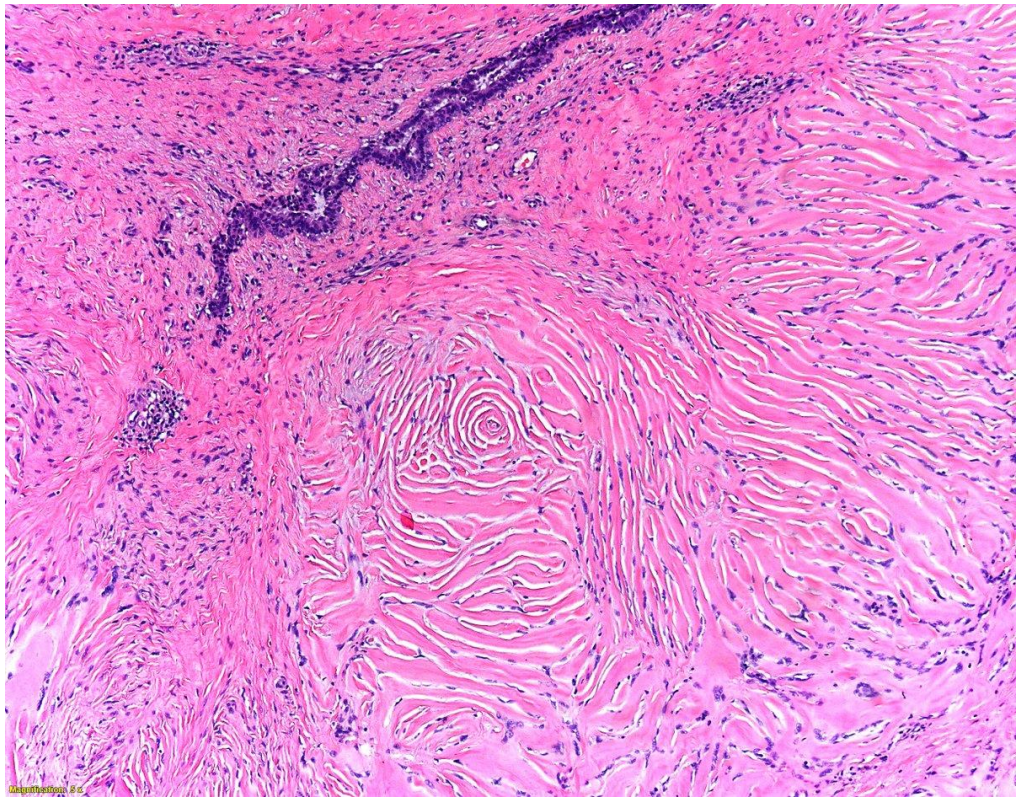
Qian et al Atypical presentation of classic Kaposi's sarcoma. *The Lancet;* 2019

