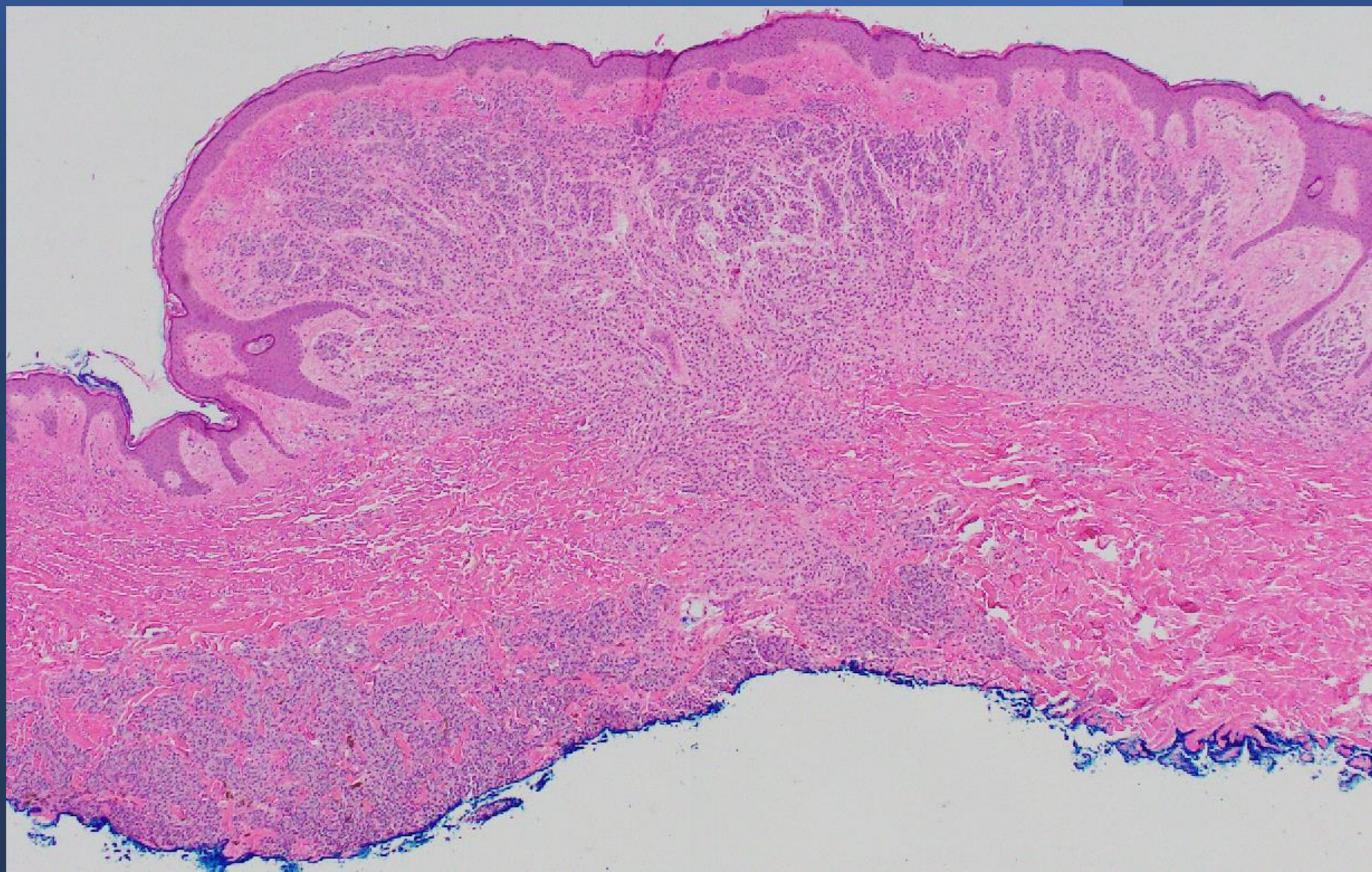
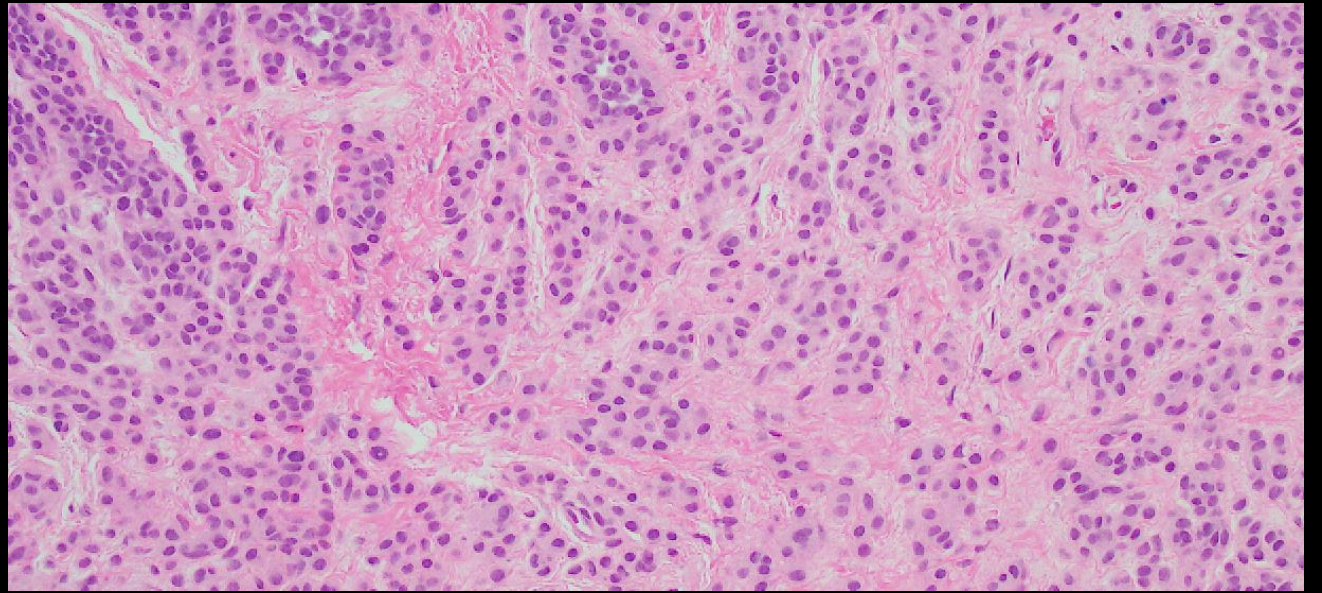
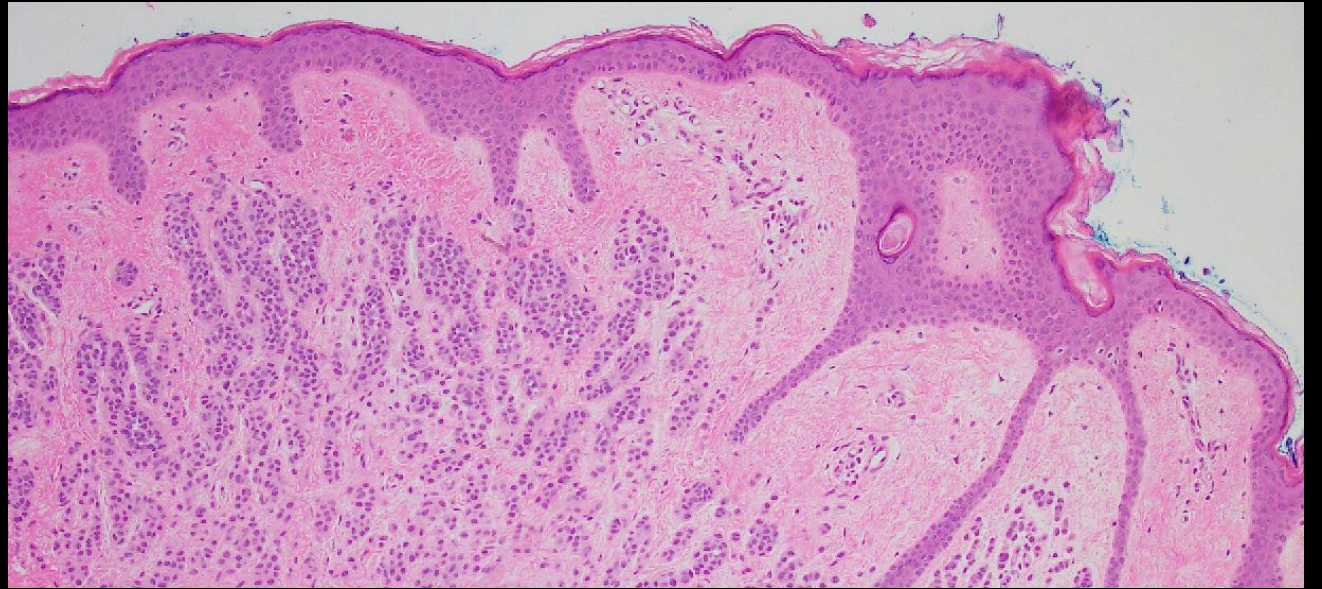
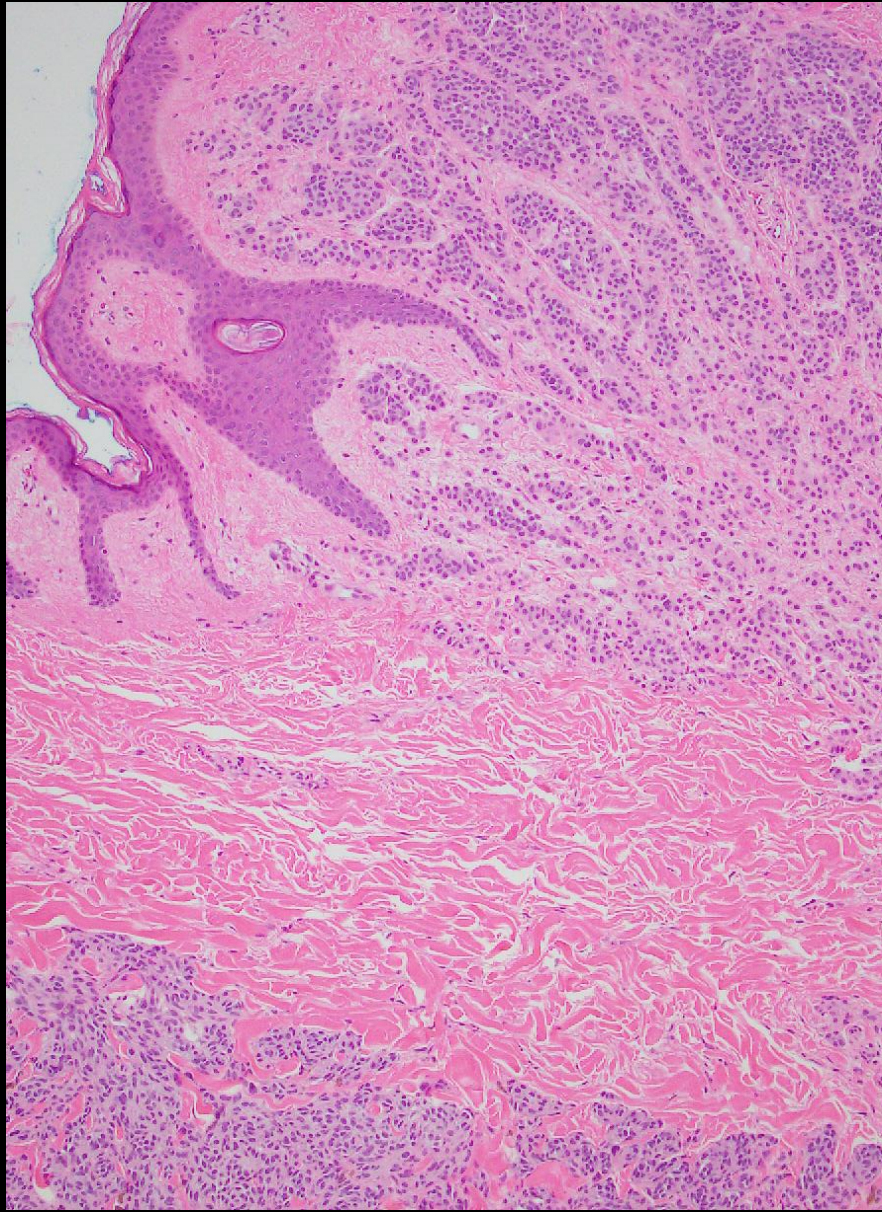


