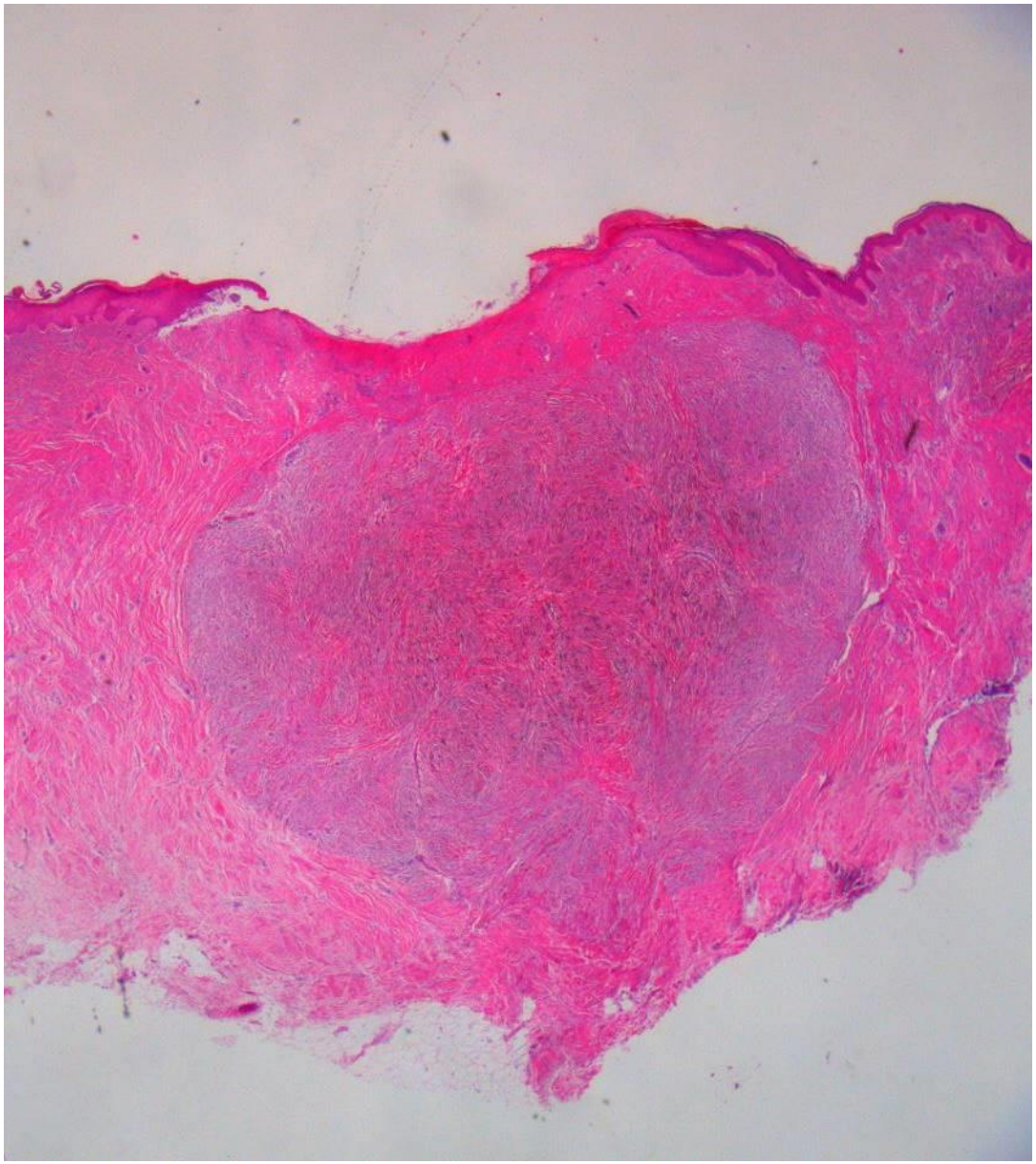
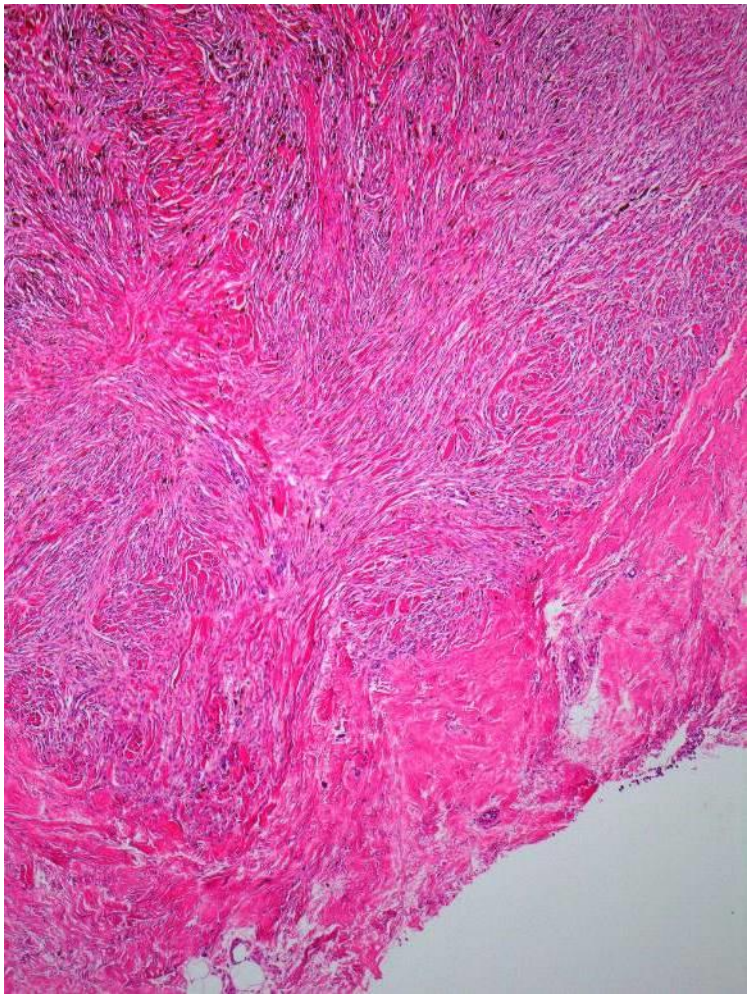
Liverpool Dermatopathology Update: Case Presentation

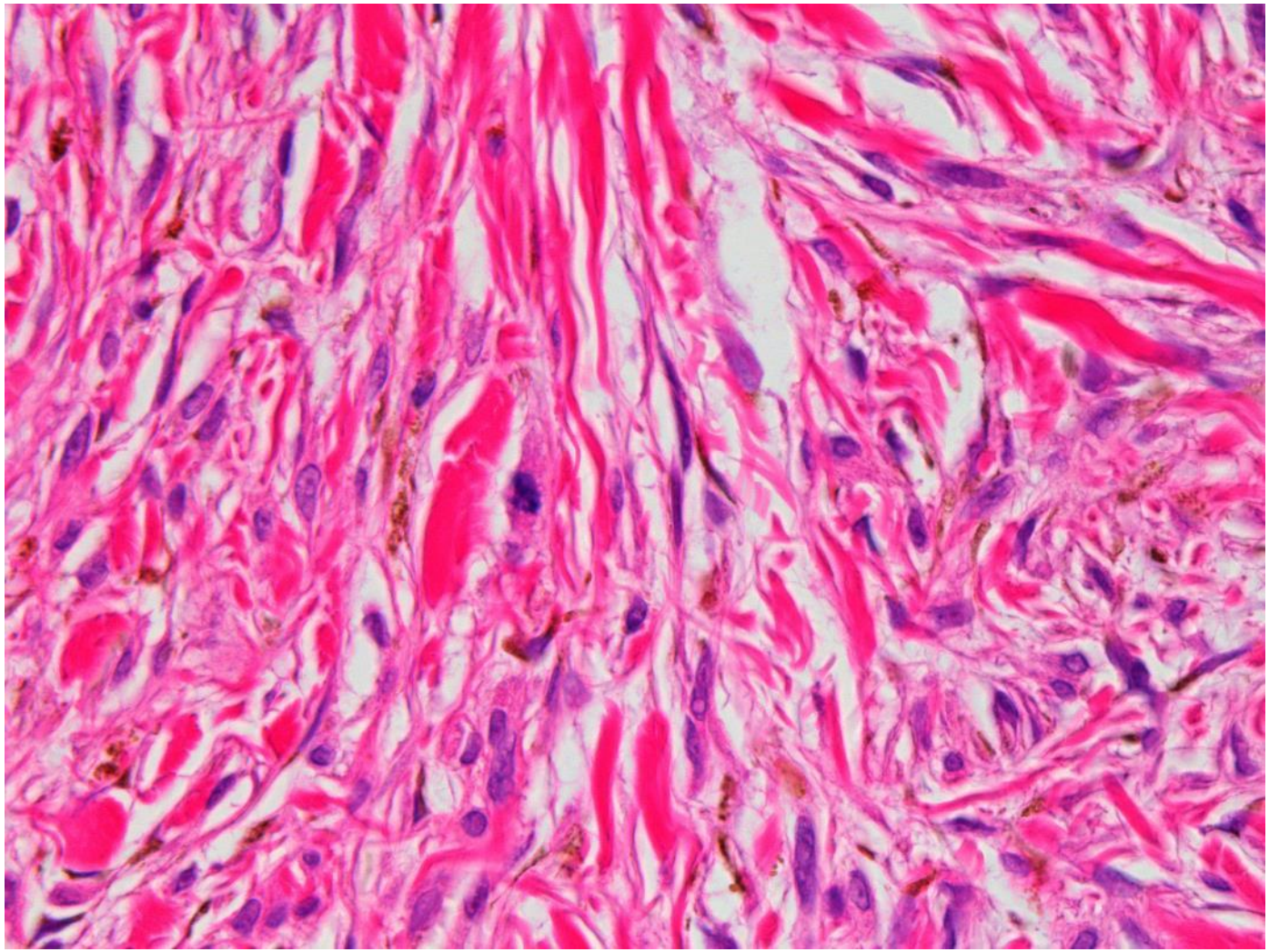
Dr P Shenjere

The Christie NHS Foundation Trust

- PS1. 60M. Excision cyst right shoulder. Cyst previously removed. ?Recurrence.

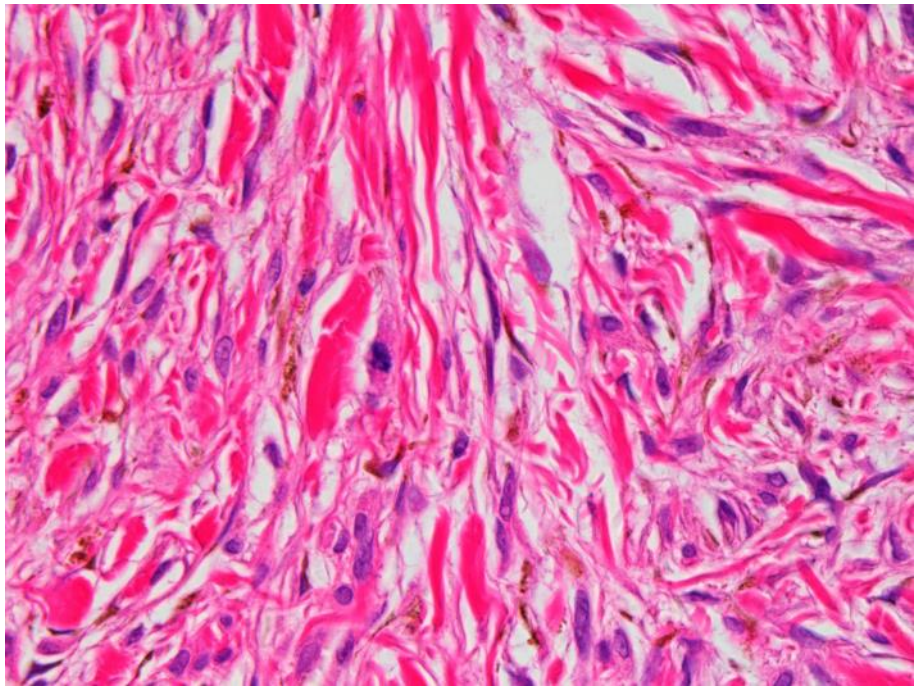






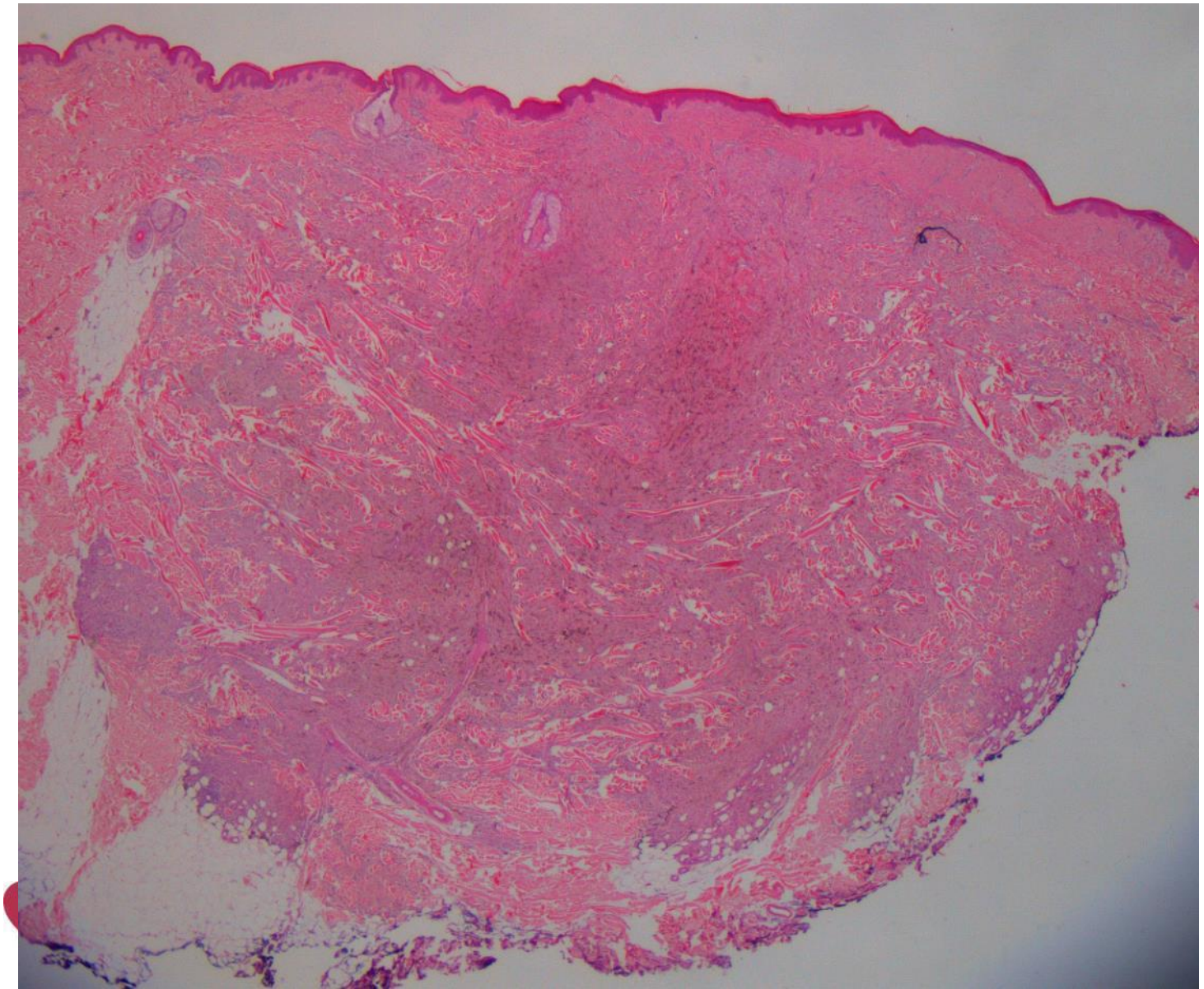
Report of previous excision: “Cellular blue naevus”

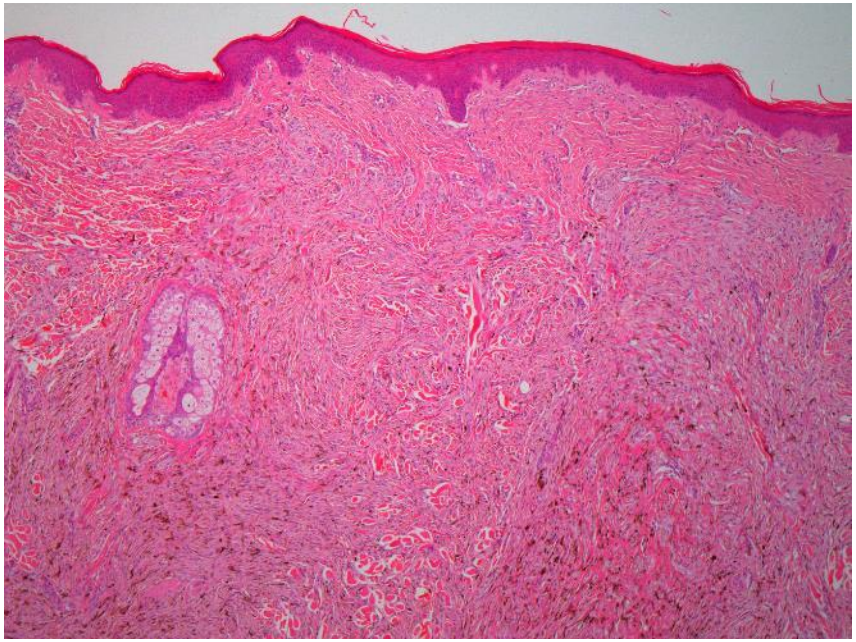
- ? Recurrent blue naevus
- ? Recurrent/metastatic melanoma with blue naevus-like features

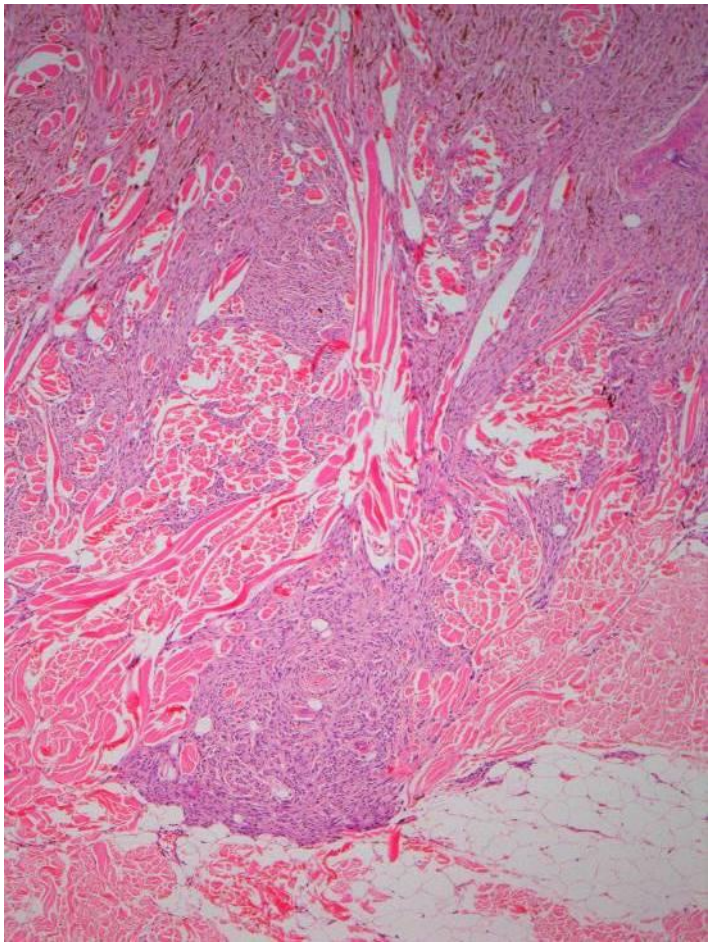


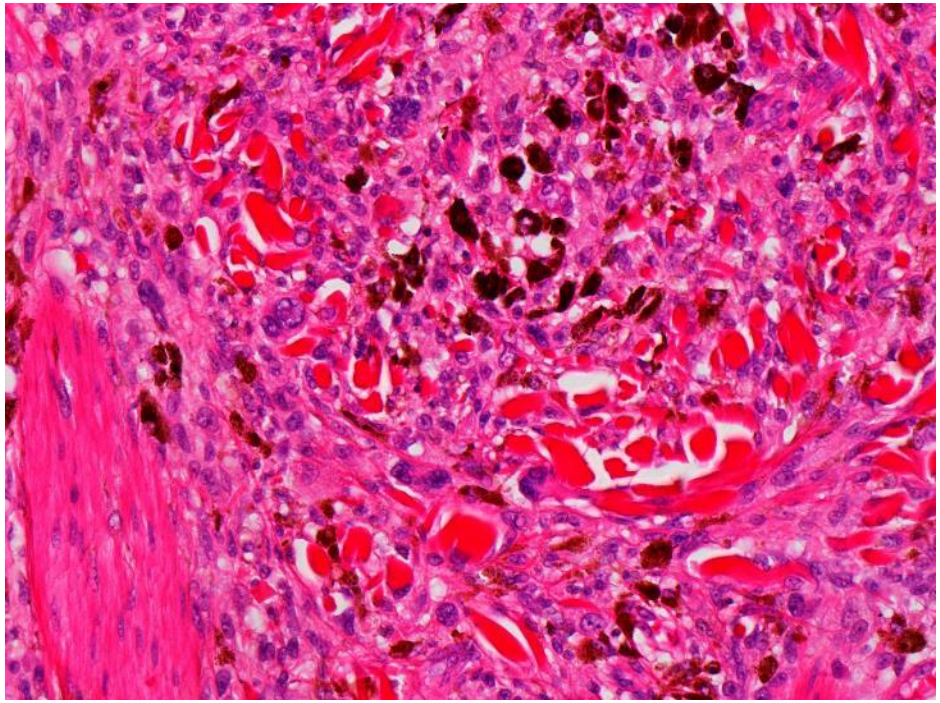
- Request material from previous resection for review