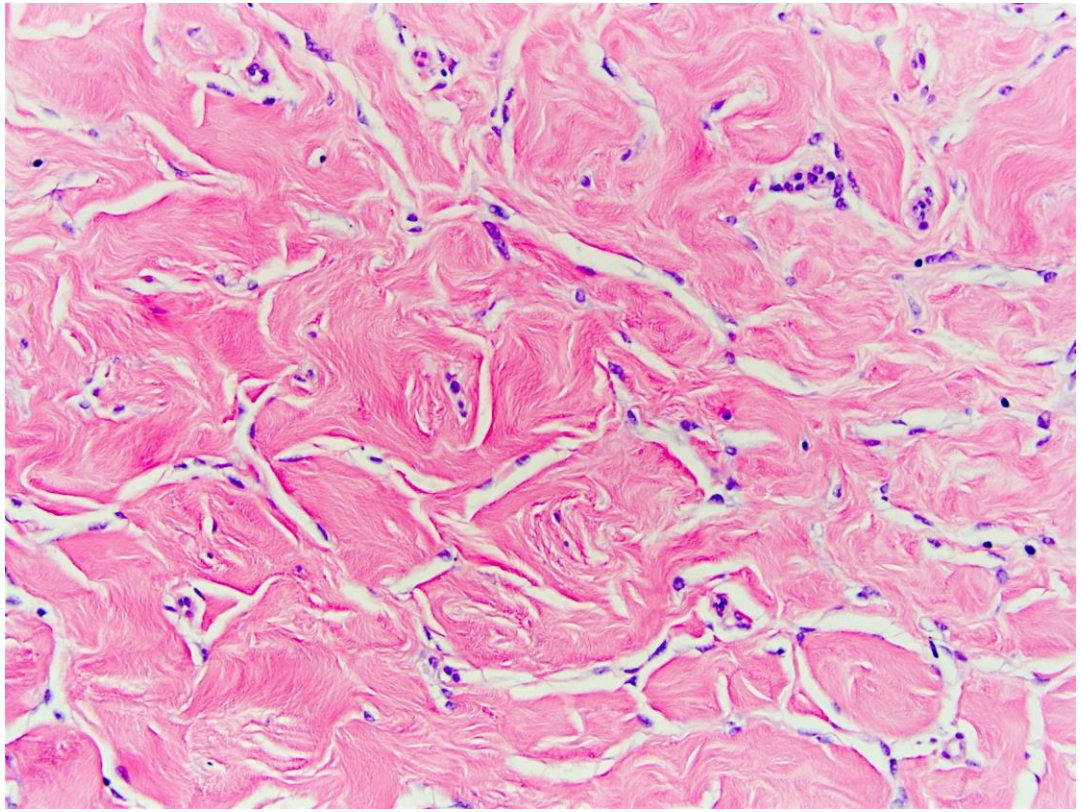


www.pathologyoutlines.com - Contributed by Michella Whisman, M.D

Non-Vascular Differential Diagnoses

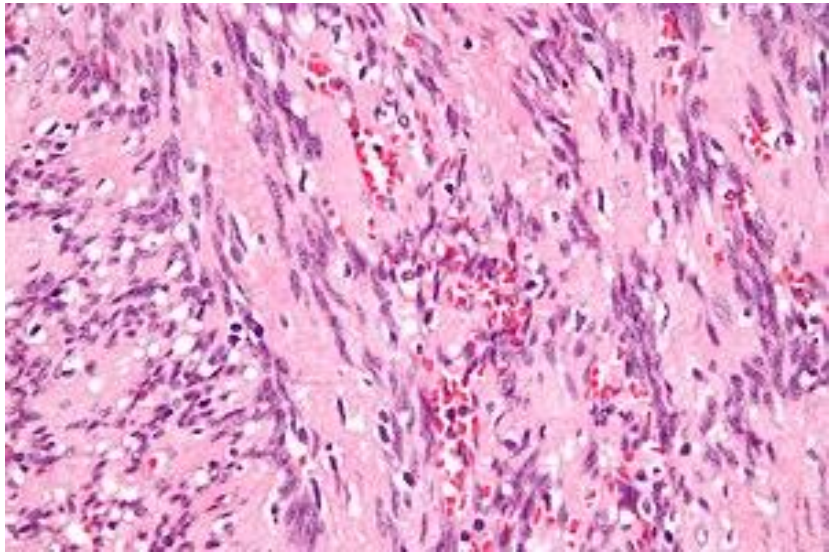
- Pseudoangiomatous stromal hyperplasia (PASH)