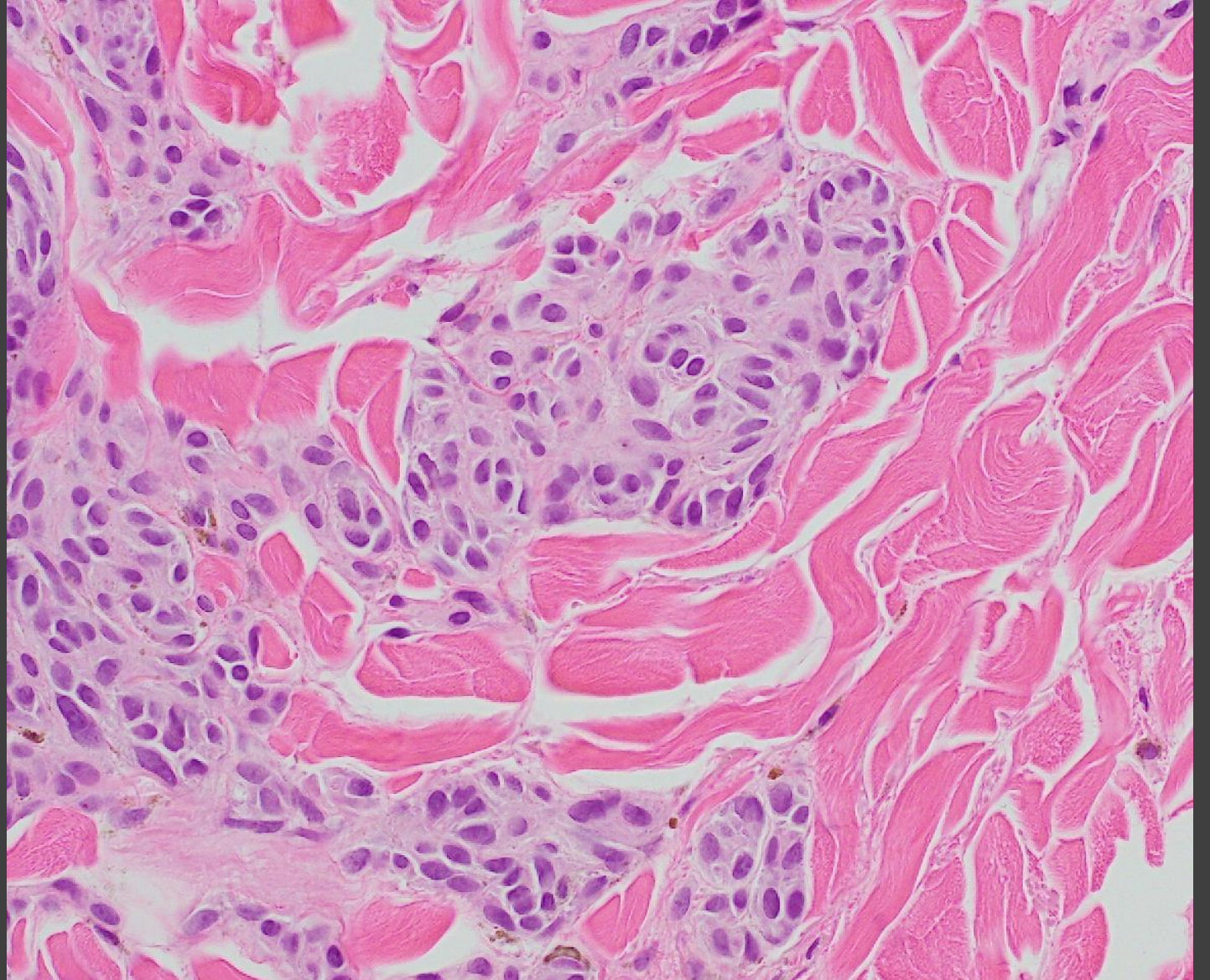
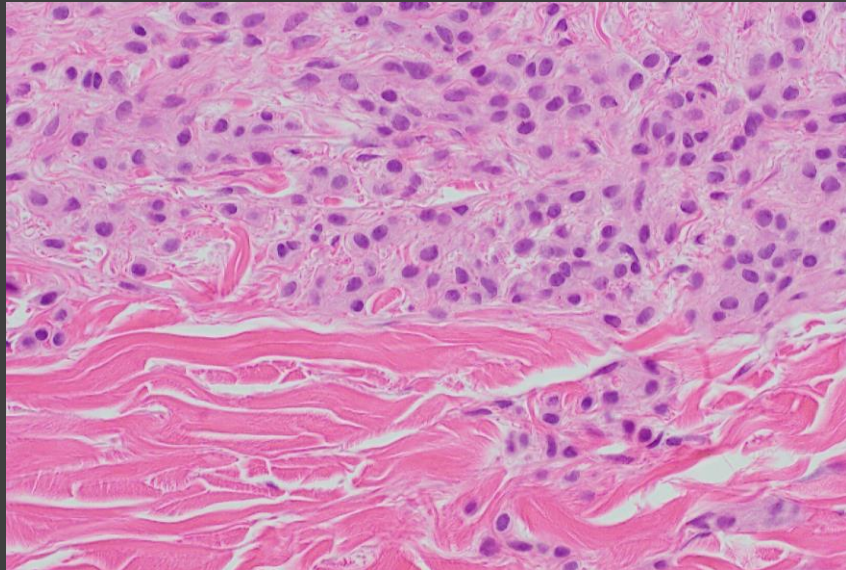
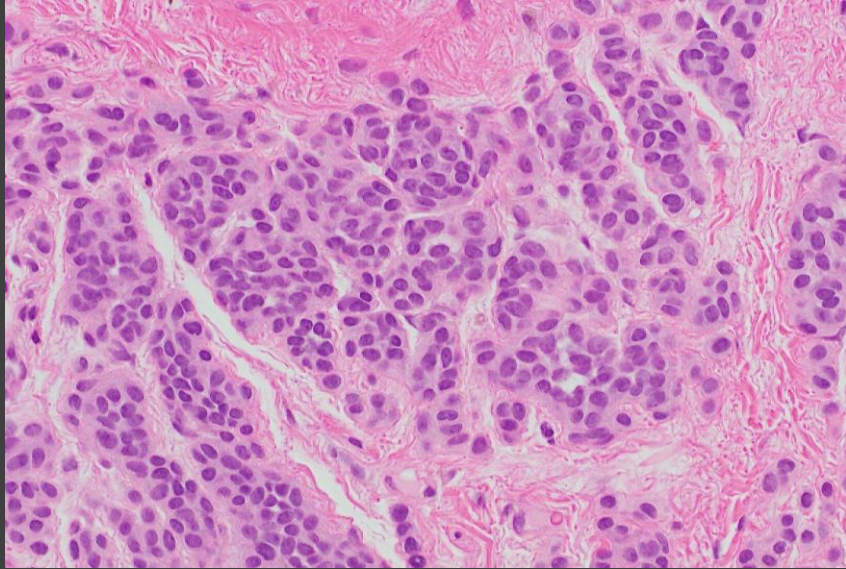
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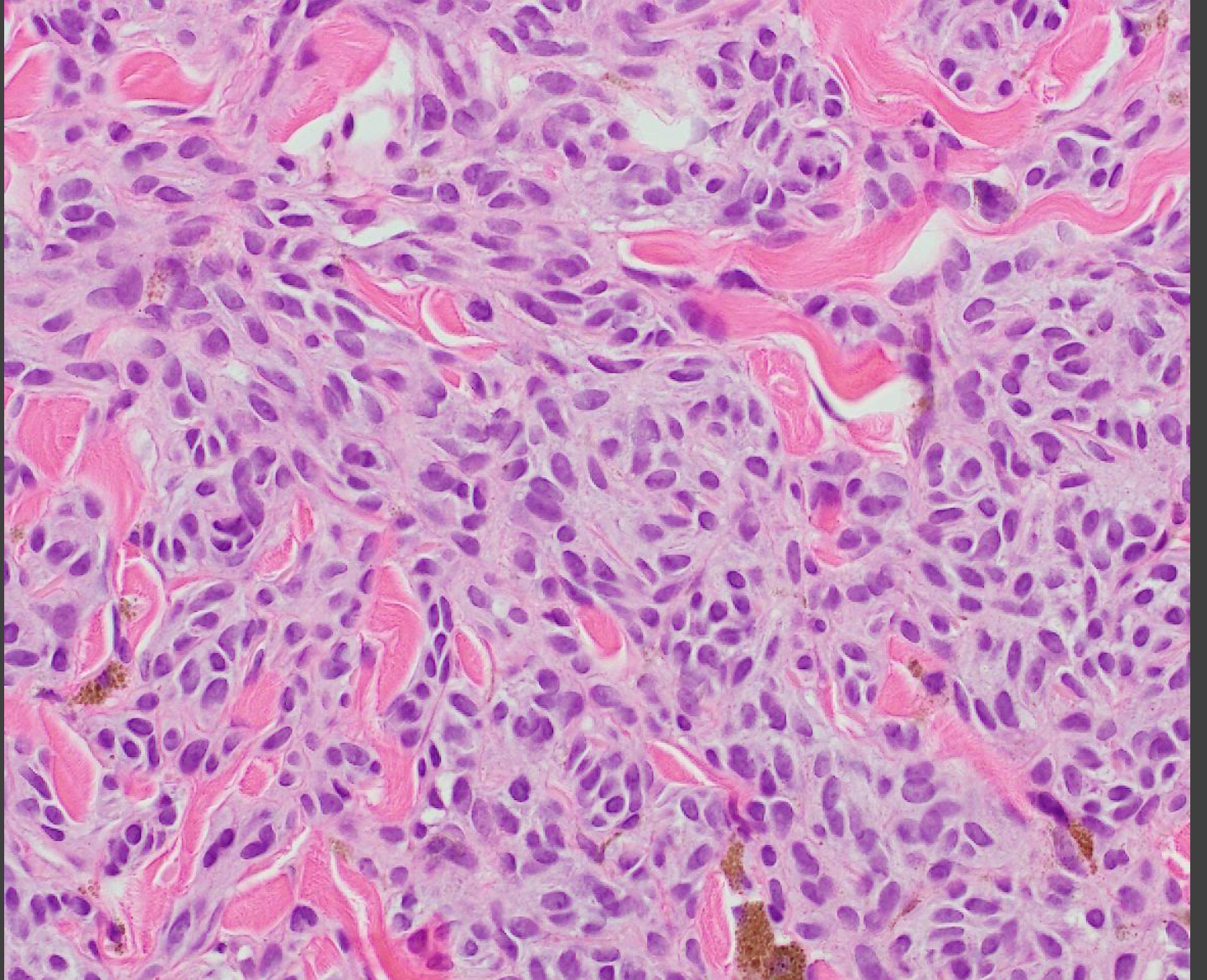
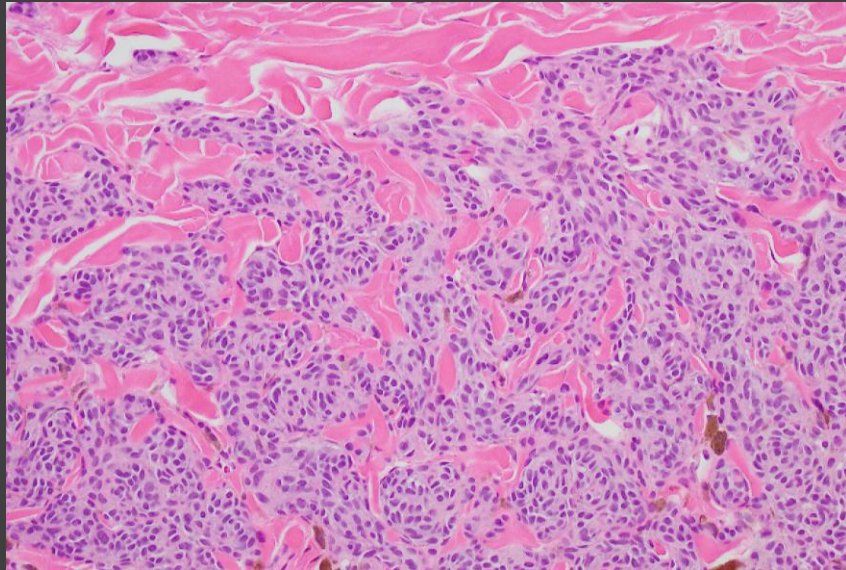
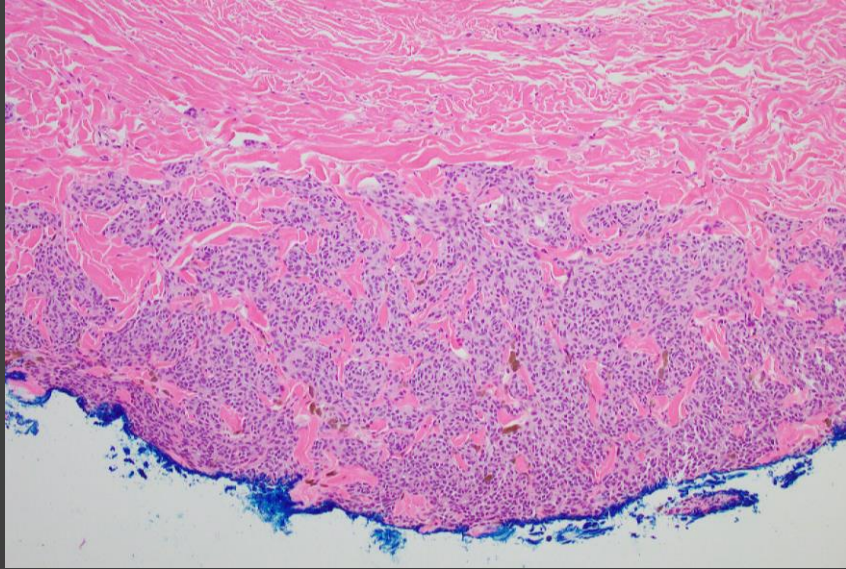
46 yo woman, pigmented lesion, left flank

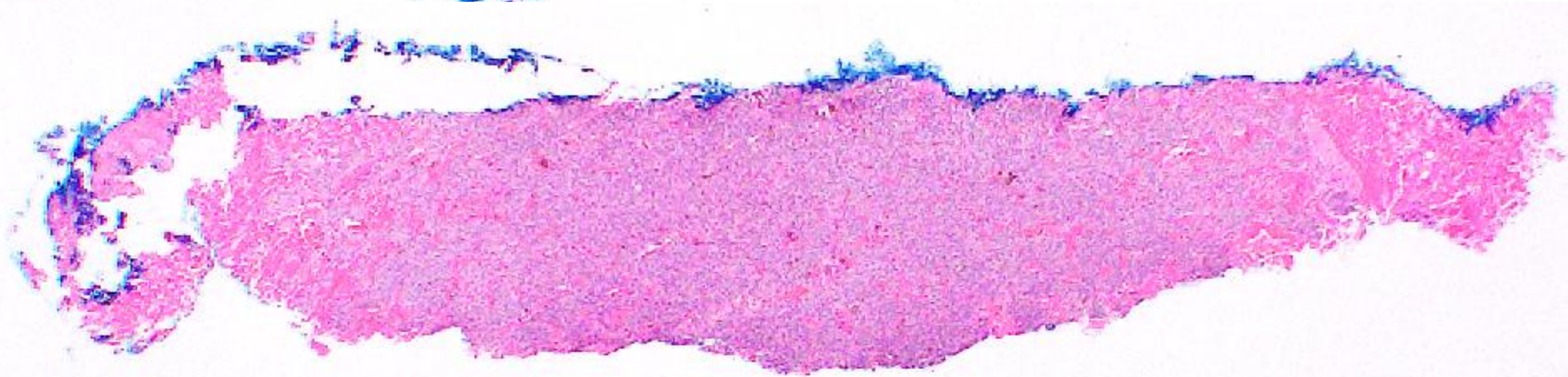
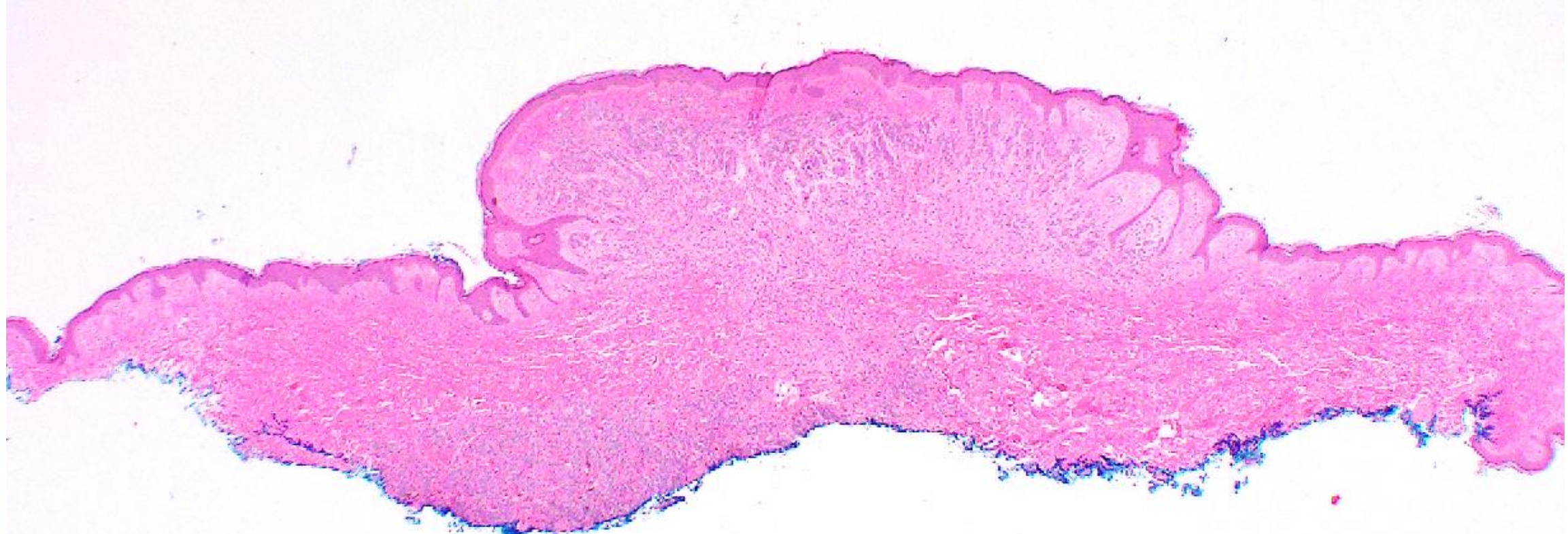
Lyn McDivitt Duncan, MD  
Professor of Pathology, Harvard Medical School  
Massachusetts General Dermatopathology Service  
Boston, MA, USA

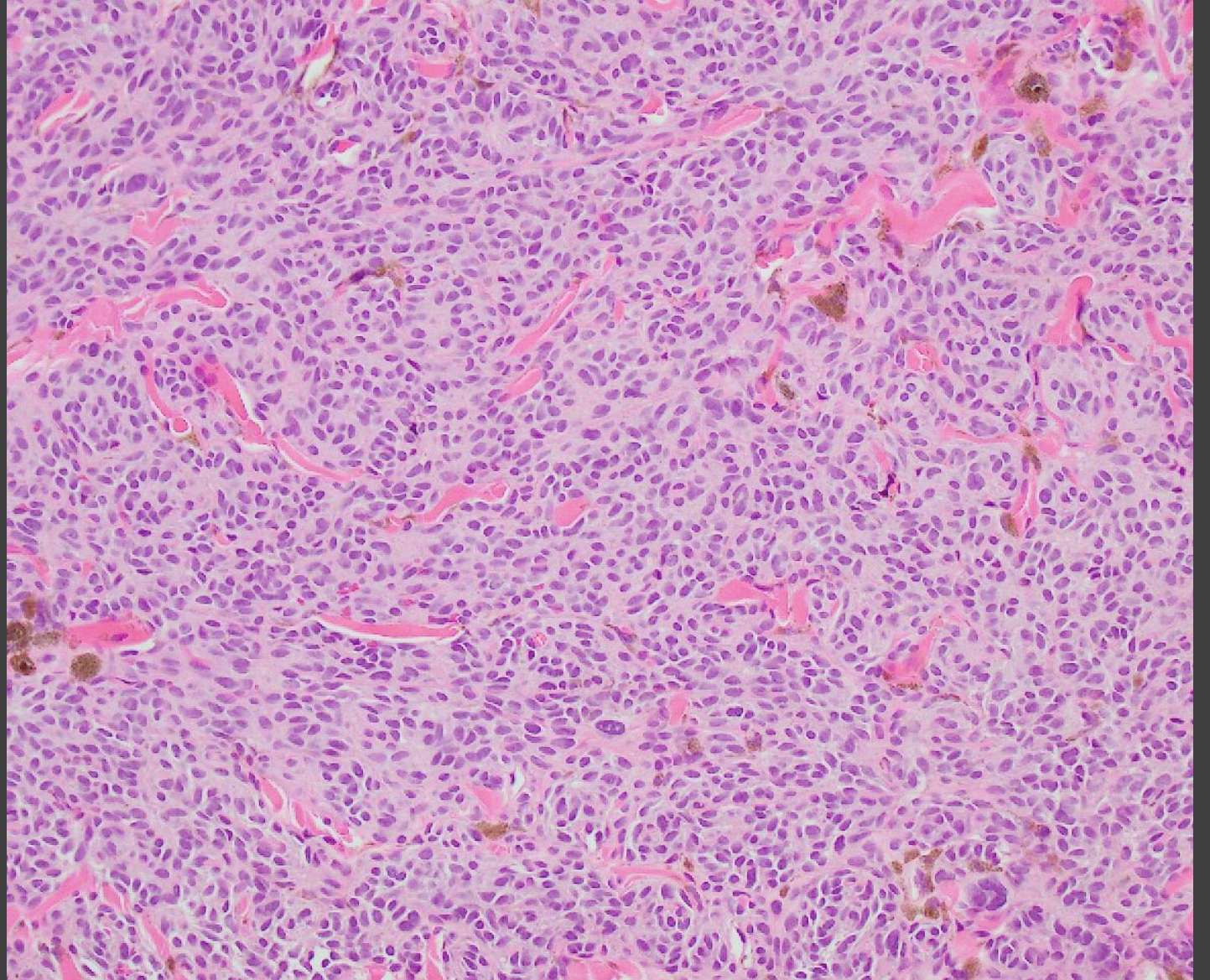
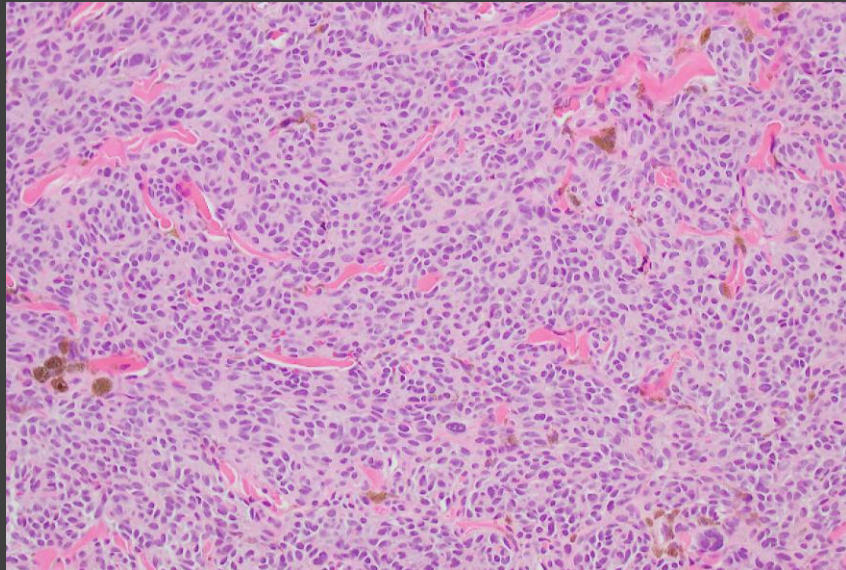
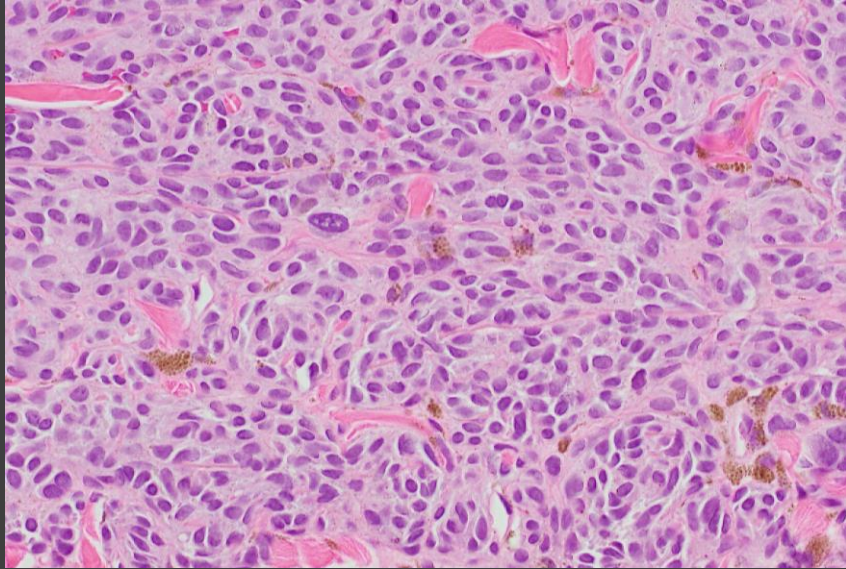


