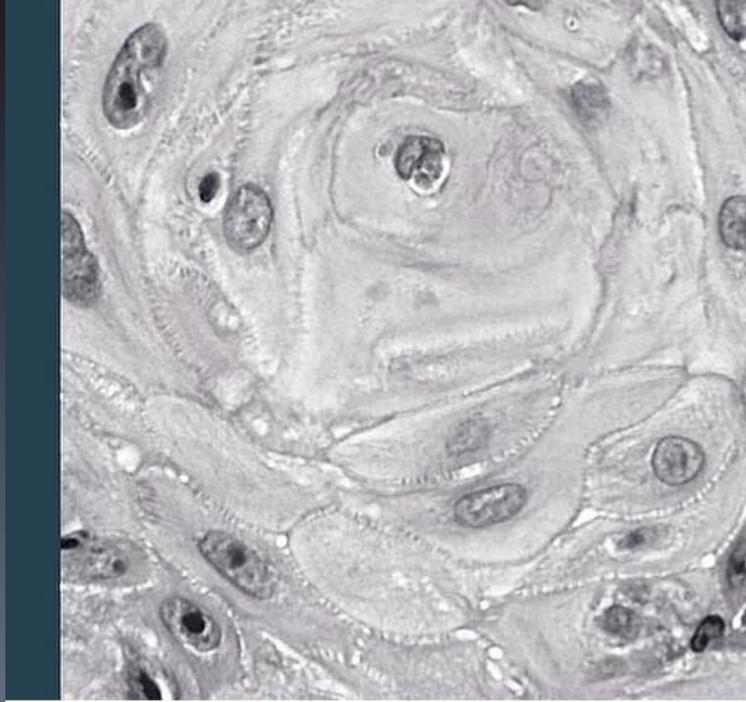


***CLAVES
IHQ DE
LESIONES
MELANOCITICAS***



**JORNADAS DE
ACTUALIZACIÓN
2020**

**CLAVES
HISTOPATOLÓGICAS EN
DERMATOPATOLOGÍA
NEOPLÁSICA**

Dr. Gonzalo de Toro Consuagra

Hospital de Puerto Montt – Universidad Austral de Chile

Inmunohistoquímica

- Ampliamente utilizada.
- Se reporta hasta en un 95% de lesiones melanocíticas más complejas.
- 42% mejoran la certeza en el diagnóstico de melanoma
- 50% de utilización en lesiones ambiguas

“La realidad es que la inmunohistoquímica es ordenada habitualmente,
pero no juiciosamente”

Zhao G, Lee KC, Kwon G, et al. J CutanPathol 2016; 43:492-407.

McCalmontTH. J CutanPathol 2012; 39: 1060-1061.

NagarajanP, et al. ActasDermosifiliogr. 2016. <http://dx.doe.org/10.1016/j.ad.2016.05.005>

UTILIZACION

- S100
- MELAN A/MART-1
- SOX-10
- MITF
- HMB-45
- KI-67
- P16
- BAP-1
- PRAME

UTILIDAD



UTILIZACION

- S100
- MELAN A/MART-1
- SOX-10
- MITF
- HMB-45
- KI-67
- P16
- BAP-1
- PRAME

Sensitivity



Antibody	Staining Pattern
S100	Nuclear/cytoplasmic staining
Sox-10	Nuclear staining
Melan A/MART-1	Cytoplasmic staining
MiTF	Nuclear staining
Tyrosinase	Cytoplasmic staining
HMB-45	Cytoplasmic staining

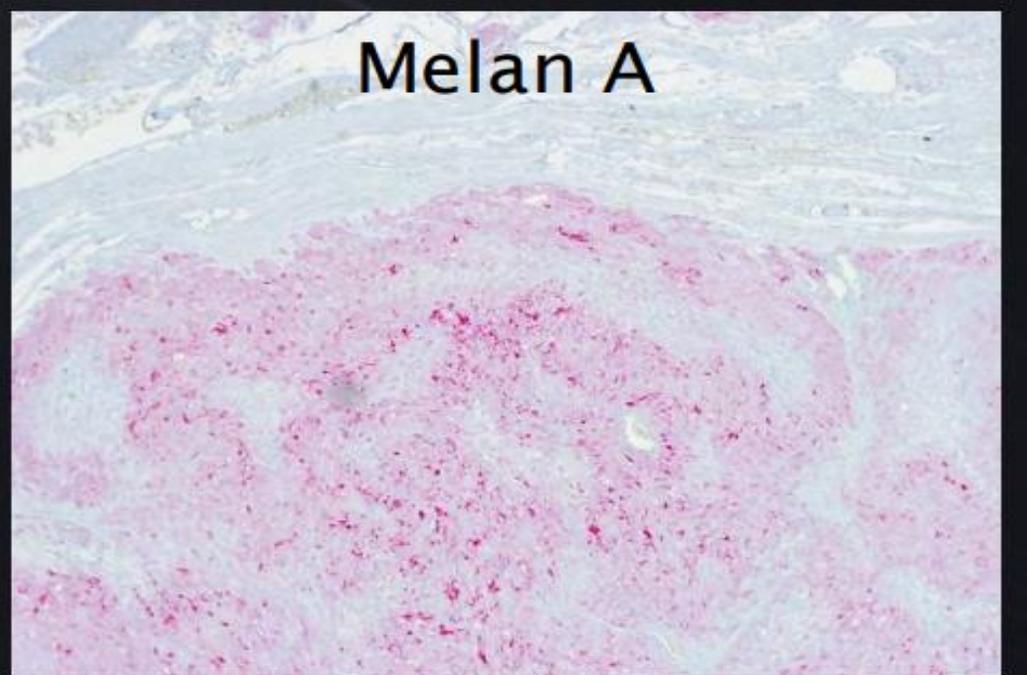
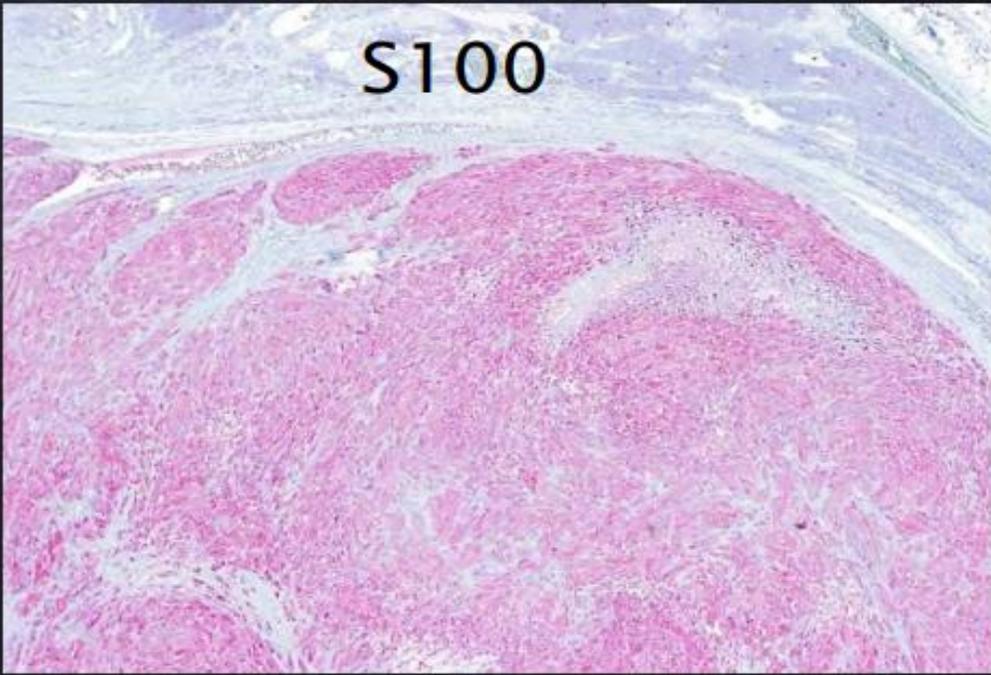
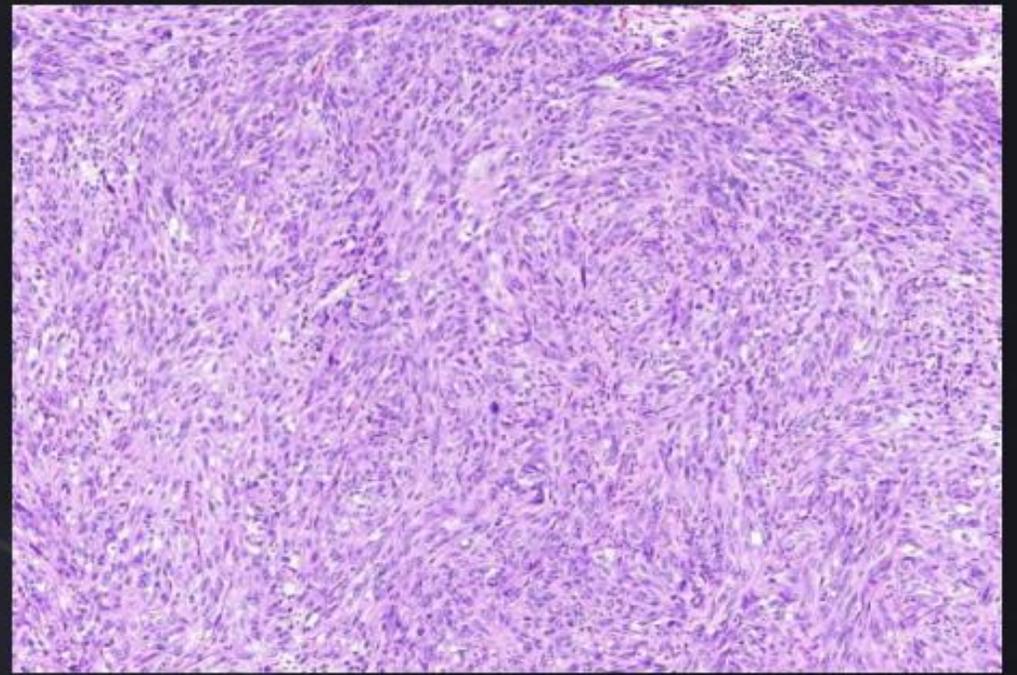
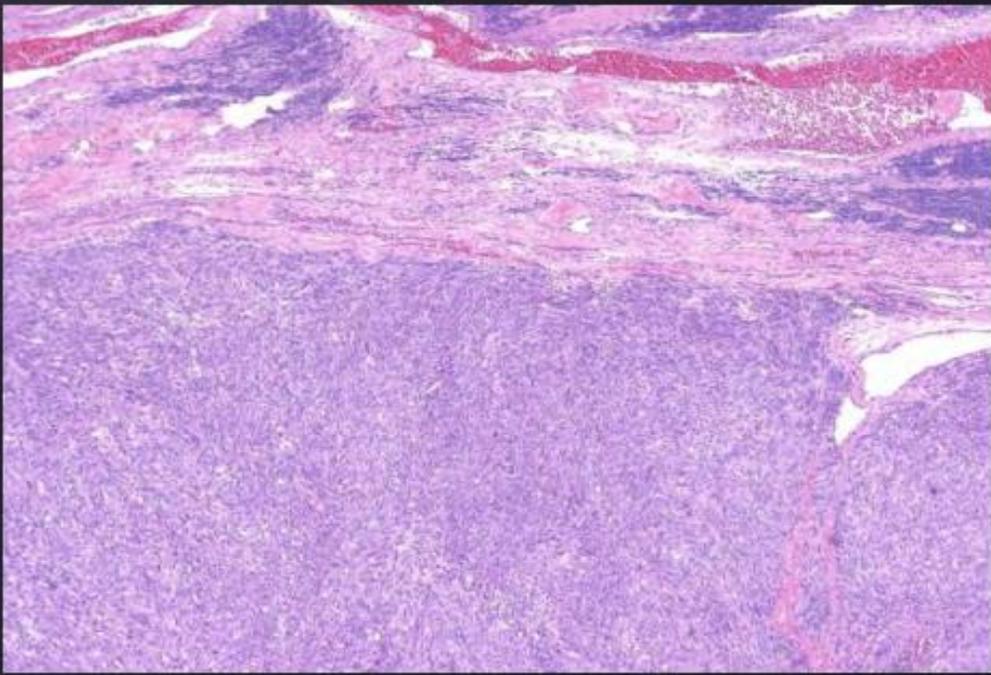
Specificity