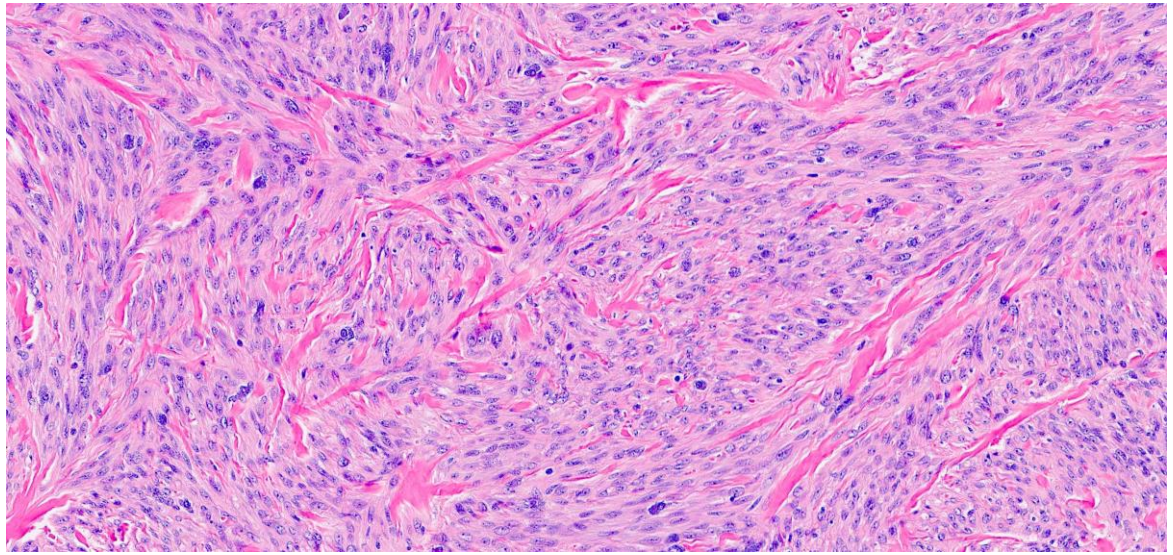




www.pathologyoutlines.comContributed by Indu Agarwal, M.D

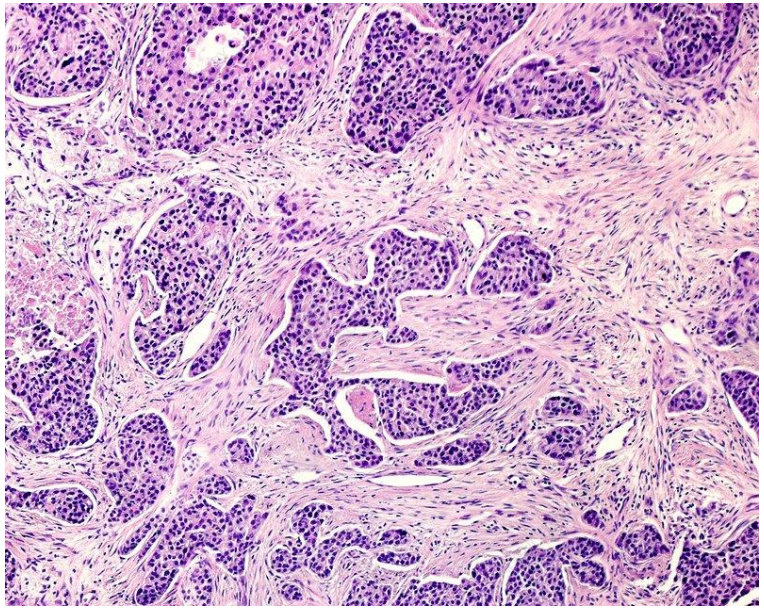
- Myofibroblastoma