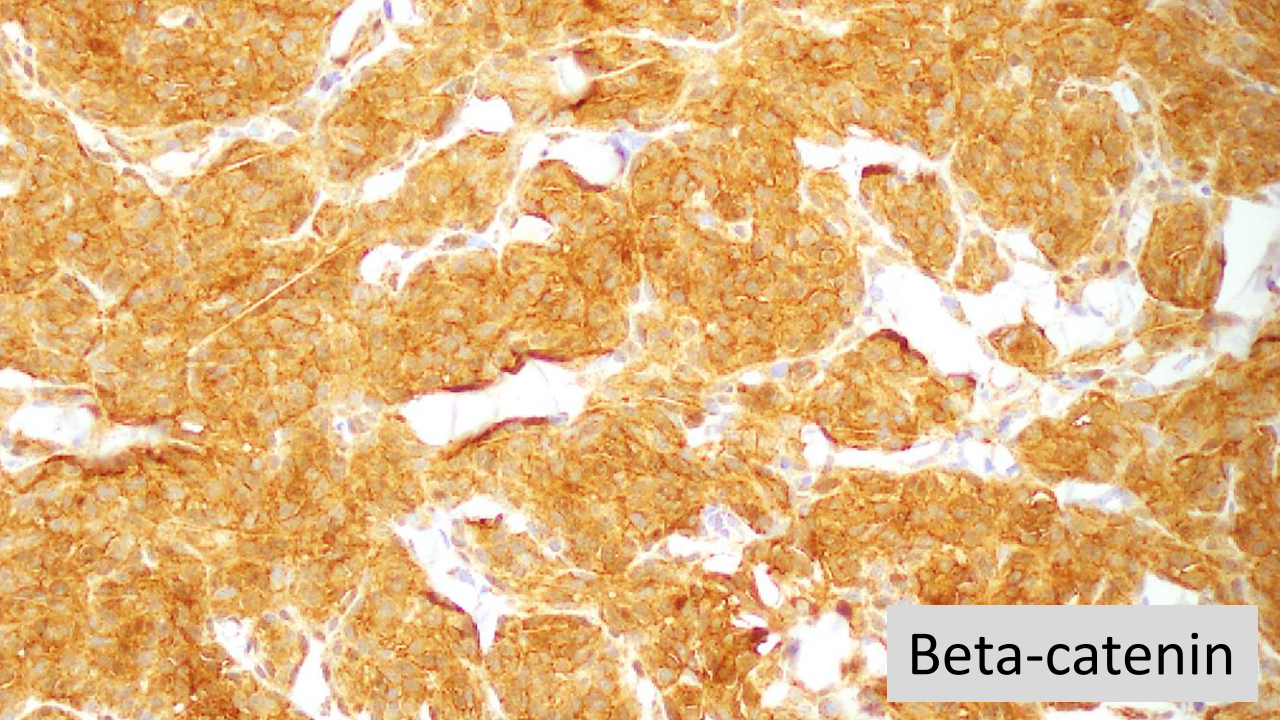
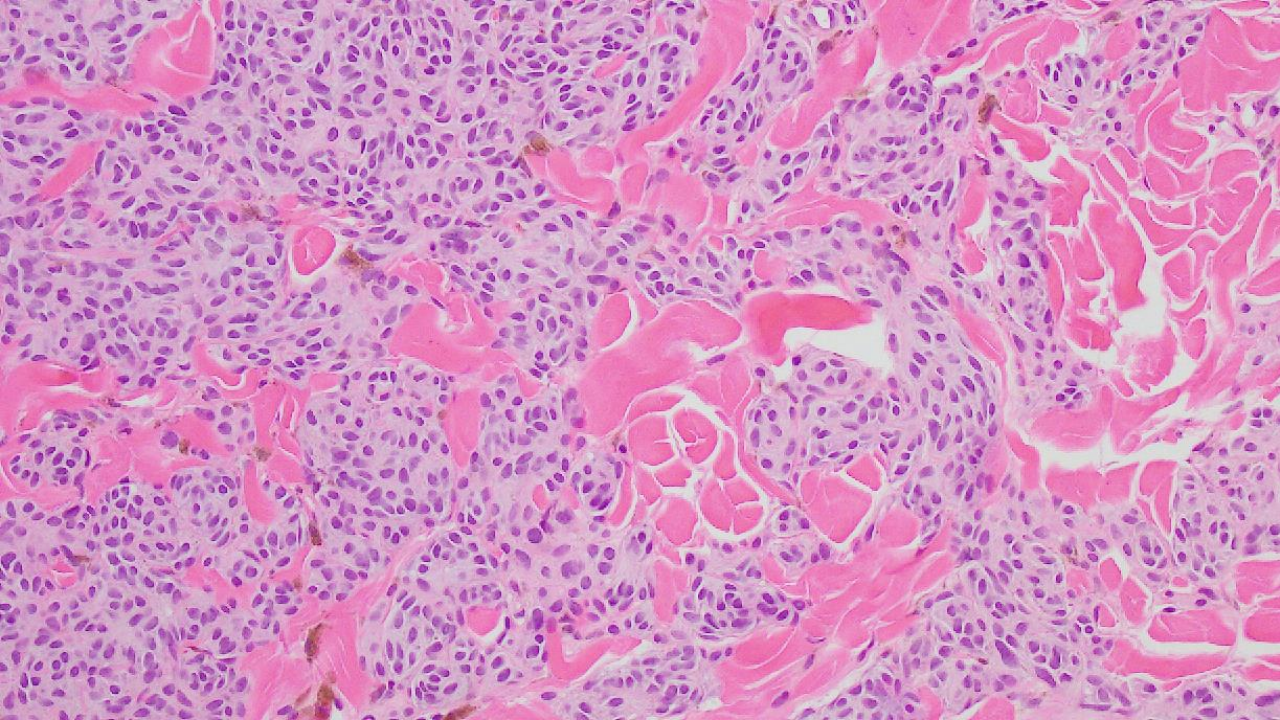




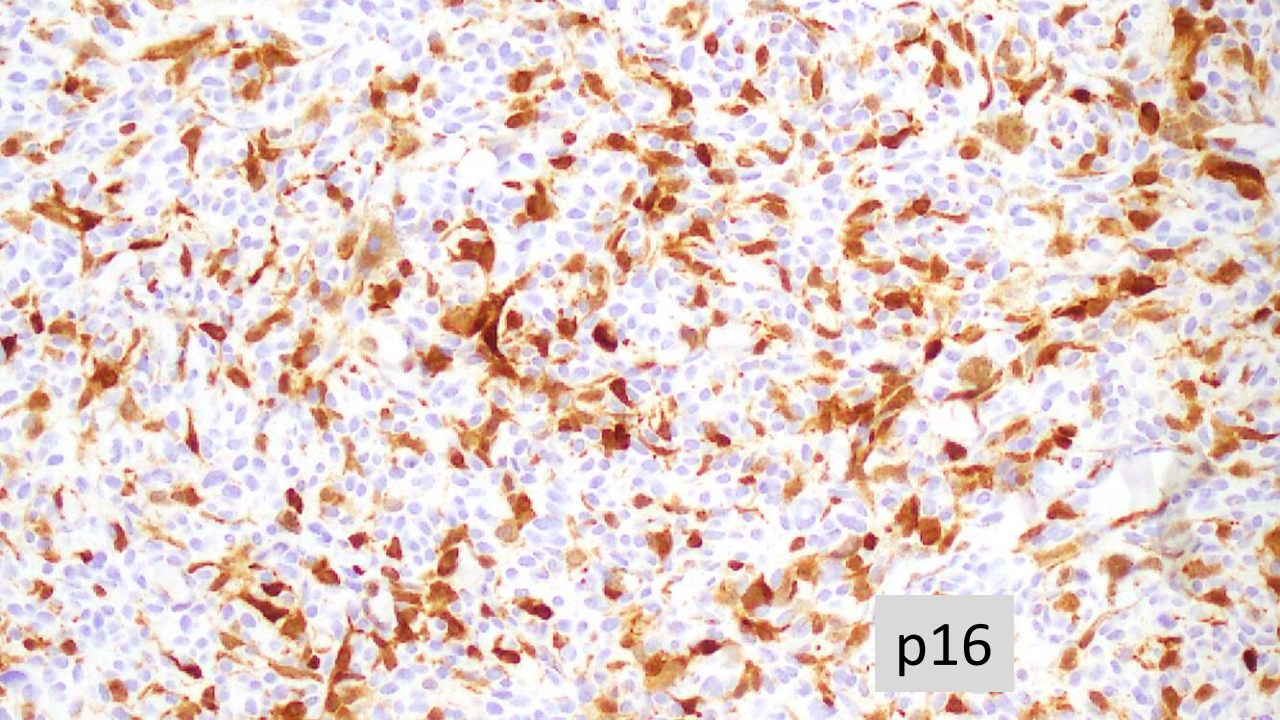




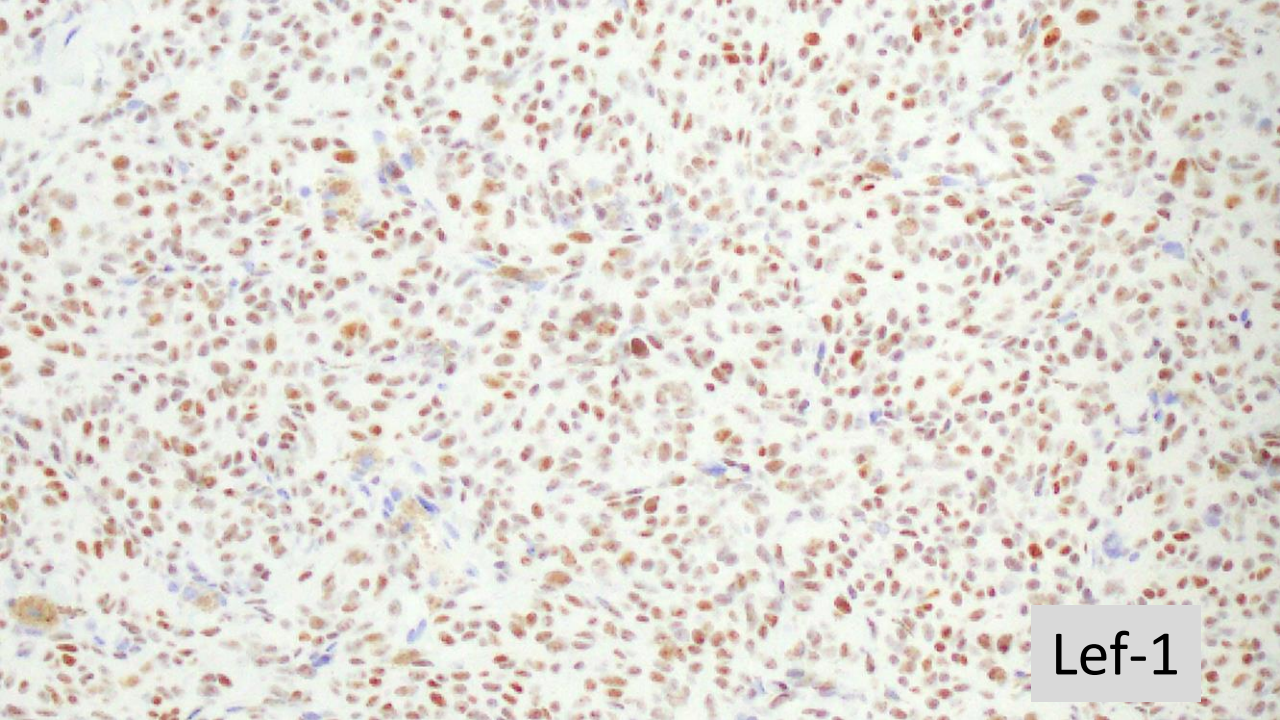




Beta-catenin



p16



Lef-1

# WHO Classification of Tumours Online – Skin Tumours 5<sup>th</sup> edition

## Nevus

- single mutation
- no other pathogenic mutations
- benign
- *very low risk* of progression to melanoma

## Melanocytoma

- initiating mutation
- additional pathogenic mutation
- intermediate
- *low risk* of progression to melanoma

WHO Classification of Tumours Editorial Board. Skin tumours. Lyon (France): International Agency for Research on Cancer; forthcoming. (WHO classification of tumours series, 5th ed.; vol. 12). <https://publications.iarc.fr>.

MELANOCYTOMA	MELTUMP (Melanocytic tumor of uncertain malignant potential)
Histomorphologically distinctive subtypes	Markedly atypical melanocytic tumors with features that fall short of diagnostic for melanoma
Genetically defined subtypes	If genomic studies are done, sufficient abnormalities for a diagnosis of melanoma do not exist
Histologically atypical, specifically defined, allow for benign diagnosis in most cases	Histologically atypical, but not outright malignant
Low incidence of melanoma in these subtypes of tumors (melanoma is associated with additional mutations)	Uncertain potential for malignancy
Not a term for histologically challenging molecularly undefined indeterminate tumors	Term may be used for histologically challenging molecularly undefined indeterminate tumors
INTERMEDIATE	UNCERTAIN

# WHO Classification– Skin Tumours 5<sup>th</sup> edition - Melanocytoma

Intermediate melanocytic neoplasms, emerge from acquisition of additional mutations  
....so called **melanocytoma** ...

Examples arising from acquired naevi (typically with BRAFp.V600E mutations):

BAP1 inactivated tumors (biallelic inactivation of BAP1)

Pigmented epithelioid melanocytoma (inactivation of PRKAR1)

Deep penetrating nevus (activation of beta-catenin or ID1)

And more:

Spitz melanocytoma (? Atypical Spitz Tumor)

Probability of malignant transformation is *very low* in nevi and *low* in melanocytomas...