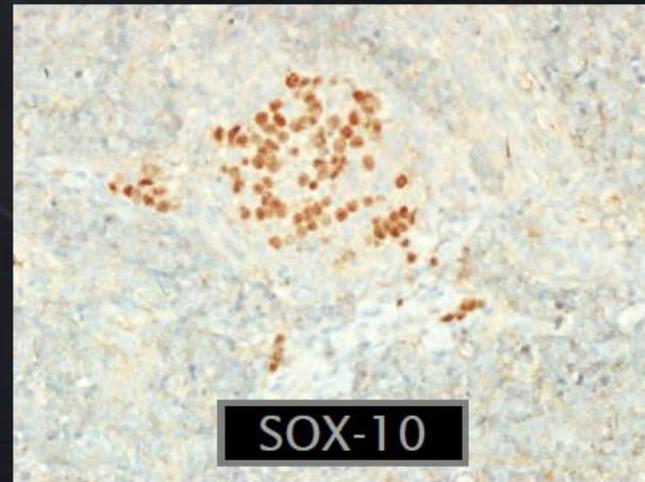
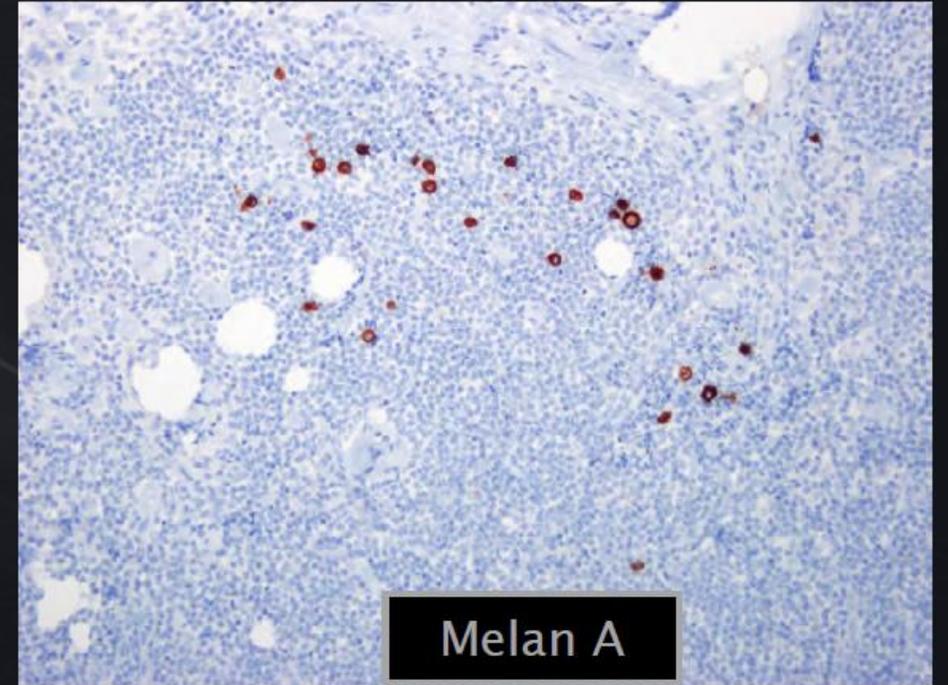
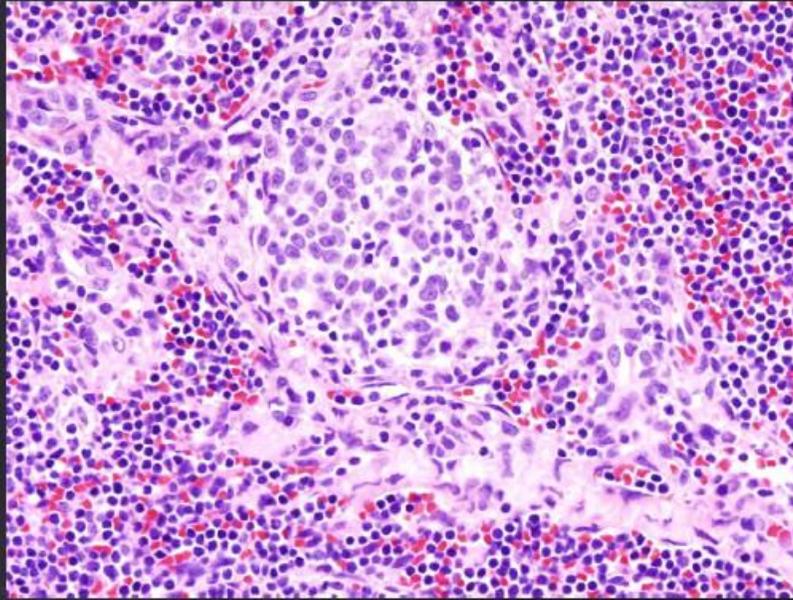
UTILIDAD

- Confirmar línea melanocítica
 - Neoplasias amelanóticas
 - Neoplasias malignas poco diferenciadas
 - Tumores malignos fusiformes
 - Lesiones metastásicas
- Evaluación de linfonodos centinelas.
- Evaluación de márgenes y profundidad (M. desmoplástico).
- Evaluación de proliferaciones melanocíticas sutiles de la unión.