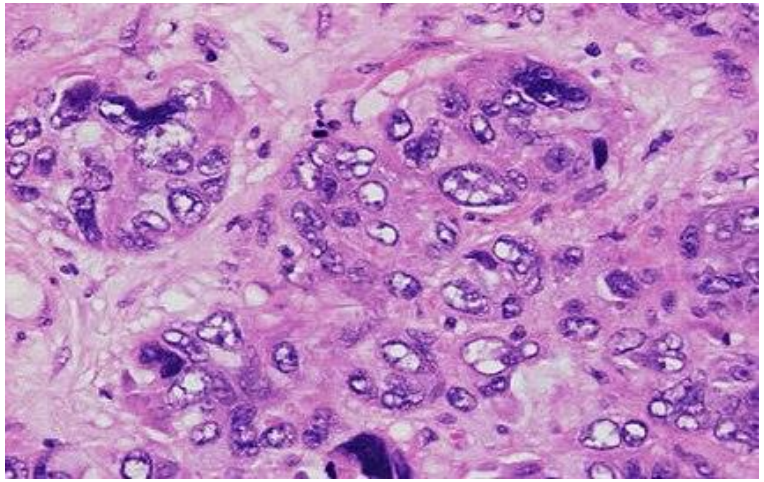




Contributed by Kristen E. Muller, D.O

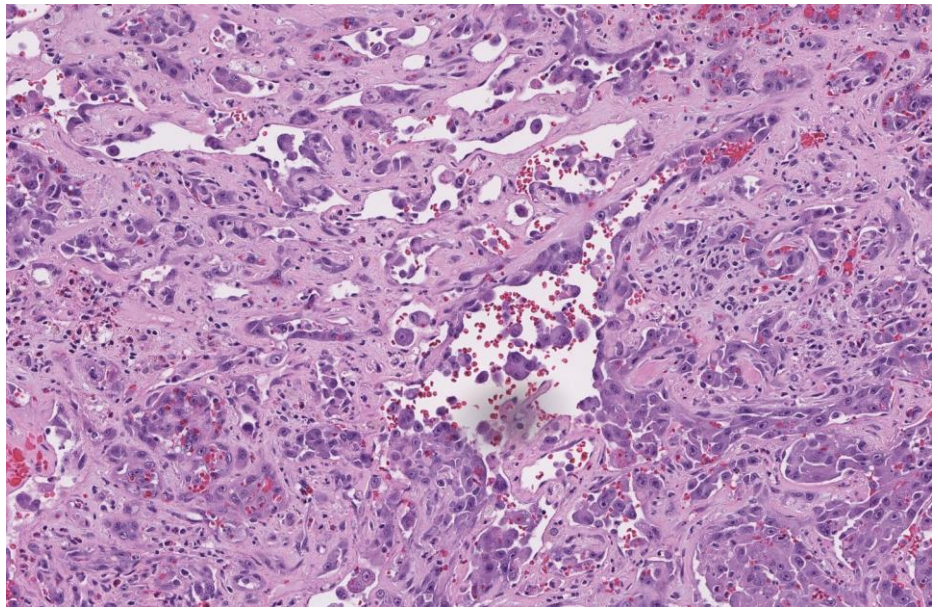
- High grade invasive carcinoma

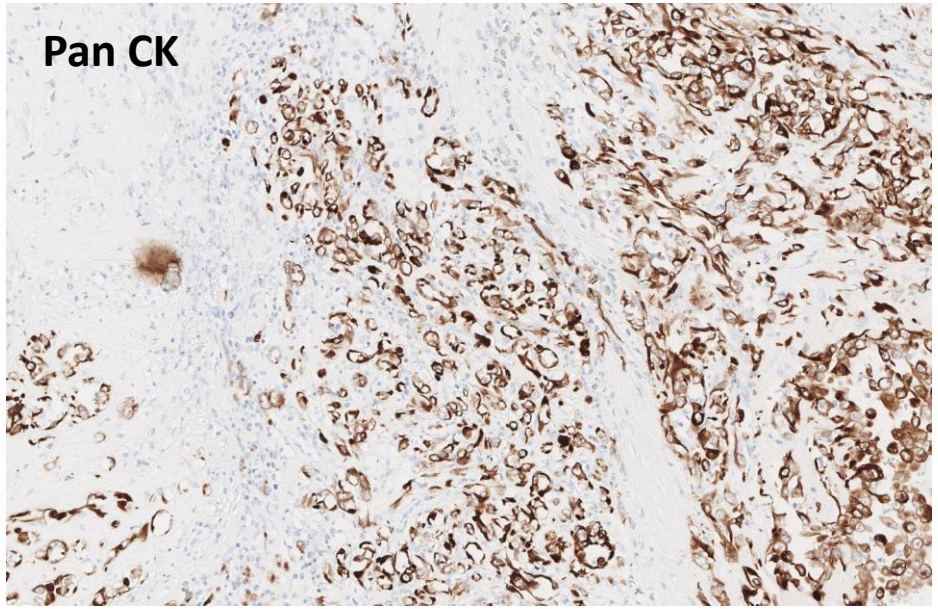