## Case 1

46 yo woman, pigmented lesion, left flank

**WNT-activated deep penetrating/plexiform melanocytoma**

May be biphasic (combined) or purely spindled, pigmented and plexiform

IHC - beta-catenin, cyclinD1 and Lef1 positive in the deep aspects

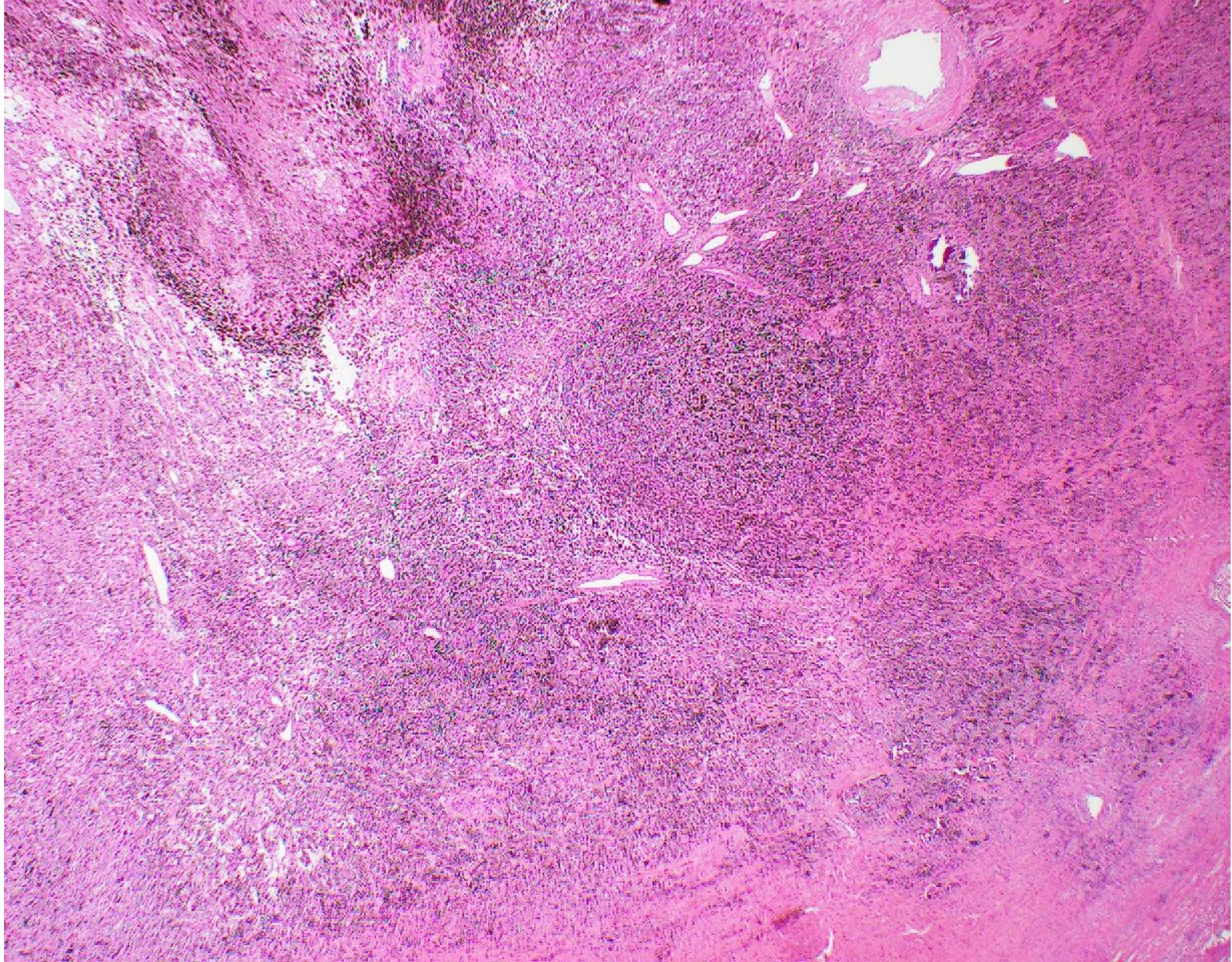
These tumors are intermediate with defined molecular abnormality (WNT-activated)

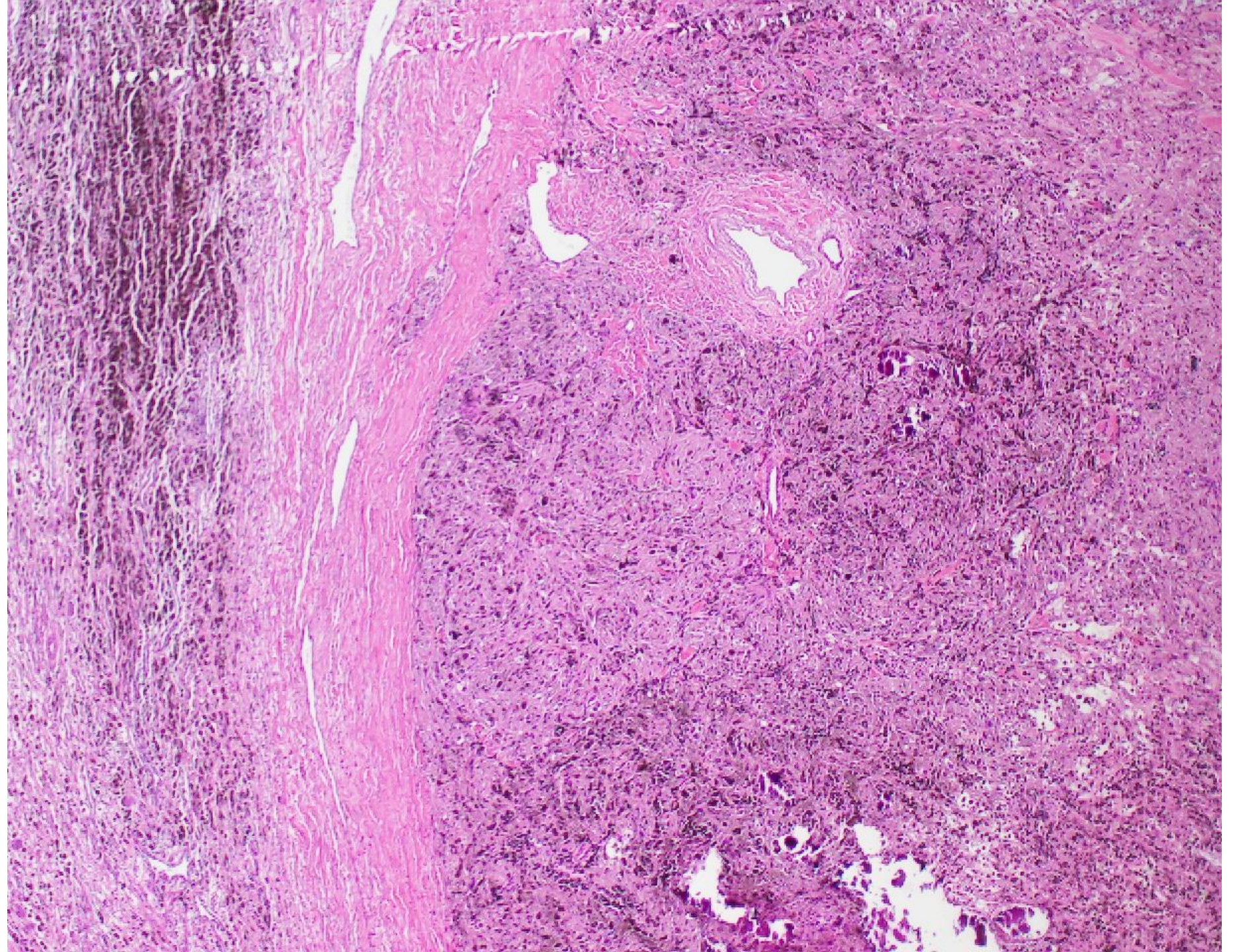


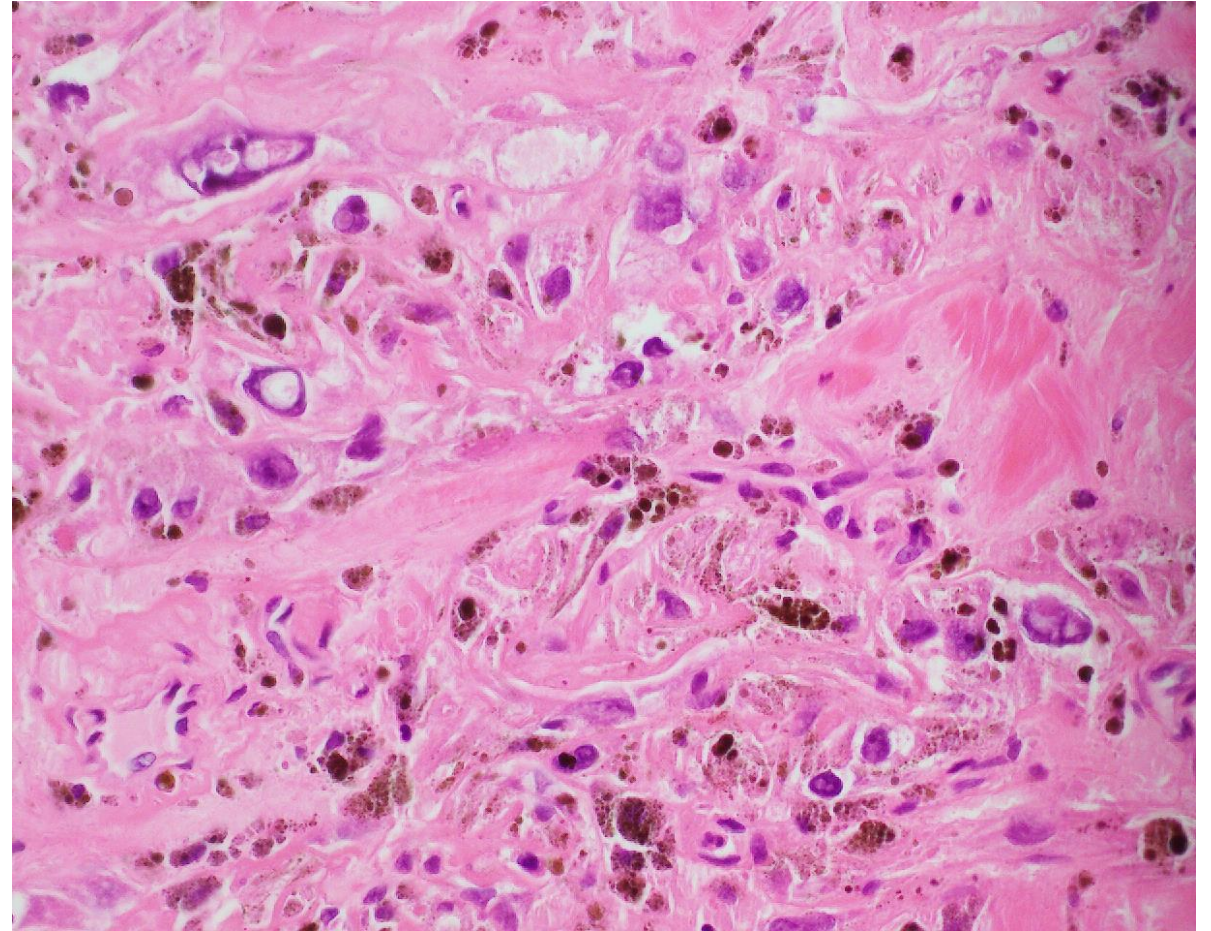
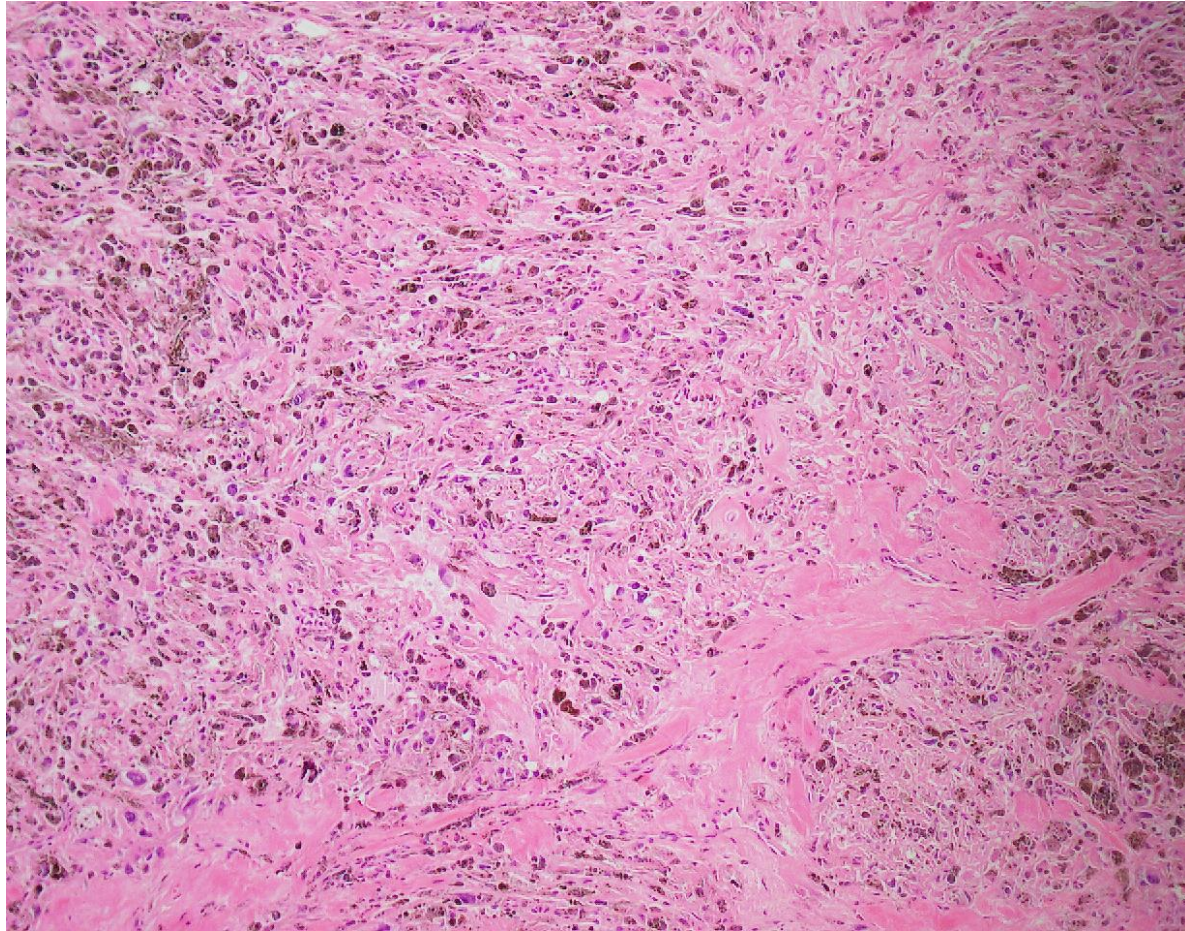
Mass General Brigham

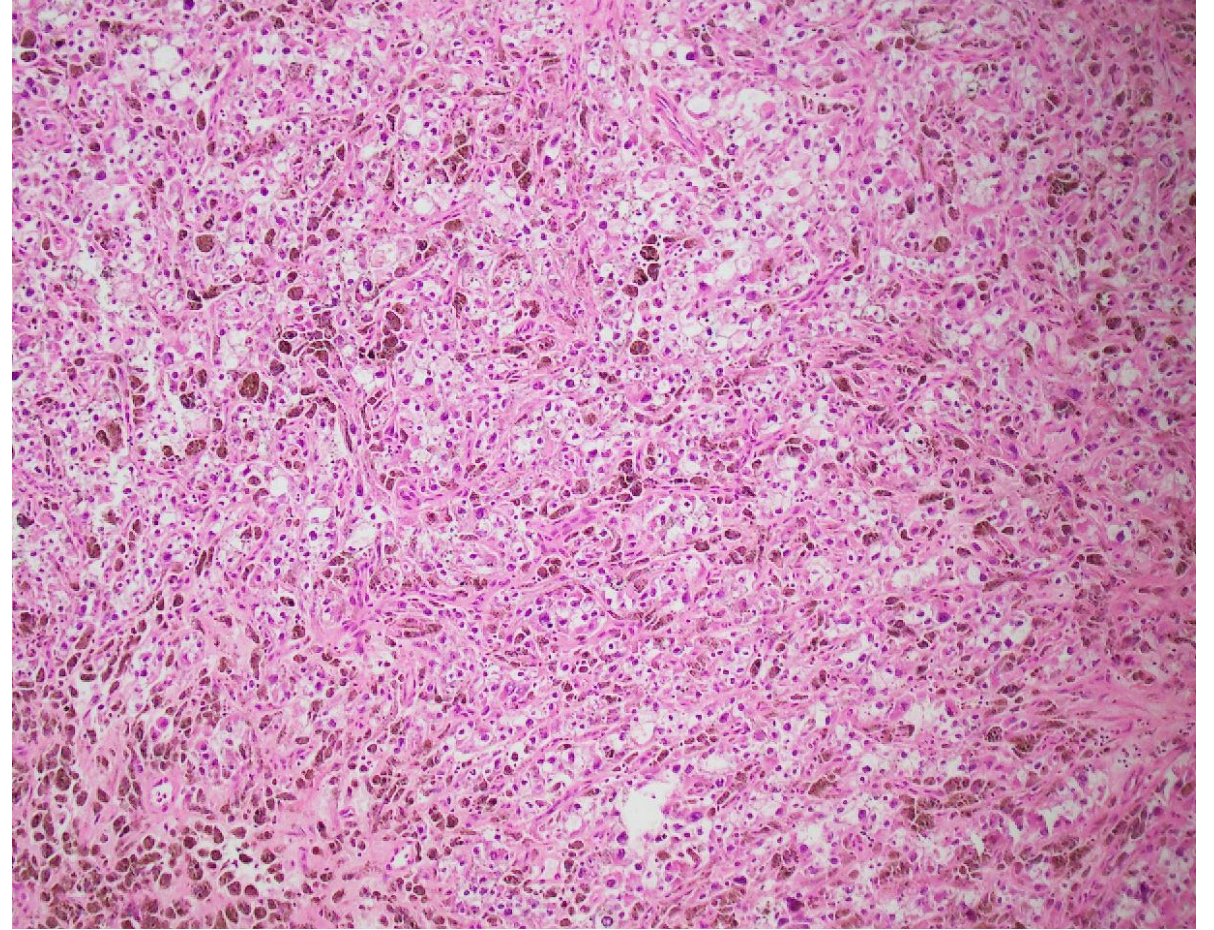
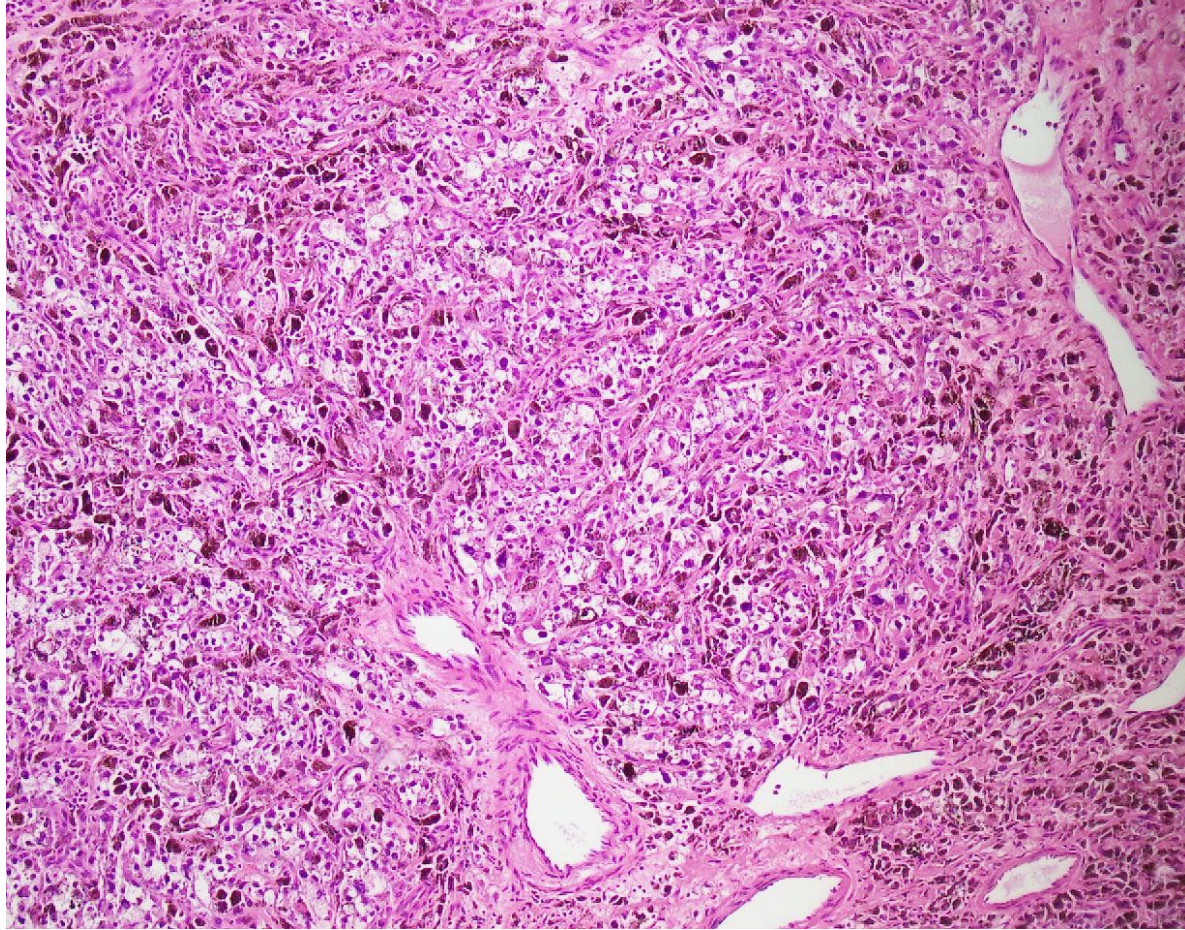
## Case 2