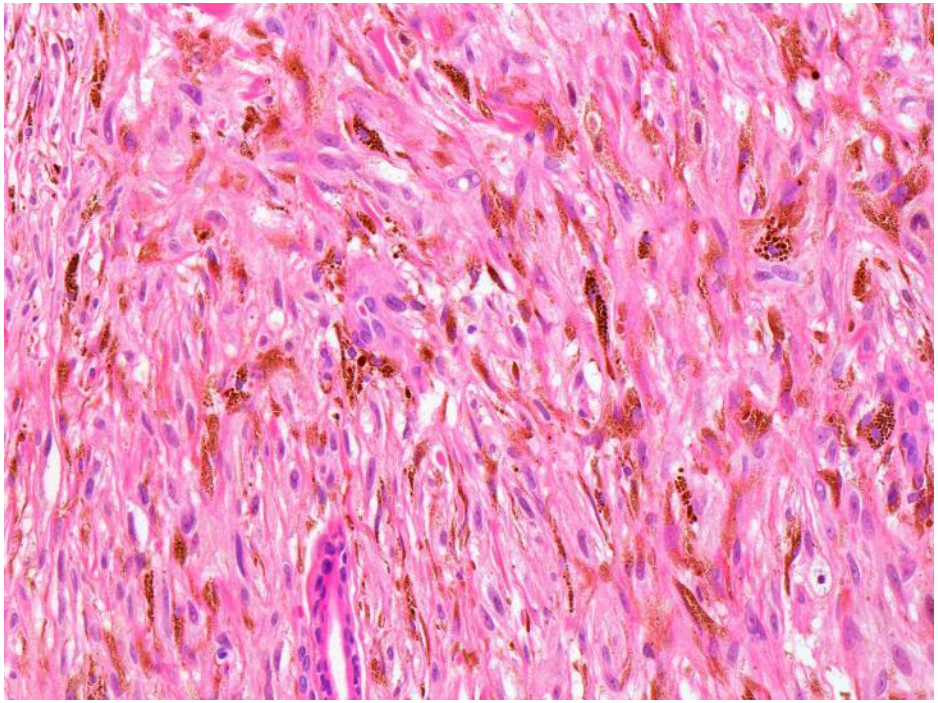
Lesion excised 5yrs before

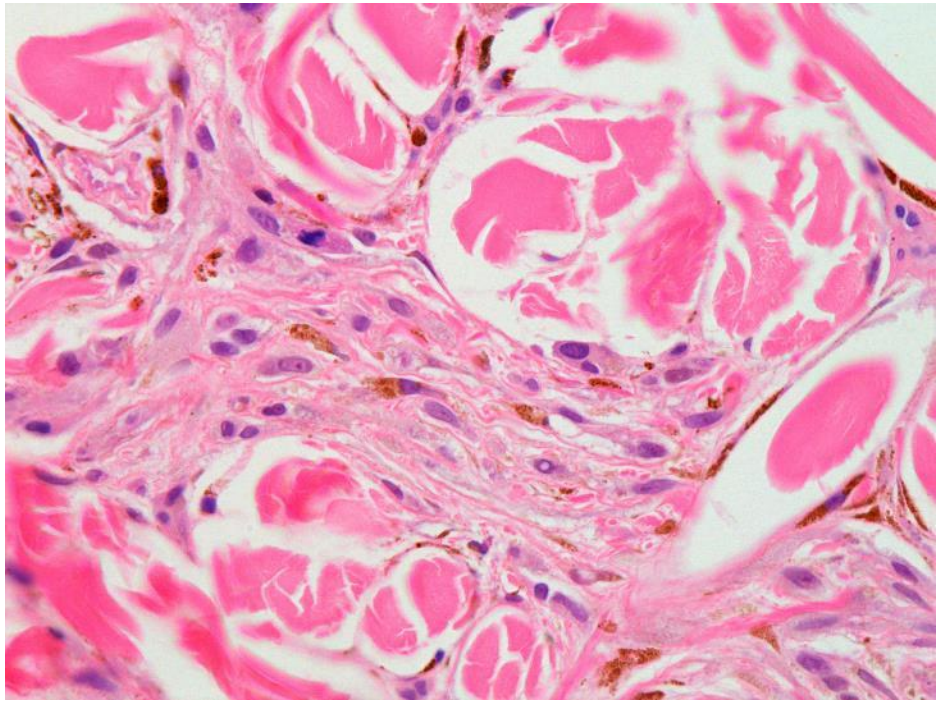


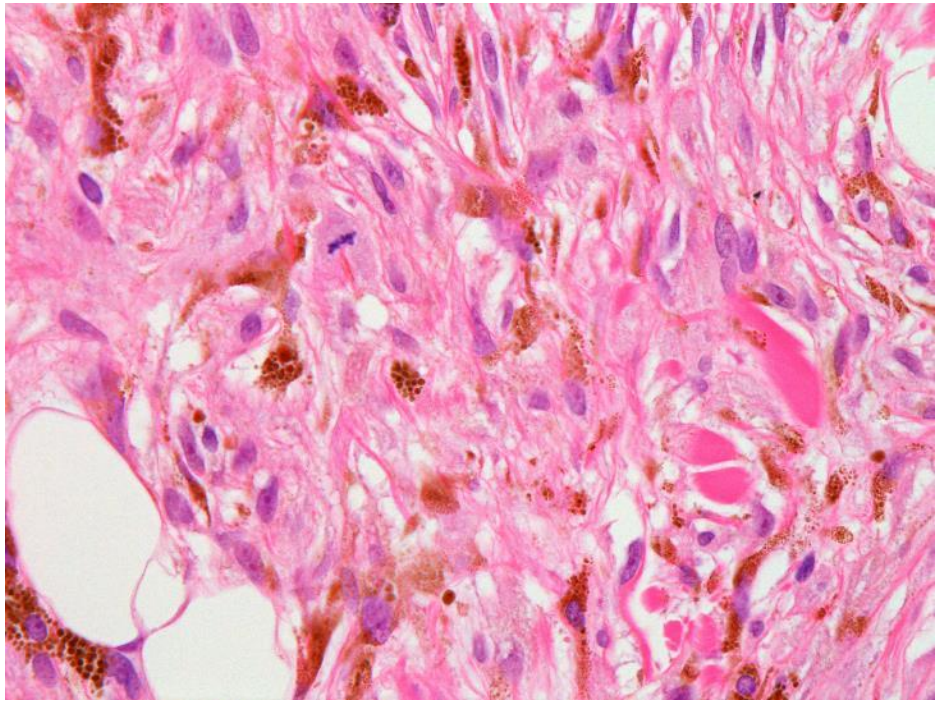


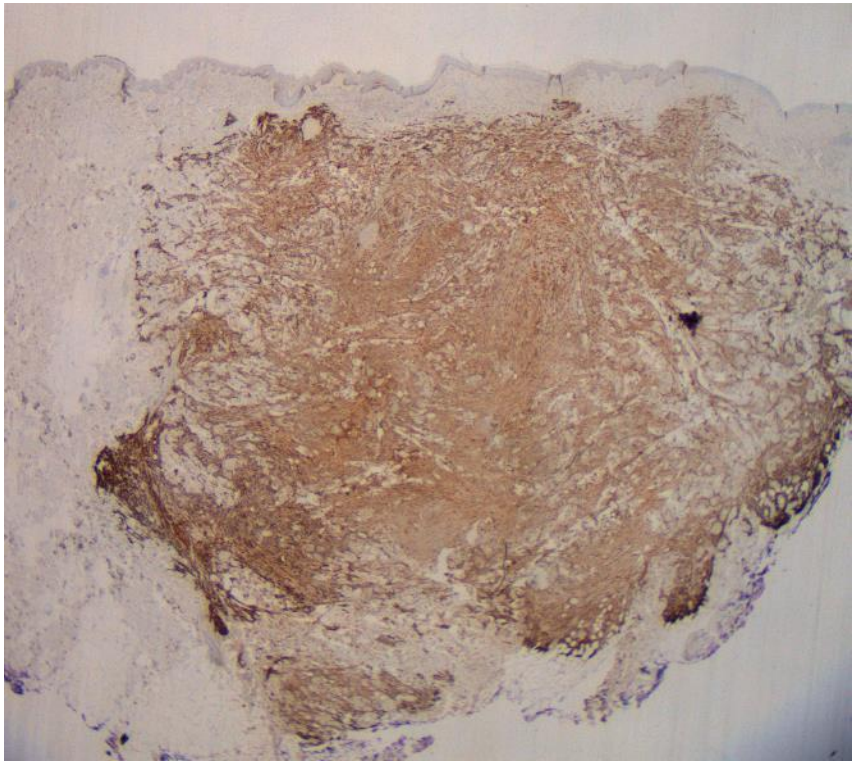


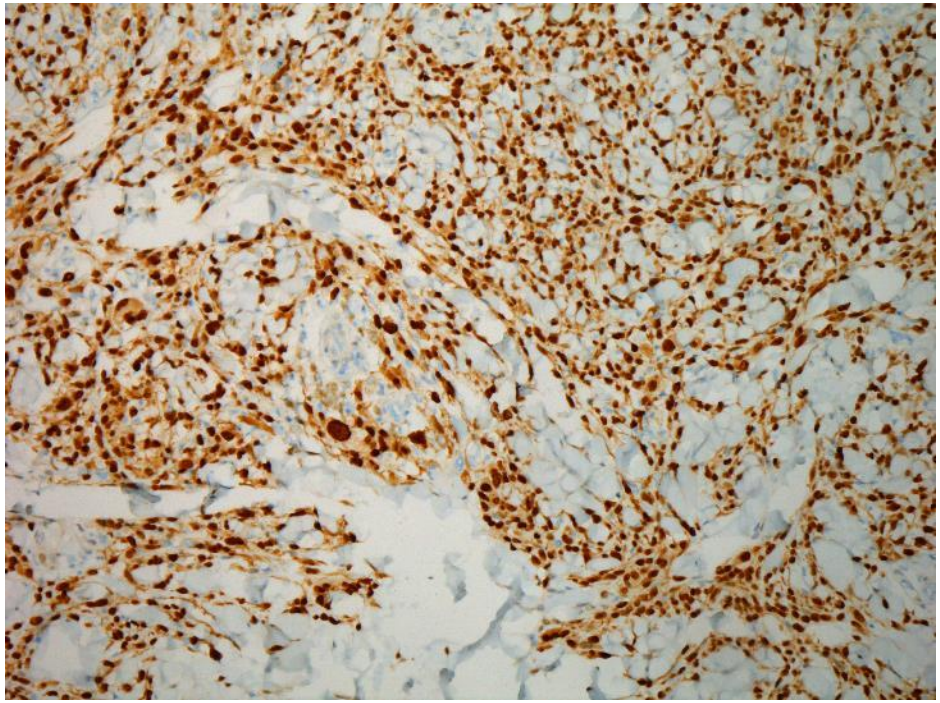




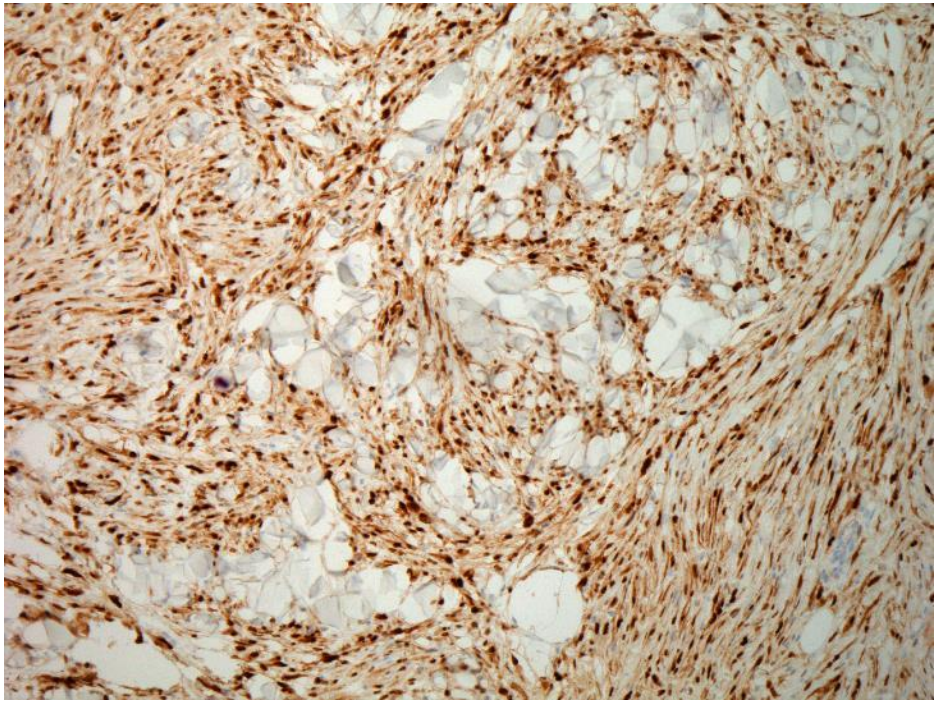






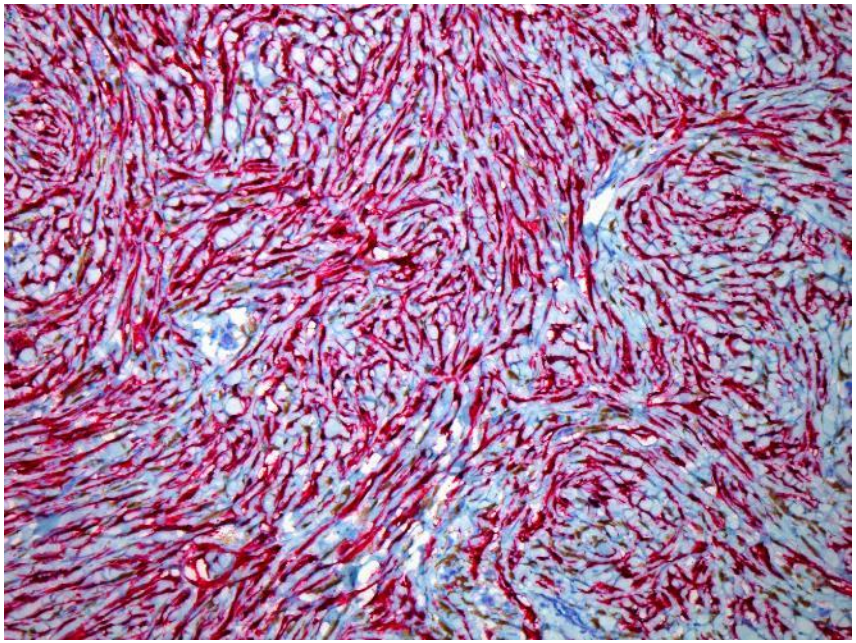


Cyclin D1

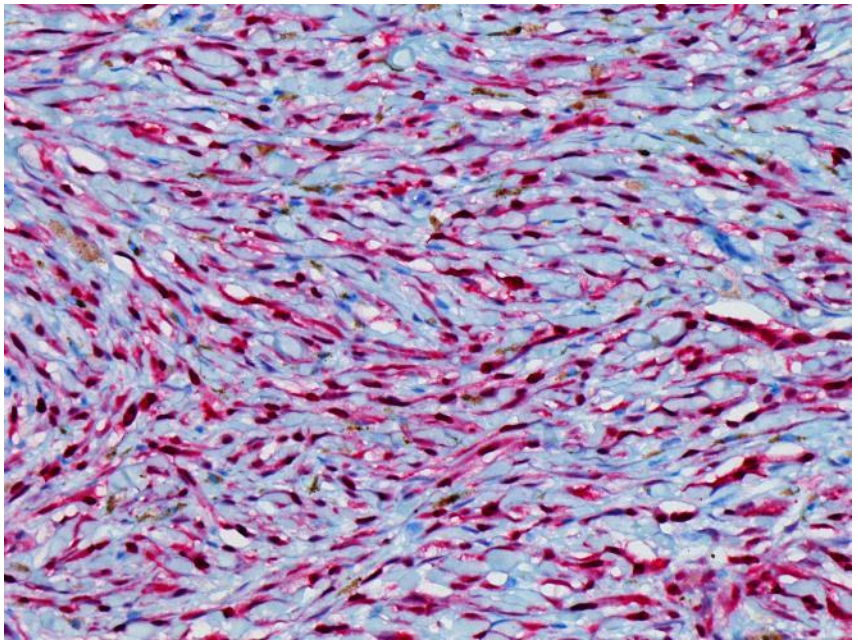


B-catenin

Recurrent lesion



B-catenin



Cyclin-D1

β-Catenin nuclear expression discriminates deep penetrating nevi from other cutaneous melanocytic tumors

Arnaud de la Fouchardière et al. Virchows Arch. 2019 May; 474(5):539-550

Abstract

Recent advances in genomics have improved the molecular classification of cutaneous melanocytic tumors. Among them, deep penetrating nevi (DPN) and plexiform nevi have been linked to joint activation of the MAP kinase and dysregulation of the β-catenin pathways. Immunohistochemical studies have confirmed cytoplasmic and nuclear expression of β-catenin and its downstream effector cyclin D1 in these tumors. We assessed nuclear β-catenin immunohistochemical expression in a large group of DPN as well as in the four most frequent differential diagnoses of DPN: “blue” melanocytic tumors, Spitz tumors, nevoid and SSM melanomas, and pigmented epithelioid melanocytomas (PEM). **Nuclear β-catenin expression was positive in 98/100 DPN** and 2/16 of melanomas (one SSM and one nevoid melanoma with a plexiform clone) and **was negative in all 30 Spitz, 26 blue, and 6 PEM lesions.** In 41% DPN, β-catenin expression was positive in more than 30% nuclei. No differences were observed in cytoplasmic and nuclear cyclin D1 expression between these tumor groups, suggesting alternate, β-catenin-independent, activation pathways. We have subsequently studied nuclear β-catenin expression in a set of 13 tumors with an ambiguous diagnosis, for which DPN was part of the differential diagnosis. The three out of four patients showing canonical DPN mutation profiles were the only β-catenin-positive cases. We c**onclude that nuclear β-catenin expression, independently from CCND1 expression, in a dermal melanocytic tumor is an argument for its classification as DPN. In ambiguous cases and in early combined DPN lesions, this antibody can be helpful as a screening tool.** β-Catenin is also potentially expressed in a subset of malignant melanomas with CTNNB1 mutations.

- ? Recurrent/persistent Atypical deep penetrating naevus/melanocytoma

- ?Melanoma with DPN-like morphology (MM with plexiform pattern)

Deep Penetrating Naevus (DPN)

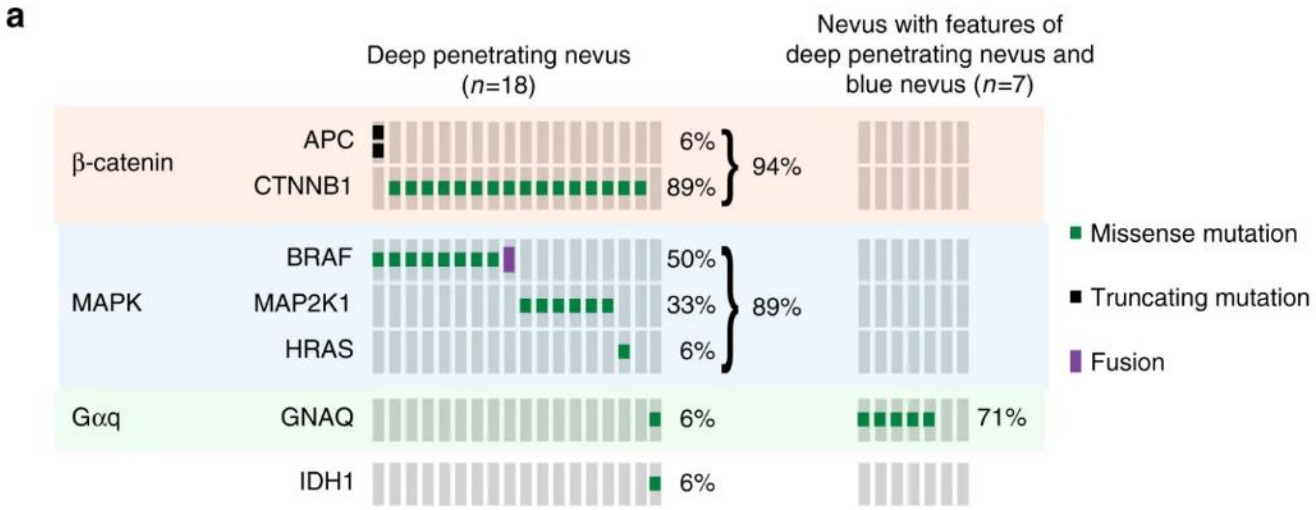
- First described by Helwig and colleagues at the AFIP in 1989
- Clinically appear as dark brown or blue papules
- Head & neck ~ 35%
- Trunk ~ 25%
- Upper extremities ~ 20.5%

DPN

- Loosely organised nests and fascicles of pigmented melanocytes with atypical vesicular nuclei
- Often involve deep reticular dermis with extension down neurovascular bundles and adnexal structures
- Many melanophages & lymphocytes
- No maturation with depth
- A significant proportion of cases occur as parts of combined naevi

- Clinically and morphologically can closely resemble blue naevi (BN)
- DPN not genetically related to BN as they do not harbour activating mutations in the G alpha Q pathway (mutations in GNAQ most common and mutations in GNA11 present in a minority of cases)
- DPN have activating mutations in BRAF, MAP2K1 or less commonly HRAS
- DPN have concomitant genetic activation of beat-catenin pathway – most commonly due to missense mutations in CTNNB1 exon 3
- A few cases have beta-catenin activation by an alternative mechanism – inactivation of the tumour suppressor APC

From: Combined activation of MAP kinase pathway and β-catenin signaling cause deep penetrating nevi



Yeh I, et al
Nat Commun. 2017 Sep 21; 8(1):644

- DPN have concomitant genetic activation of beat-catenin pathway – most commonly due to missense mutations in CTNNB1 exon 3
- A few cases have beta-catenin activation by an alternative mechanism – inactivation of the tumour suppressor APC