Credit: Jose Calvo

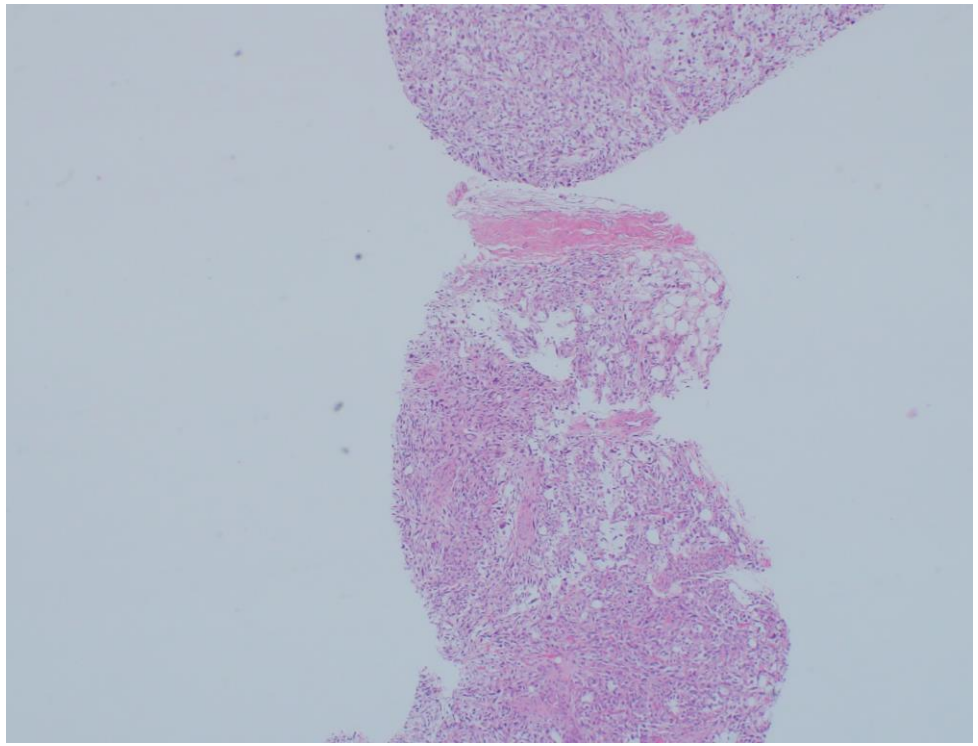
Epithelioid angiosarcoma

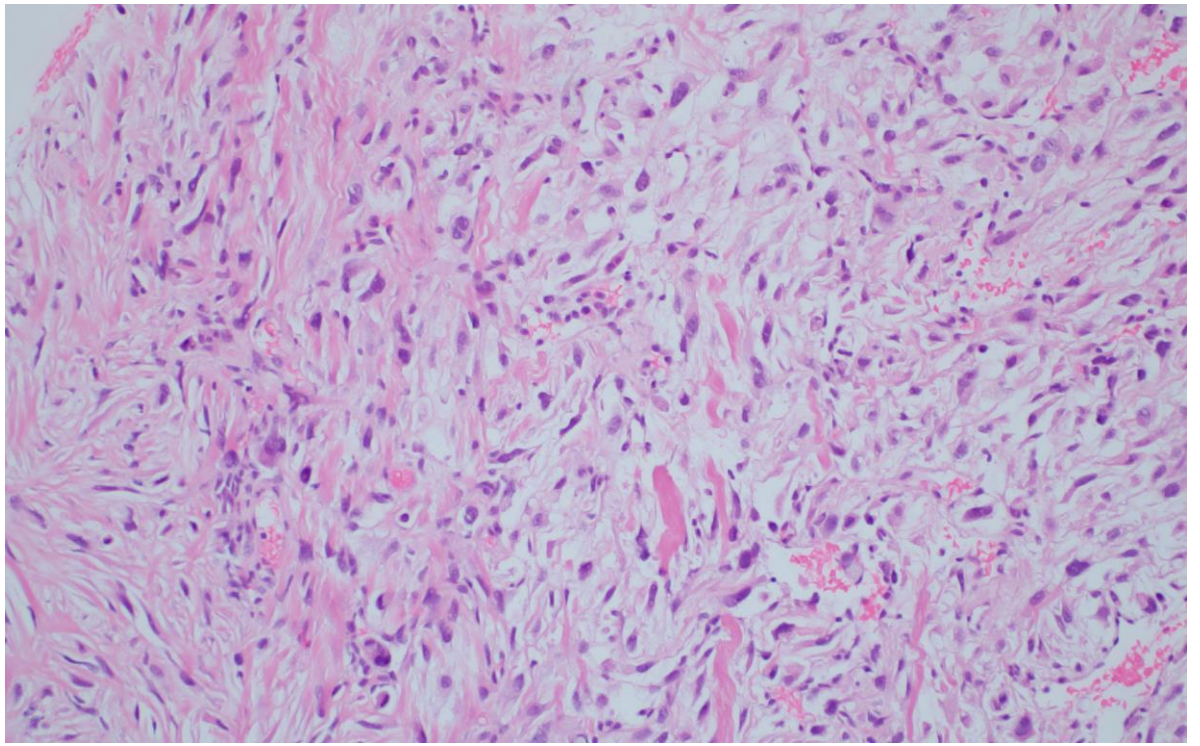


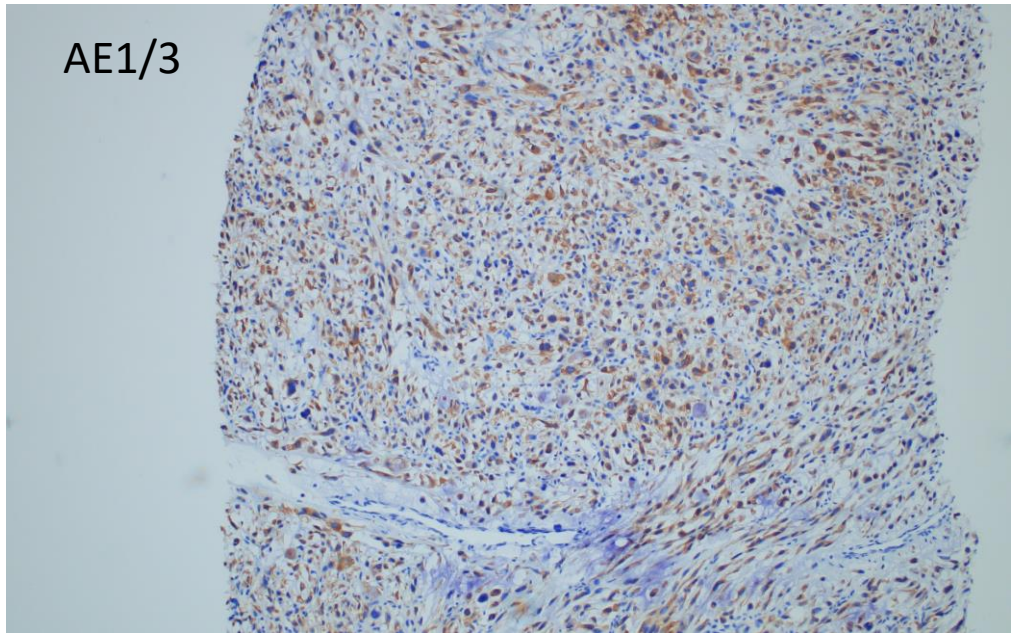