38 yo man, right pharyngeal space tumor









Immunohistochemical stains revealed a SOX10+ S100+HMB45+ MITF+ pigmented tumor with tumoral necrosis: diagnosis metastatic melanoma

PET/CT, ocular examination and skin examination all normal with no evidence of primary melanoma

Sought second opinion: additional immunohistochemistry and molecular studies explored

# Immunohistochemistry in Differential Diagnosis

Diagnosis	Immunophenotype
Melanoma	S100, SOX10, Mart1, HMB45
Poorly differentiated Carcinoma	p63, p40, p16, cytokeratins
Diffuse large B cell lymphoma	CD20, PAX5
Malignant peripheral nerve sheath tumor	S100, SOX10 (loss of H3K27m33)
Follicular dendritic cell sarcoma	CD21, CD23, CD35, claudin-4, D2-40, SSTR2
Neuroendocrine carcinoma	INSM1, chromogranin, synaptophysin, cytokeratins
Malignant melanotic nerve sheath tumor	S100, SOX10, Mart1, HMB45 (loss of PRKAR1A, no BRAFm)

Sought second opinion: additional immunohistochemistry and molecular studies explored

RAS61R negative

IHC for PKR1A equivocal, not diagnostic

PRKAR1A c.962delC pathogenetic variant reported through Caris Life Sciences molecular genetic testing studies

# Malignant Melanotic Nerve Sheath Tumor

## Definition

Peripheral nerve sheath tumor composed of Schwann cells with melanocytic differentiation

Rare and aggressive

50% associated with Carney complex

## 2013

Classified as a benign tumor

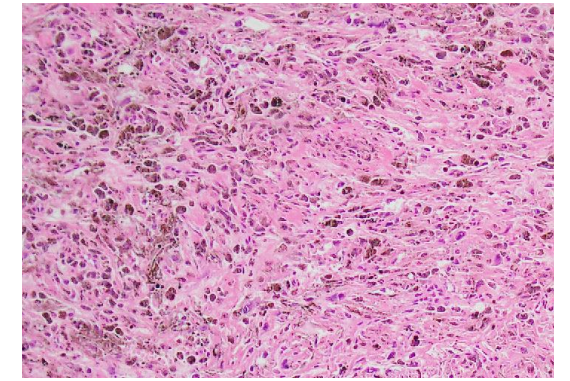
Melanotic Schwannoma

## 2020

Classified as malignant

Malignant melanotic nerve sheath tumor

# Malignant Melanotic Nerve Sheath Tumor



## Essential features

- Peripheral nerve sheath tumor neoplasm, Schwannian with melanocytic differentiation
- Often associated with spinal or visceral autonomic nerves
- Fascicular to sheet-like proliferation of heavily pigmented, relatively uniform plump spindle cells
- Expression of S100 / SOX10 and other melanocytic markers (HMB45, MelanA)
- Metastases may occur even in morphologically banal tumors
- Loss of PRKAR1a, molecular analysis may be needed to look for PRKAR1a mutation

# Malignant Melanotic Nerve Sheath Tumor

## **Immunophenotype**

- 100% HMB45+
- 100% Tyrosinase+
- 92% MelanA+
- 84% S100+
- Negative for GFAP
- Negative for EMA
- 100% SMARCB1 retained
- 35% with loss of PRKAR1A expression
- 92% with Ki-67 <5%

# Malignant Melanotic Nerve Sheath Tumor

## **Histopathology**

- Epithelioid and spindled cells
- Abundant pigmented tumor cell cytoplasm and melanophages
- Arranged in nodules and fascicles
- Psammoma bodies may be present
- Low mitotic index
- Tumor- type necrosis in 30%
- In the skin can mimic melanoma, pigmented neurofibroma, and pigmented epithelioid melanocytoma

# Differential Diagnosis: Malignant Melanotic Nerve Sheath Tumor (MMNST)

	Histopathology	Immunophenotype	Molecular
<b>MMNST</b>	Pigmented epithelioid and spindled cells Low mitotic rate	Express melanocytic markers Loss of Prkar1a	PRKAR1A alterations, no BRAF mutation
<b>Melanoma arising in blue nevus</b>	Pigmented epithelioid and spindled cells Prominent dendritic cytology	Express melanocytic markers	70% with GNAQ/GNA11-activating mutations, BAP1, EIFIAX, SF2B1 mutations
<b>Melanoma</b>	Pigmented epithelioid and spindled cells Higher mitotic rate	Express melanocytic markers	May have BRAF, NRAS, MAP2K1 activating alterations, TERT promoter mutations, CDKN2A alterations, copy number variations

# Malignant Melanotic Nerve Sheath Tumor

## Clinical features

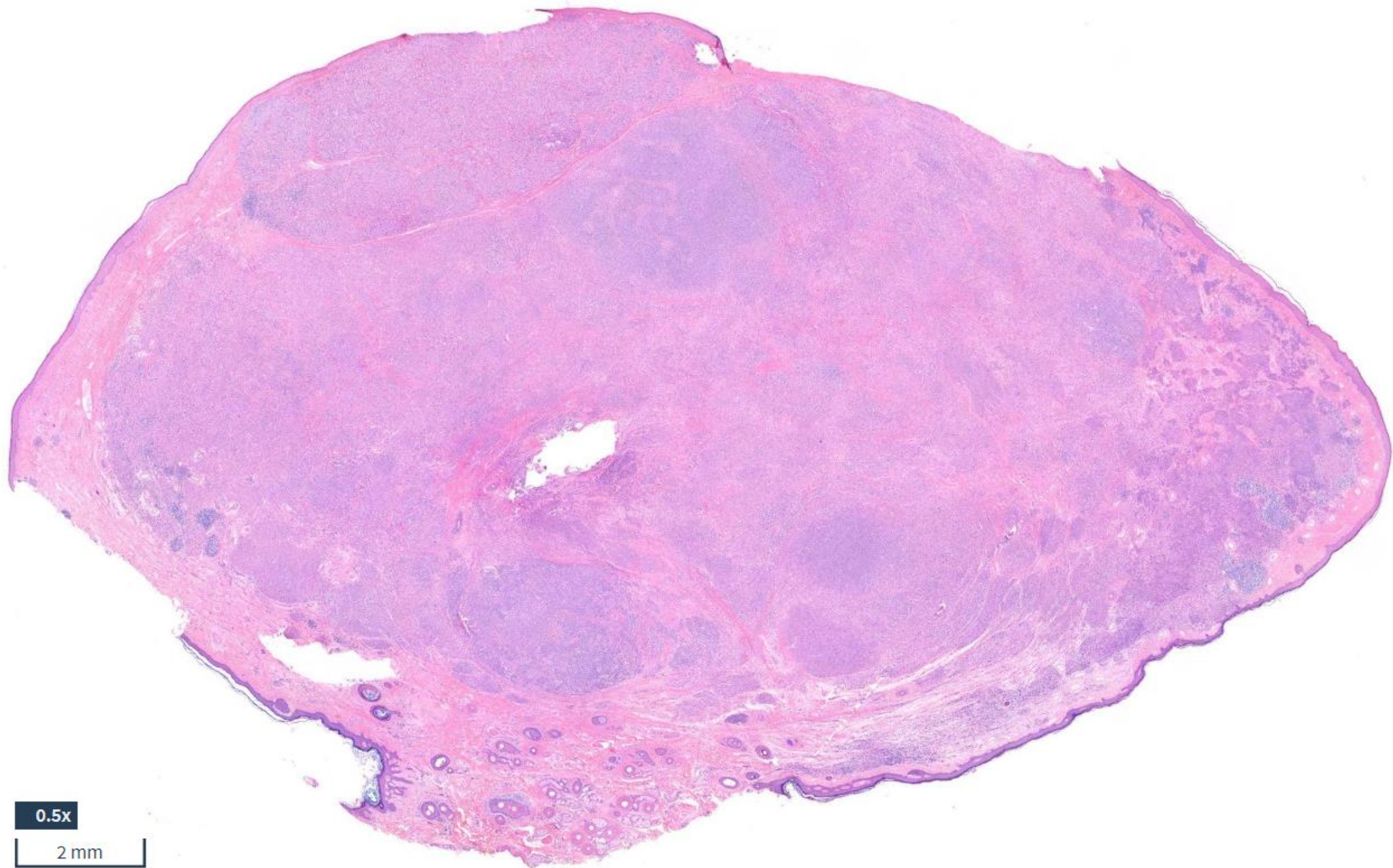
- Mean age 40 years (11-85 years)
- Localized mass with pain, pressure or neurological symptoms
- Cutaneous tumors can mimic melanoma
- 30% are identified as a tumor without symptoms
- 2.5% arise in the skin

## Prognosis

- 35% recur locally
- 44% metastasize, sometimes decades after diagnosis (lung, pleura, bone, liver)
- Only mitotic rate  $> 2/10$  hpf correlates with metastasis
- Surgical treatment, adjuvant radiotherapy remains controversial