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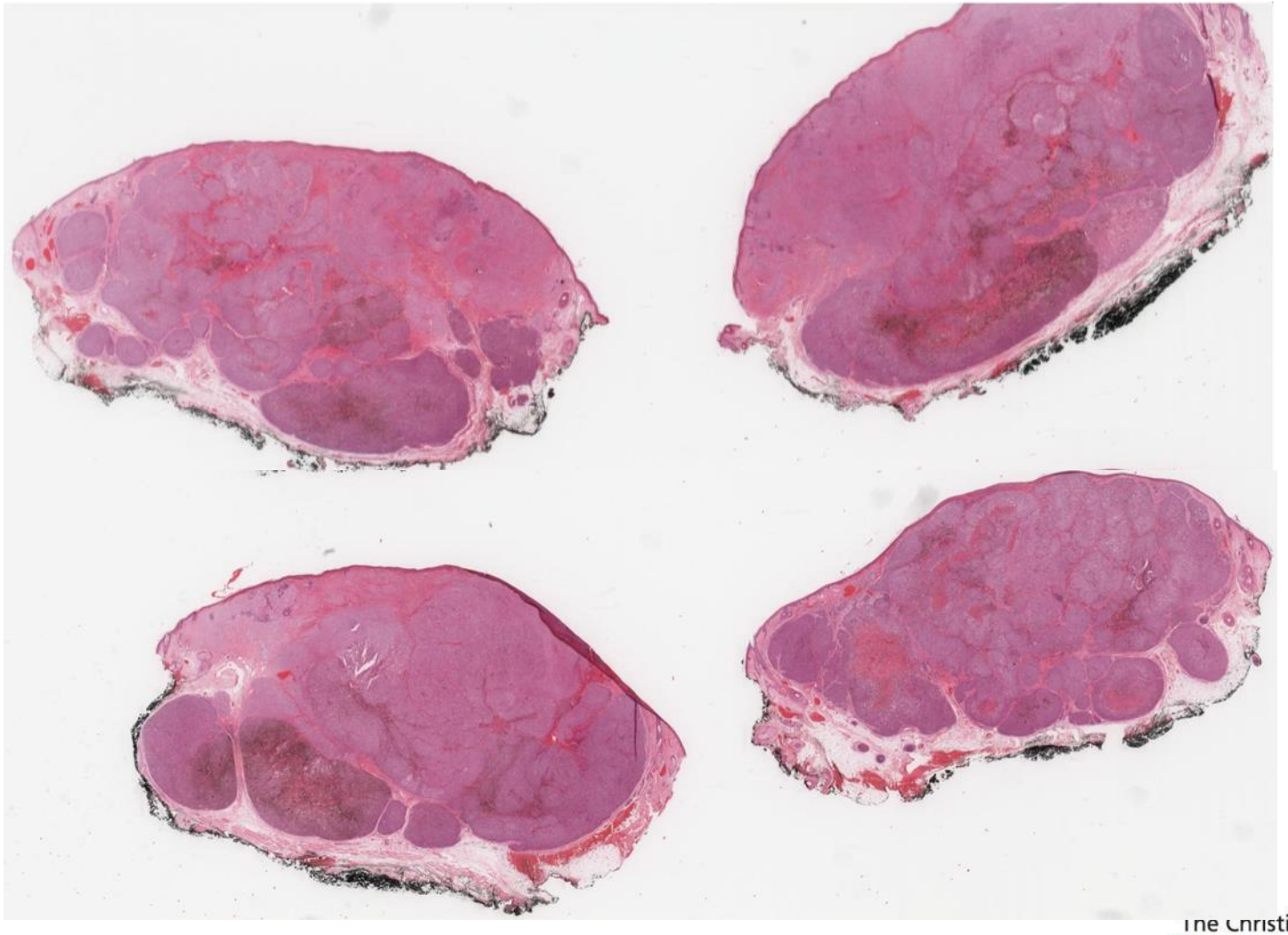
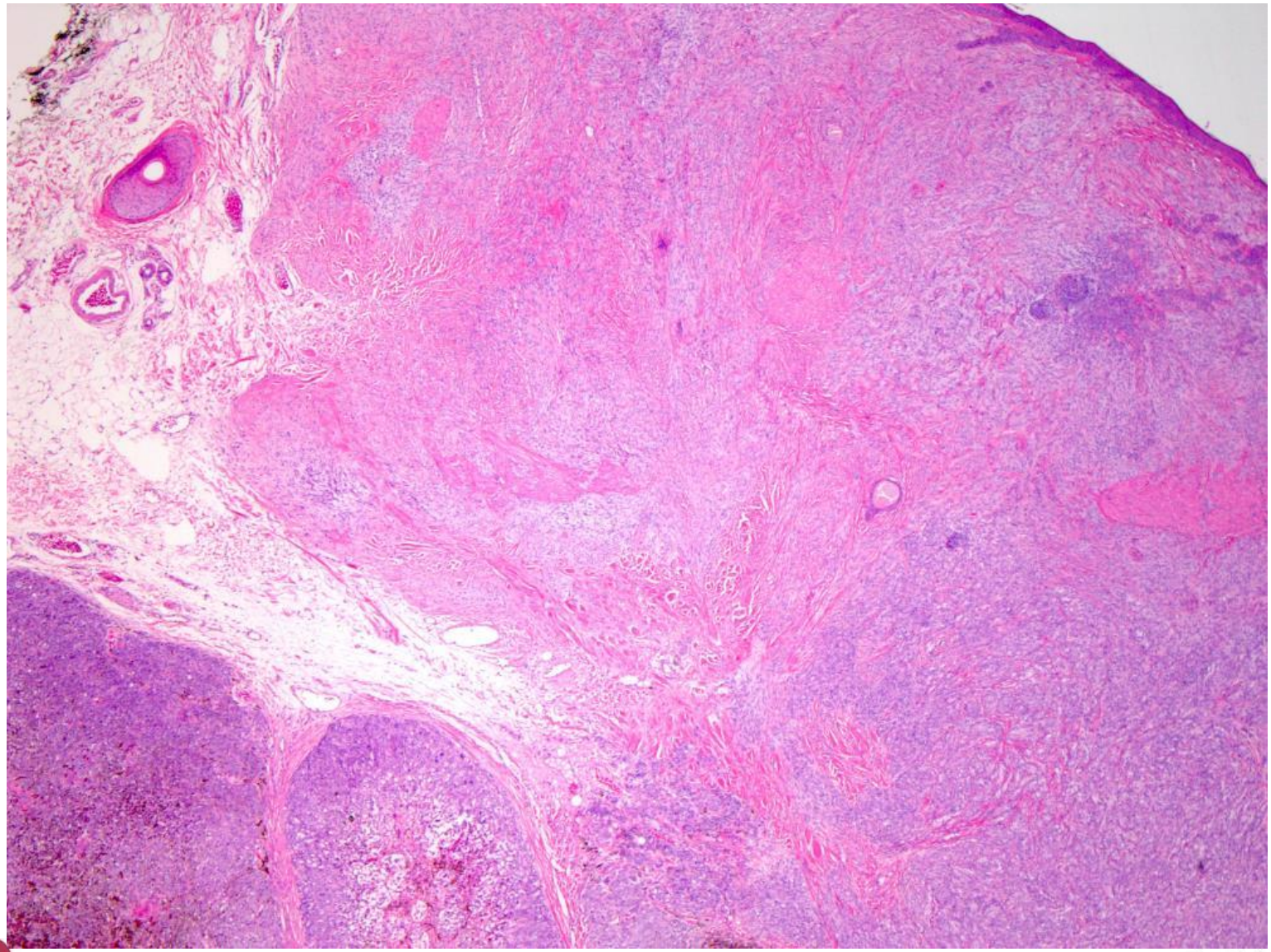
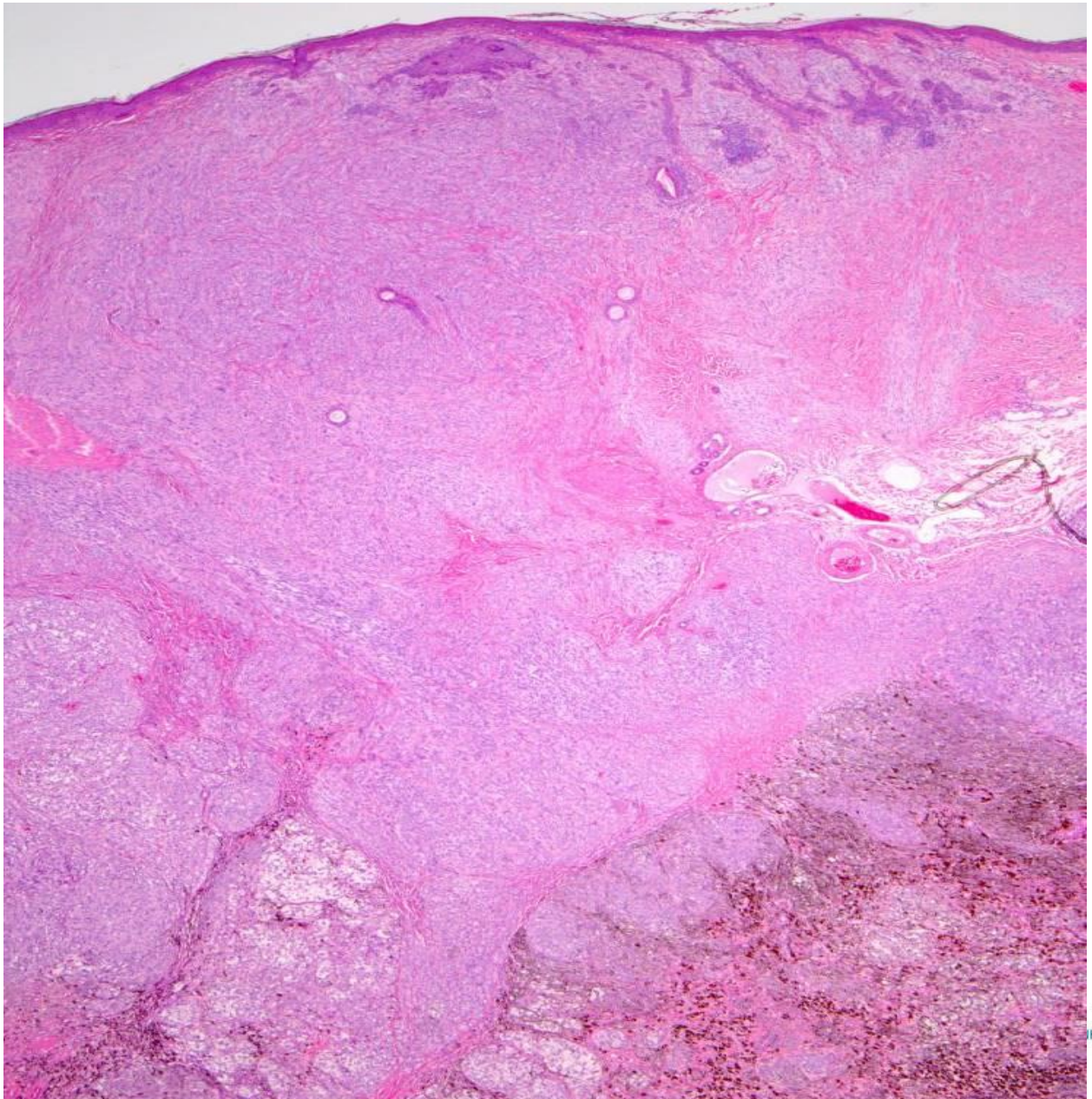
- Immunohistochemical overexpression of cyclin D1 (whose transcription is mediated by the β-catenin-LEF1 complex)
- Since oncogenic mutations additional to BRAF and CTNNB1 can lead to overt malignancy, DPN can be regarded as an intermediate stage in the stepwise progression from naevus to melanoma – hence the designation of DPN/melanocytoma

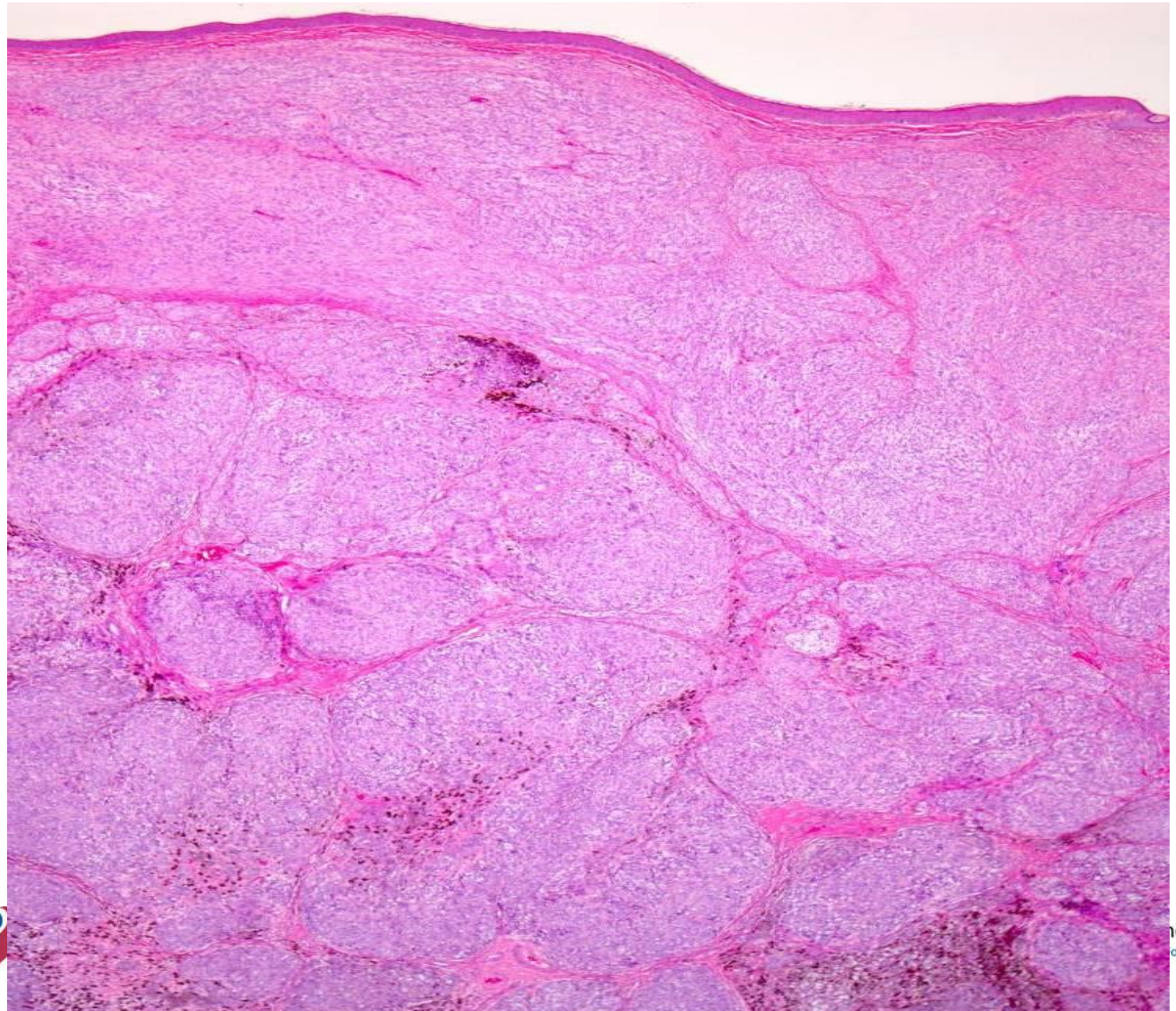
- ?? Beta-catenin activated melanocytoma

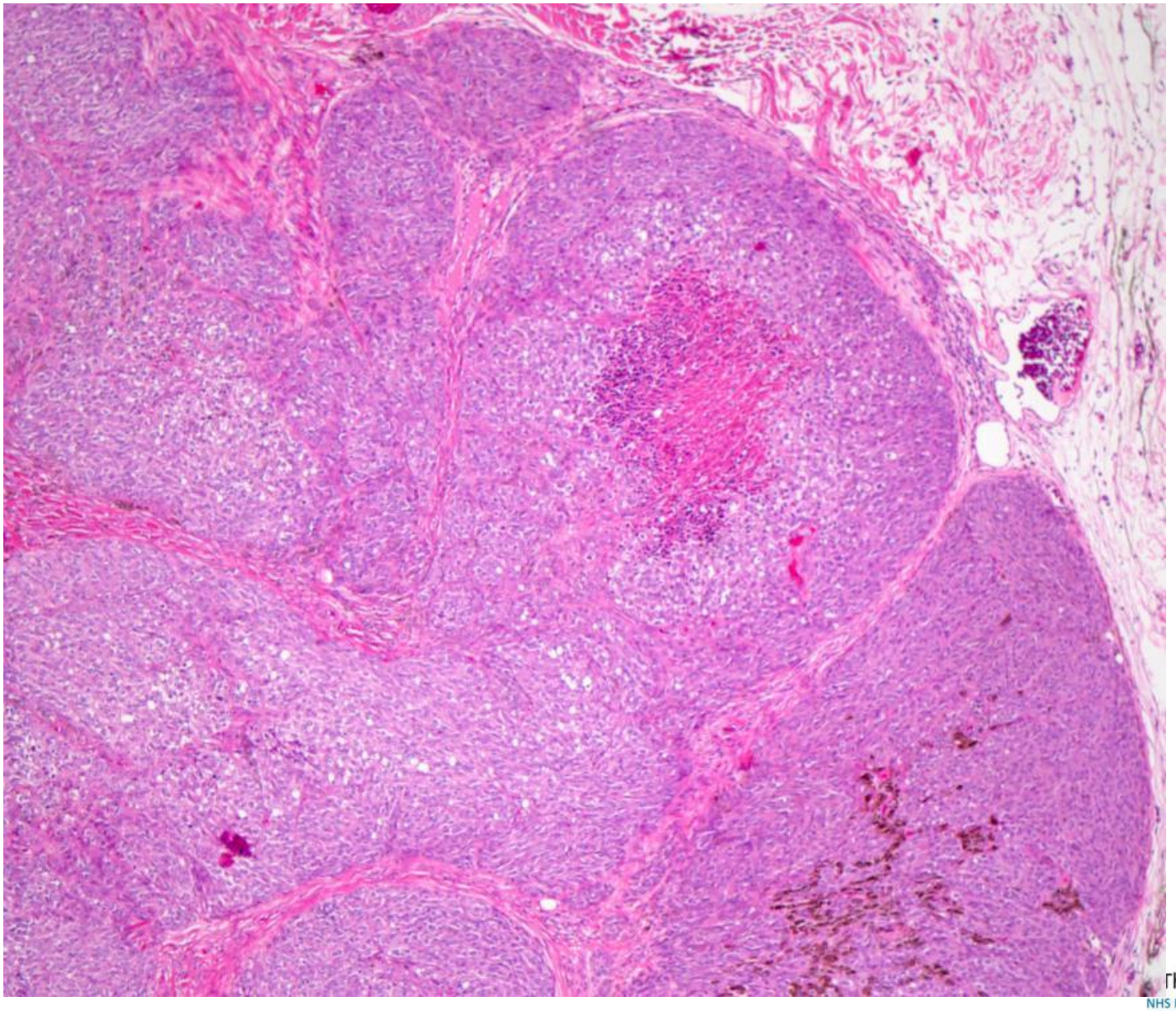
PS2. 49F. “Cystic lesion” left temple, excision