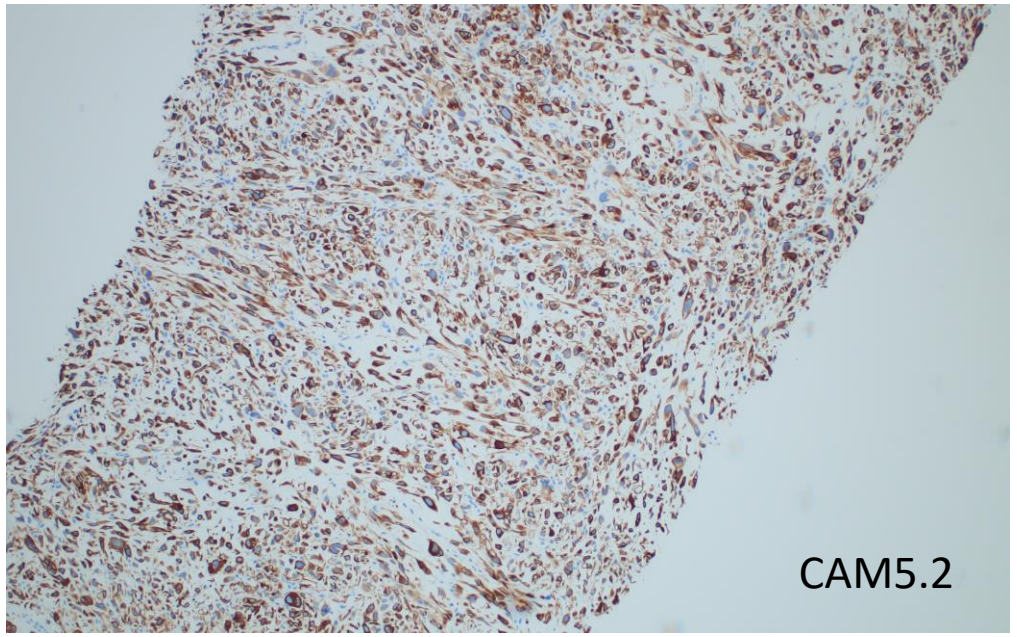
Credit: David Loeffler

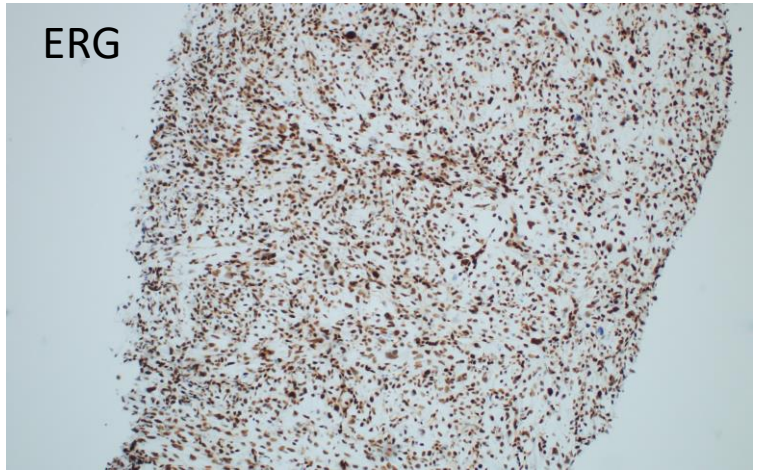
- Metaplastic spindle cell carcinoma

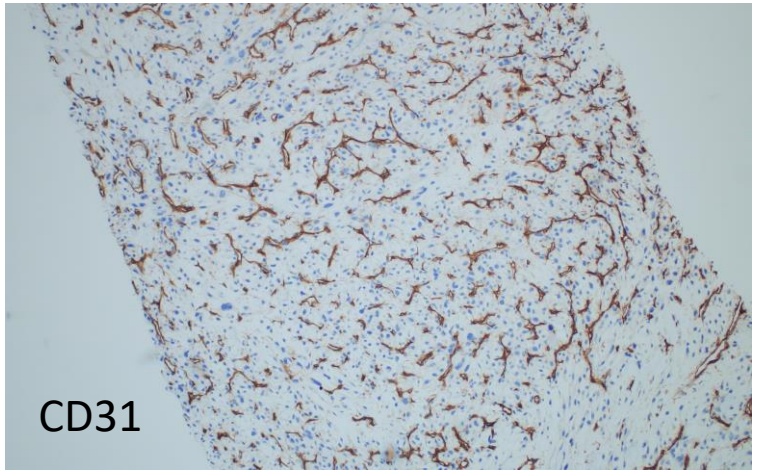