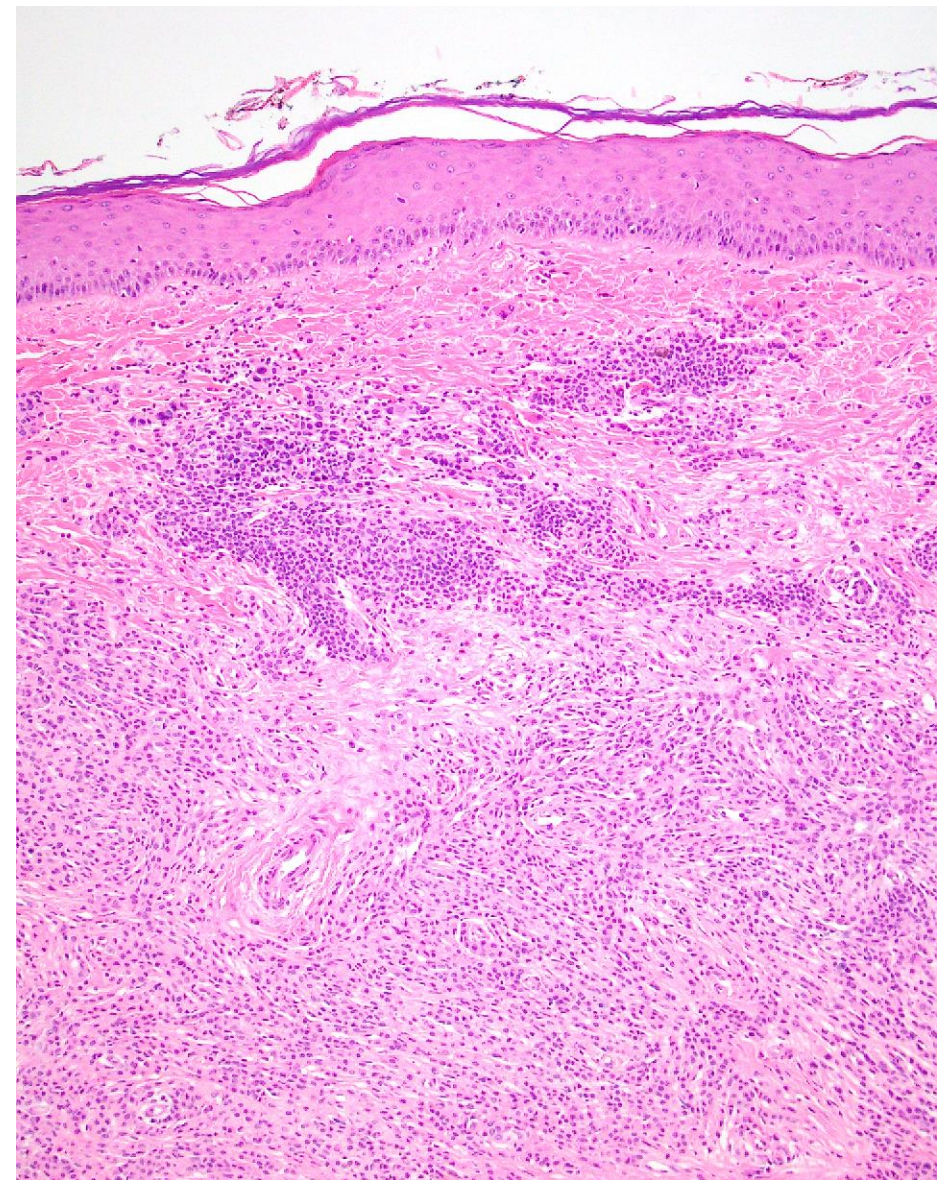
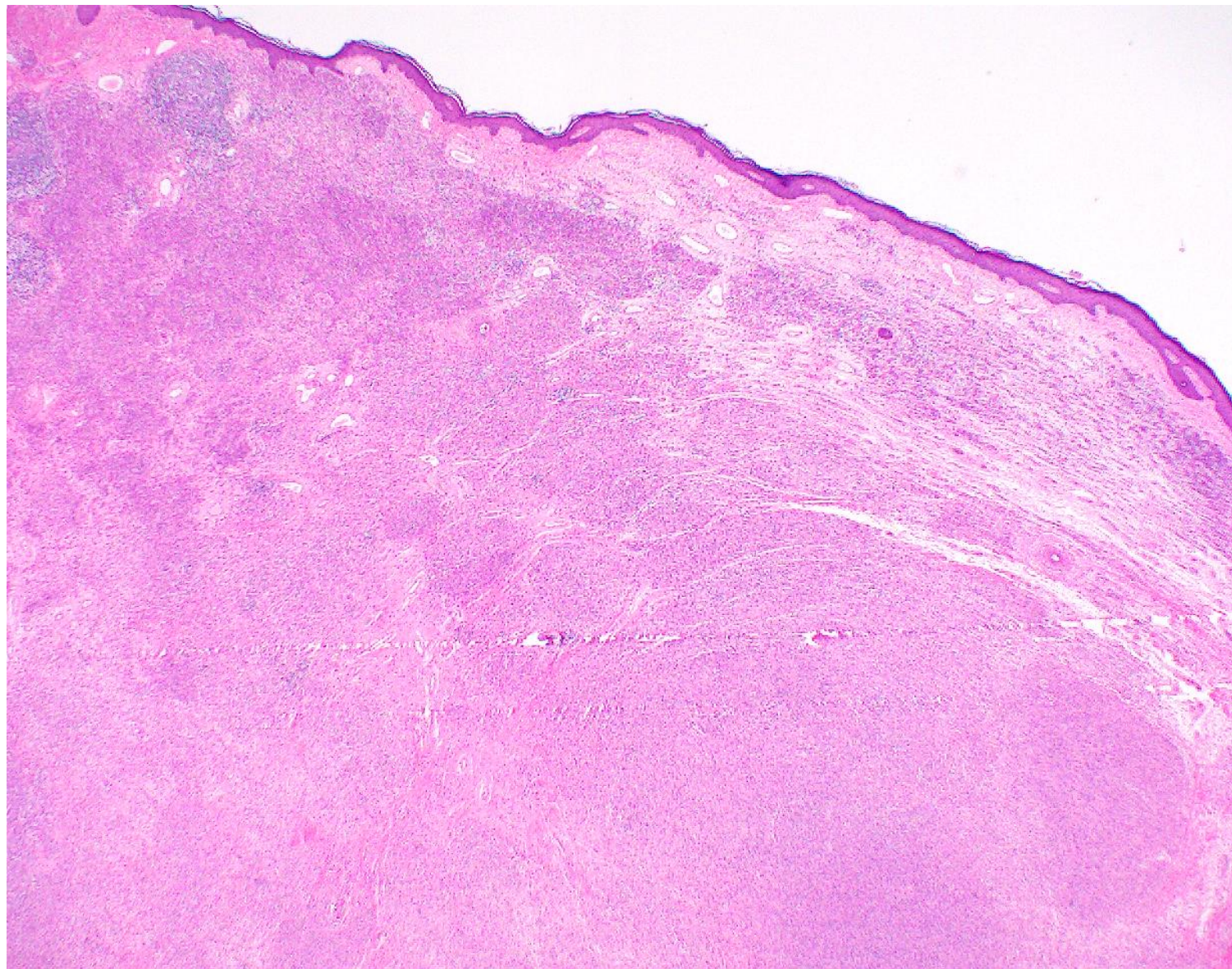
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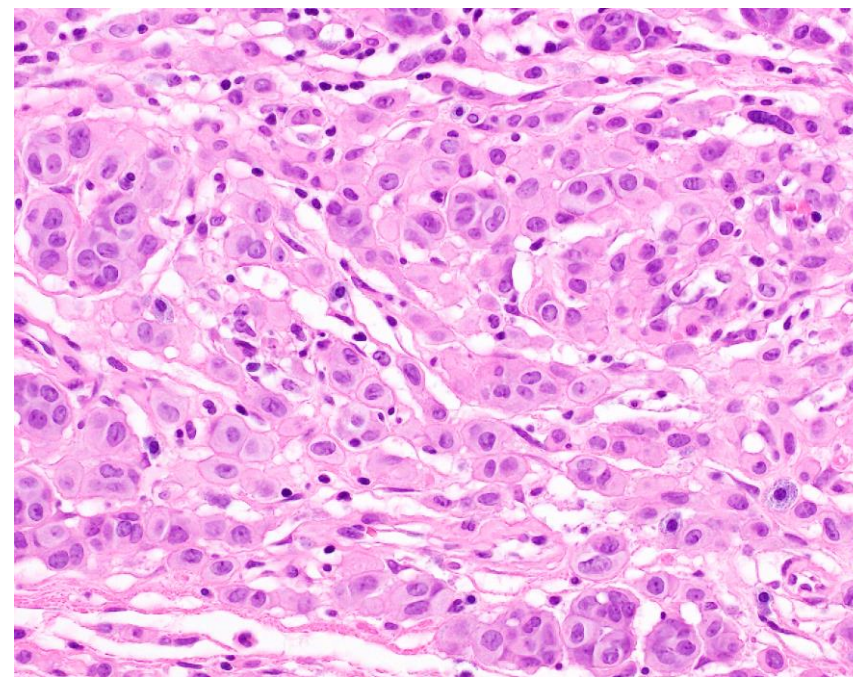
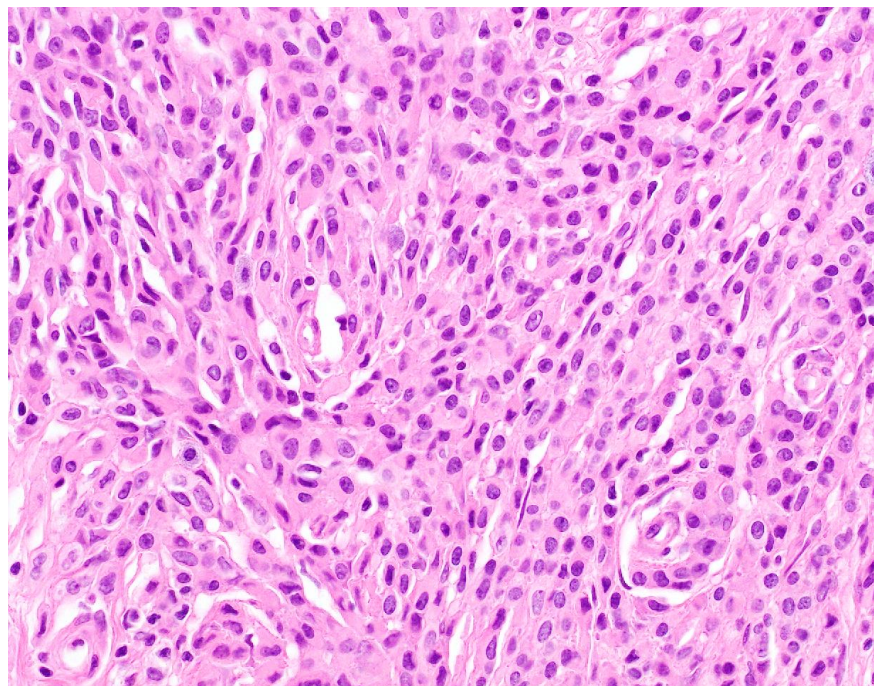
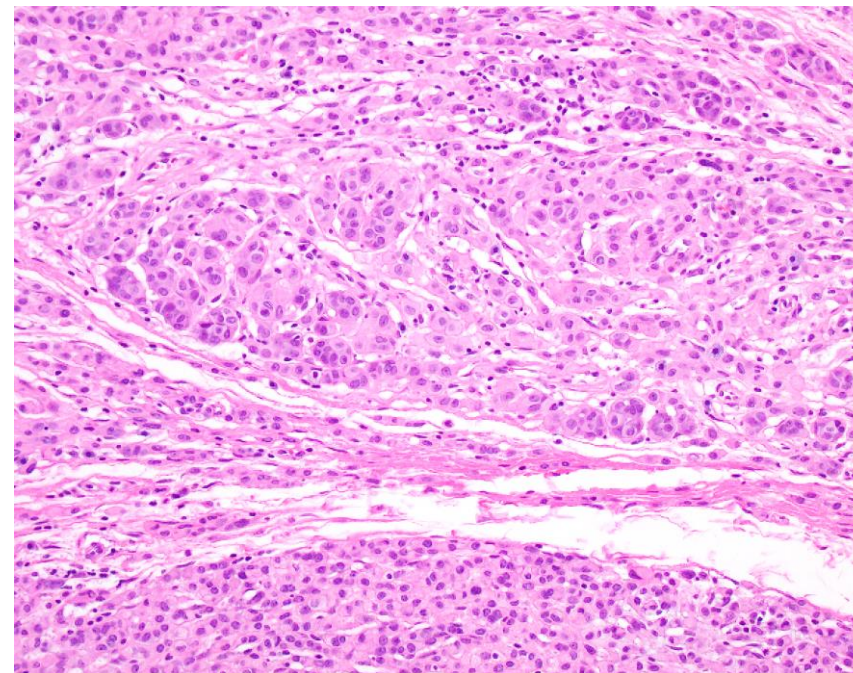
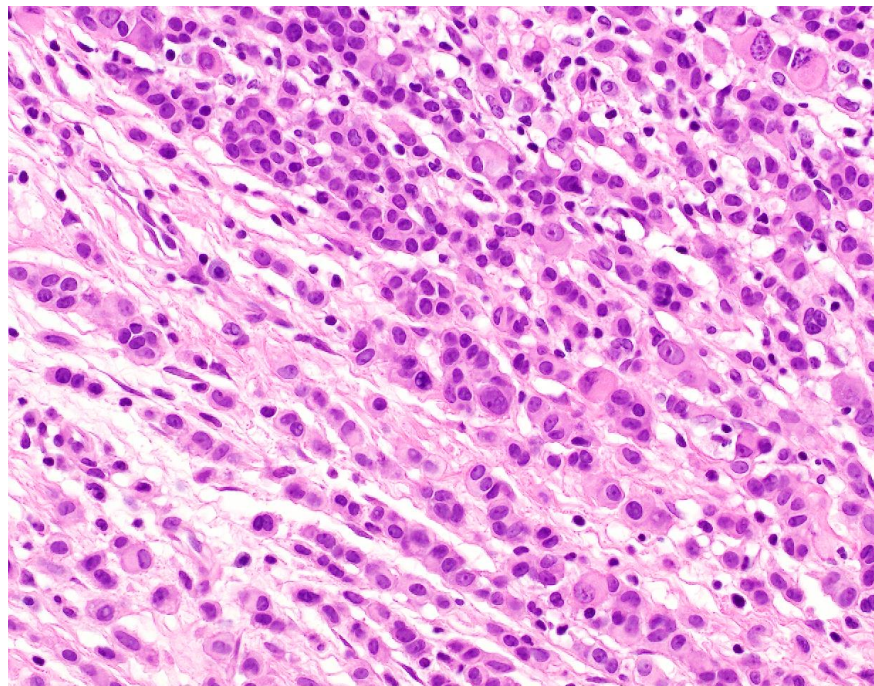
24 year old woman with lesion on occiput

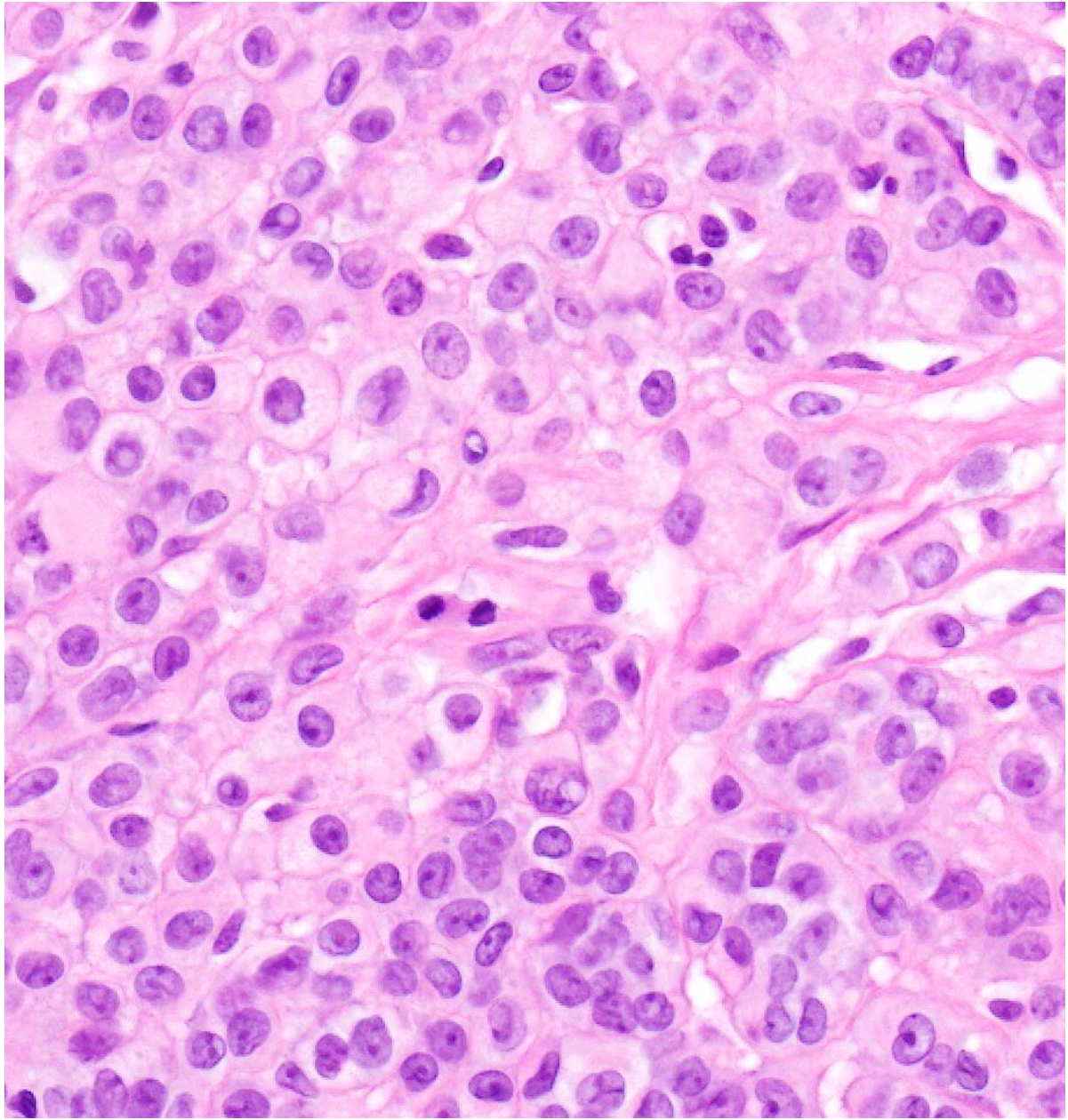
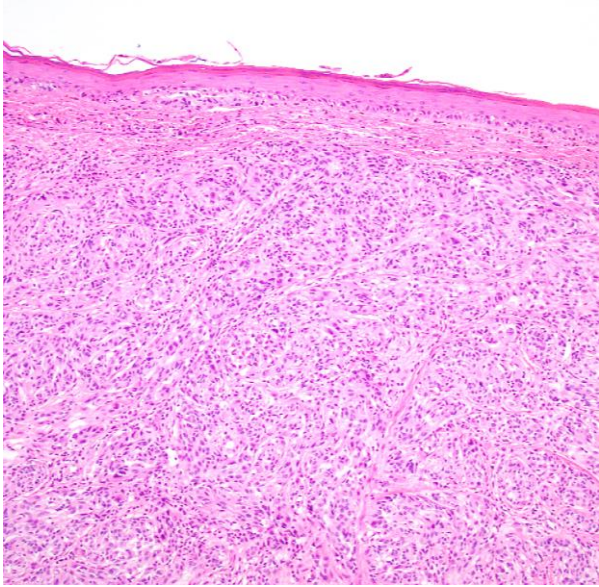
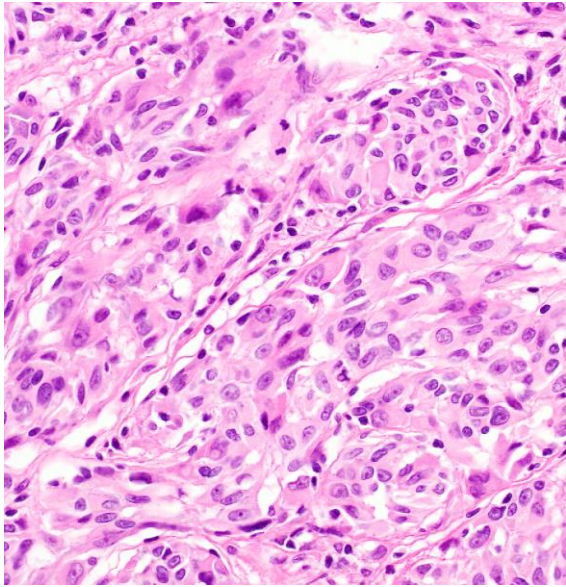
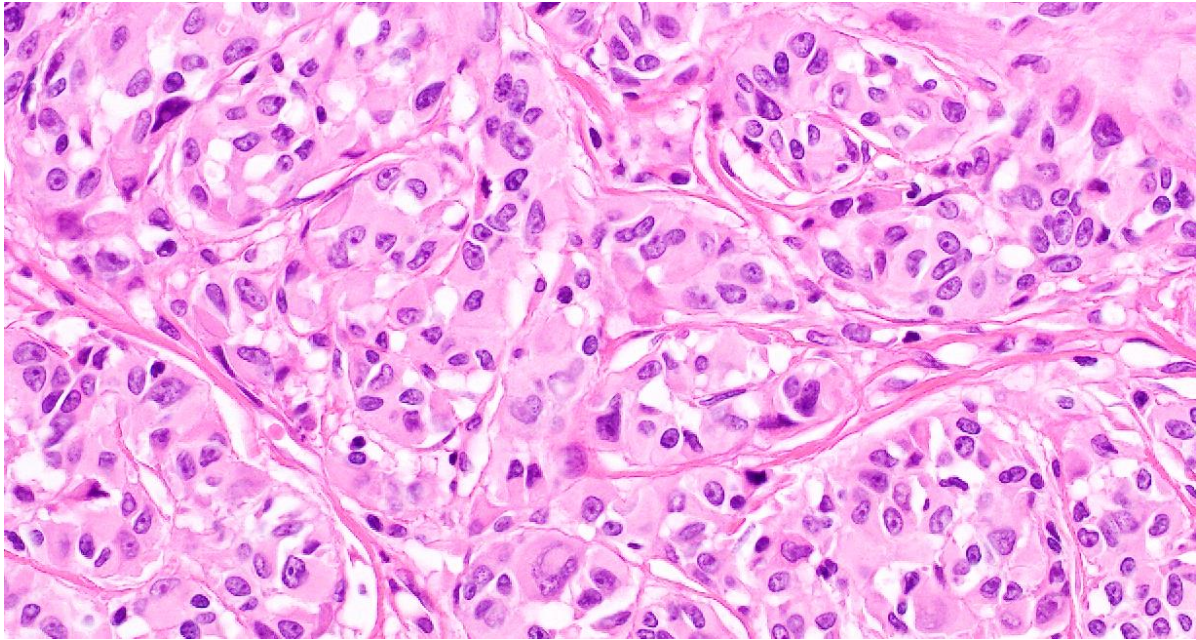