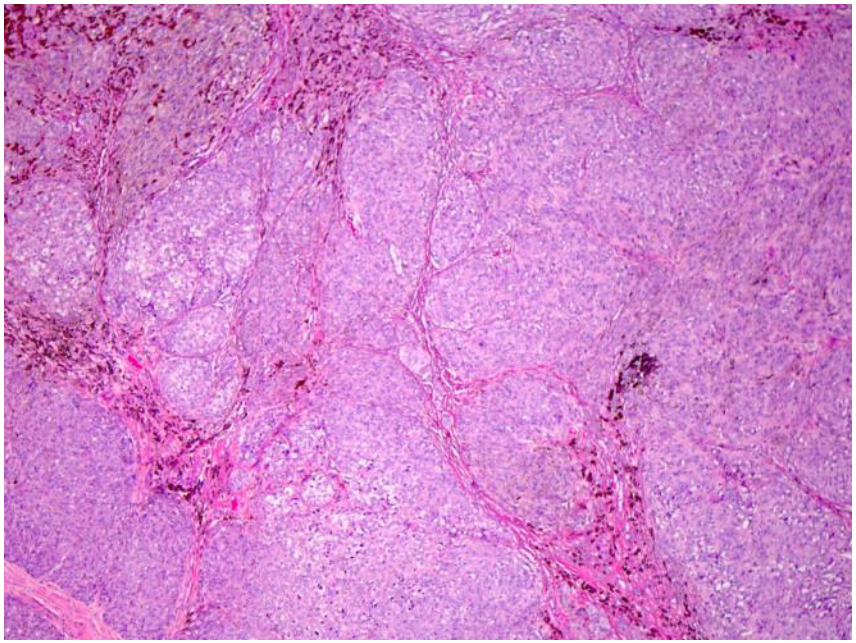


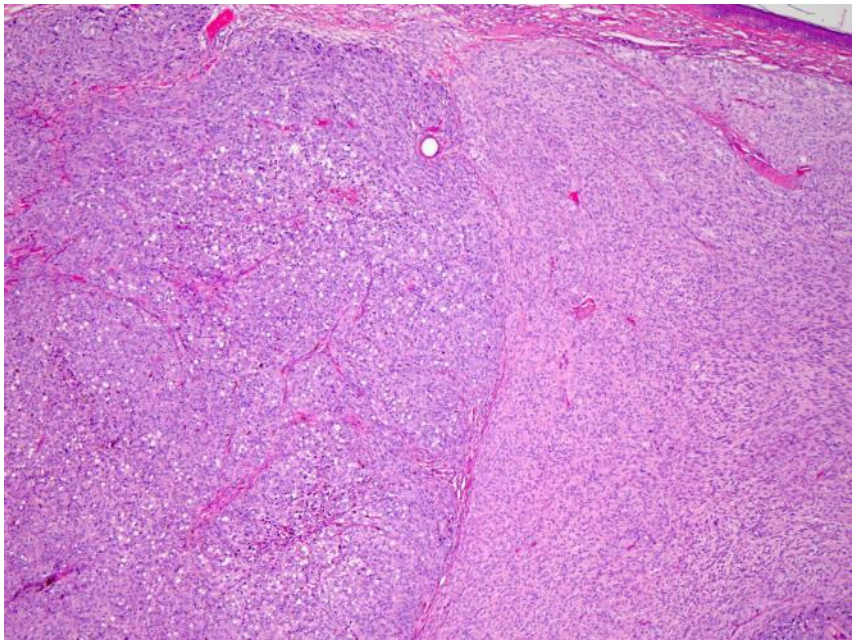


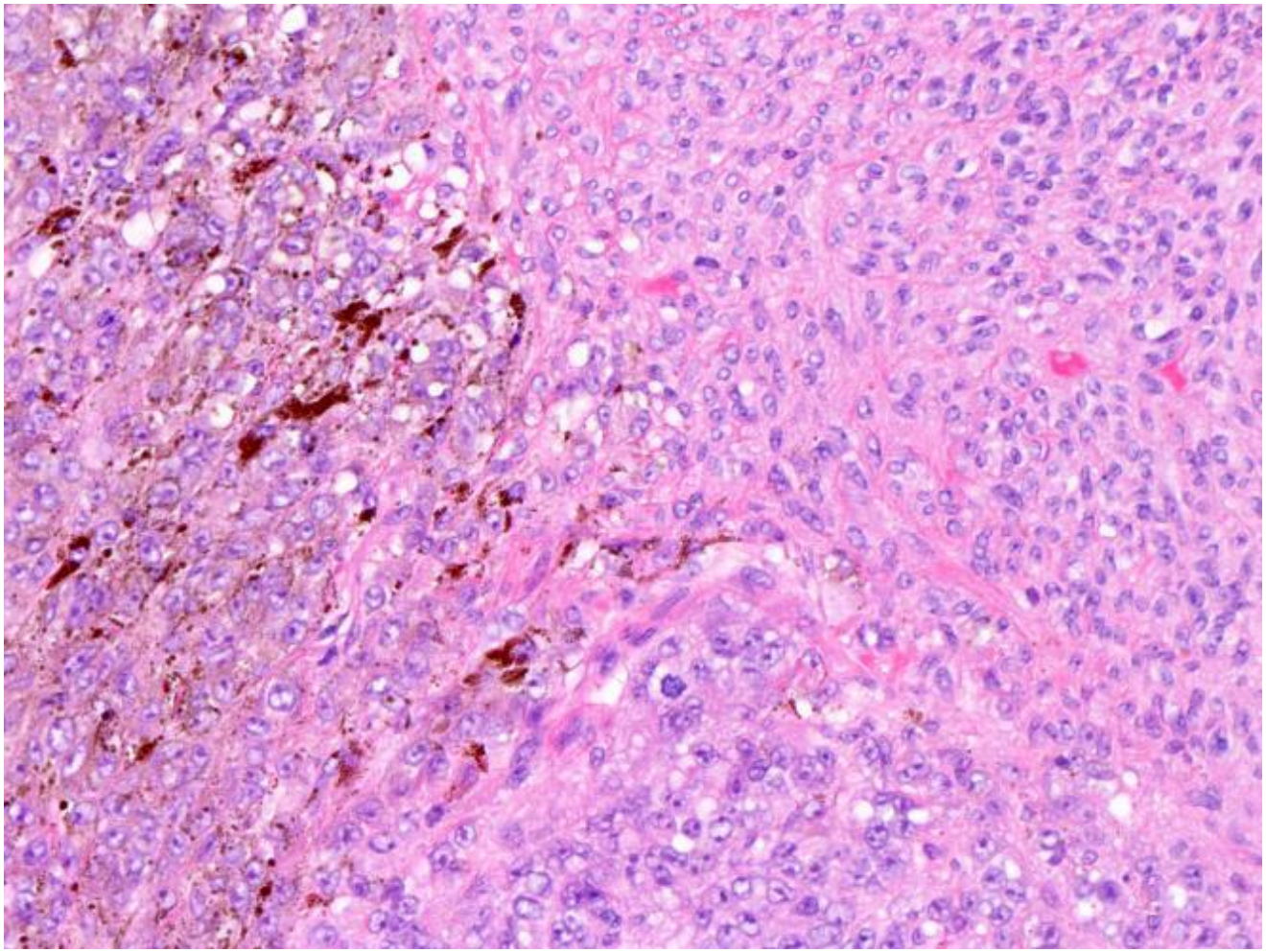


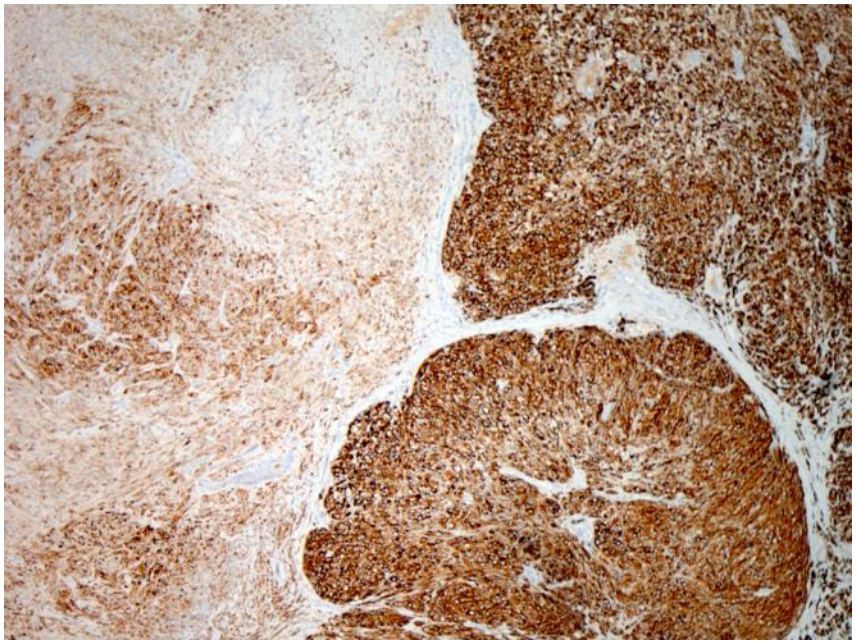




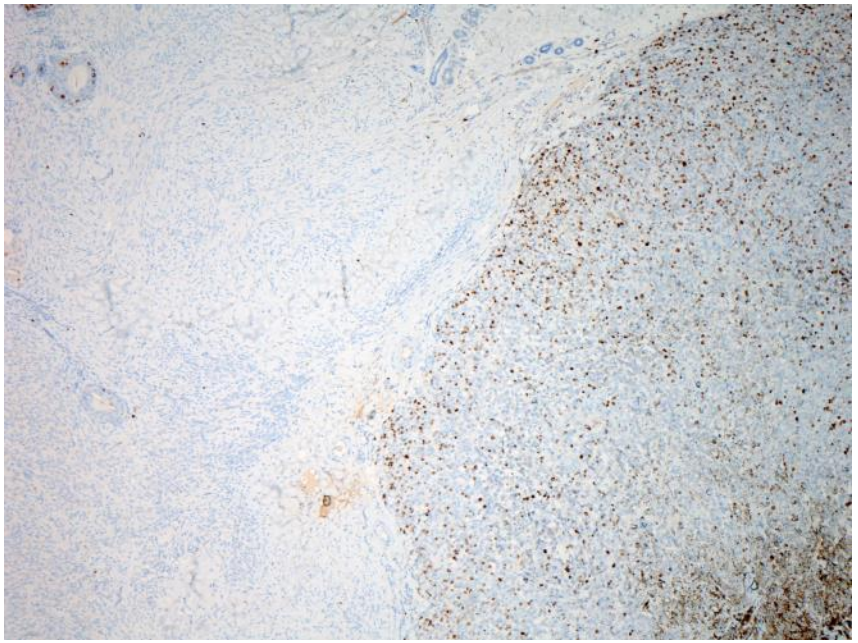




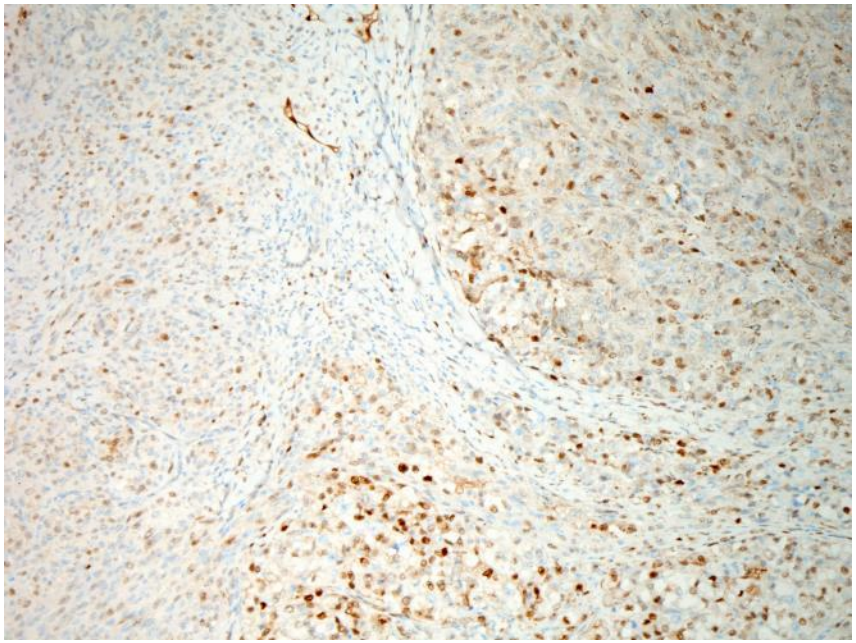


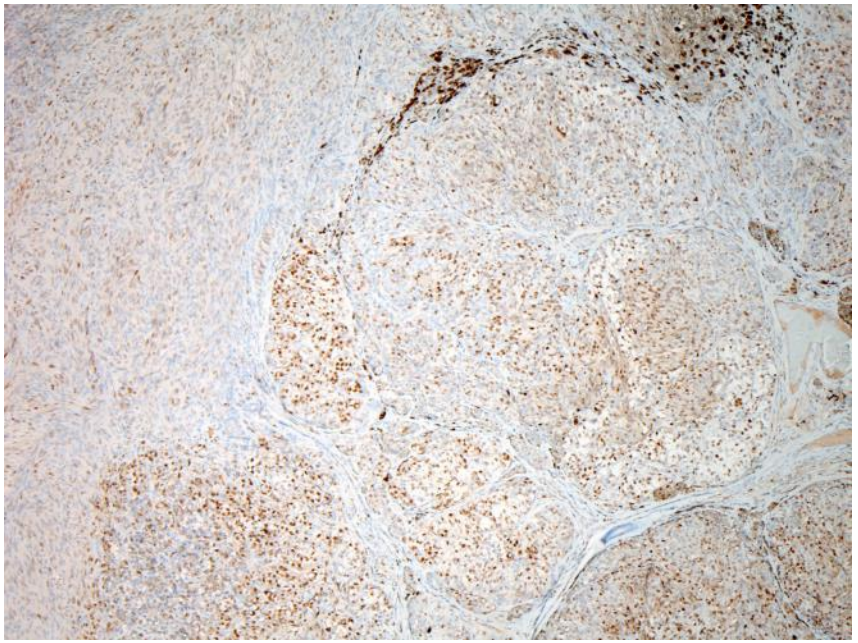


HMB45

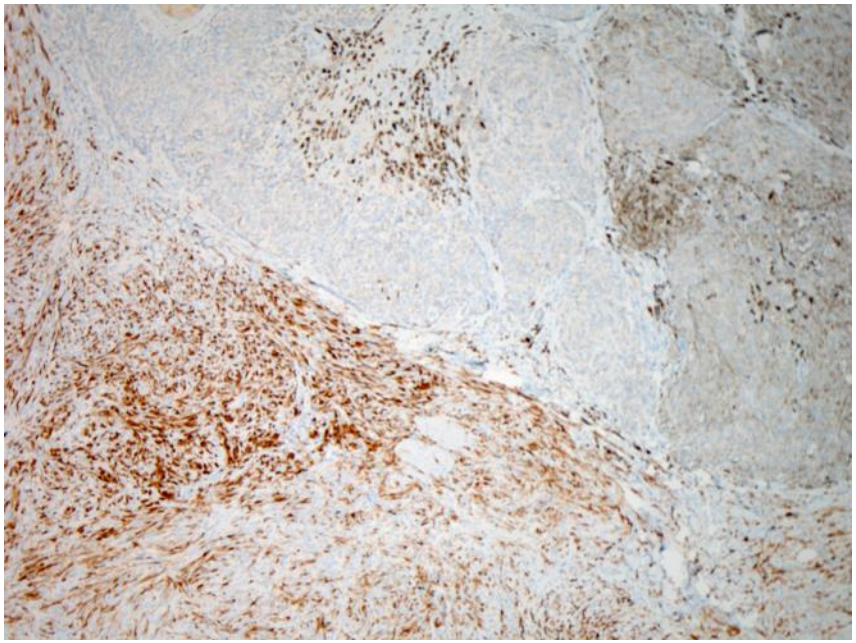


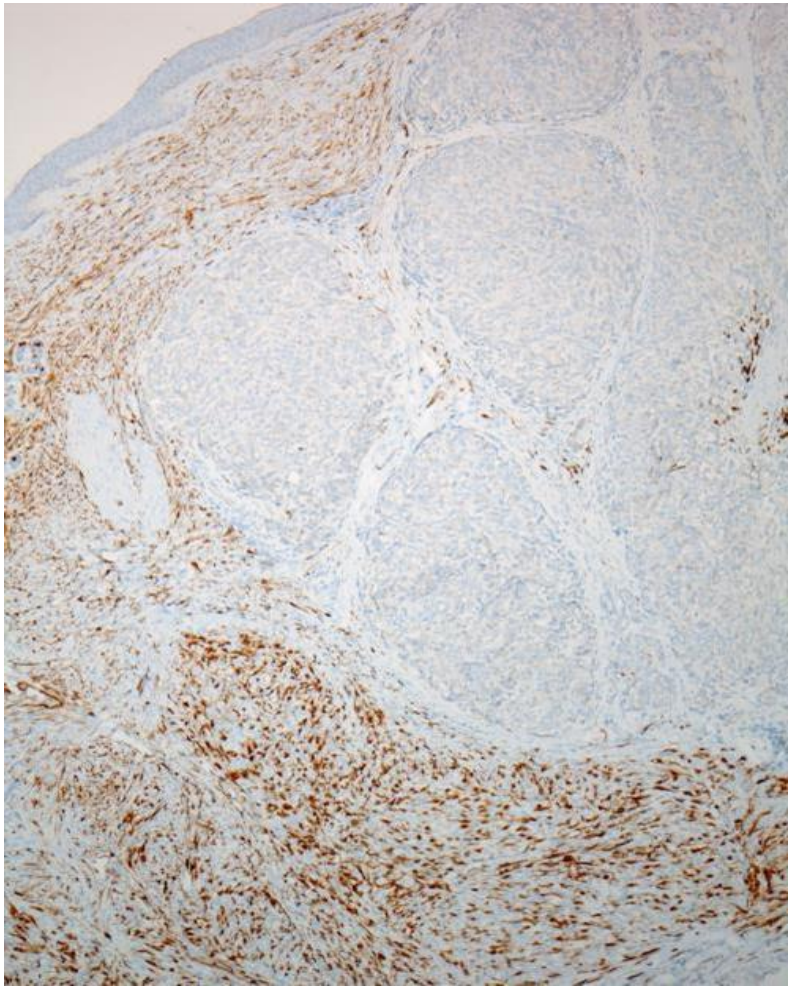
MiB1





Cyclin D1





p16

Diagnosis

- Melanoma ex blue naevus/melanoma arising in a blue naevus

(melanoma simulating BN/malignant blue naevus or malignant blue tumour)

- Fisher ER. Arc Dermatol 1956 :
- Connelly and Smith. Cancer 1991
- Granter et al Am J Surg Path 2001: 10 cases
- Martin et al. Cancer 2009: 23 cases
- Loghavi et al Mod Pathol 2014: 24cases

MODERN PATHOLOGY (2014) 27, 1468–1478

Melanoma arising in association with blue nevus: a clinical and pathologic study of 24 cases and comprehensive review of the literature

Sanam Loghavi[1], Jonathan L Curry[1], Carlos A Torres-Cabala[1], Doina Ivan[1], Keyur P Patel[2], Meenakshi Mehrotra[2], Roland Bassett[3], Victor G Prieto[1] and Michael T Tetzlaff[1]

[1]Department of Pathology, Section of Dermatopathology, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Hematopathology, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA and [3]Department of Biostatistics, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Melanomas arising in association with blue nevi or mimicking cellular blue nevi comprise a relatively rare and heterogeneous group of melanomas. It remains controversial which prognostic indicators predictive of outcome in conventional cutaneous melanomas are applicable to this type of melanoma. Here, we describe the clinical and histopathologic features of 24 melanomas arising in association with blue nevi and correlate these with clinical outcome. The mean patient age was 49 years (range: 23–85) with a slight female predominance (15 females:9 males). The most common anatomic locations included the head and neck region (50%), the trunk (21%), and the buttock/sacrococcygeum (17%). Histologically, the tumors were typically situated in the mid to deep dermis with variable involvement of the subcutis, but uniformly lacked a prominent intraepithelial component. The mean tumor thickness (defined as either the standard Breslow thickness or, if not available due to the lack of orientation or lack of epidermis, the largest tumor dimension) was 20.9 mm (range: 0.6–130 mm). The mean mitotic figure count was 6.5/mm^2 (range: 1–30/mm^2). Perineural invasion was common (38%). Follow

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- Most cases located the head and neck (~50%)
  - trunk (~21%)
  - buttock (~17%)
- Heterogeneous group in which there remains controversy regarding diagnostic and prognostic features

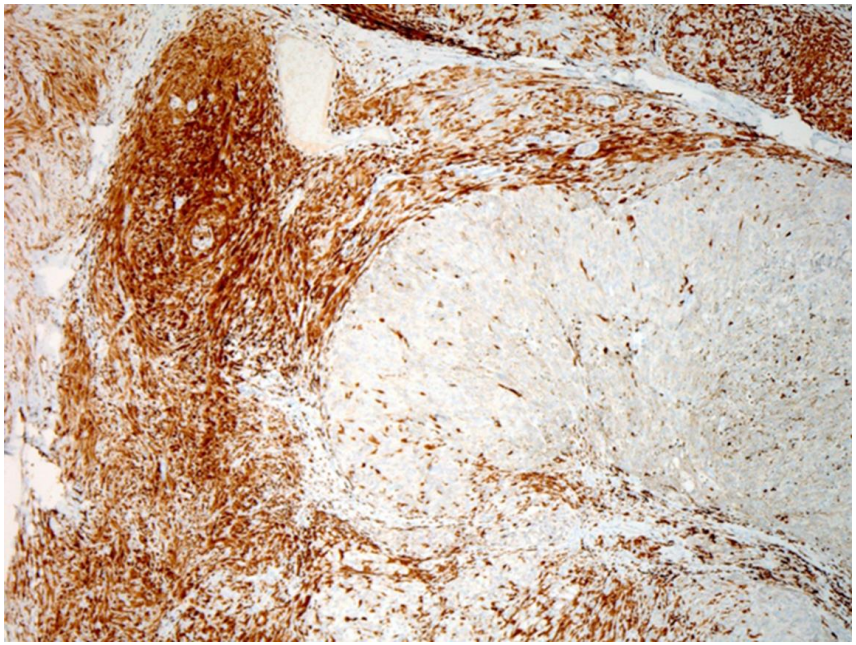
Melanomas Associated With Blue Nevi or Mimicking Cellular Blue Nevi

Clinical, Pathologic, and Molecular Study of 11 Cases Displaying a High Frequency of GNA11 Mutations, BAP1 Expression Loss, and a Predilection for the Scalp

Sebastian Costa, MD, Michelle Byrne, MBBS,† Daniel Pissaloux, PhD,* Veronique Haddad, PharmD,* Sandrine Paindavoine, Msc,* Luc Thomas, MD, PhD,‡ Francois Aubin, MD, PhD,§ Thierry Lesimple, MD,‖ Florent Grange, MD, PhD,¶ Bertille Bonniaud, MD,# Laurent Mortier, MD, PhD,** Christine Mateus, MD,†† Brigitte Dreno, MD,‡‡ Brigitte Balme, MD,§§ Beatrice Vergier, MD, PhD,‖‖ and Arnaud de la Fouchardiere, MD, PhD**

Abstract: Melanomas associated with blue nevi (MABN) or mimicking cellular blue nevi (MMCBN) represent exceptional variants of malignant cutaneous melanocytic tumors. Uveal and leptomeningeal melanomas frequently have somatic mutations of *GNAQ* or *GNA11*, which are believed to be early driver mutations. In uveal melanomas, monosomy 3, linked to the *BAP1* gene, is an adverse prognostic factor. We have studied the clinical, histologic, BAP1 expression profile, and molecular data of 11 cases of MABN/MMCBN and 24 cellular blue nevi. Most of the cases of MABN/MMCBN occurred on the scalps of adult patients and presented as rapidly growing nodules, typically ≥1 cm, often arising at the site of a preexisting melanocytic

large dermal atypical melanocytes, in some cases lying adjacent to a blue nevus. Four patients developed metastatic disease, and 2 died from their disease. A *GNA11* mutation was found in 8/11 cases and a *GNAQ* mutation in 1 case. Seven of 11 cases showed loss of nuclear BAP1 immunohistochemical (IHC) expression in the malignant component, sparing the adjacent nevus. Array comparative genomic hybridization revealed recurrent deletions of chromosomes 1p, 3p, 4q, 6q, 8p, 16q, and 17q and recurrent gains of chromosomes 6p, 8q, and 21q. The 24 cases of cellular blue nevi frequently occurred on the sacrum, had *GNAQ* mutations, and showed normal positive IHC staining for BAP1. These results underscore overlapping features in all blue-like



Am J Surg Pathol. 2016 Mar;40(3):368-77 BAP1

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- Hx of recent change in a long standing lesion

D/D

Atypical cellular blue naevus

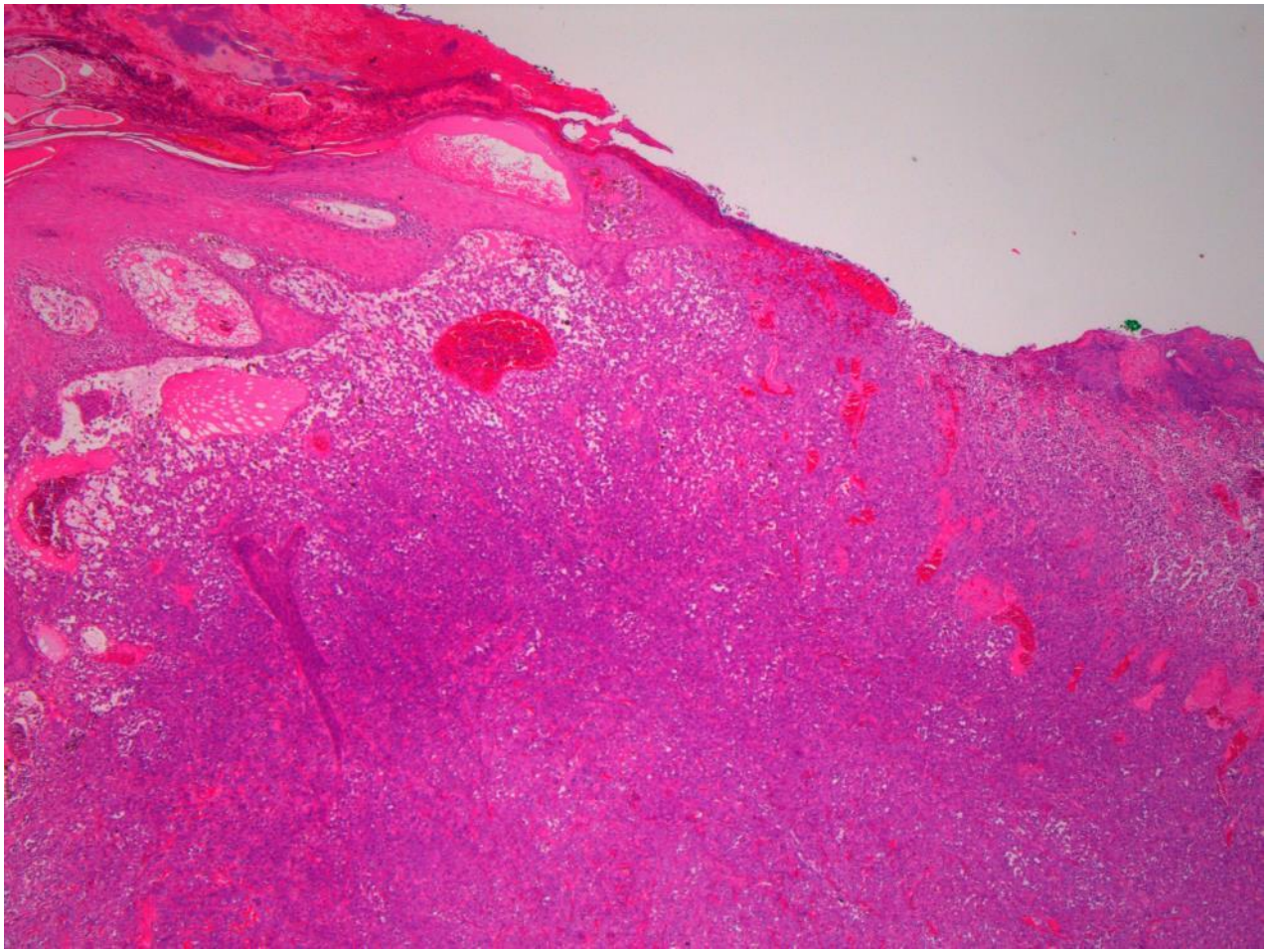
-cellular BN with no expansile nodules of atypical cells

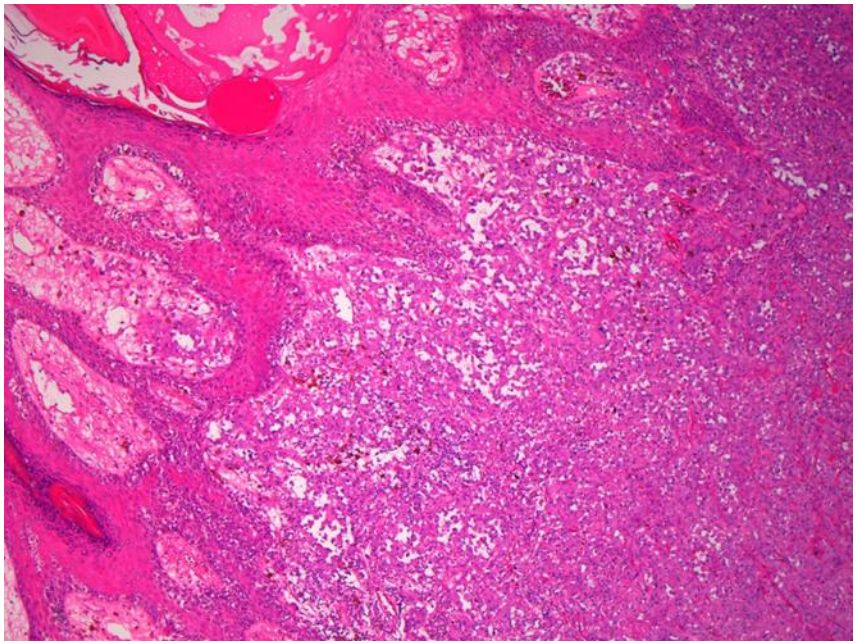
-large lesions with hypercellularity and infiltrative borders

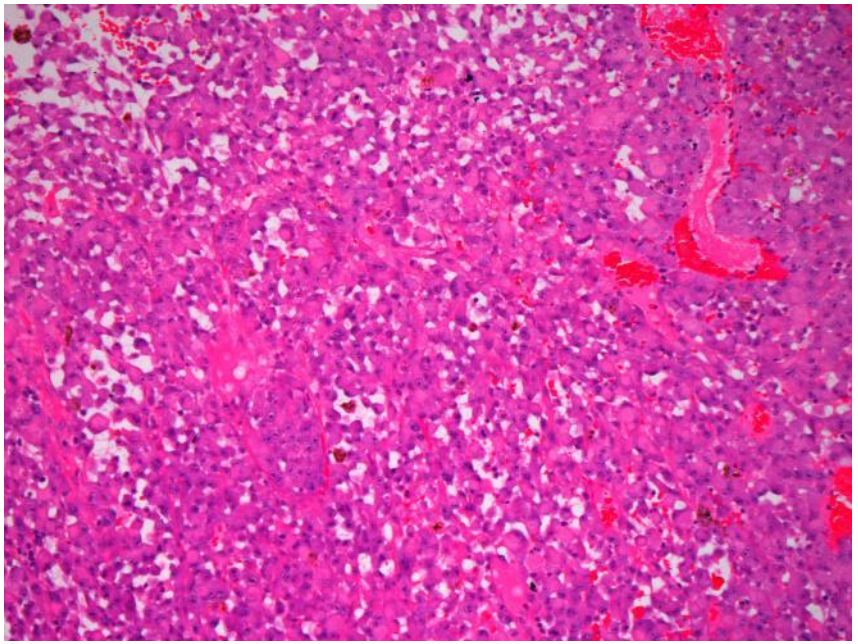
-scattered atypical cells

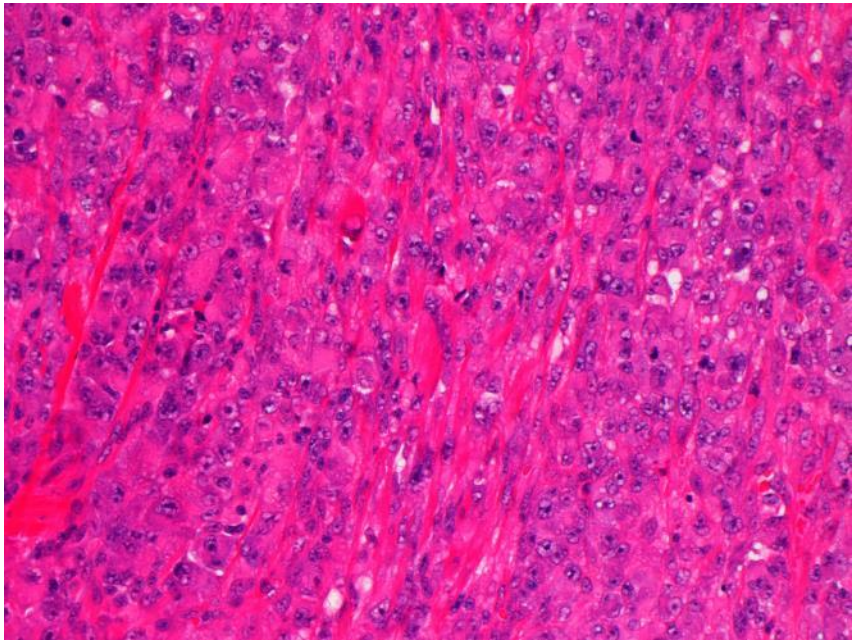
Occasional mitotic figures (up to 2/sq. mm)