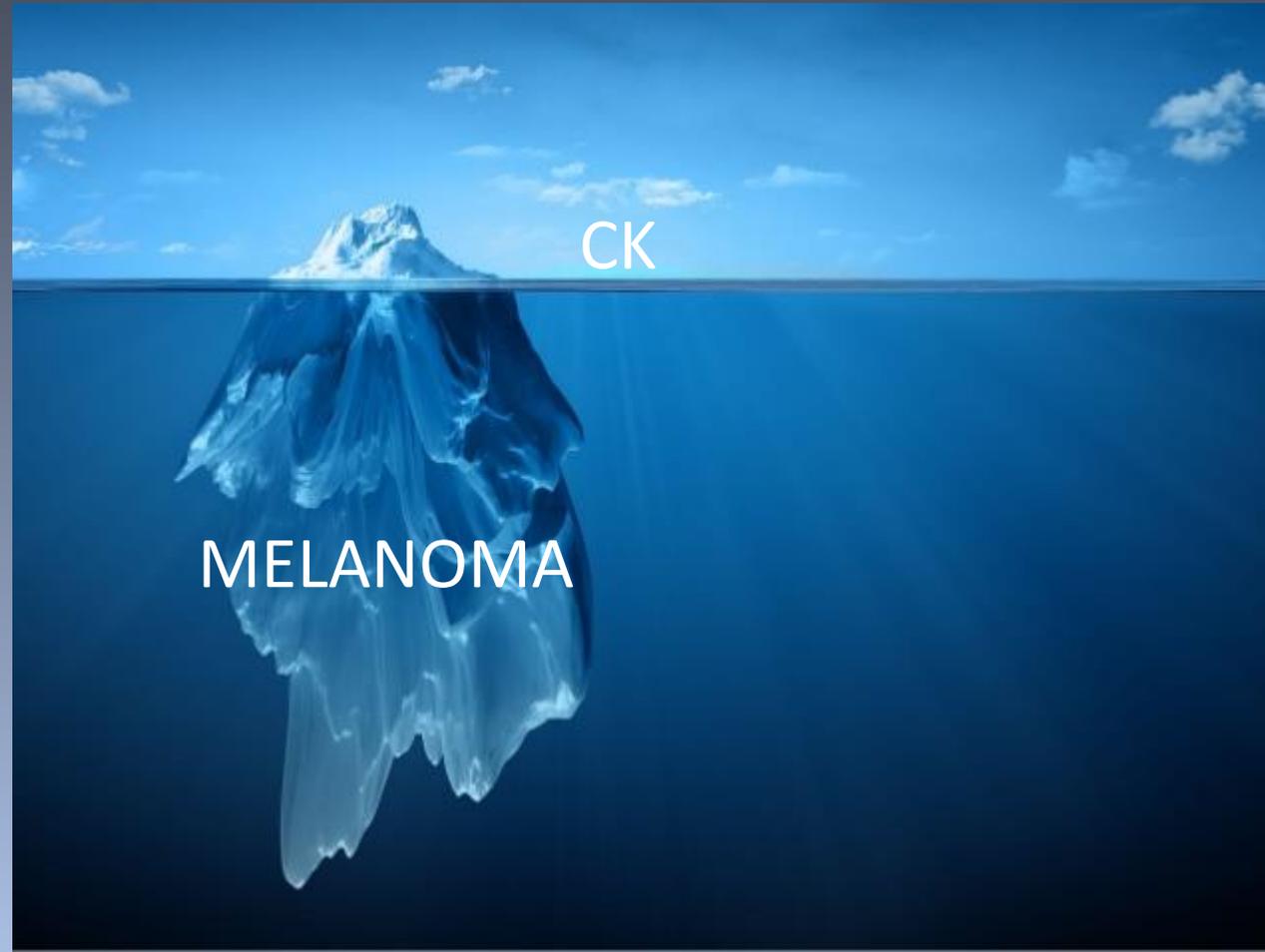


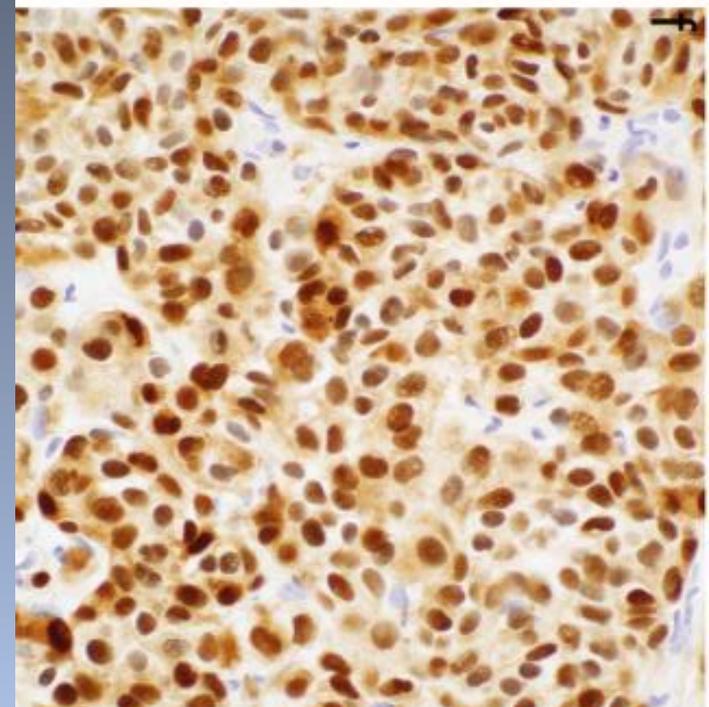
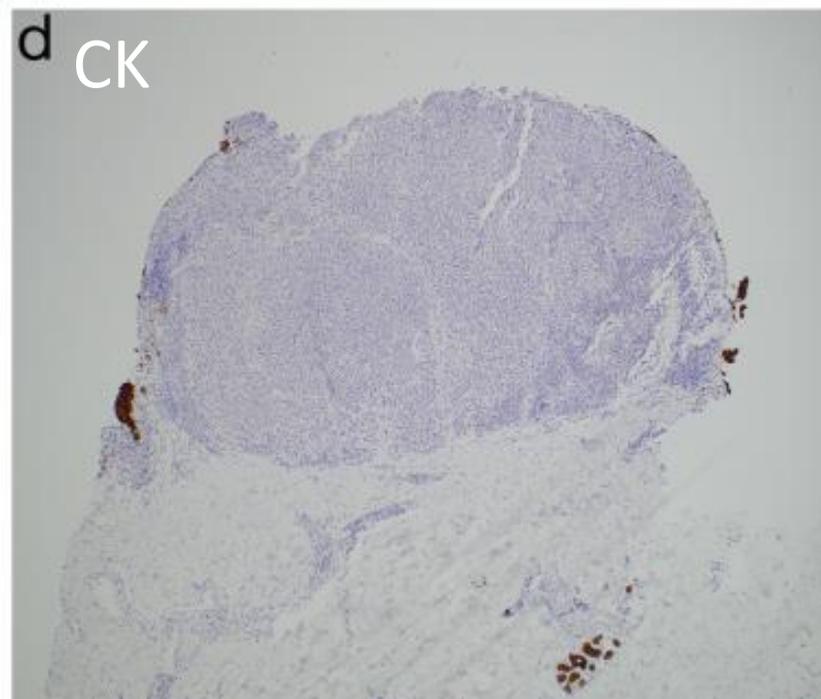
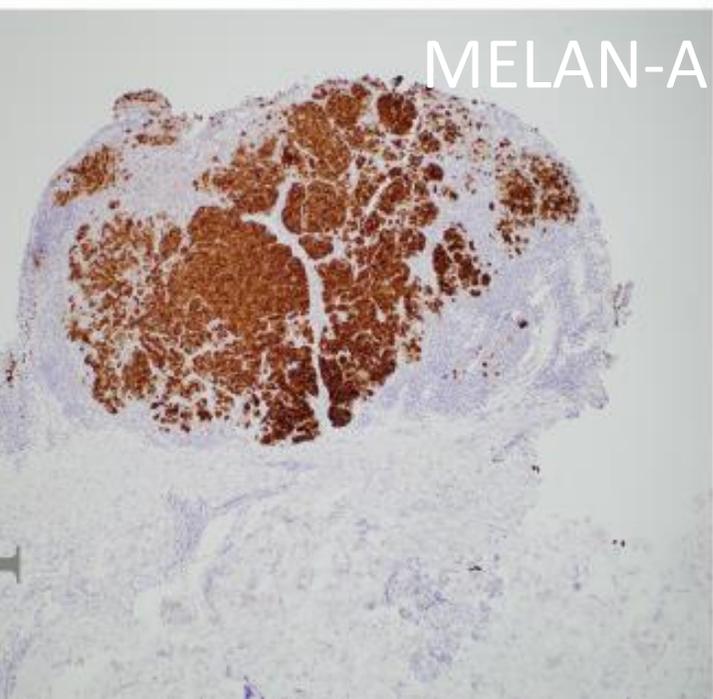
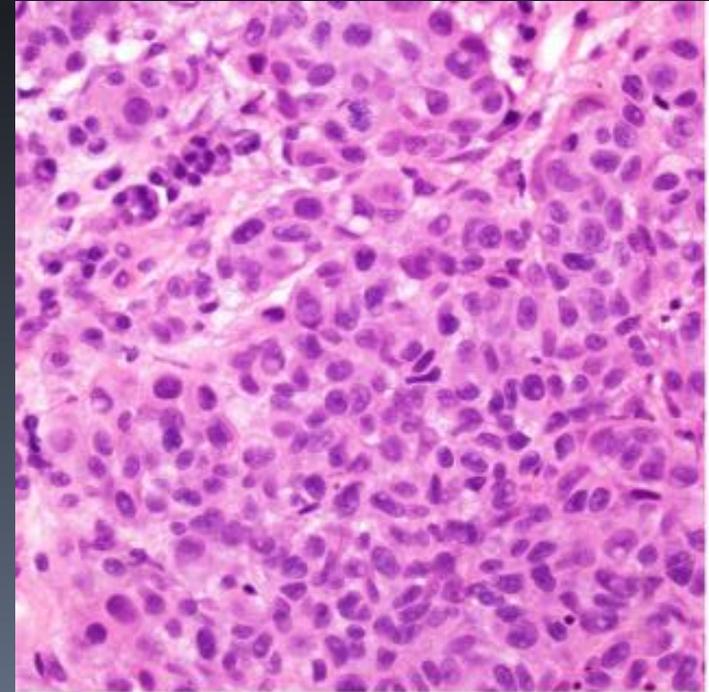
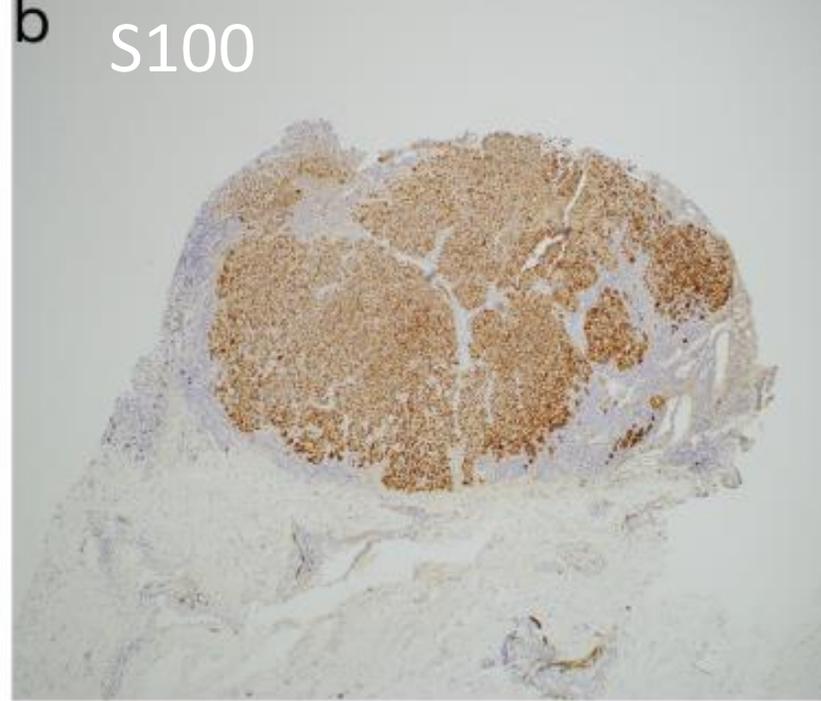
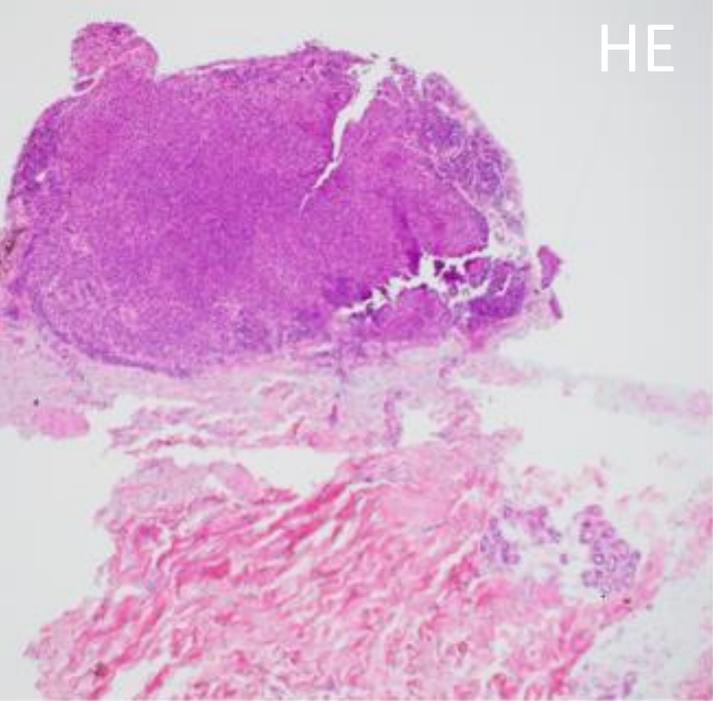
METASTASIS DE MELANOMA EN LINFONODO CENTINELA