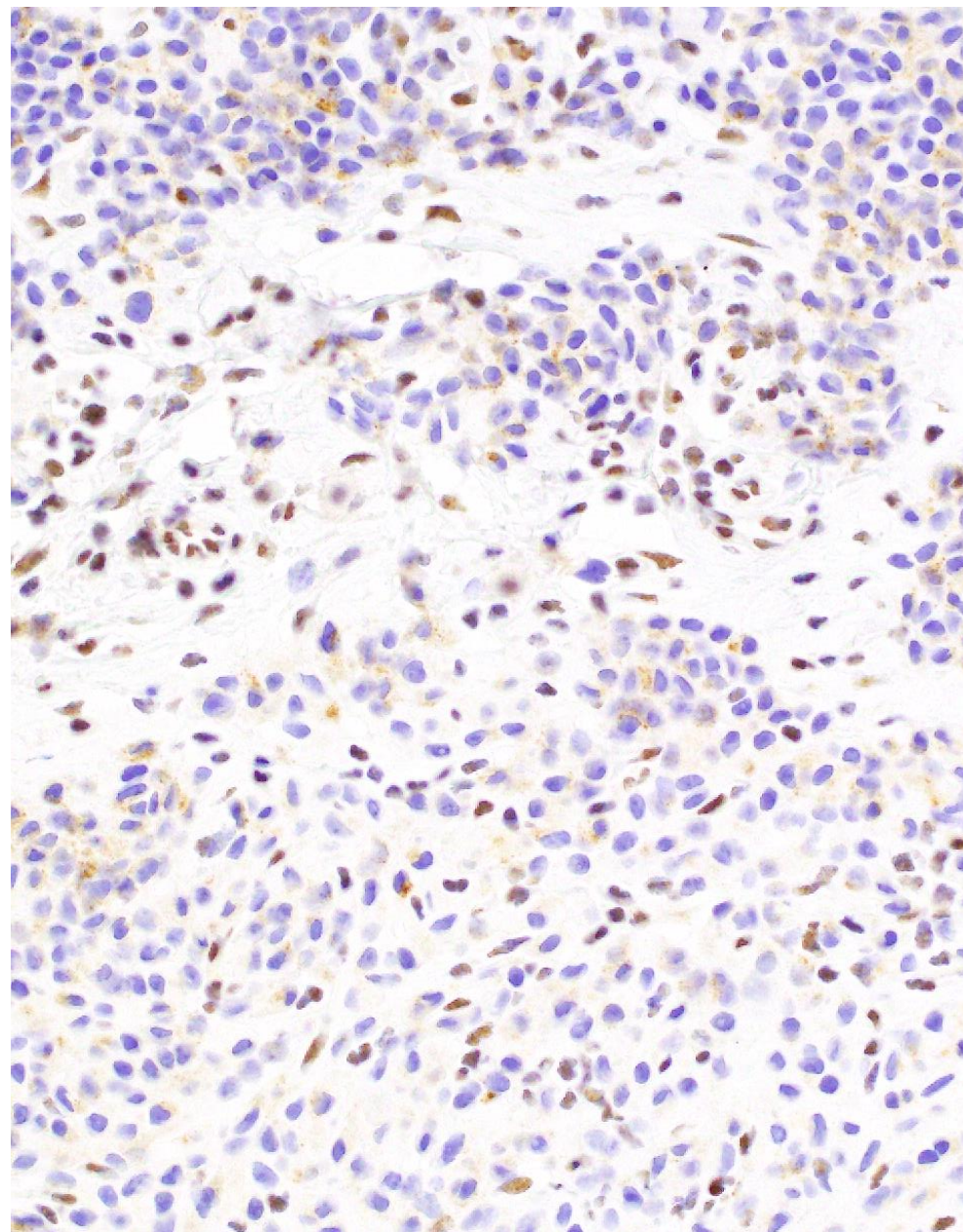
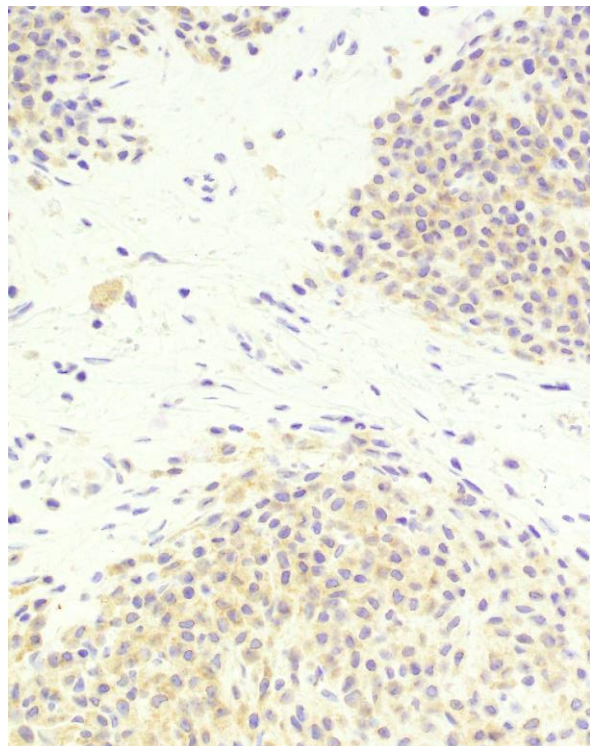
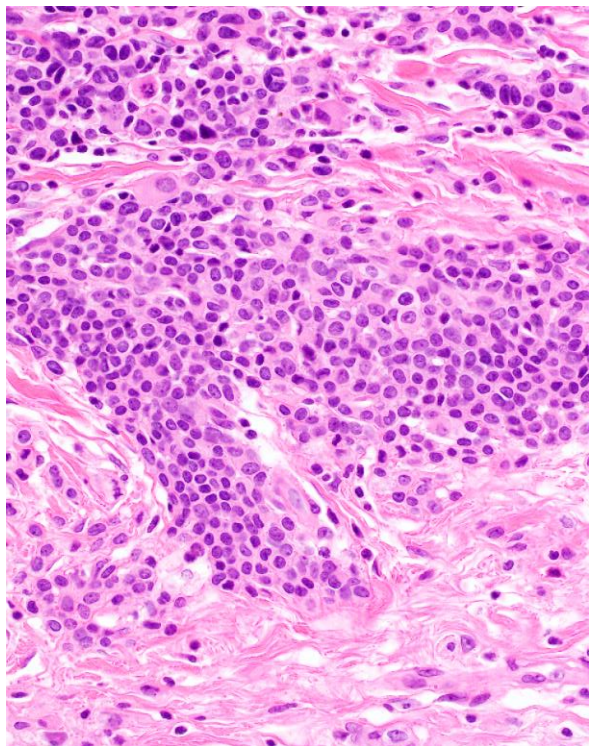
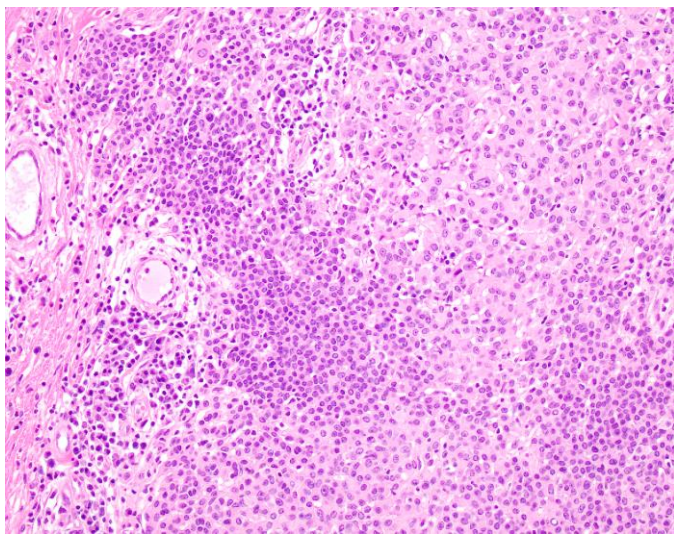
0.5x

2 mm



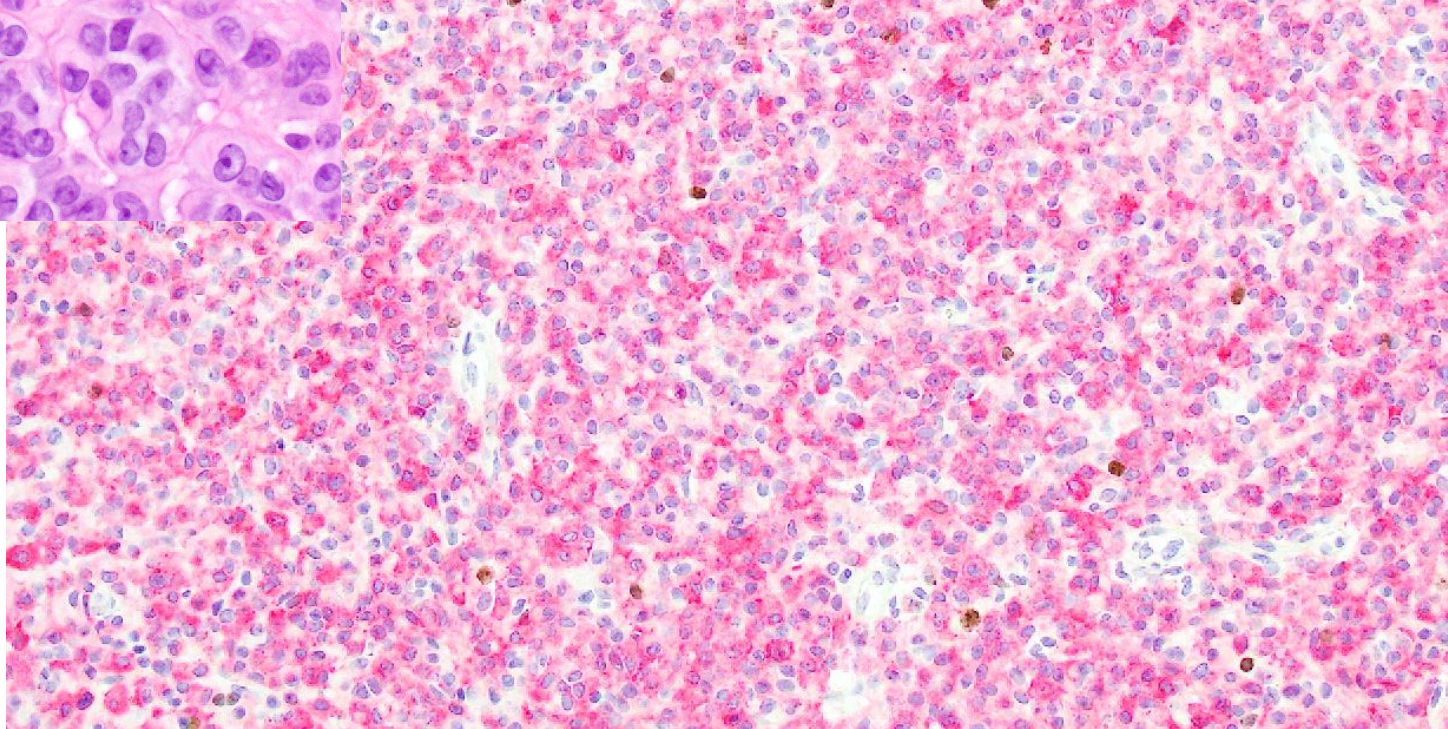
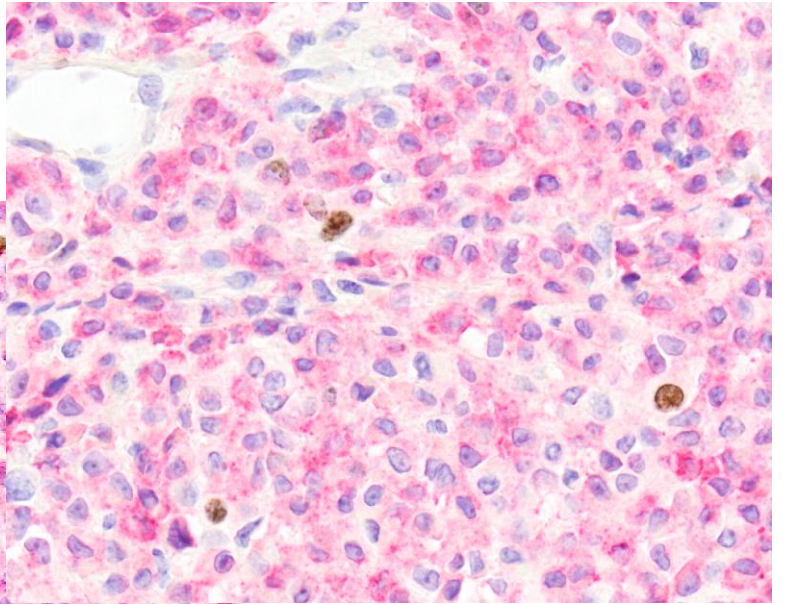
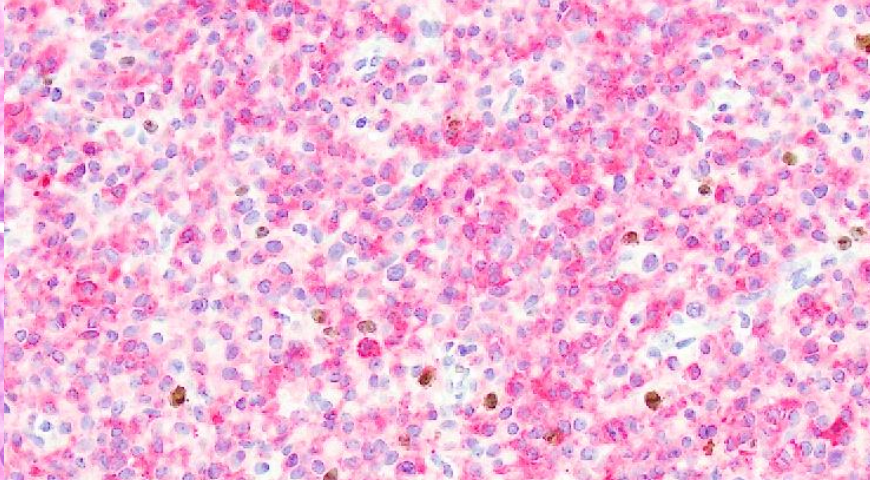
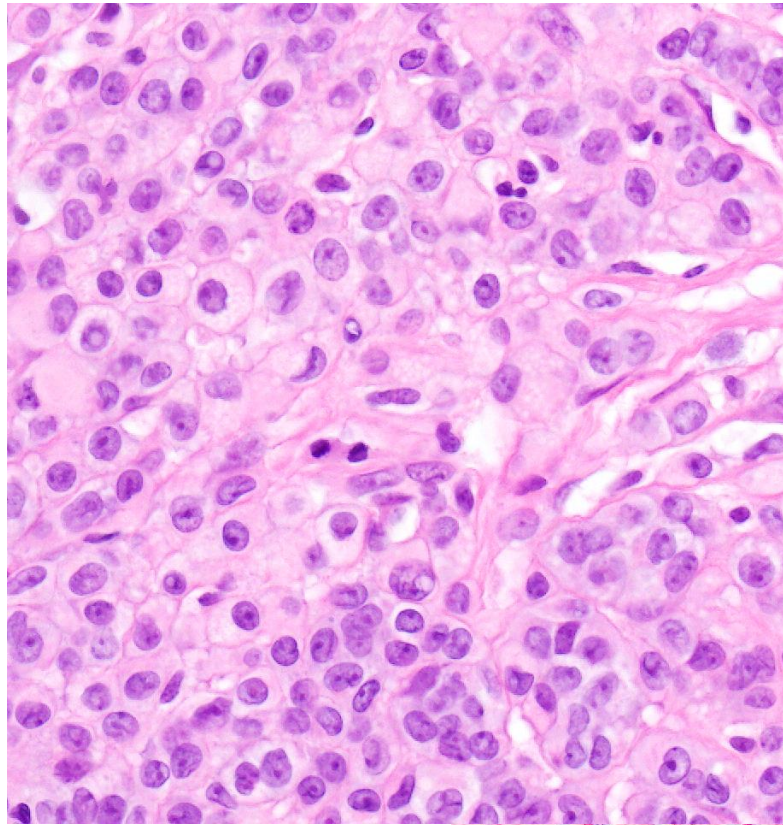