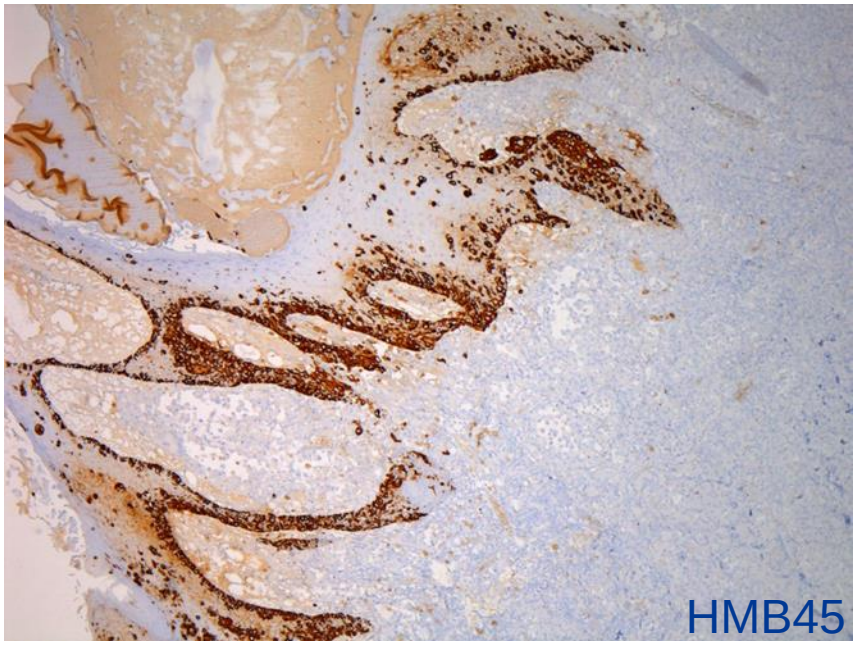
- PS3. 19M. Excision of nodular lesion Rt temple. Clinical Information: Biopsy showed discohesive sheets of tumour cells with epithelial, plasmacytoid and rhabdoid morphology ? Rhabdomyosarcoma







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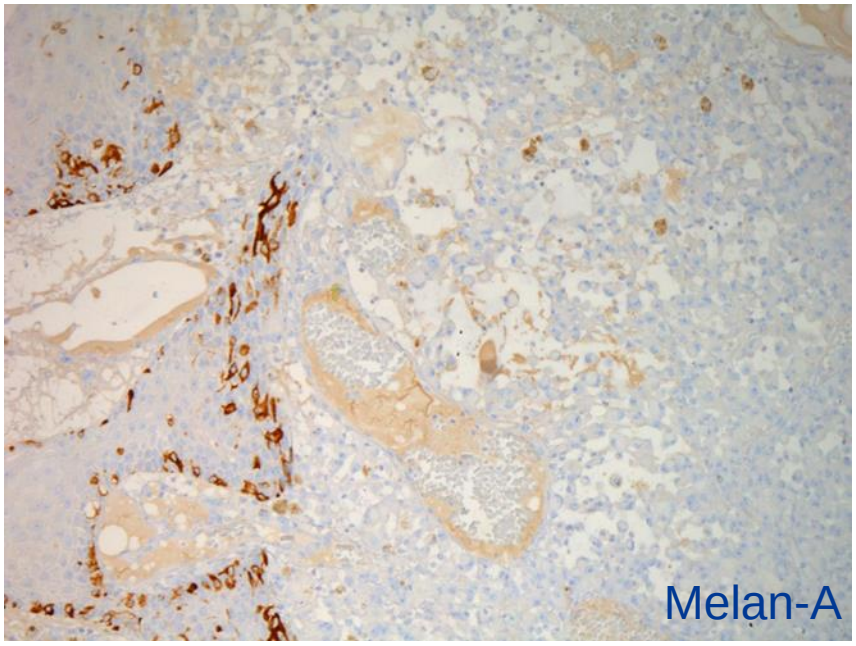
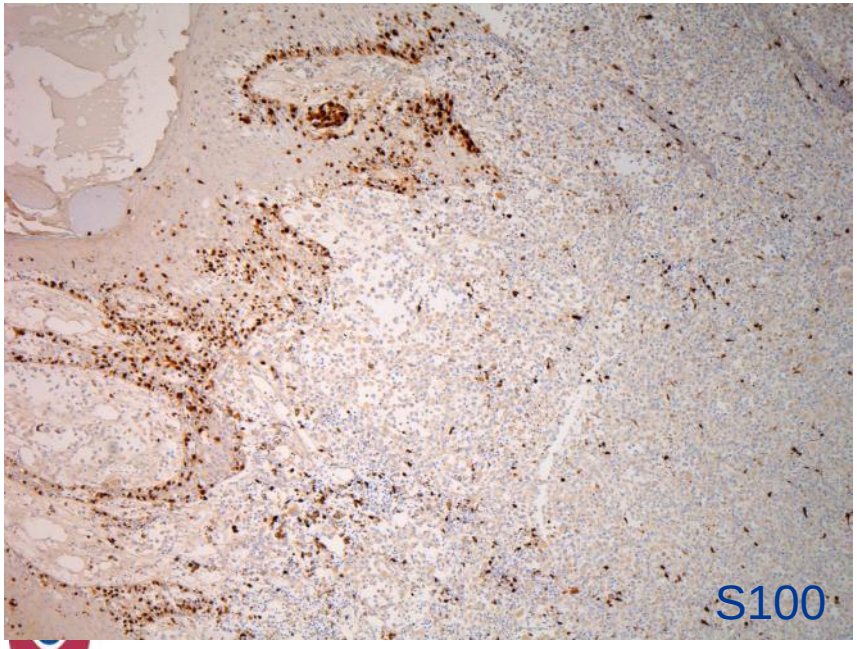
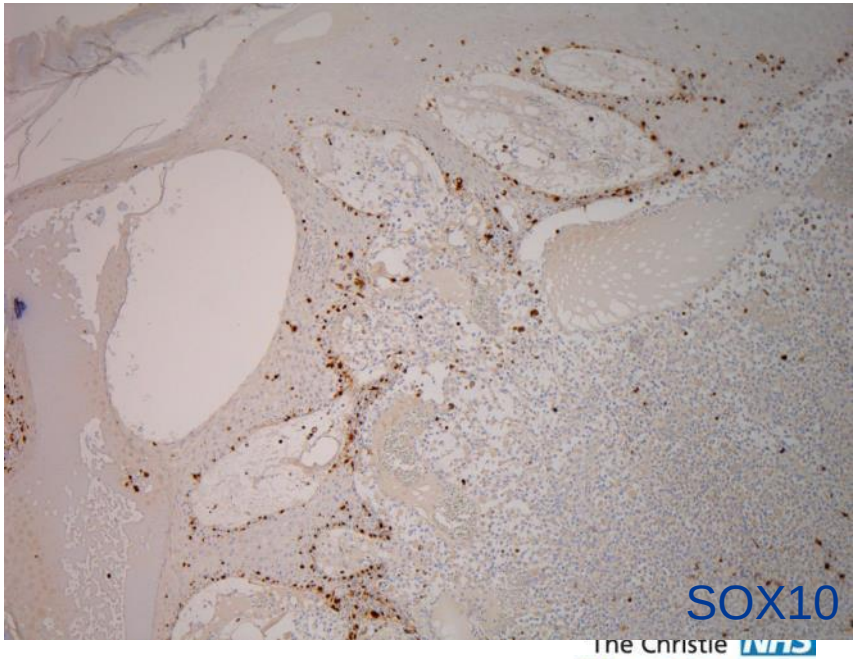
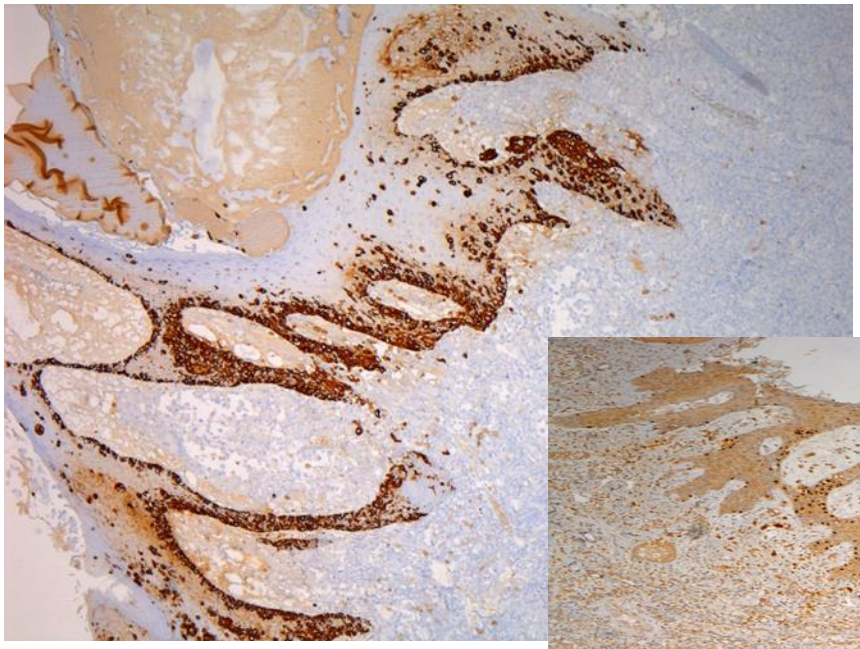
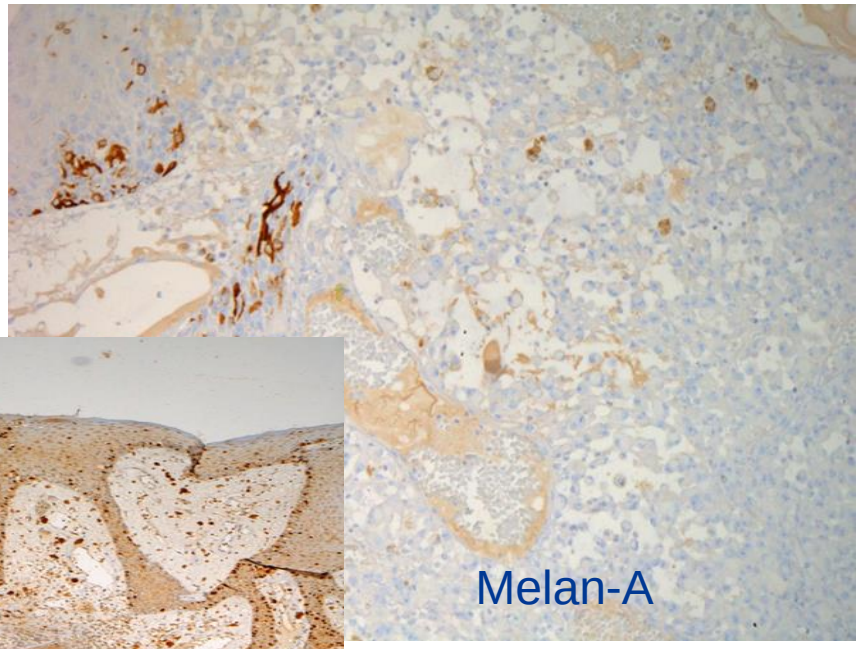

Melan-A


S100


SOX10

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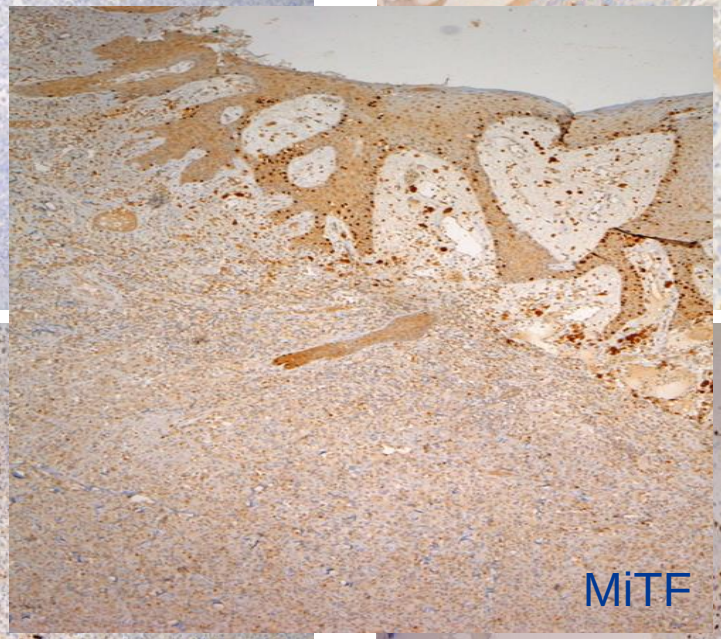
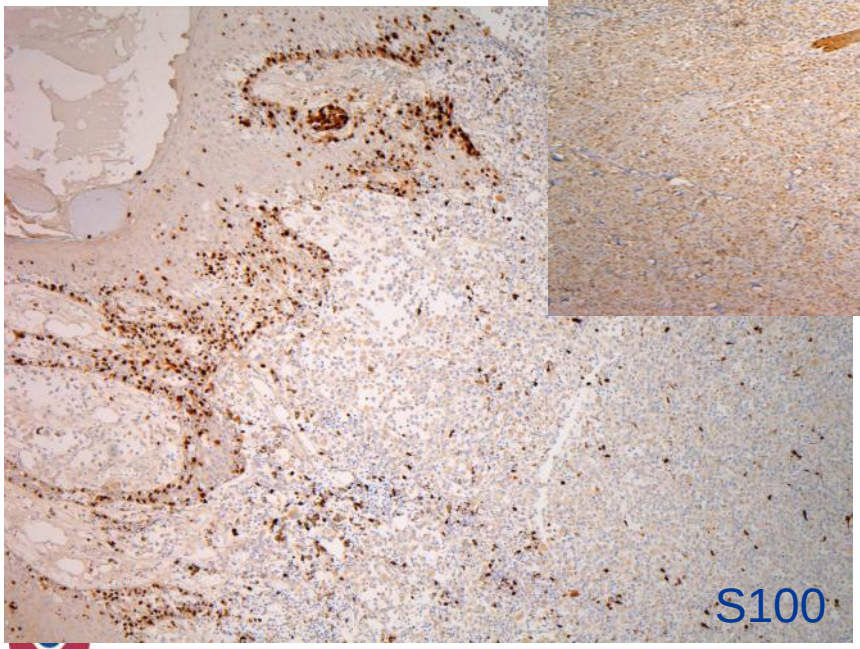

MiTF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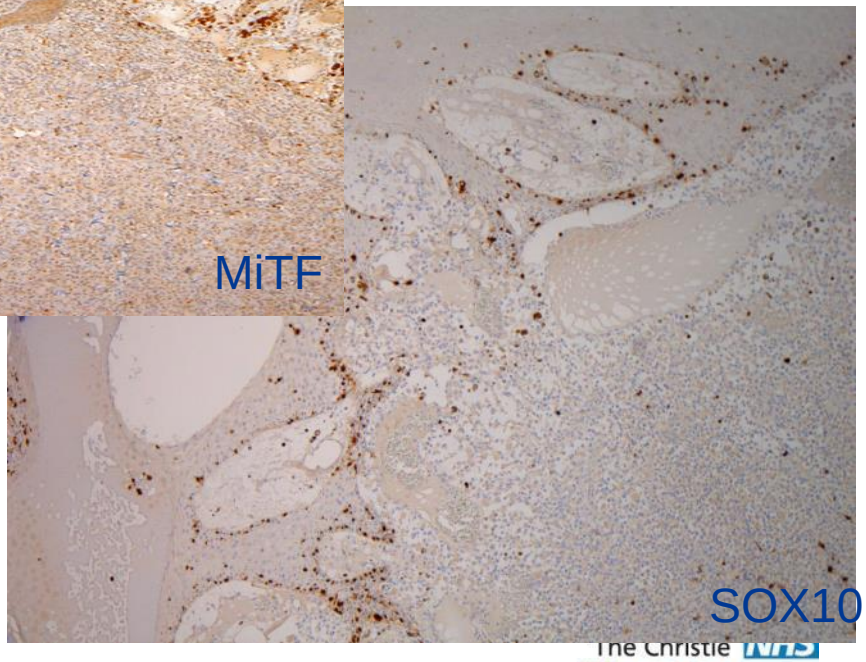
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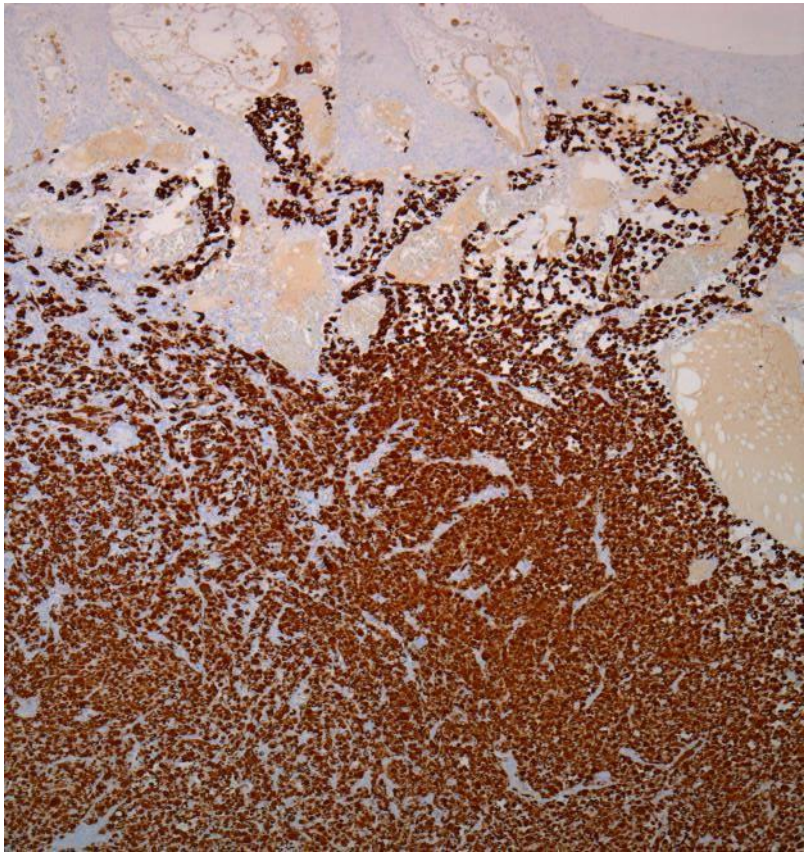
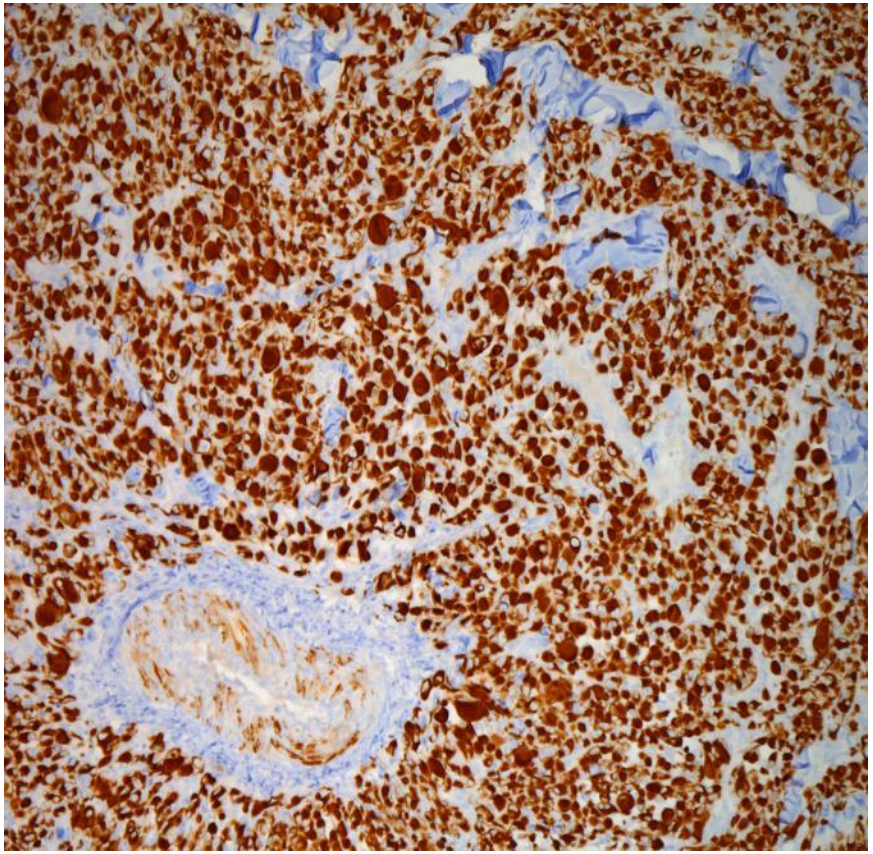
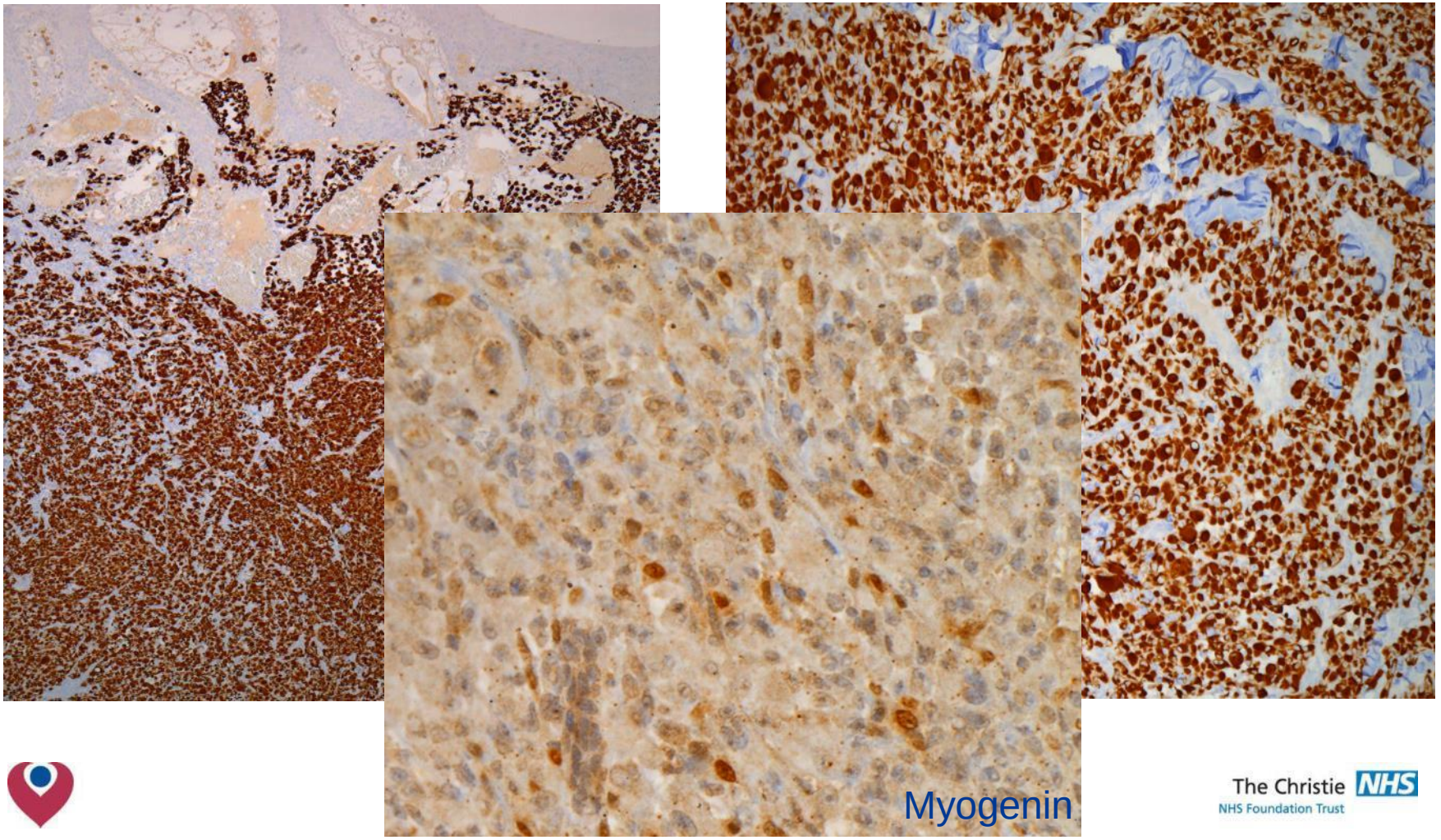