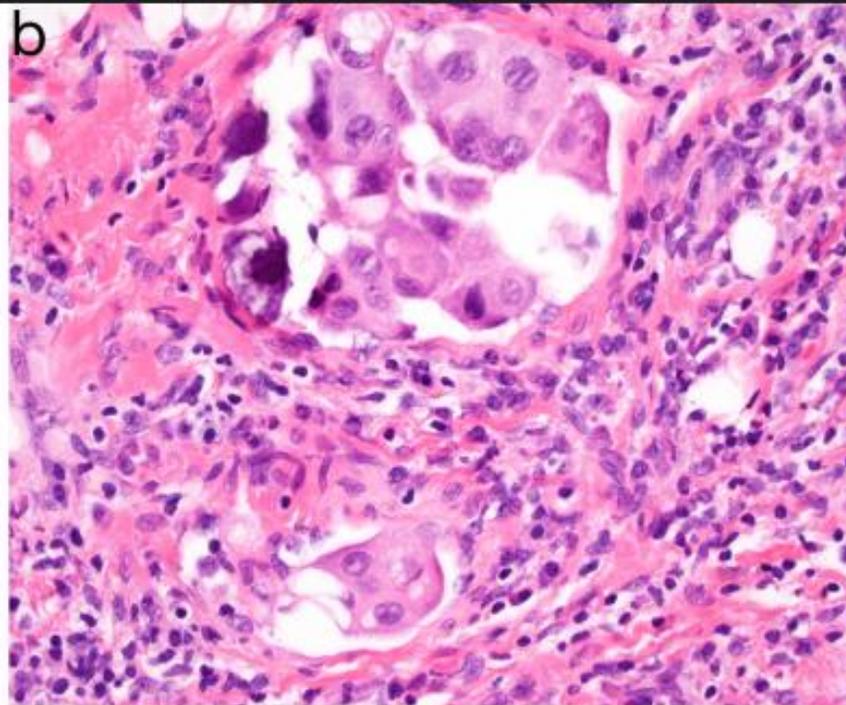
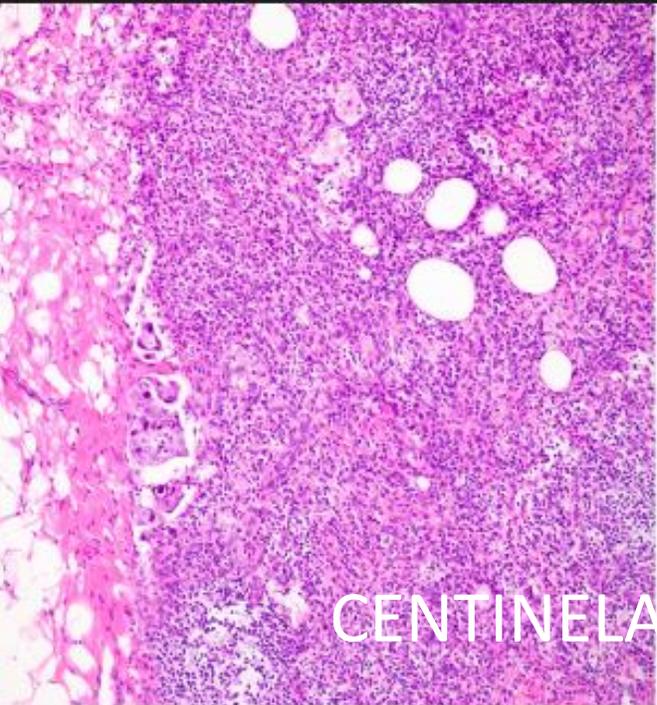


PEARLS AND PITFALLS

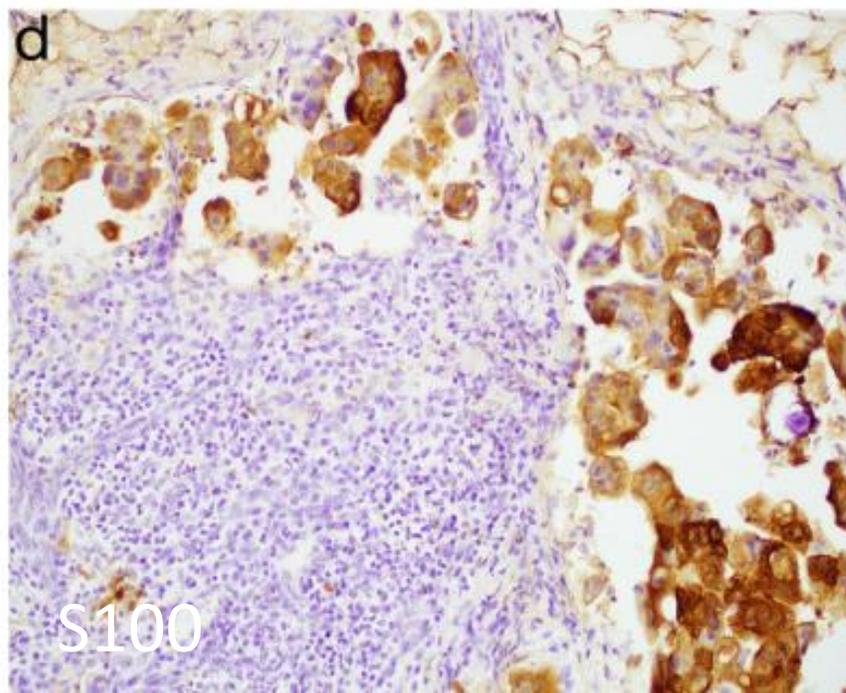
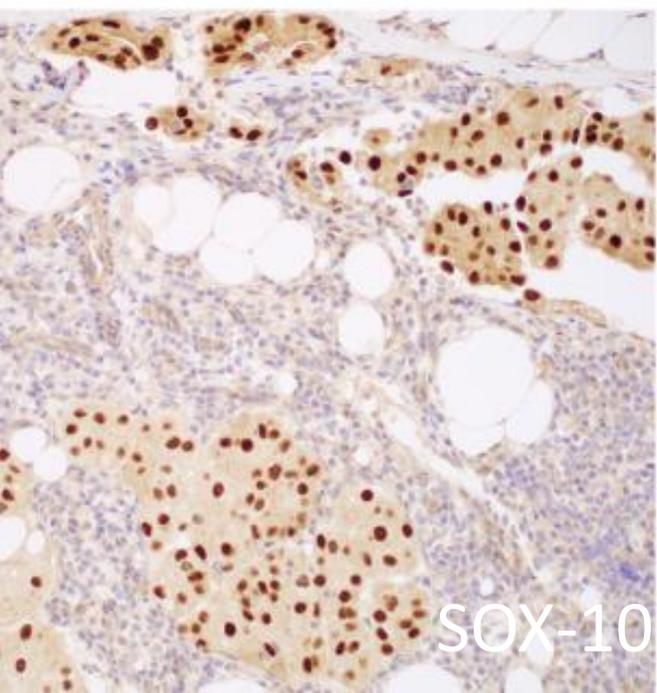
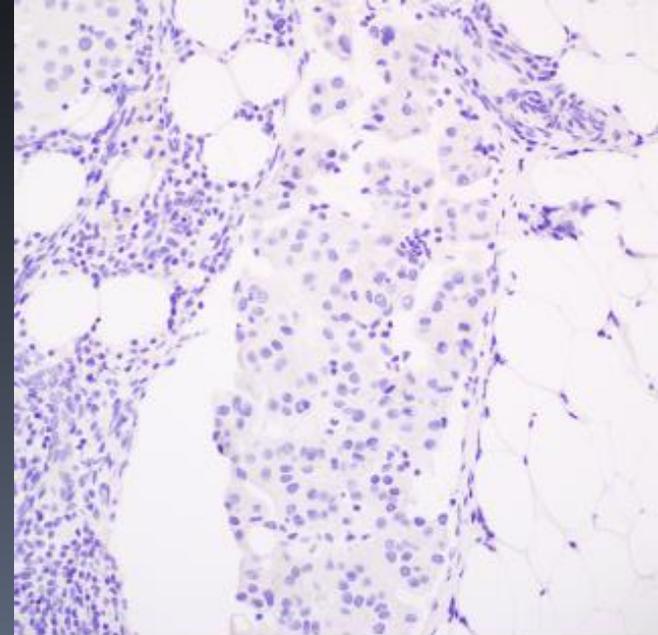
- PEARL: 20% DE LOS MELANOMAS EXPRESAN MARCADORES EPITELIALES



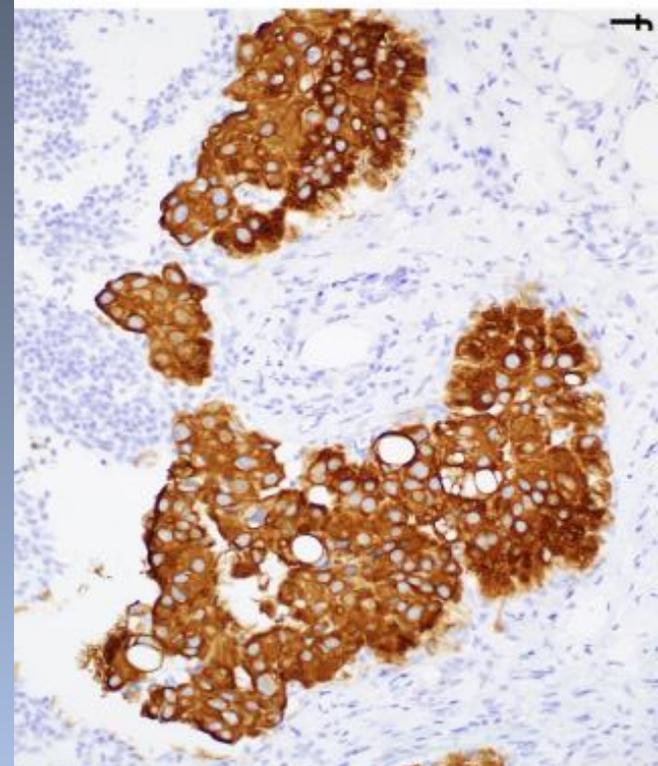




MELAN-A



CK7



Pitfalls:

Case Reports

> J Cutan Pathol. 2020 Jul 24. doi: 10.1111/cup.13822. Online ahead of print.