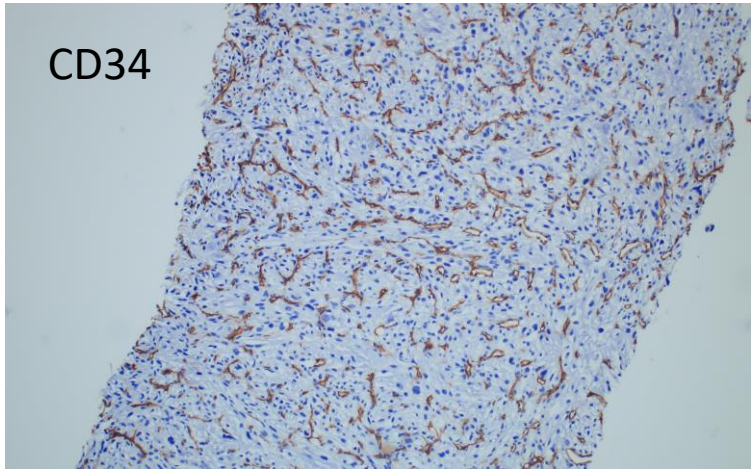




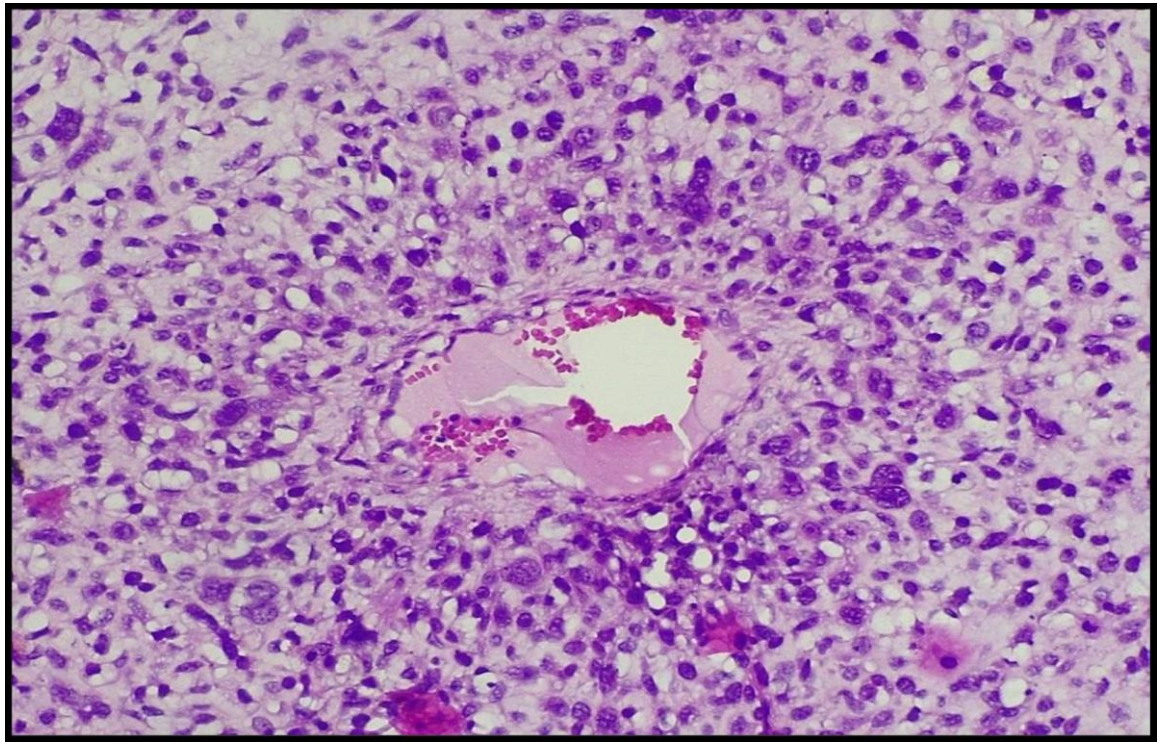








- Malignant phyllodes tumor



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