Desmin


Myogenin

Diagnosis

- PS3: Malignant melanoma with divergent rhabdomyosarcomatous differentiation

Definition of Divergent Differentiation in Melanomas

- Development of morphologically, immunohistochemically and or ultrastructurally recognisable non melanocytic cell or tissue components

Banerjee S S & Eyden B, Histopathology 2008;52:119 –129

Rhabdomyoblastic Differentiation

- Mainly described in congenital nevi in children with or without neurocutaneous melanosis syndrome
- Very rarely seen in melanomas occurring in adults
- IHC: Desmin, myogenin, MYO-DI ± myoglobin
- EM: Thick and thin filaments + Z-bands

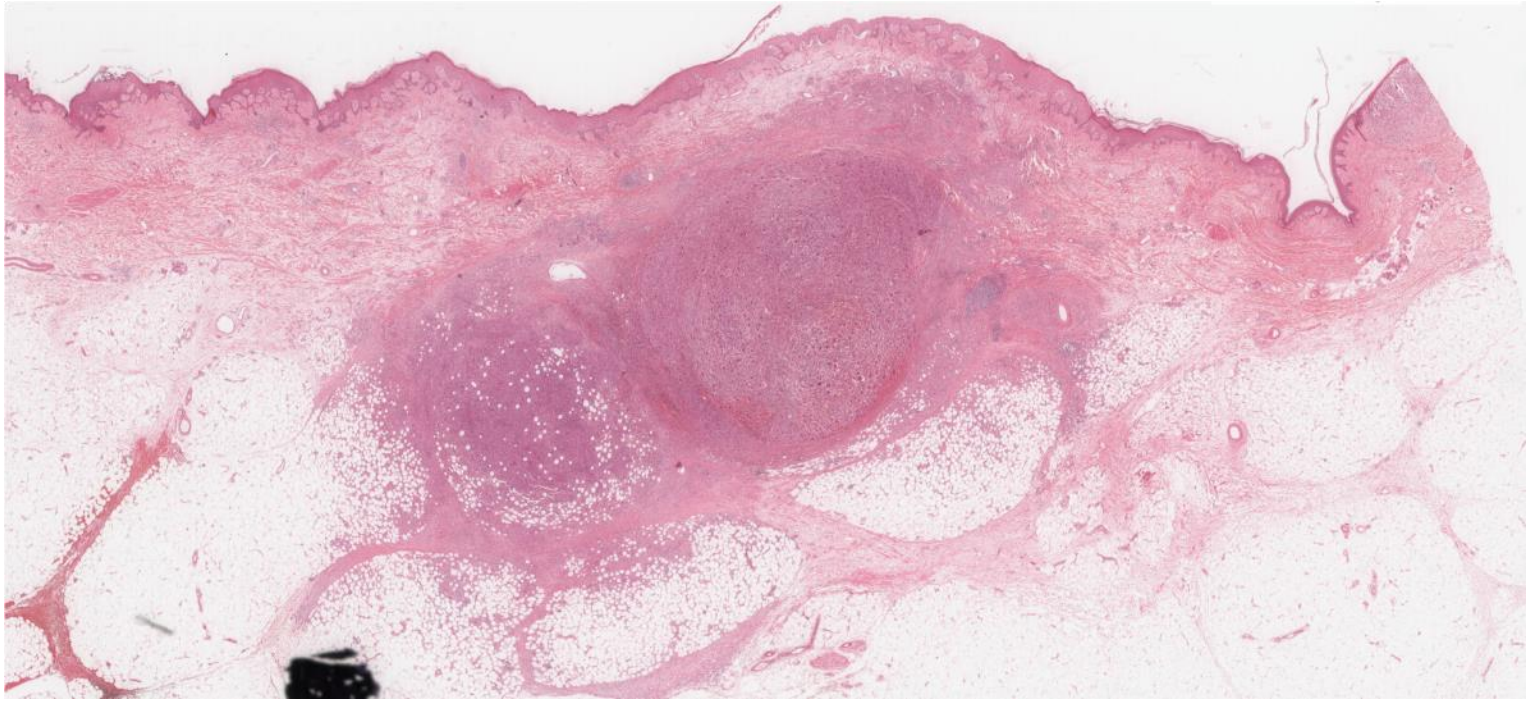
Tran TAN et al. Am J Dermatopathol. 2018. Campbell K et al. J Cutan Pathol. 2018. Antonov NK et al. Am J Dermatopathol. 2016. **Shenjere P et al. Int J Surg Pathol. 2014**. Gharpuray-Pandit D et al. Int J Surg Pathol. 2007. Gattenlohner, S & Brocker, EB. N Engl J Med. 2008. Reilly, DJ et al Int J Surg Pathol. 2013. Kuwadekar A et al. BMJ Case Rep. 2018

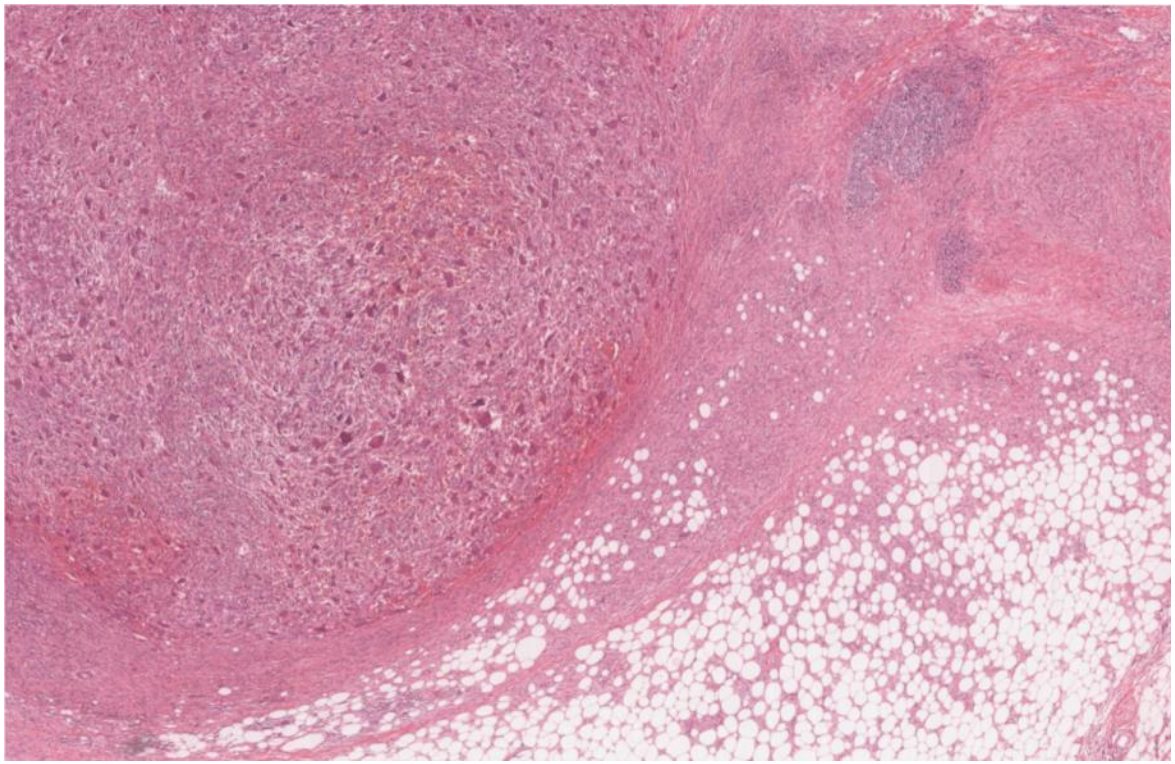
- Should be differentiated from rhabdoid melanomas
- Other D/D: malignant Triton tumor

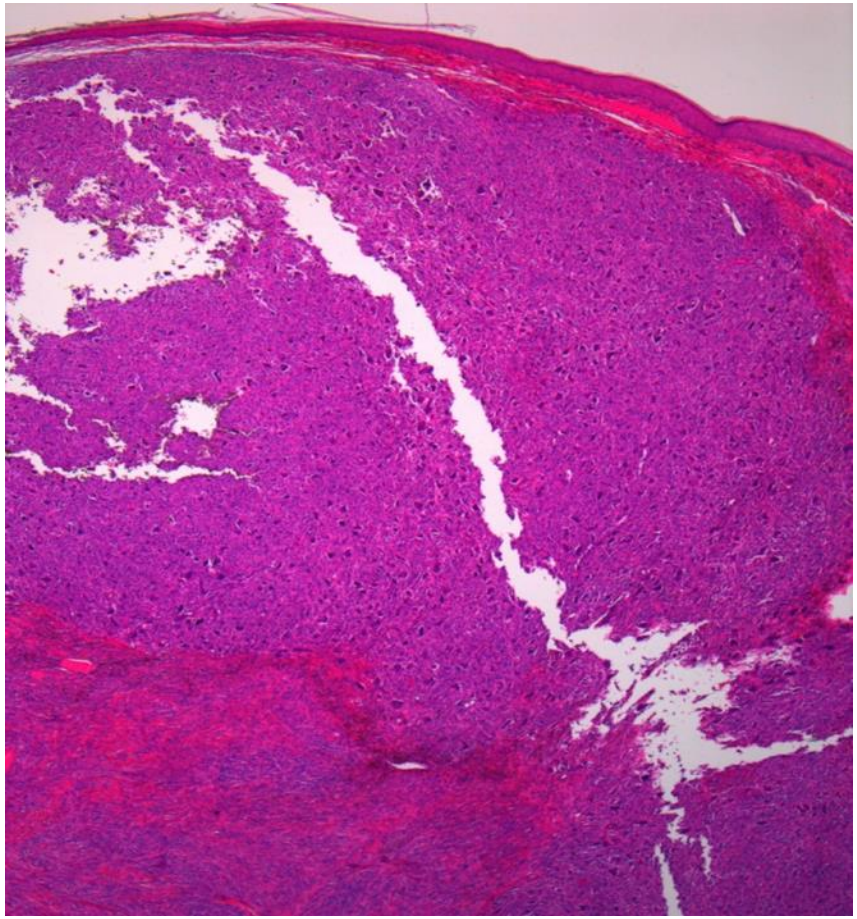
Different Non-melanocytic Components Detected In Malignant Melanomas

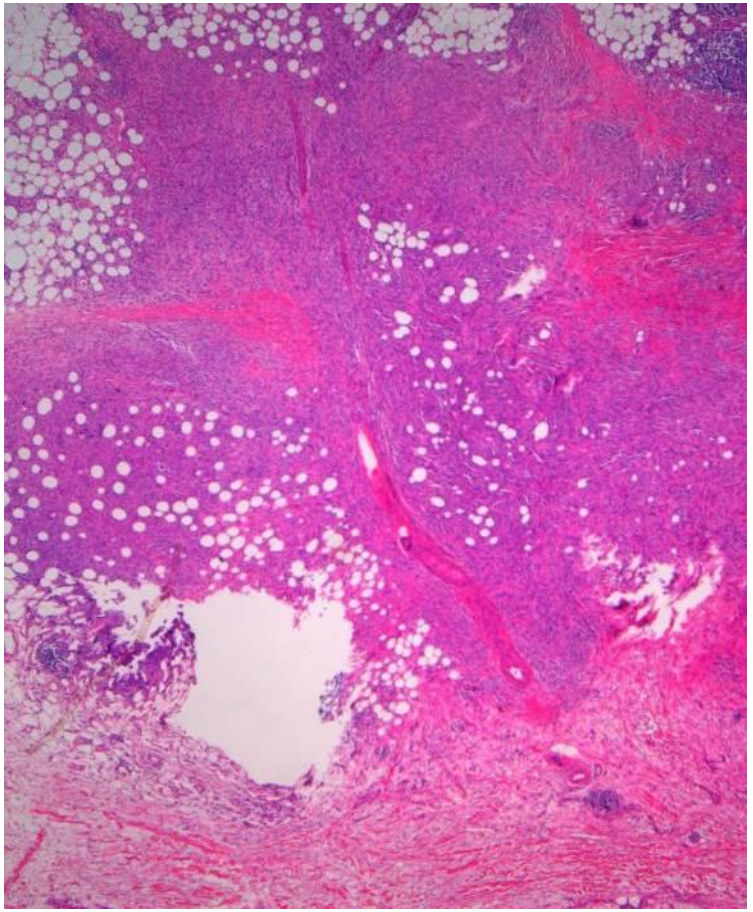
- Fibroblastic/ myofibroblastic
- Smooth muscle
- Osteocartilaginous
- Schwannian & Perineurial
- Ganglionic and ganglioneuroblastic
- Neuroendocrine
- Epithelial

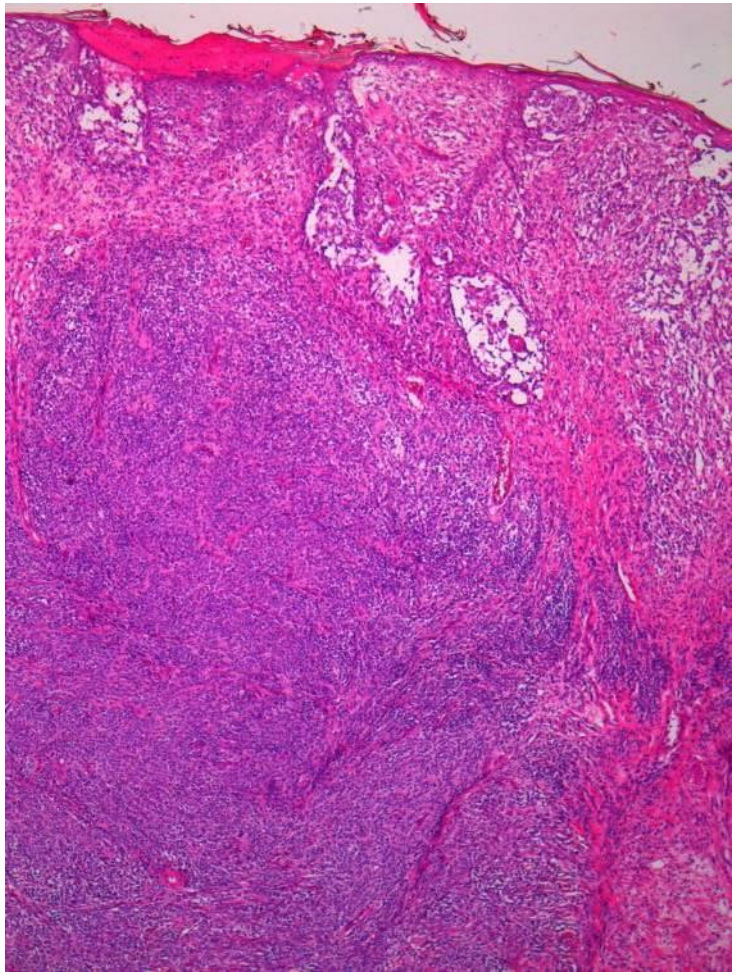
- PS4. 70M. Left lower leg lesion, excision.