S-100 Protein and SOX10-positive Breast Carcinoma Mimicking Metastatic Melanoma

John Newman¹, Meera Brahmbhatt², Benjamin K Stoff^{2 3}, Anthony P Martinez^{2 3}

Affiliations + expand

PMID: 32710508 DOI: [10.1111/cup.13822](https://doi.org/10.1111/cup.13822)

Abstract

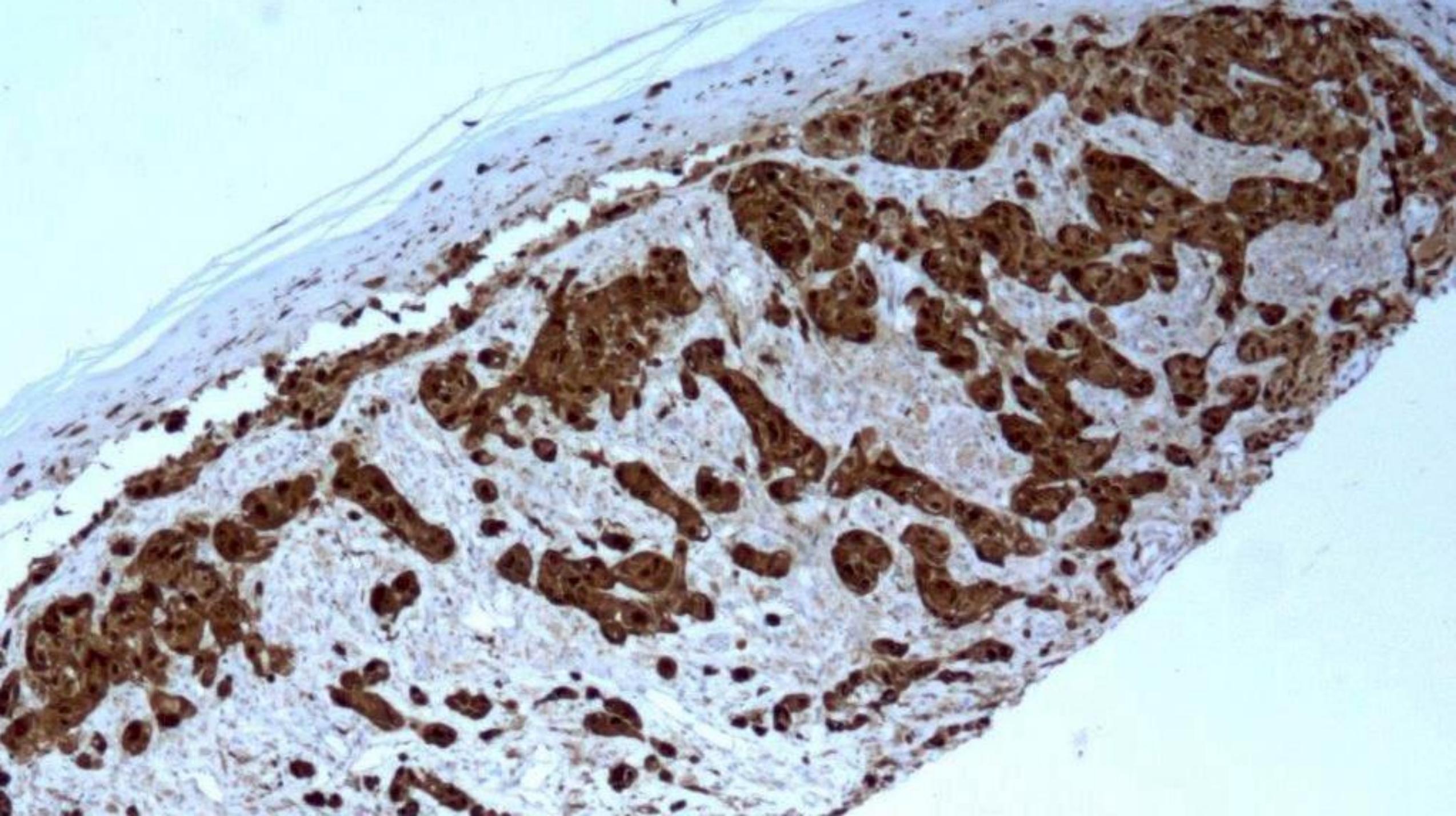
We present a case detailing a 70-year-old female with a history of triple negative breast carcinoma (TNBC) of the left breast and contralateral stage pT2a nodular melanoma of the right upper arm that underwent sentinel lymph node biopsy of the right axilla demonstrating a metastatic epithelioid tumor that was strongly positive for S-100 protein and SOX10. The tumor cells were negative for HMB-45 and Melan-A and positive for CK7 and other breast markers (GCDFP15, mammaglobin, and GATA3). While concerning for metastatic melanoma based on clinical history and initial immunohistochemistry, tumor morphology and subsequent immunohistochemistry was supportive of metastatic breast adenocarcinoma. This case demonstrates a rare but perilous diagnostic pitfall of triple negative breast carcinomas that strongly and diffusely express S-100 protein and SOX10 mimicking melanoma. This article is protected by copyright. All rights reserved.

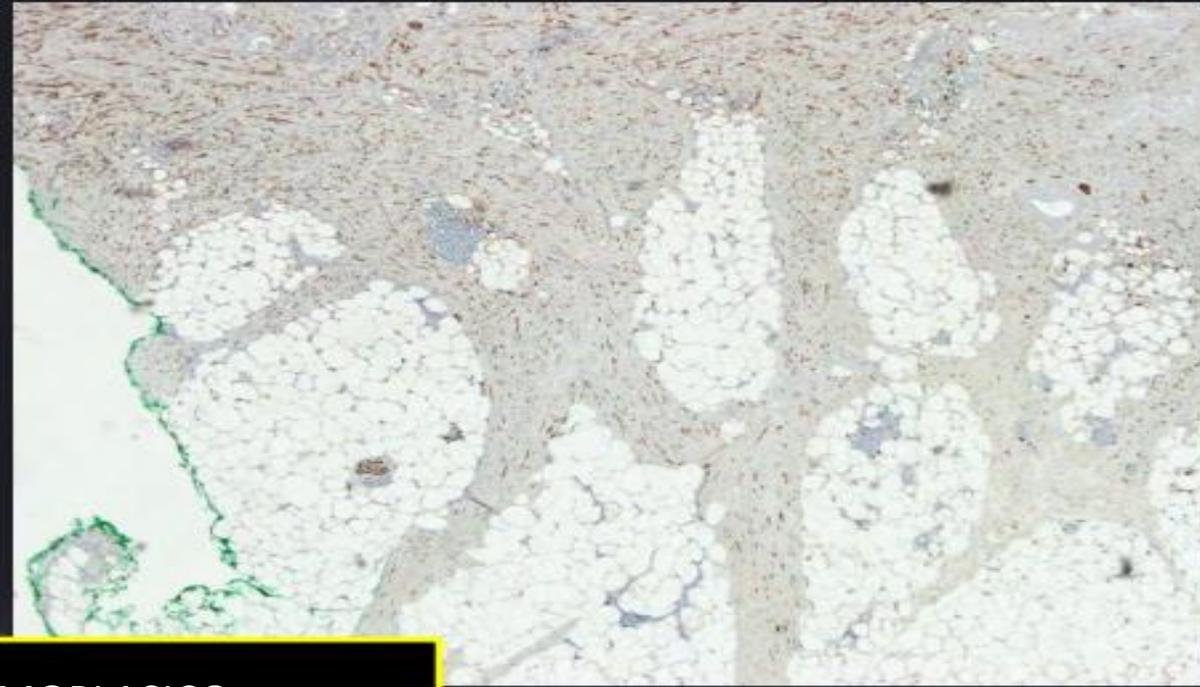
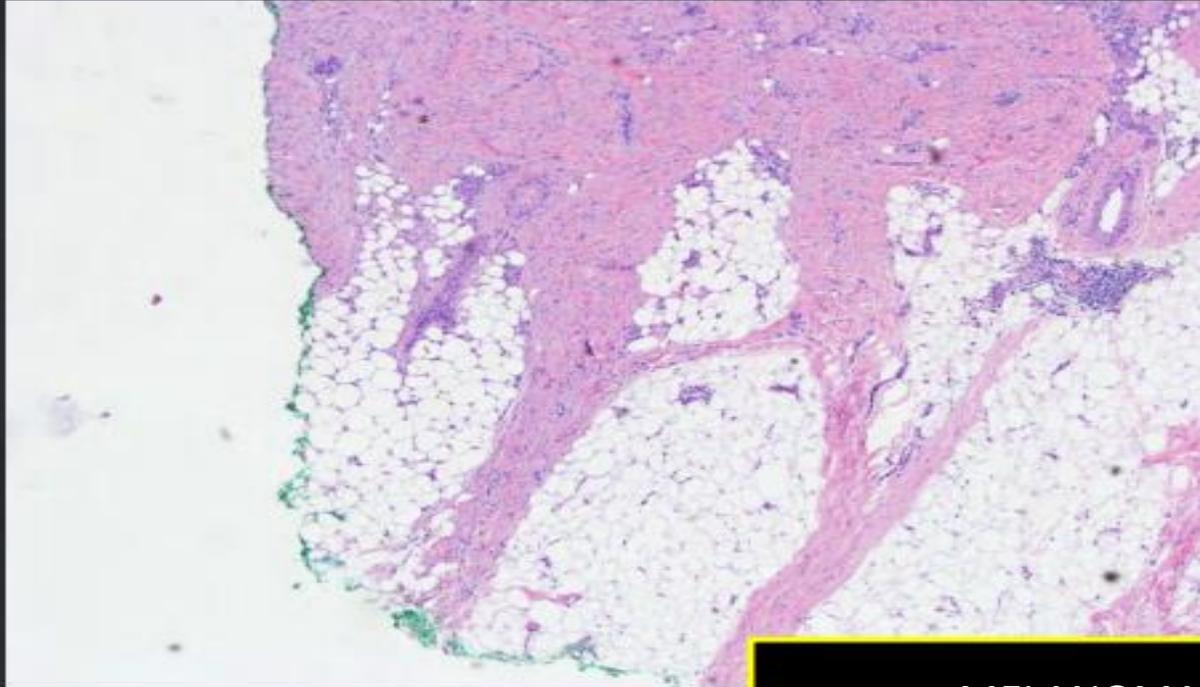
Keywords: Breast carcinoma; S-100; SOX10; melanoma; metastasis.

This article is protected by copyright. All rights reserved.

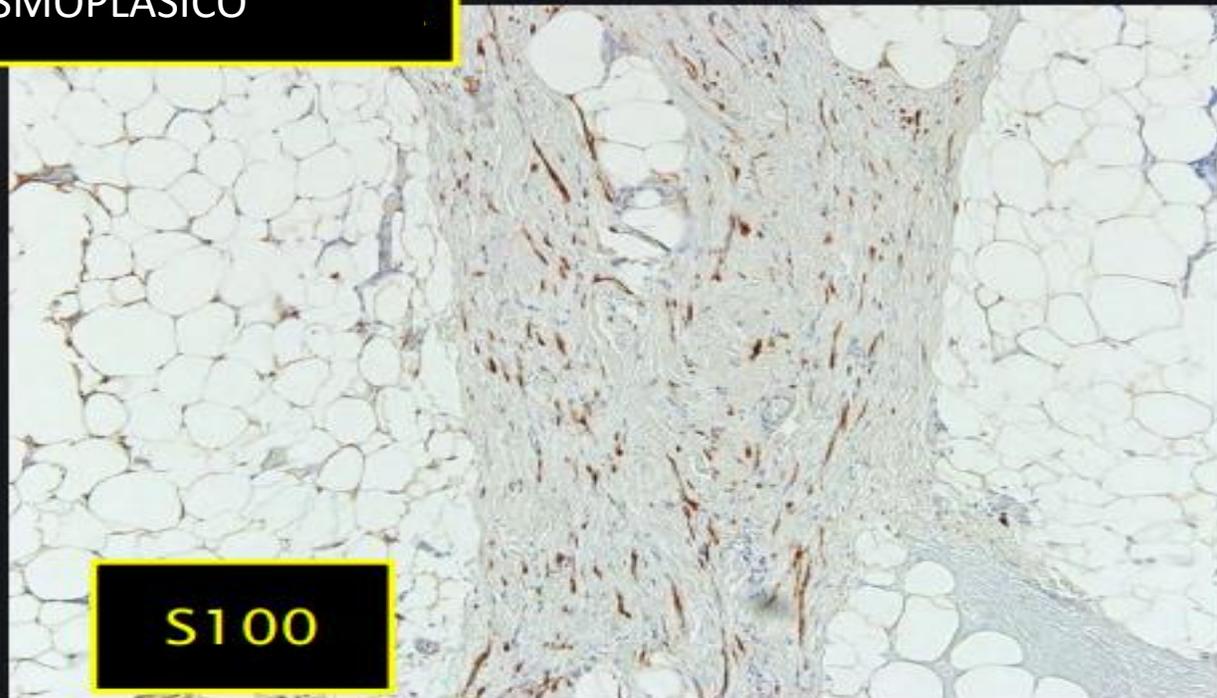
PROTEINA S100

- Más del 95% de los melanomas cutáneos primarios expresan S100.
- Sin embargo, varias condiciones pueden afectar su expresión:
 - Demasiado o muy poco tiempo de fijación,
 - Tejido previamente congelado y
 - Pretratamiento enzimático con tripsina
- De los varios antígenos detectados por anti-S100, A6 se expresa en algunas lesiones melanocíticas y también es un marcador muy útil para detectar neurotequeomas.