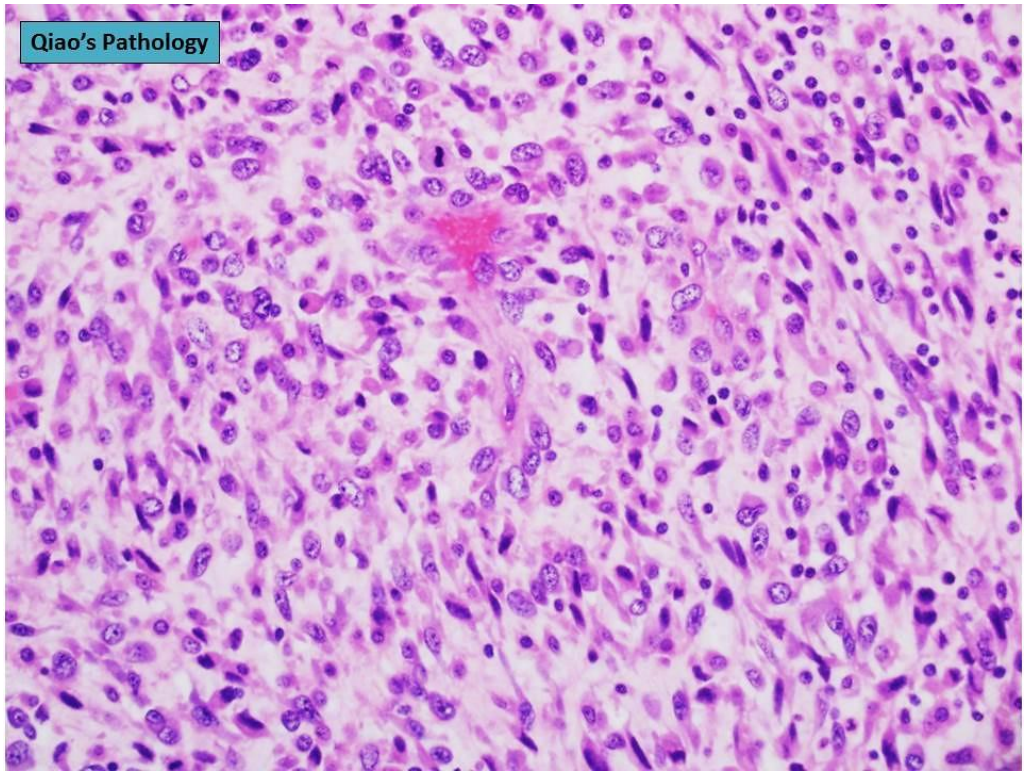
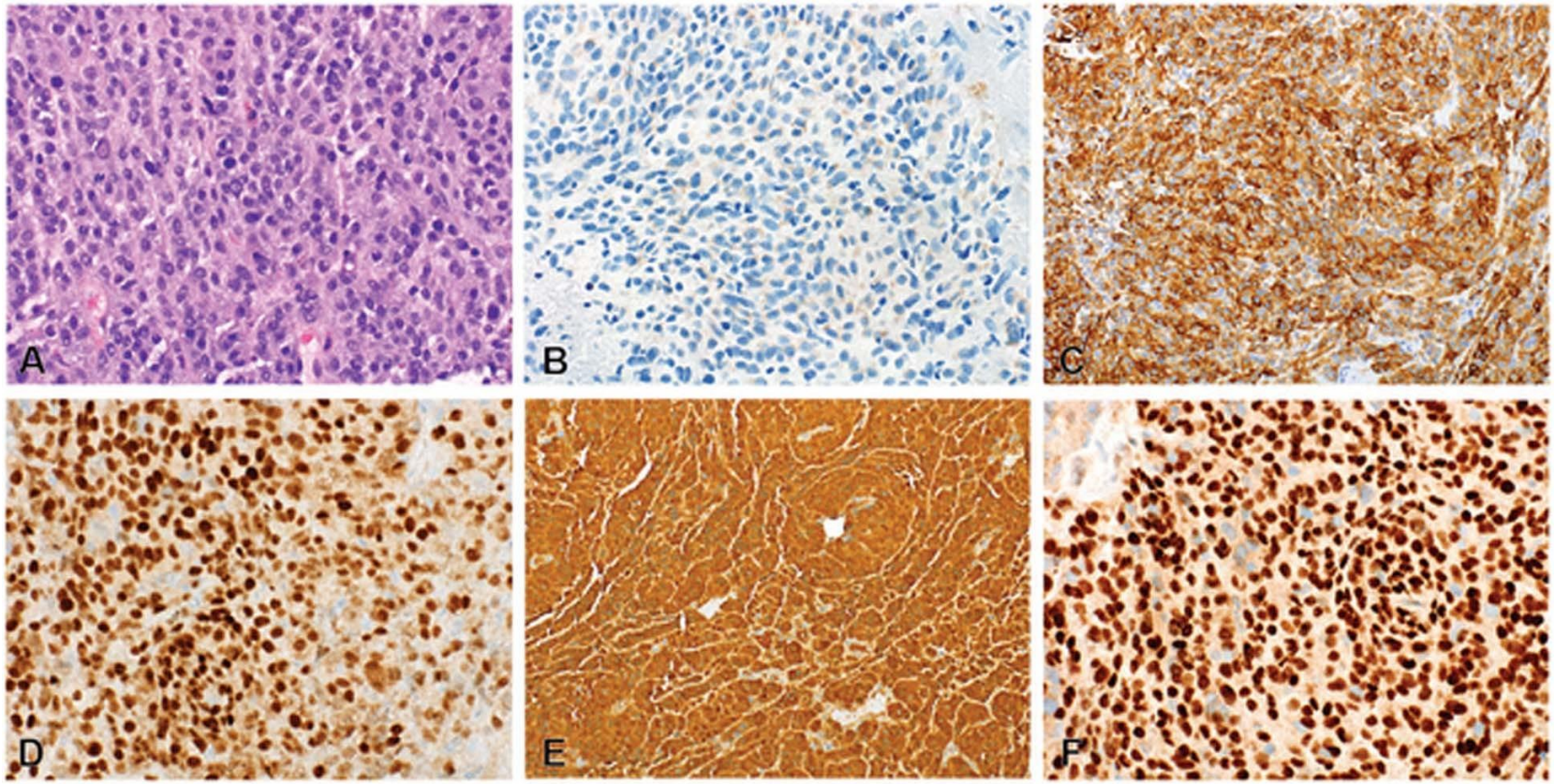


- Metastatic melanoma



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Thank you!