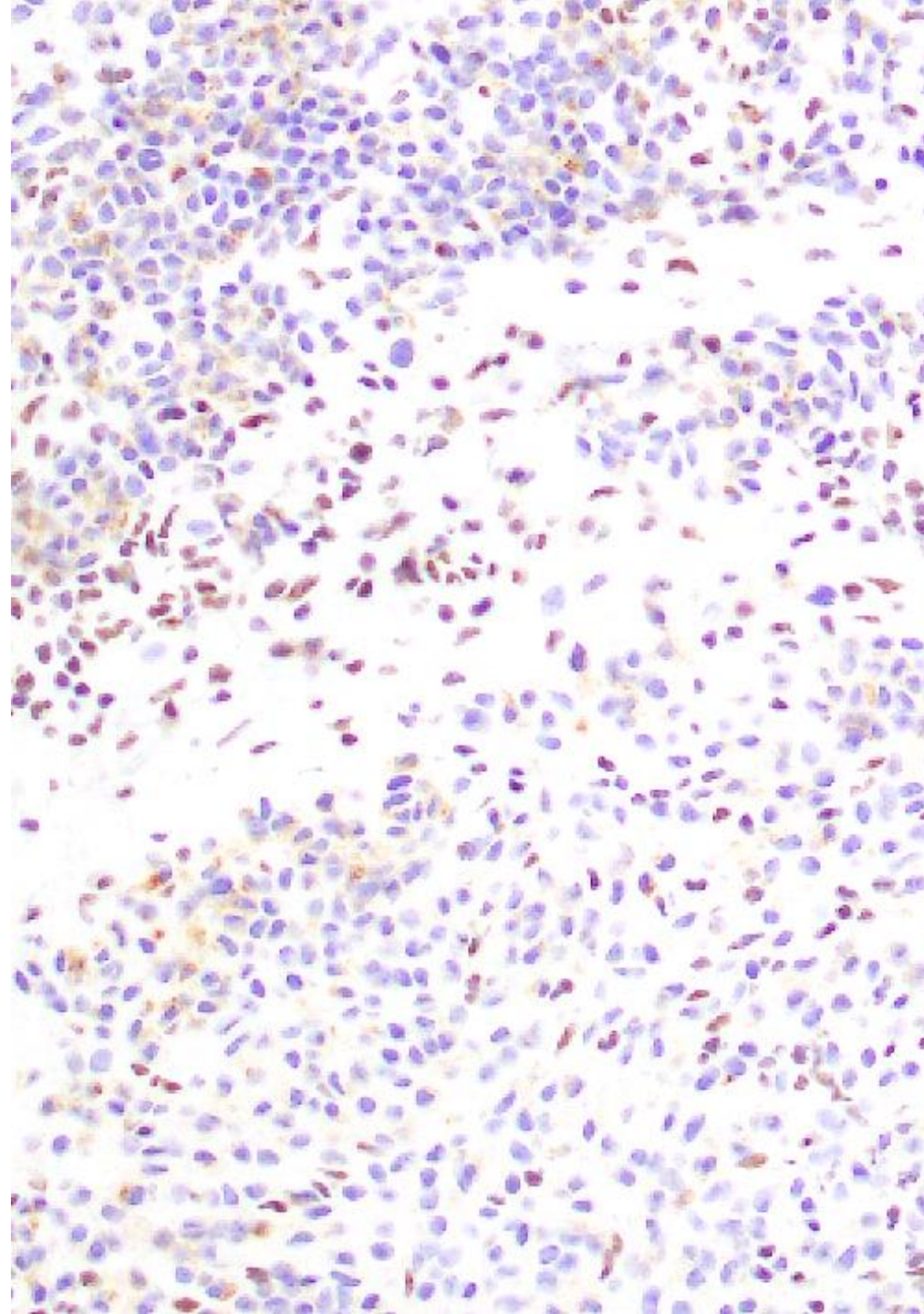


BRAFV600E

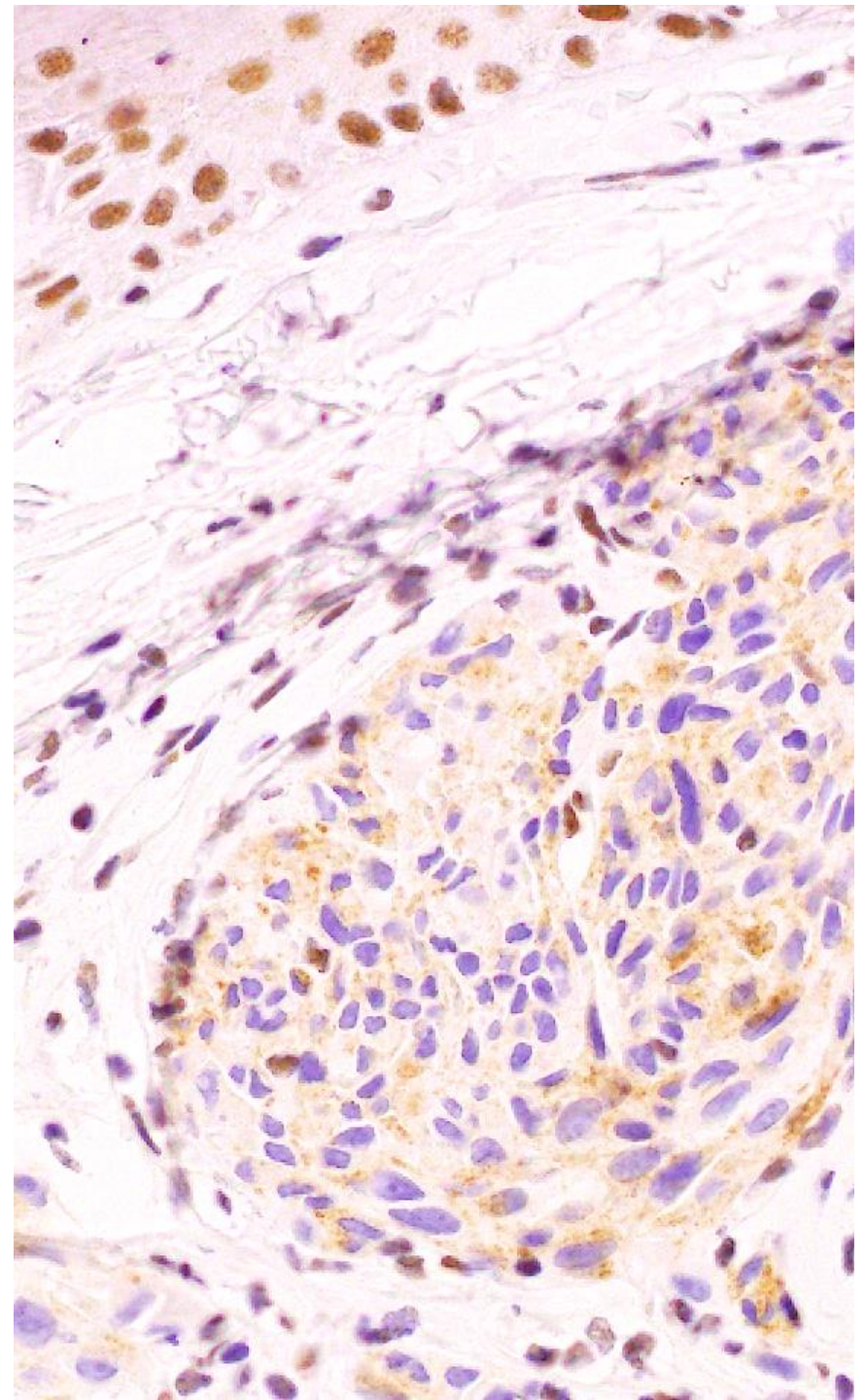
BAP1

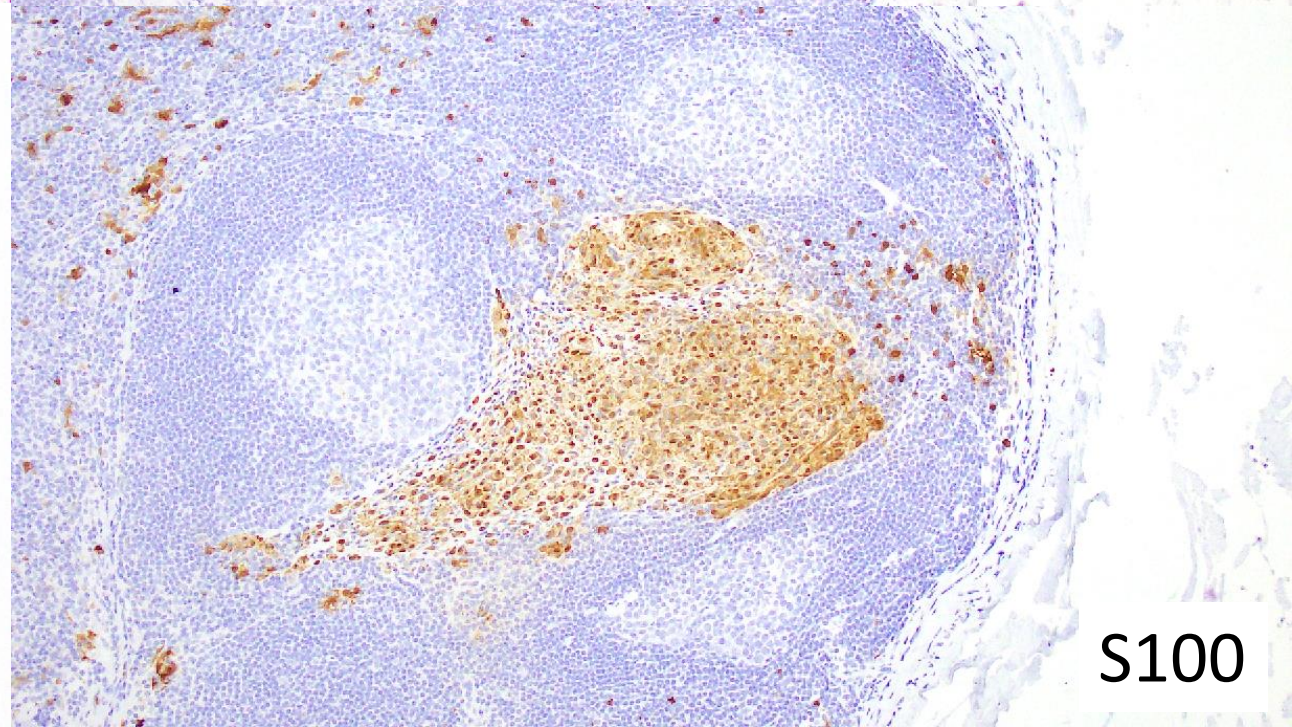
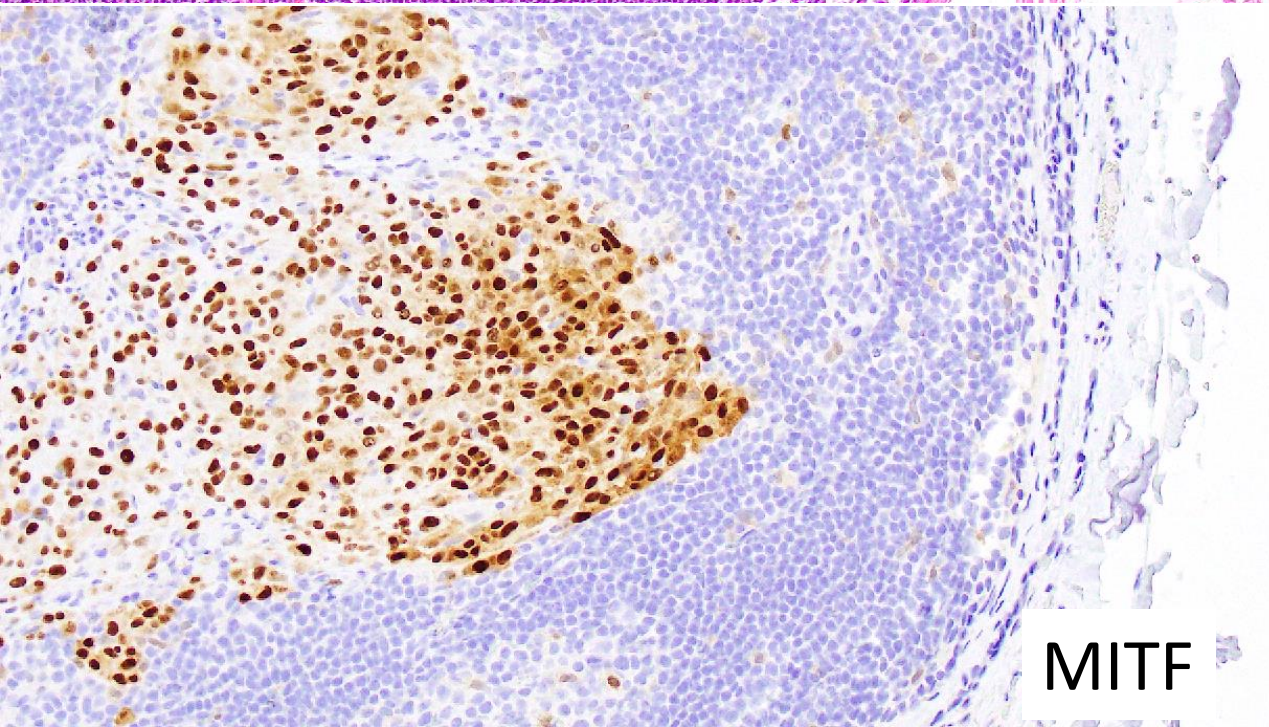
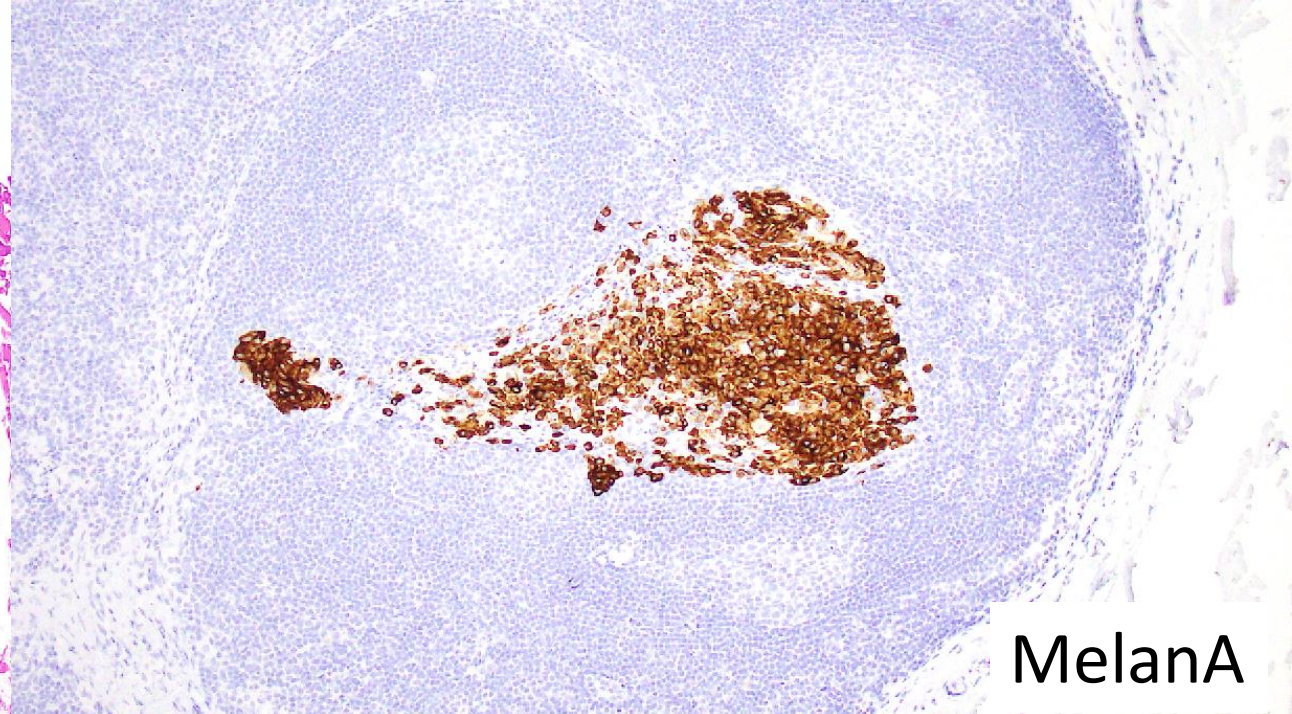
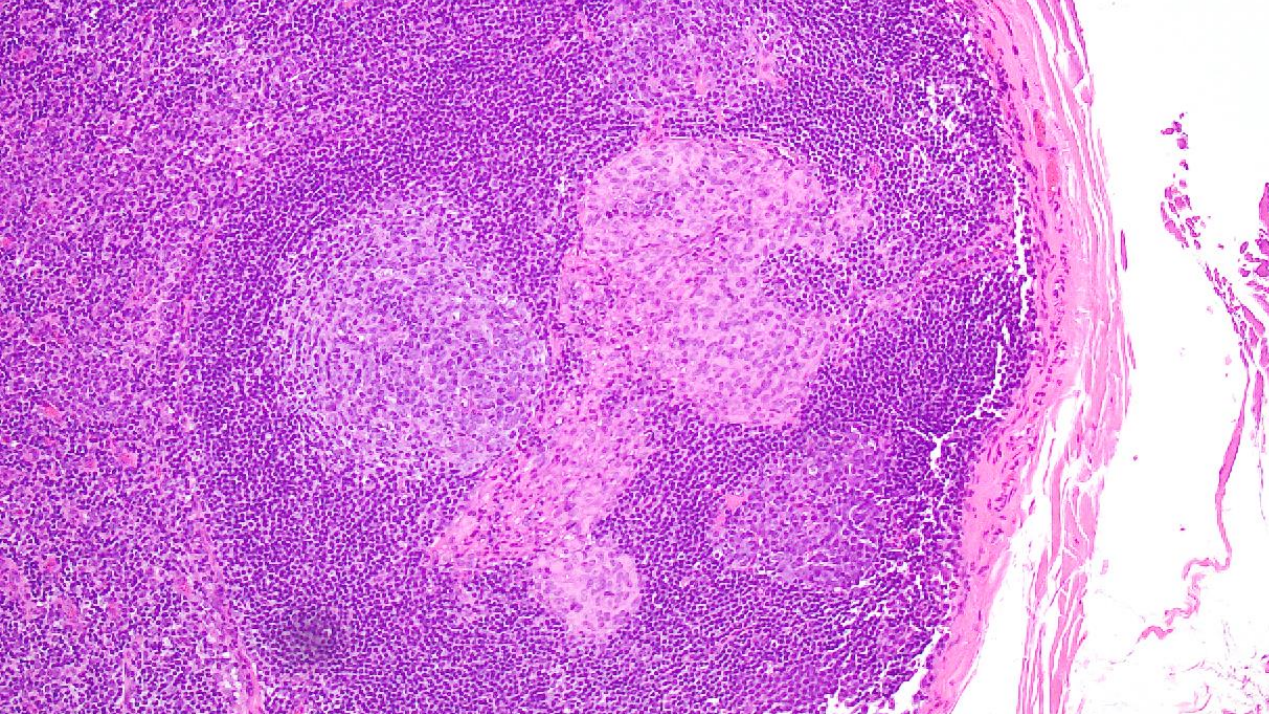


Ki67/MelanA



BAP1





# **BIMT Histopathology –other cutaneous tumors**

## **BAP1 Inactivated Melanoma**

Histopathologically obvious melanoma – mitoses, ulcer, LVI, in situ component, genomic abnormalities by FISH or CGH

## **Blue nevus-like melanoma**

GNAQ and GNA11 mutations

BAP1 loss ~malignant behavior (similar to uveal melanoma)

# BAP1 tumor predisposition syndrome (BAP1-TPDS)

## Genetic counseling and germline testing recommendations:

- Two or more cutaneous BIMT
- Family history of mesothelioma or uveal melanoma

71% (12/17) germline BAP1 mutation using these criterion

0% (0/32) with only one BIMT and no other malignancy history

*Cabaret & de la Fouchardiere et al. Genes Chromosomes Cancer. 2017*

## Known tumor associations include:

Uveal melanoma 28-36%

Mesothelioma 22-36%

Cutaneous melanoma 18-43%

Cutaneous BIMT 17%

Basal cell carcinoma 14%

Renal cell carcinoma 9%

.... also meningioma, lymphoma, cholangiocarcinoma  
carcinoma of the colon, breast, thyroid, prostate,  
pancreas, lung