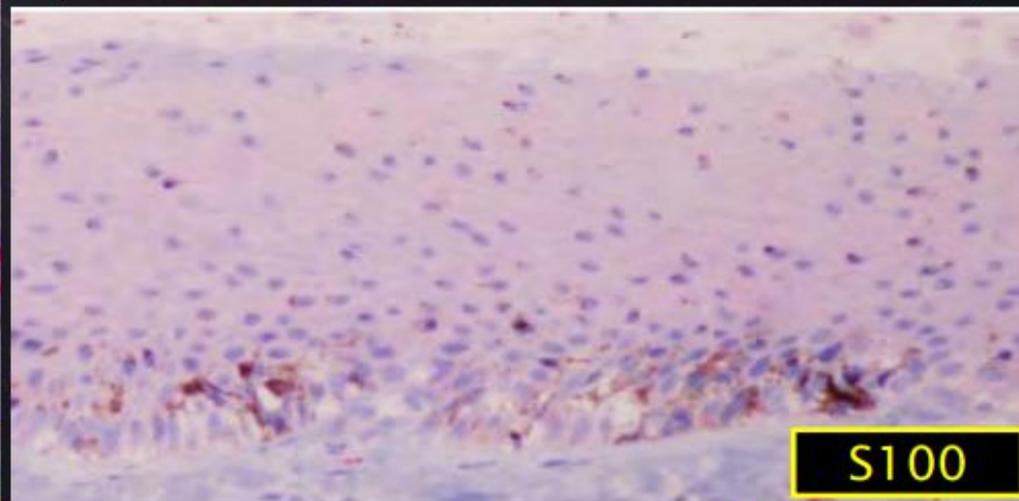
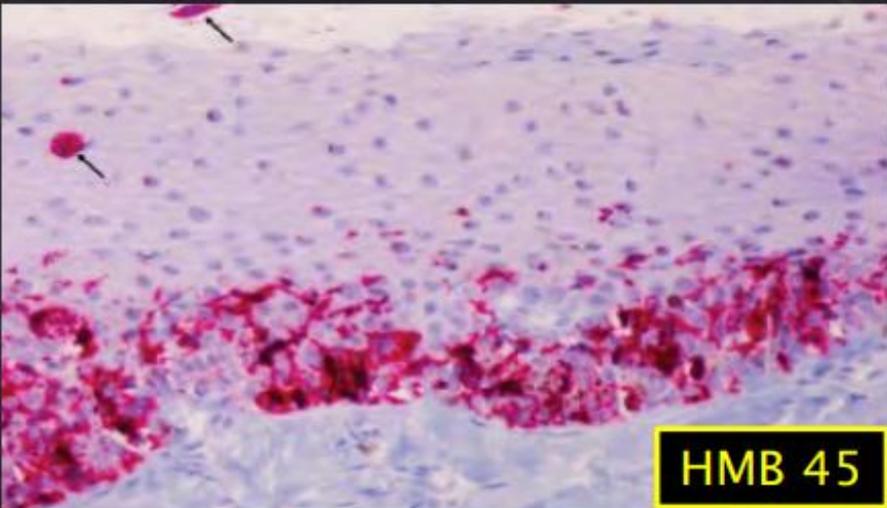
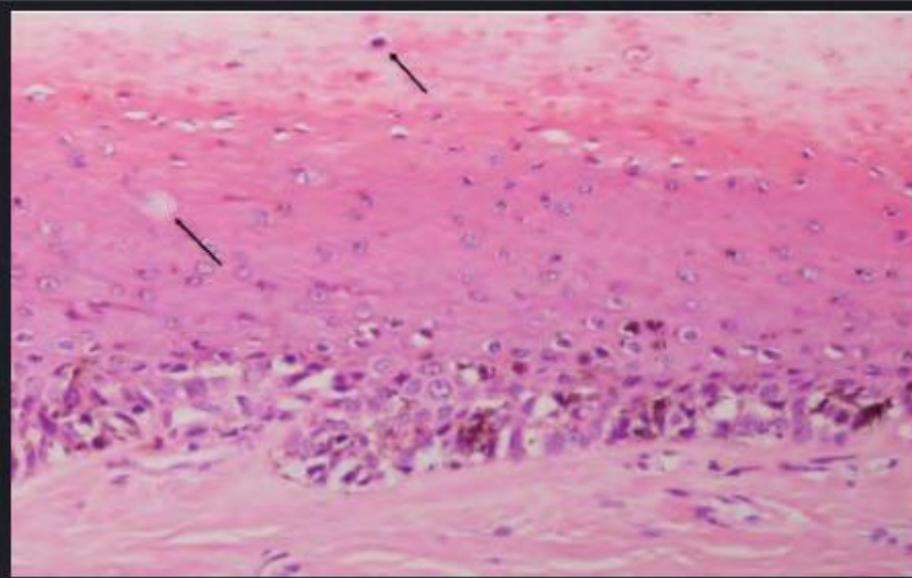
MELANOMA DESMOPLASICO



S100

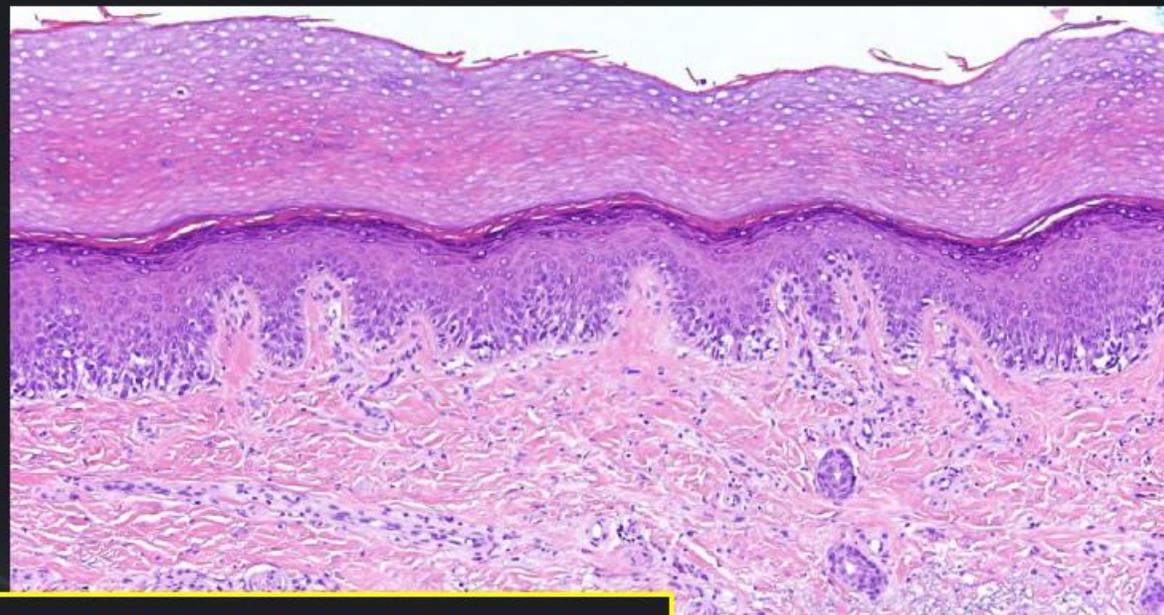
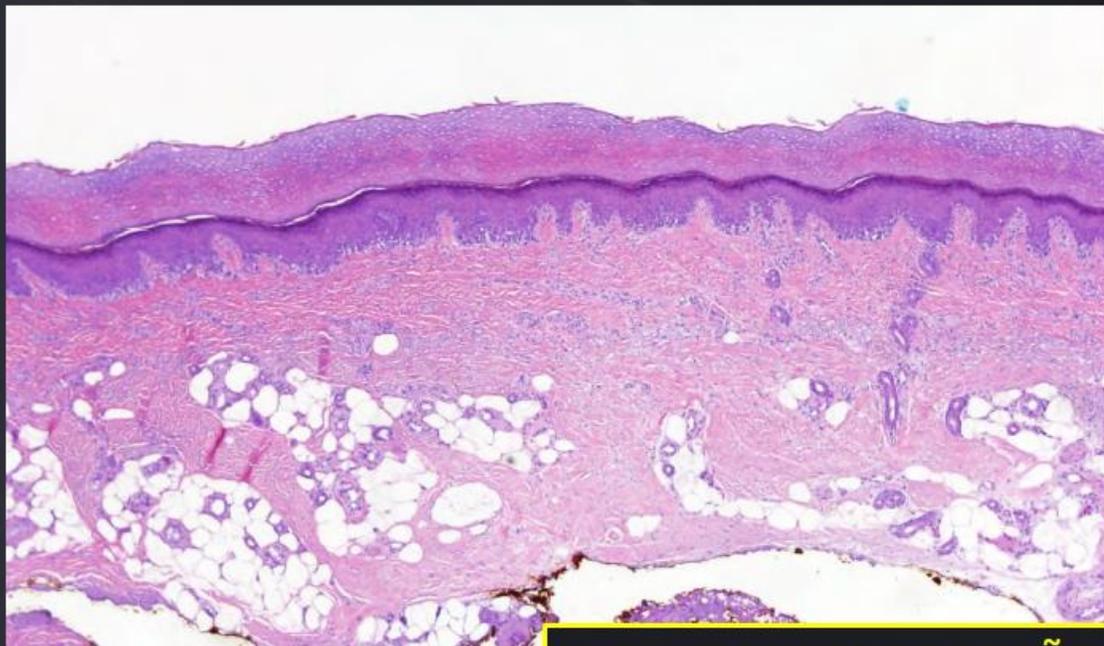
PROTEINA S100