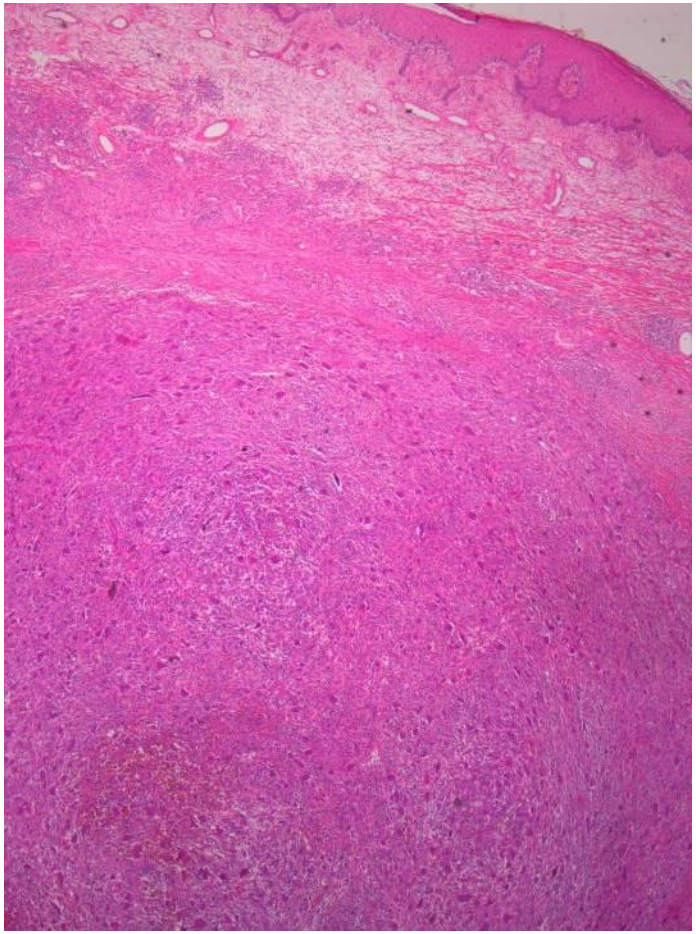


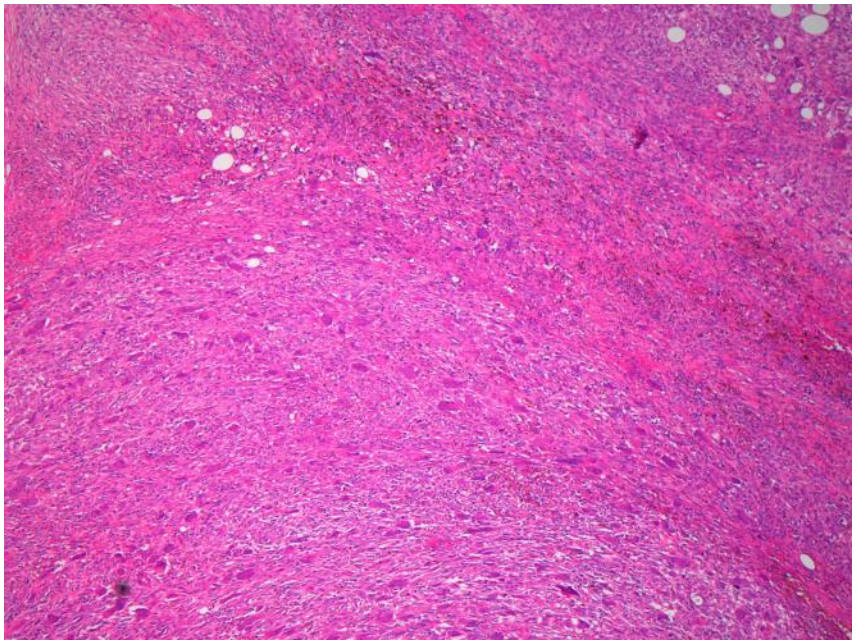


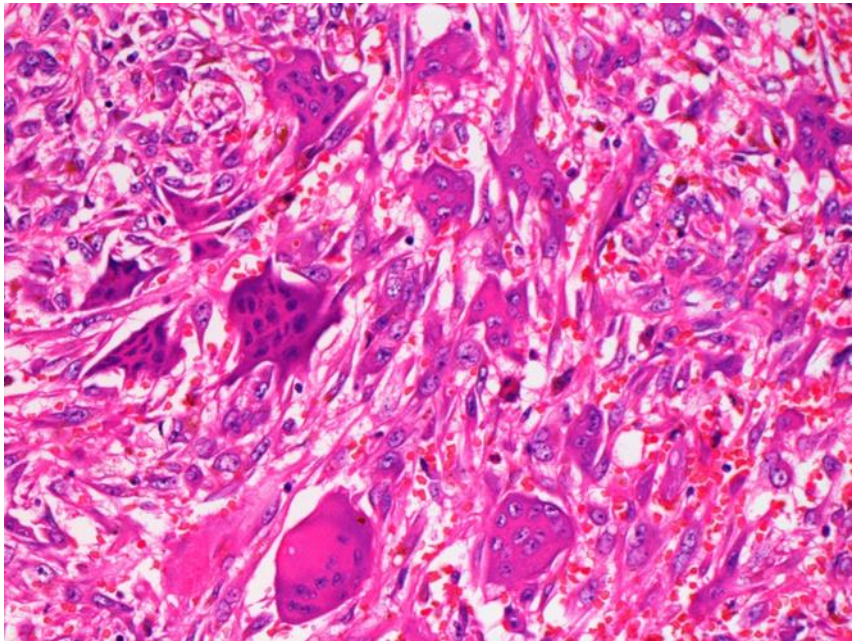


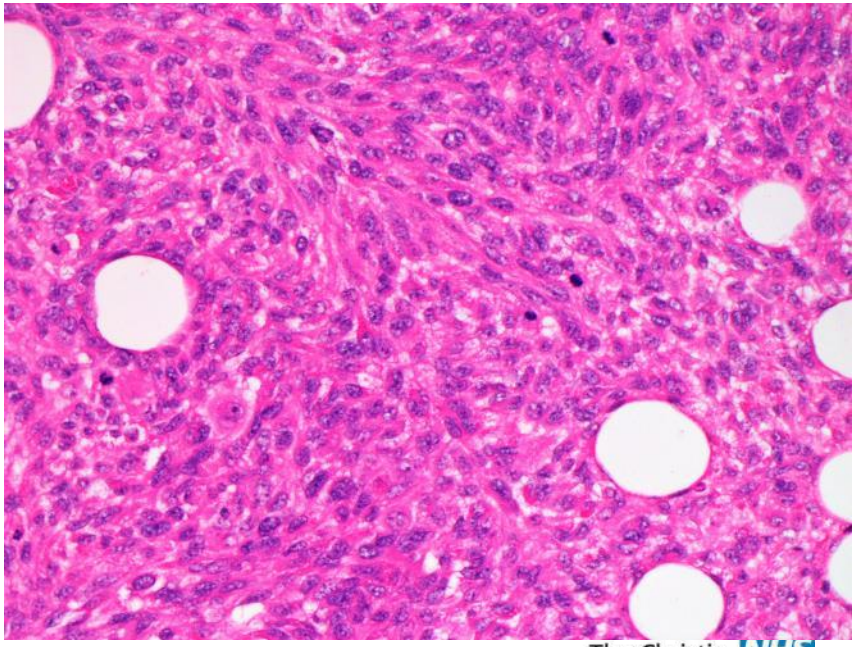


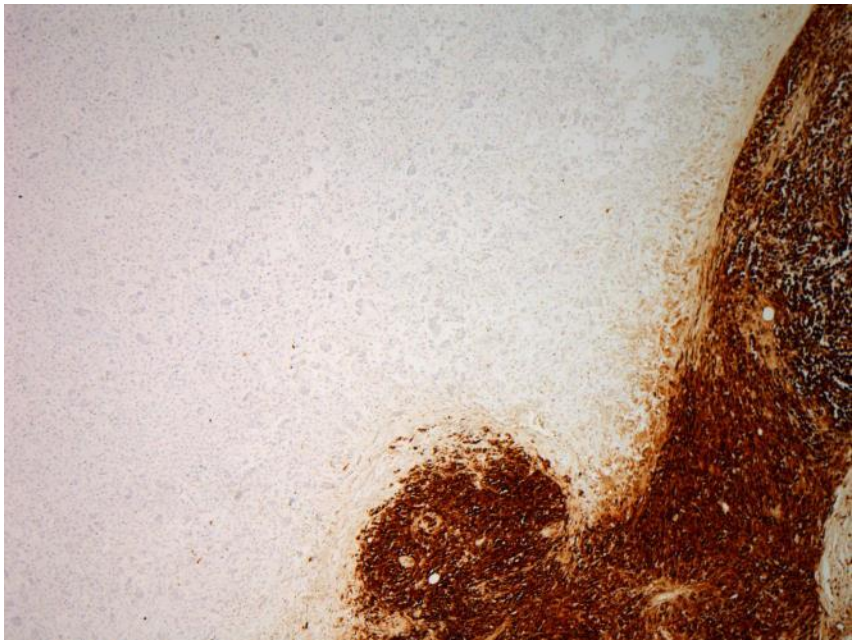


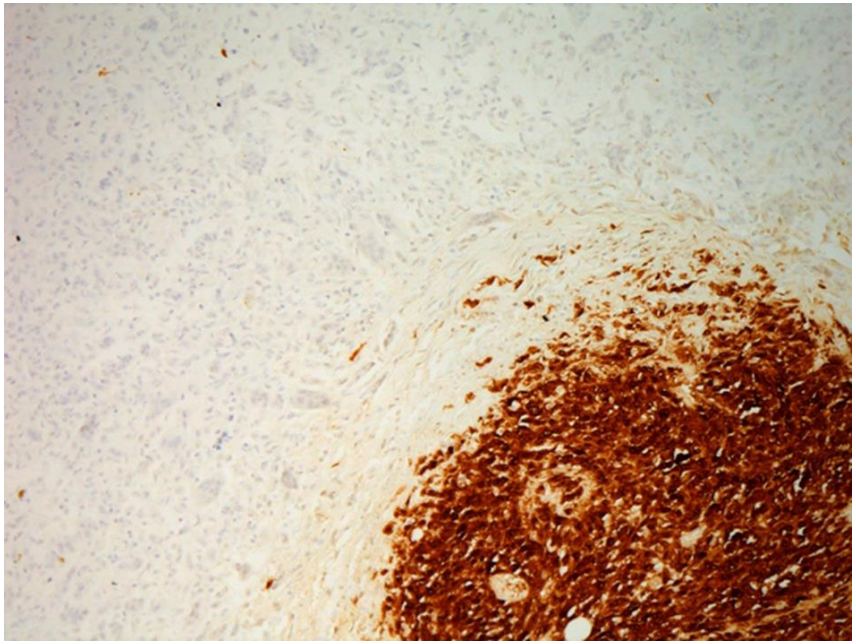










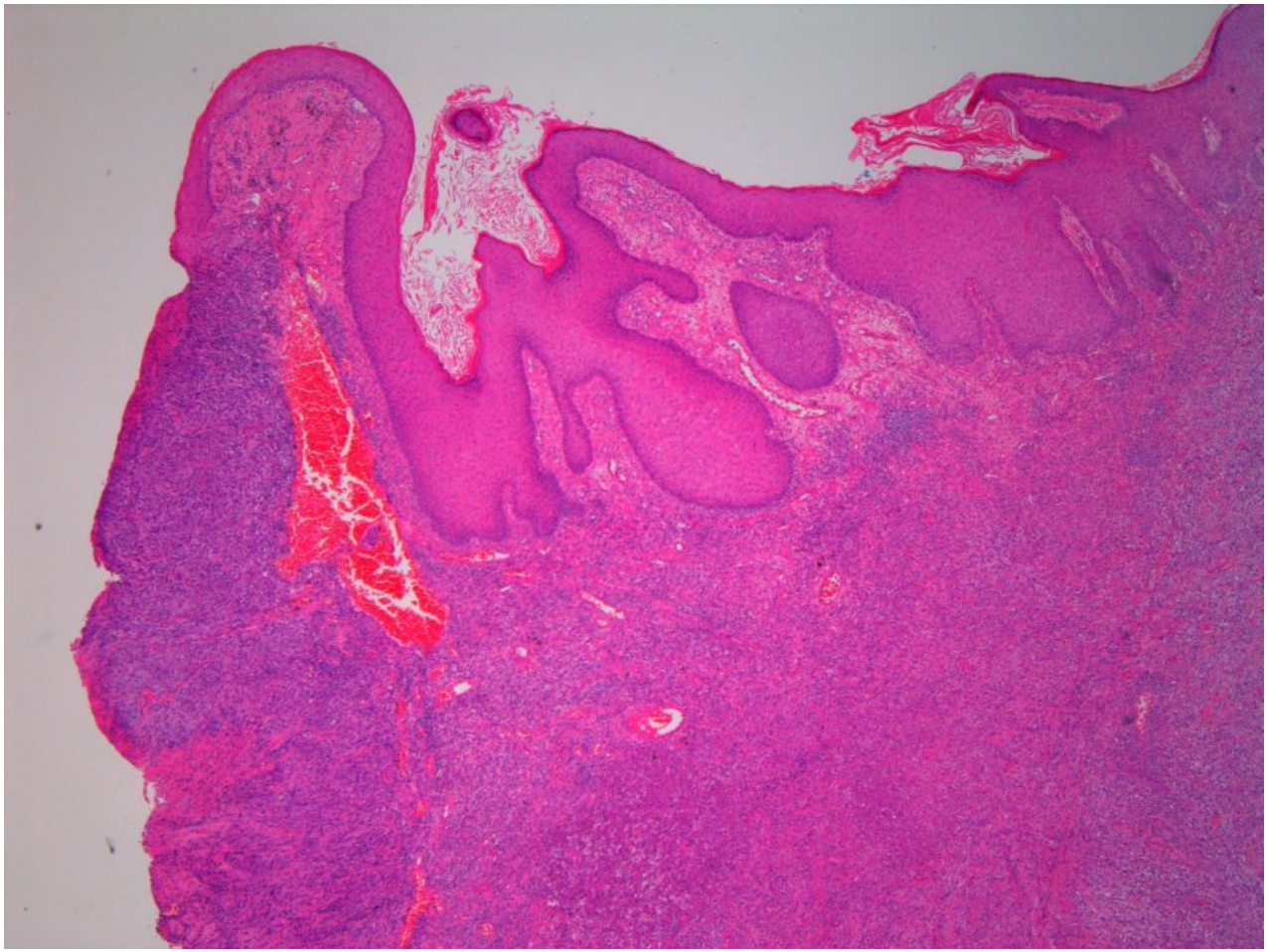


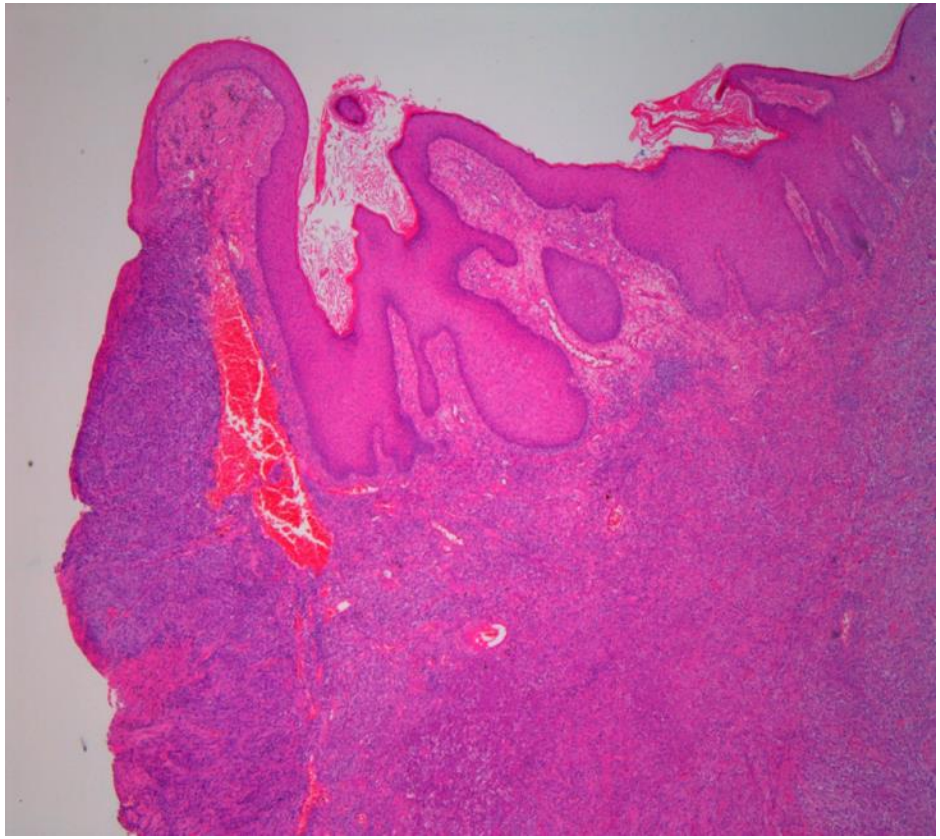
S100

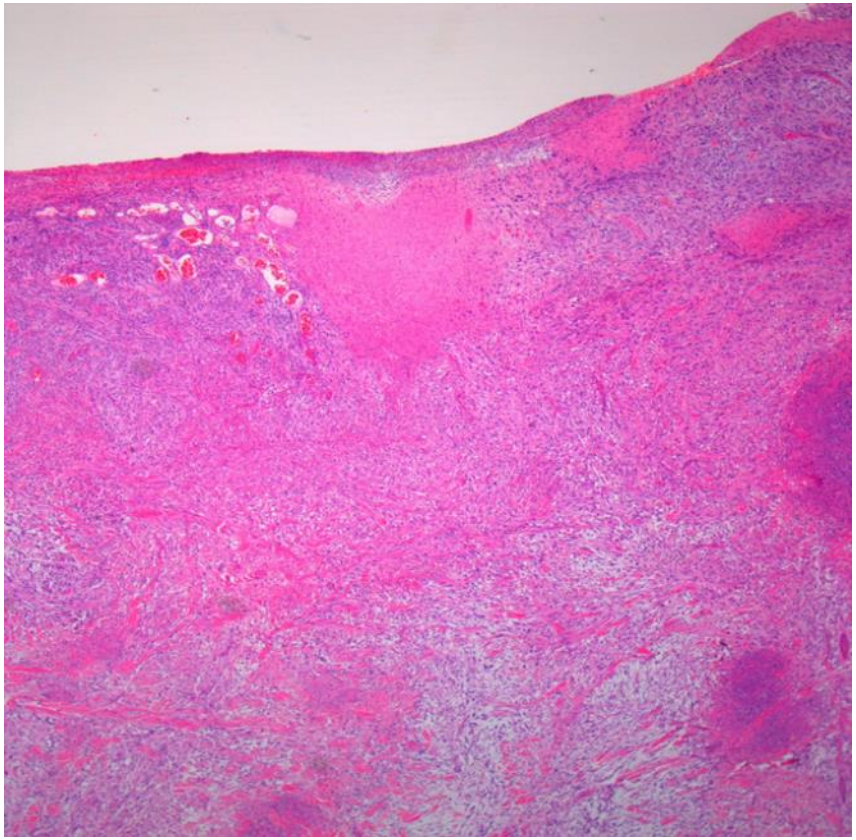
Diagnosis

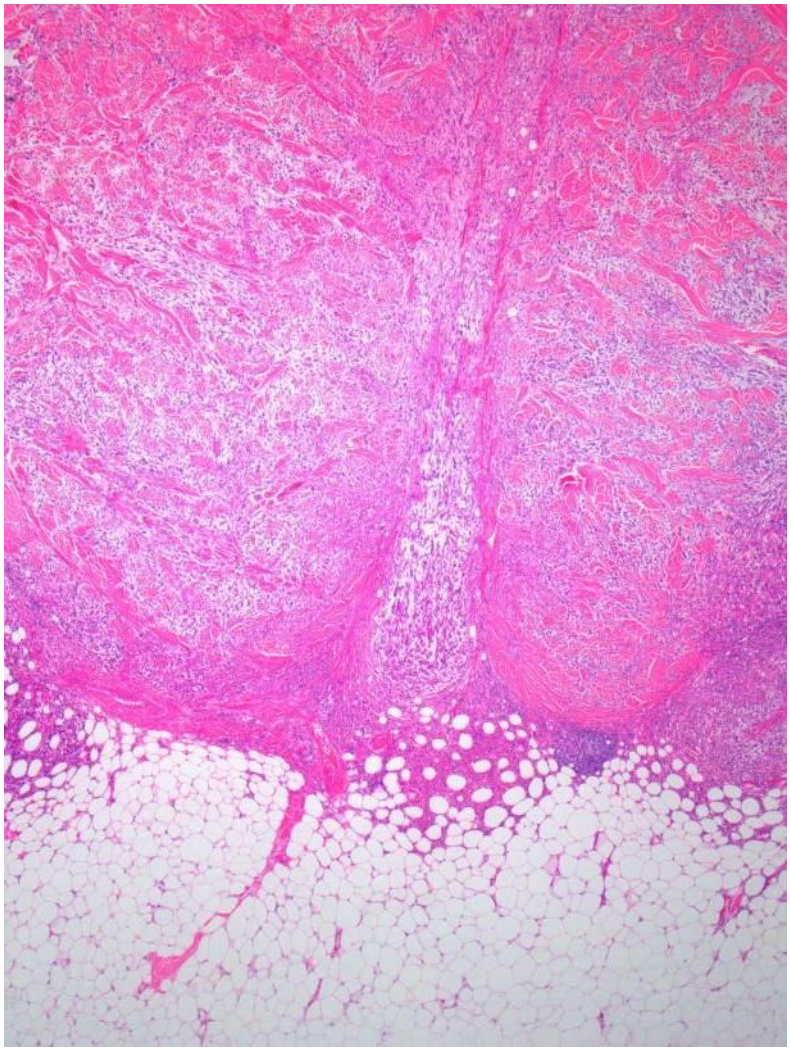
- Sarcomatoid malignant melanoma (melanoma with sarcomatoid dedifferentiation), with prominent osteoclast type giant cells