- MARCADOR IHQ MELANOCITICO ALTAMENTE SENSIBLE
- **PITFALL**
- CUIDADO con lesiones melanociticas de la matriz ungueal
- La sensibilidad de S100 es débil en las proliferaciones melanociticas de la unión en matriz ungueal

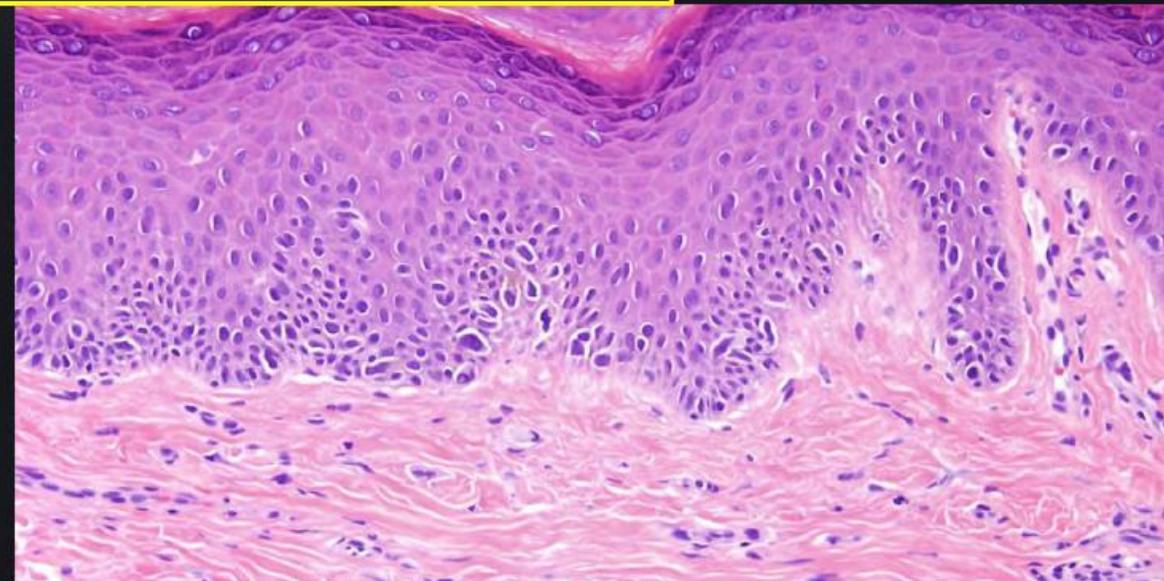
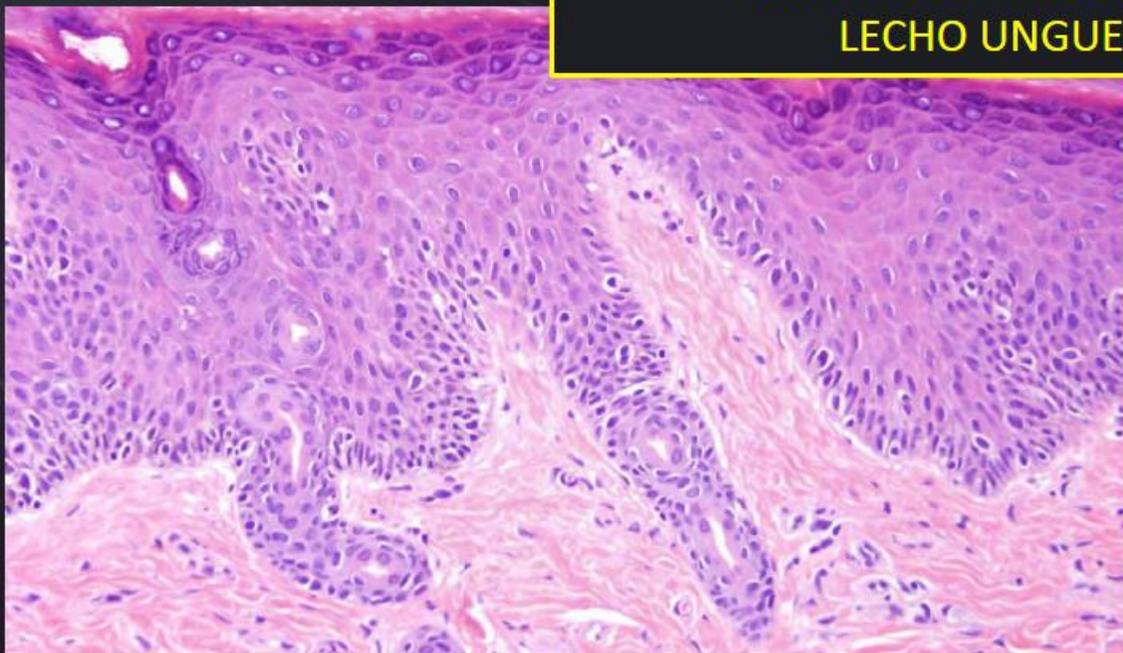


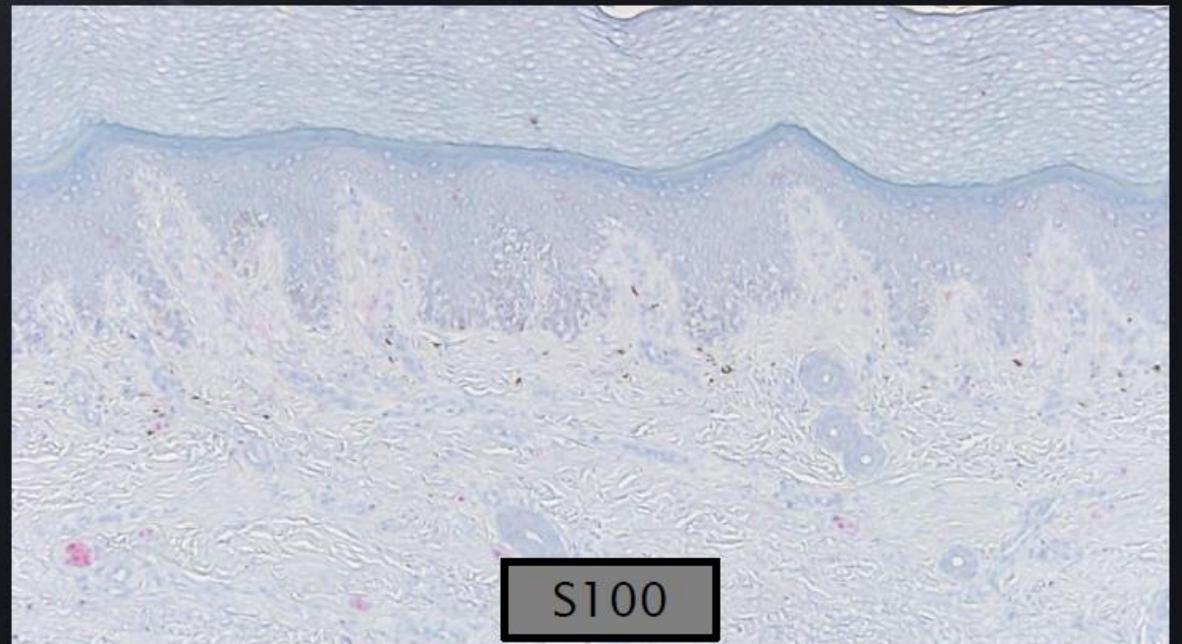
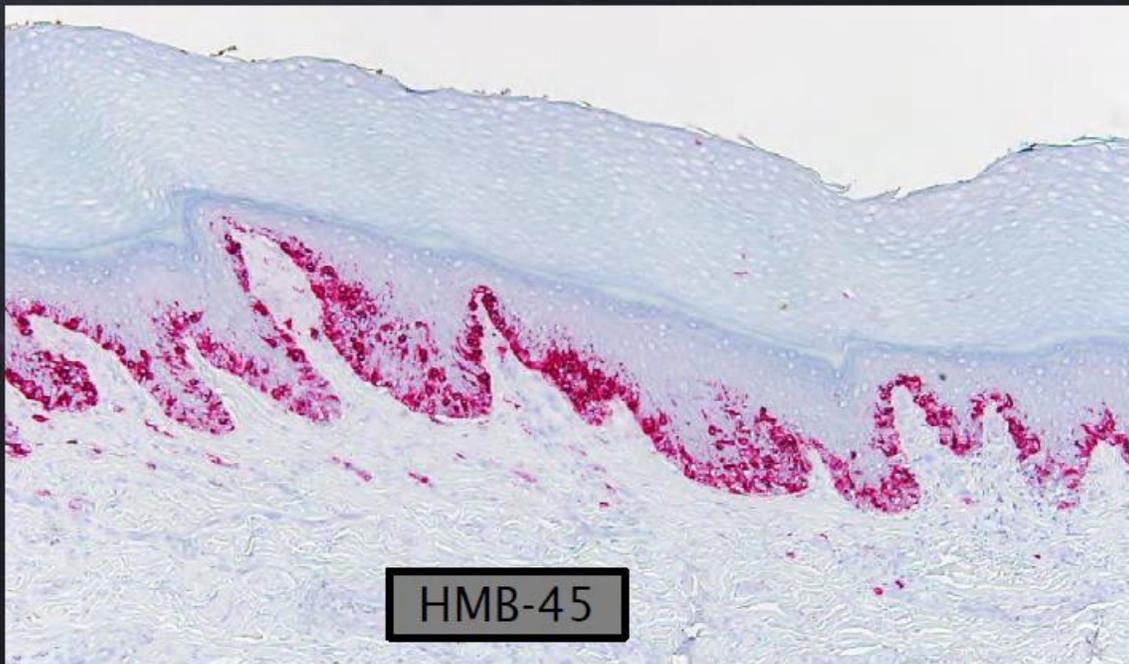
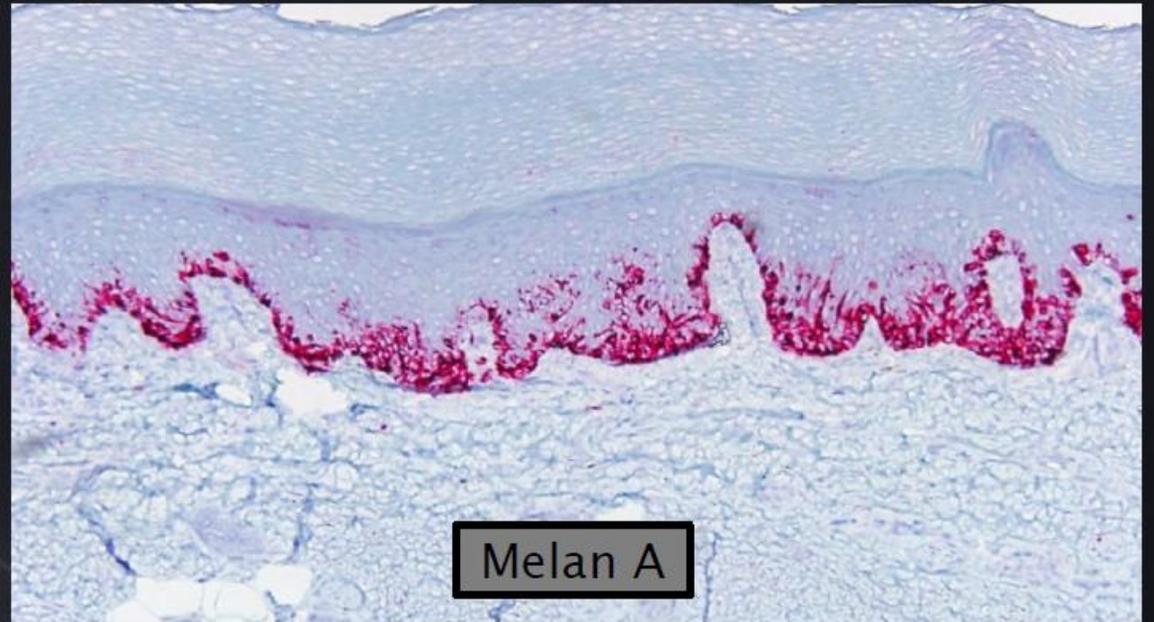
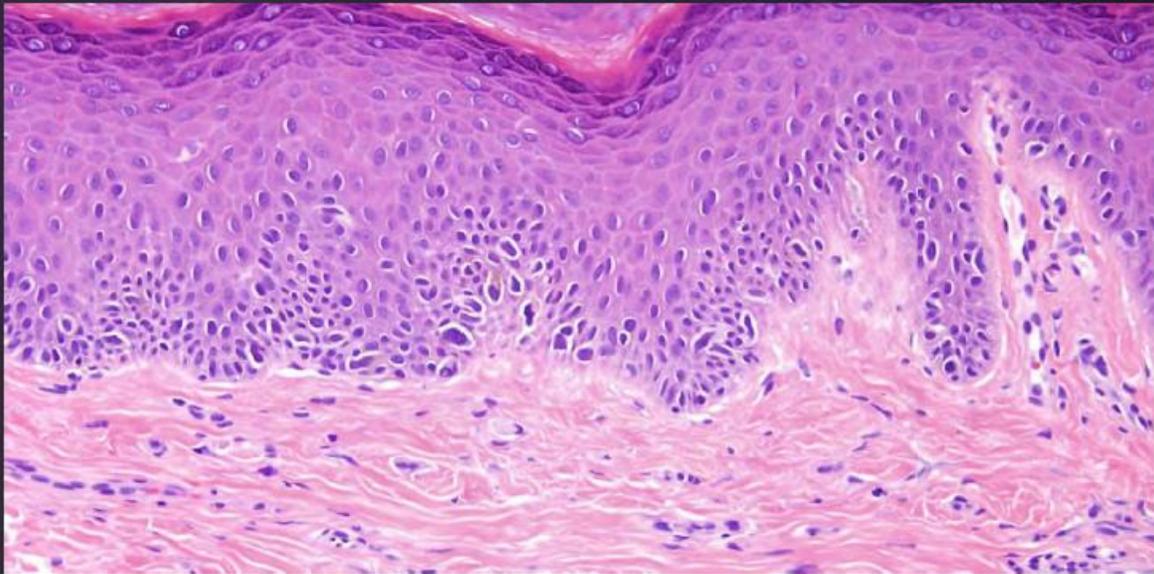
Immunohistochemical Study of 40 Cases of Longitudinal Melanonychia