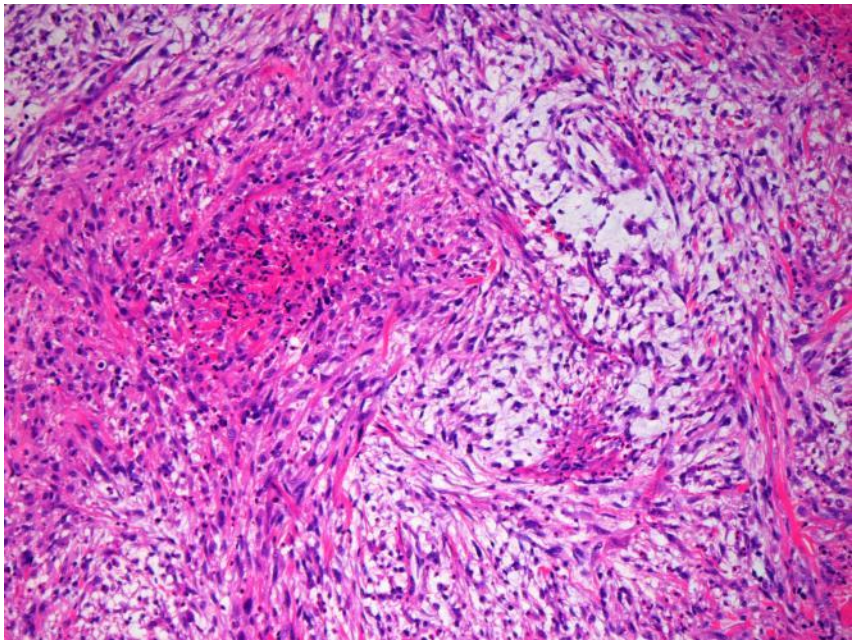
- PS5. 77M.Skin lesion, back, WLE

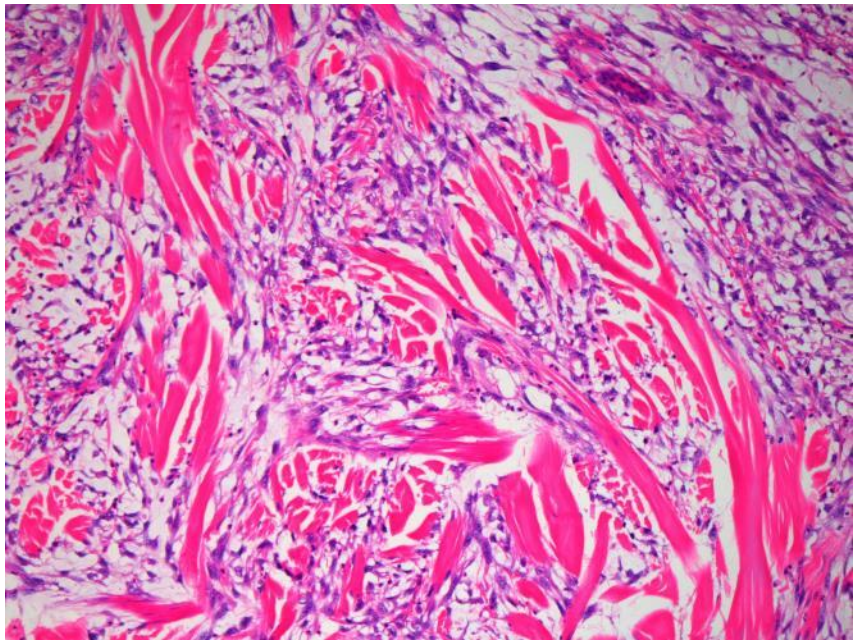


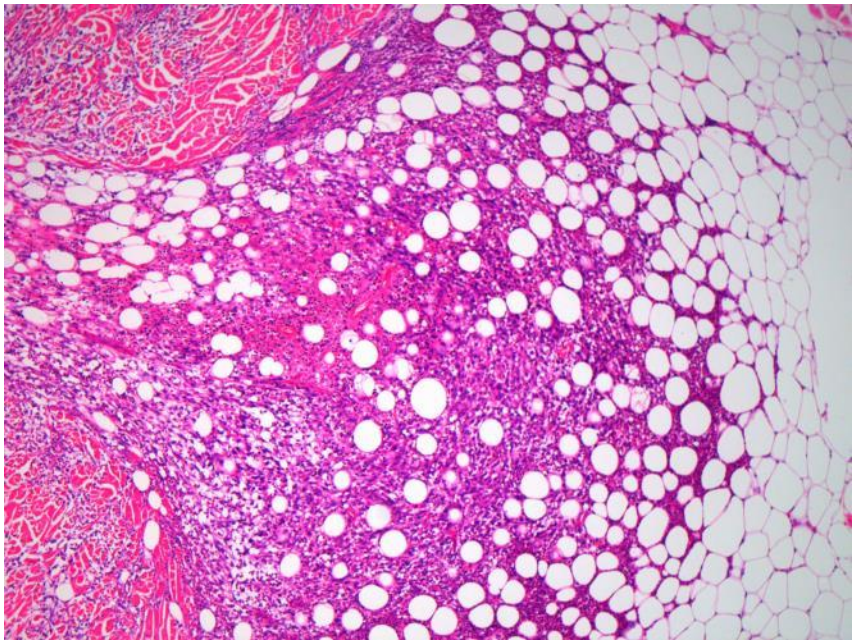


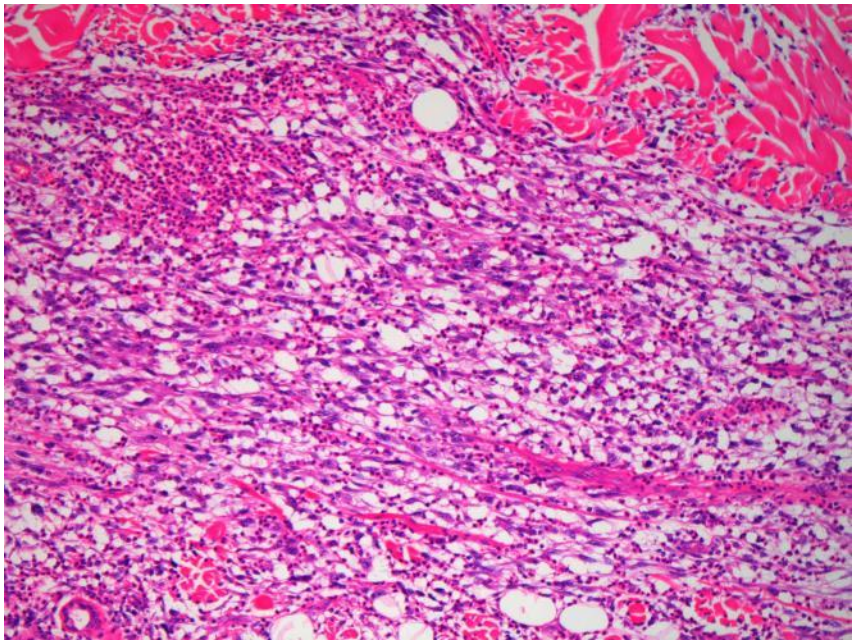


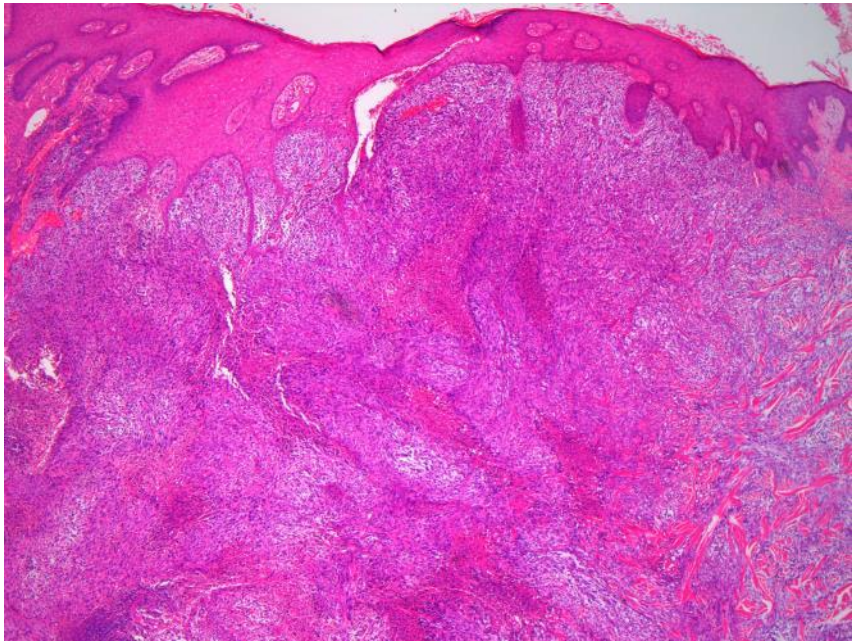


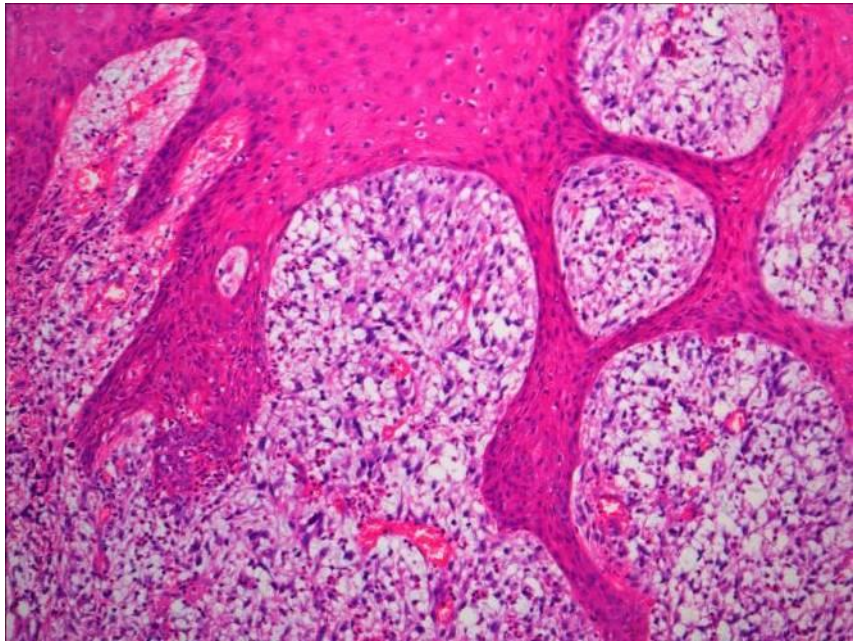


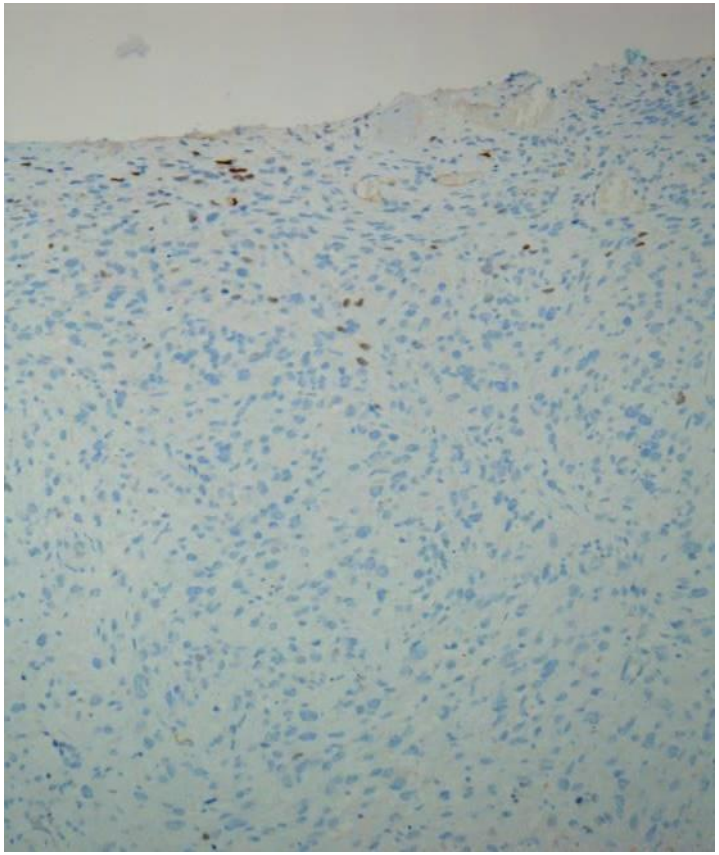




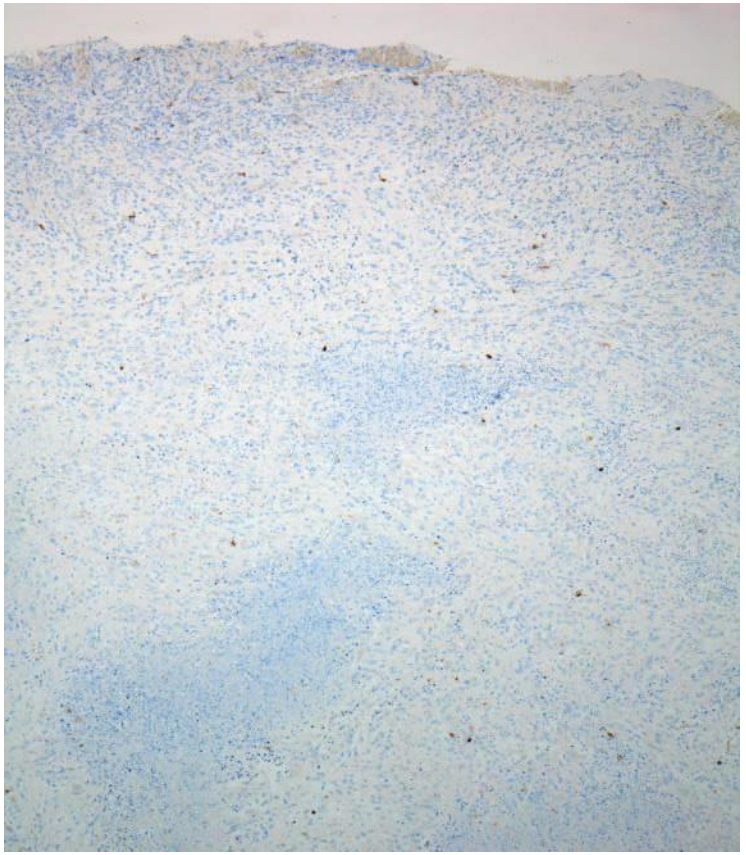








SOX10



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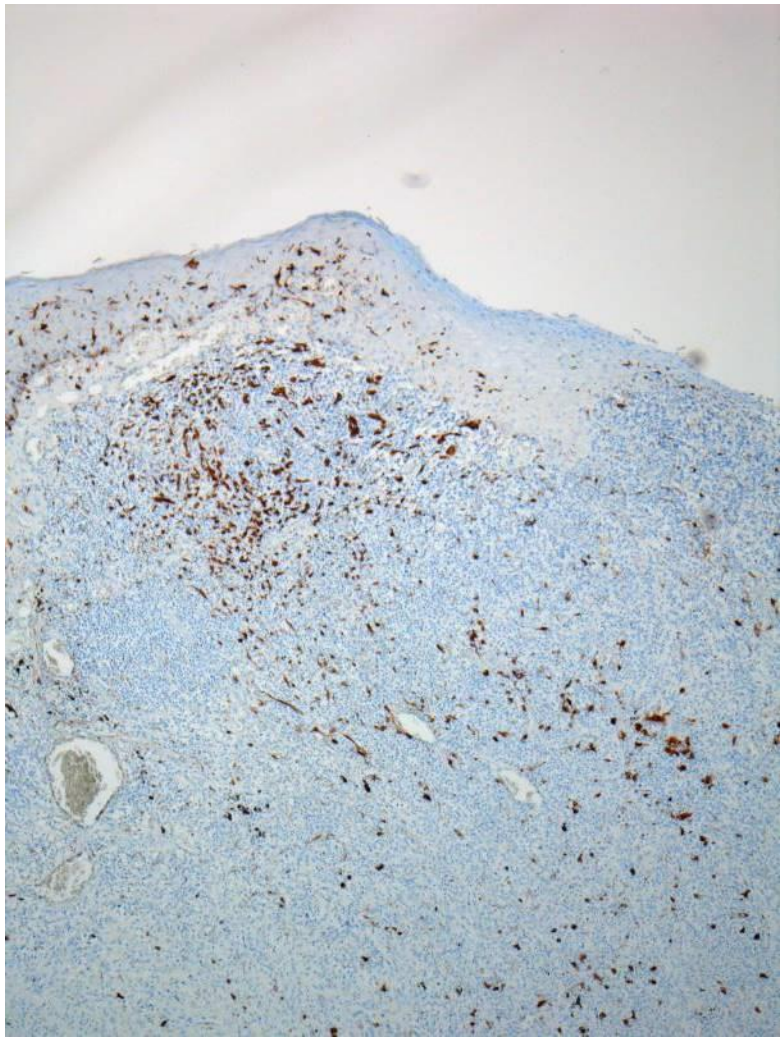

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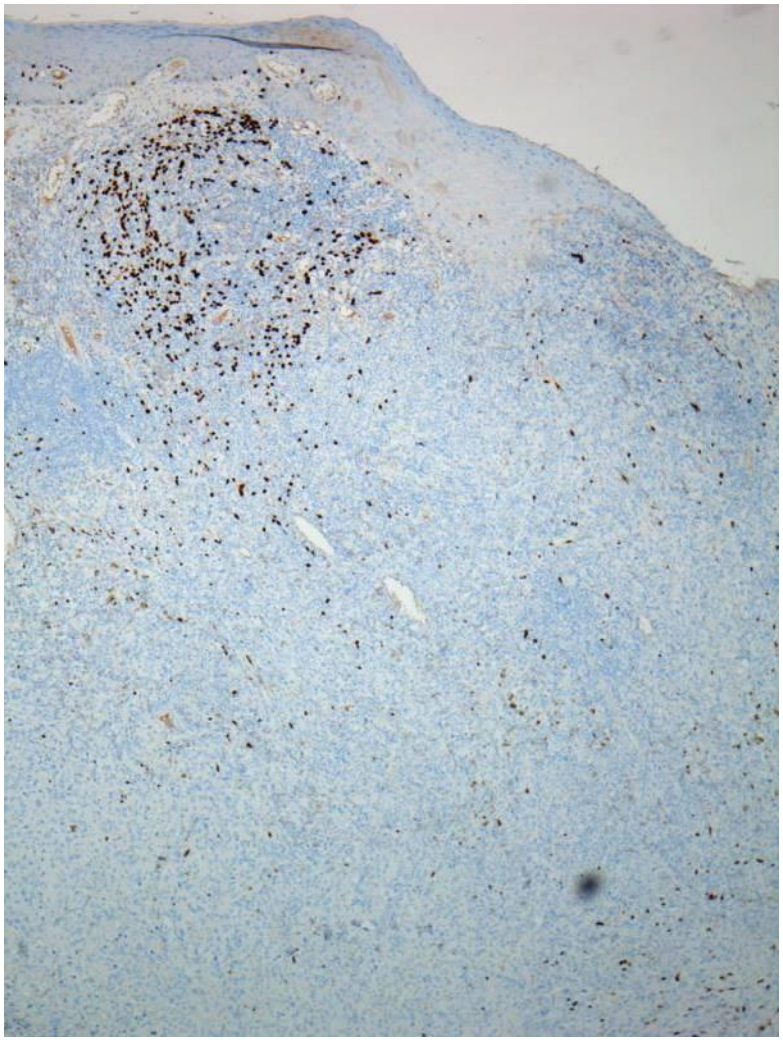

SOX10

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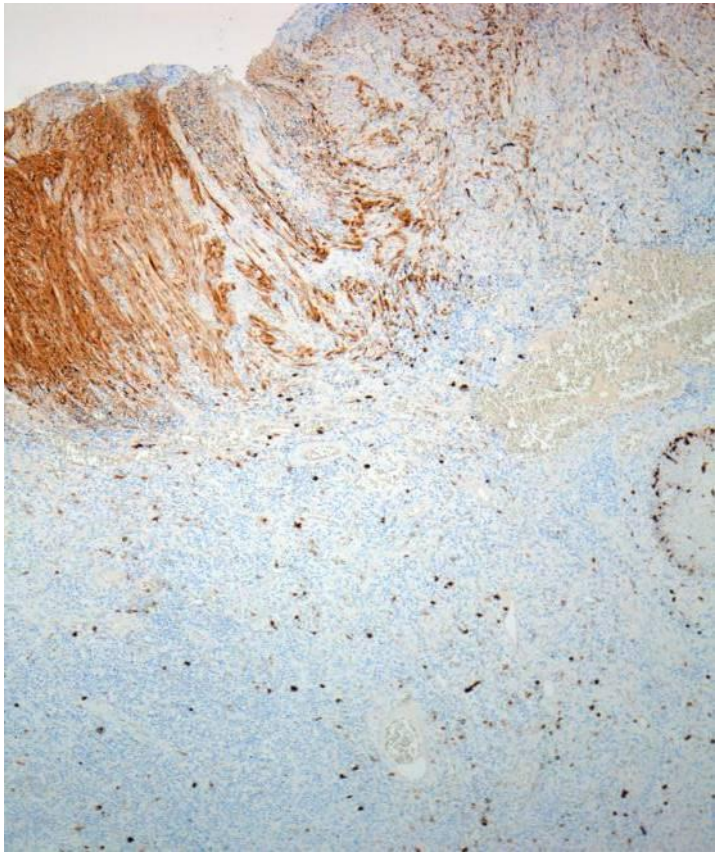
NHS Foundation Trust



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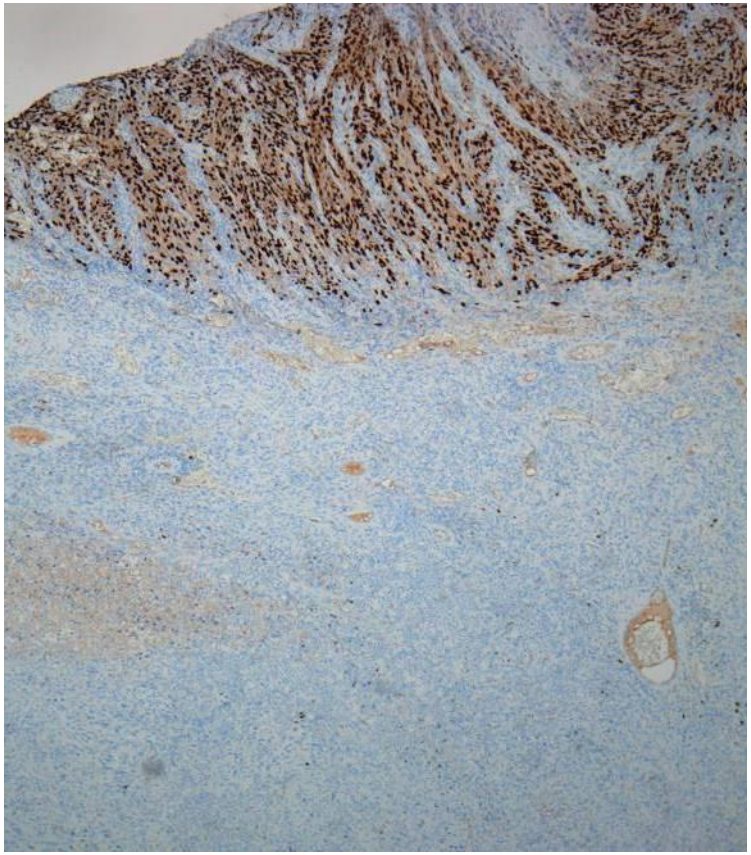

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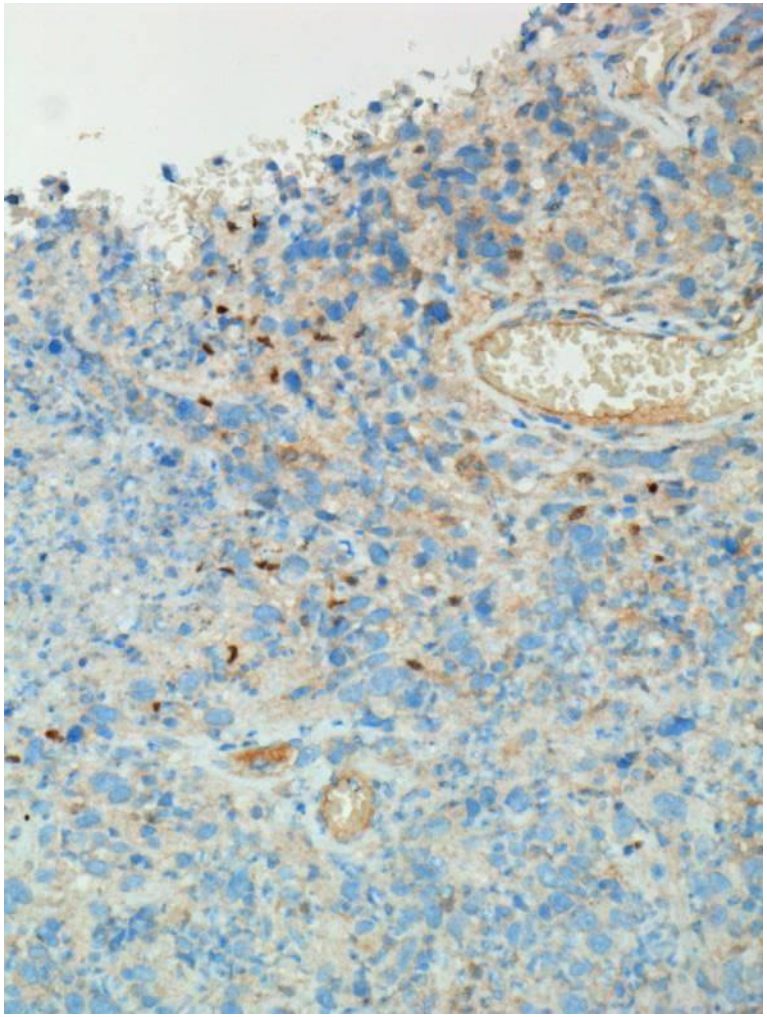

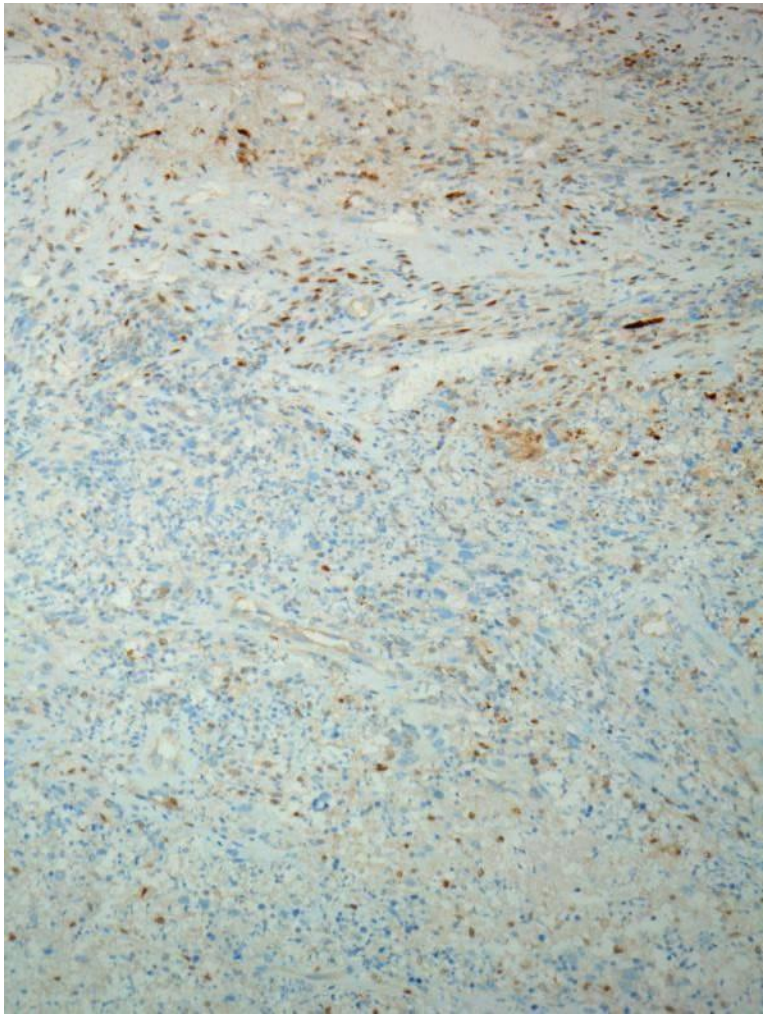

MiTF

Diagnosis

- Sarcomatoid malignant melanoma (melanoma with sarcomatoid dedifferentiation)

Desmoplastic Melanoma with Sarcomatoid De-differentiation

Maija Kiuru, MD PhD[1], **Gregory McDermott, BA**[1], **Michael Berger, PhD**[1,2], **Allan C Halpern, MD**[3], and **Klaus J Busam, MD**[1]

[1]Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York

[2]Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, New York

[3]Department of Medicine, Dermatology Service, Memorial Sloan-Kettering Cancer Center, New York, New York

Abstract

Desmoplastic melanoma (DM) is a variant of melanoma, which typically affects chronically sun-damaged skin of elderly patients. Pure DM displays a low density of fusiform melanocytes in a collagen-rich matrix. In mixed DM, tumor cell density is higher, and parts of the tumor lack abundant stromal fibrosis. Both pure and mixed DM usually express S100 protein homogeneously. We report herein an unusual bi-phenotypic tumor characterized by the association of a pure DM with an undifferentiated solid spindle cell nodule. It occurred on the scalp of a 66 year-old man. A biopsy of the undifferentiated spindle cell nodule was initially interpreted at a commercial laboratory as atypical fibroxanthoma. The pure DM was seen only in the excisional specimen. All cells of the pure DM stained for S100 protein and SOX10. The adjacent solid sarcomatoid spindle cell nodule lacked expression of S100 protein, SOX10, as well as melan-A, gp100 and microphthalmia transcription factor in more than 95% of its tumor cells. While focal expression of melanocyte differentiation antigens in the solid tumor component made us favor a combined DM with sarcomatoid de-differentiation, we also considered the possibility of a collision scenario, i.e., a pleomorphic dermal sarcoma incidentally colliding with a DM. To further assess a possible relationship of the sarcomatoid nodule with the DM, we performed next-generation sequencing analysis on each component separately. The analysis revealed shared chromosomal copy number changes and a high number of common mutations, thereby supporting the concept of a DM with a de-differentiated sarcomatoid component. An interesting finding is the presence of mutations of the neurofibromin gene in both tumor components

Am J Surg Pathol. 2014

The Christie NHS
NHS Foundation Trust

Living on the Edge: Diagnosing Sarcomatoid Melanoma Using Histopathologic Cues at the Edge of a Dedifferentiated Tumor: A Report of 2 Cases and Review of the Literature

Emily M. Erstine, MD, MBA, Michael T. Tetzlaff, MD, PhD,† Jennifer S. Ko, MD, PhD,* Victor G. Prieto, MD, PhD,† Alison L. Cheah, MBBS,‡ and Steven D. Billings, MD**

Abstract: Sarcomatoid melanoma is a rare type of melanoma lacking typical histologic features of melanoma and often lacks expression of S100 protein and melanocyte-specific markers. Given the rarity of this entity, its clinicopathologic findings are not well defined. We report 2 cases of sarcomatoid melanoma received in consultation: a 65-year-old woman with a right breast mass and a 62-year-old man with a left plantar heel mass. Both lesions were ulcerated, pedunculated, highly cellular proliferations of atypical spindle cells arranged as fascicles and/or sheets. The tumor cells of the breast mass expressed CD10 and vimentin diffusely but S100 protein only focally. The tumor cells of the heel mass lacked expression of melanocytic markers altogether, except for weak, very focal S100 protein expression. At the junctional edge of the breast mass and in the ulcer base of the heel mass, focal precursor melanoma was present and exhibited melanocytic differentiation. We report these cases to emphasize the importance of meticulous histologic inspection at the lesion's edge and/or ulcer base to correctly identify the conventional precursor melanoma in these rare lesions to ensure appropriate diagnosis and subsequent clinical management as treatment options may be significantly different from those offered for sarcomas.

differential diagnosis of primary cutaneous pleomorphic spindle-cell neoplasms. Therefore, making a correct diagnosis of sarcomatoid melanoma is not only essential for initiating appropriate clinical management but also for contributing meaningful data to the existing scarce literature regarding its clinicopathologic behavior. Although because of its rarity, the efficacy of targeted immunotherapies recently approved for melanoma is unknown, accurate diagnosis would potentially allow a chemotherapeutic option that could positively affect patient outcome. Herein, we describe 2 cases of sarcomatoid melanoma and review of the literature.

MATERIALS AND METHODS

Two cases were received in consultation in 2013 and 2014 at the Cleveland Clinic Foundation, Cleveland, OH, and at The University of Texas MD Anderson Cancer Center, Houston, TX. Sarcomatoid melanoma was defined as a primary cutaneous pleomorphic spindle-cell neoplasm with focal, weak, or absence of expression of neural crest or melanocytic markers in the sarcomatoid component with an

Take Home Message

- Divergent differentiation/trans-differentiation and dedifferentiation can rarely occur in melanomas
- MM may contain mesenchymal, neuroectodermal & epithelial components

- Such tumours may cause diagnostic confusion:

  -awareness of the possibility important
  -sampling
  -use of panel of IHC
  -clinical context

- Prognostic significance still uncertain – more experience required