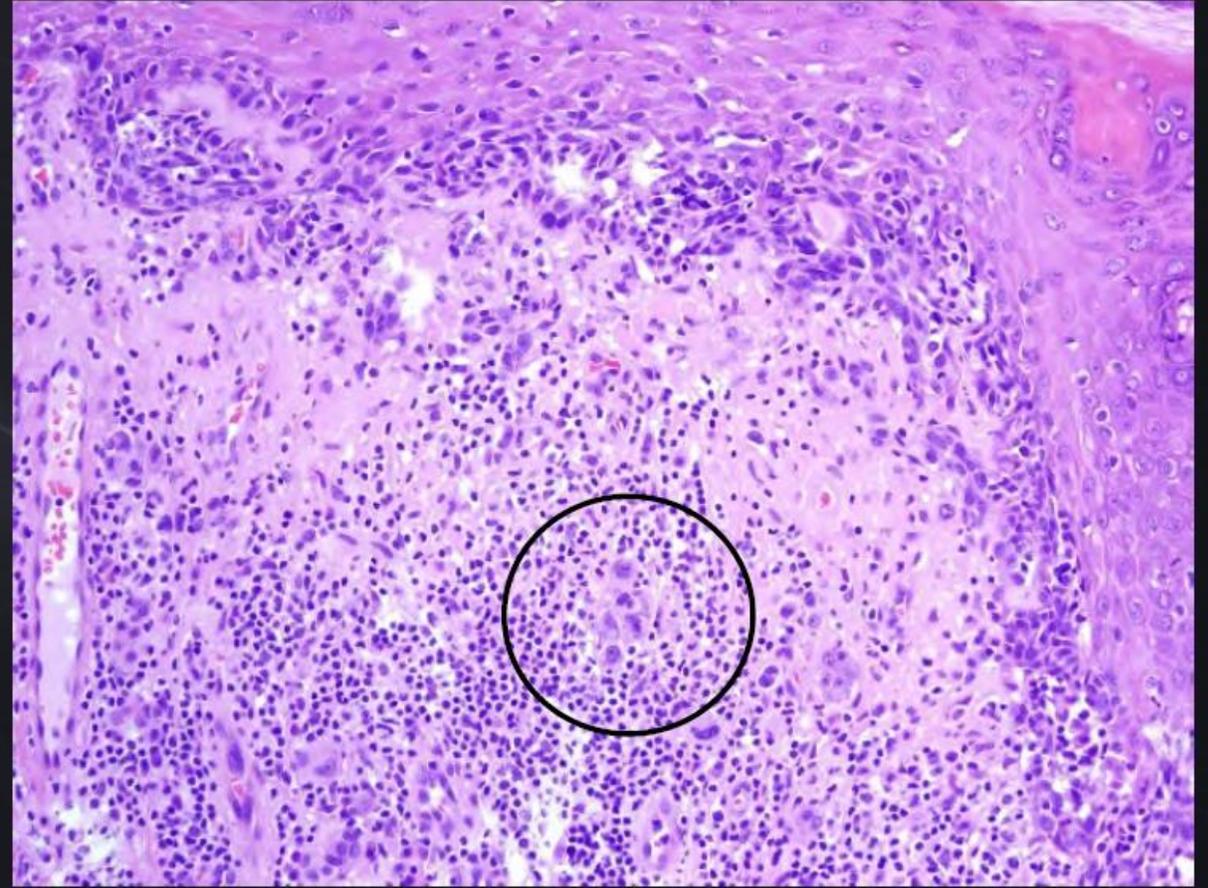
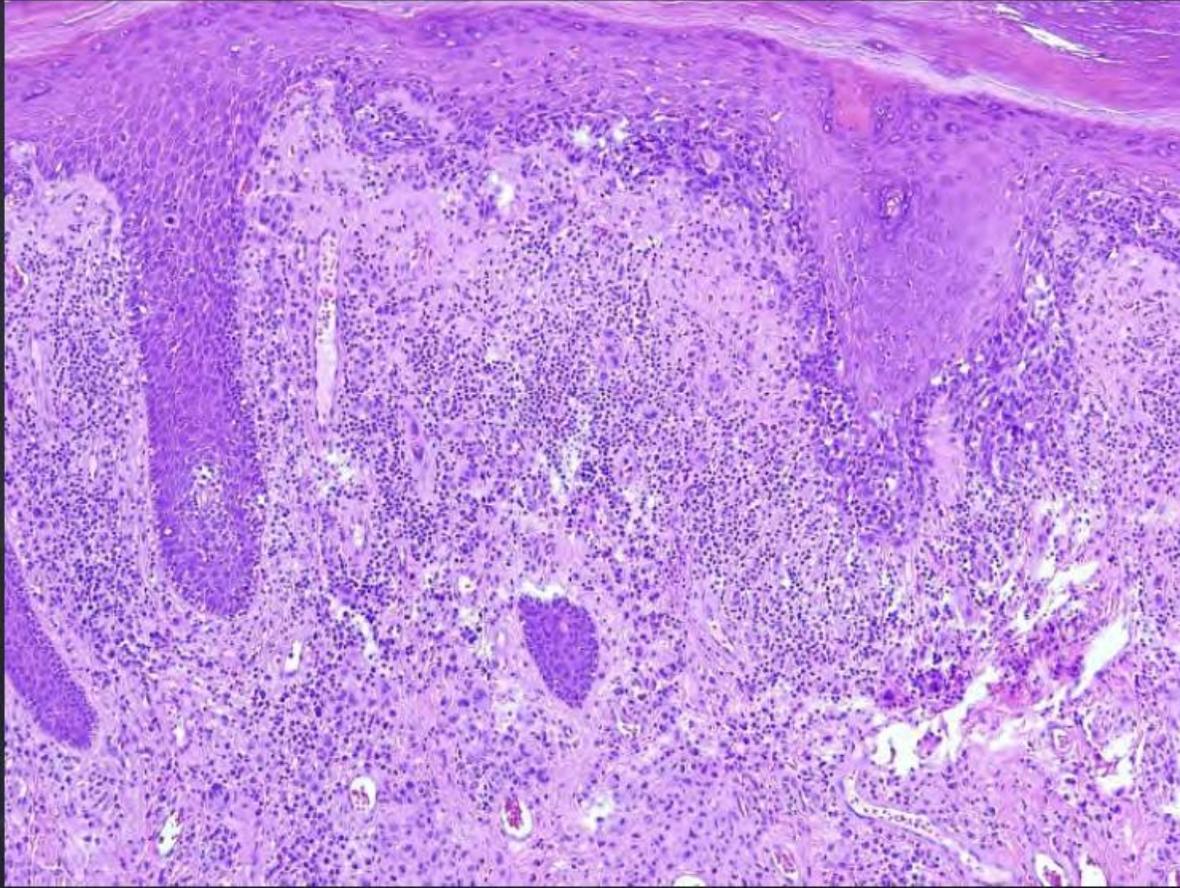
Anne Theunis, MD, Bertrand Richert, MD,† Ursula Sass, MD,* Nadine Lateur, MD,*
François Sales, MD,‡ and Josette André, MD**
Am J Dermatopathol 2011; 33: 27-34.



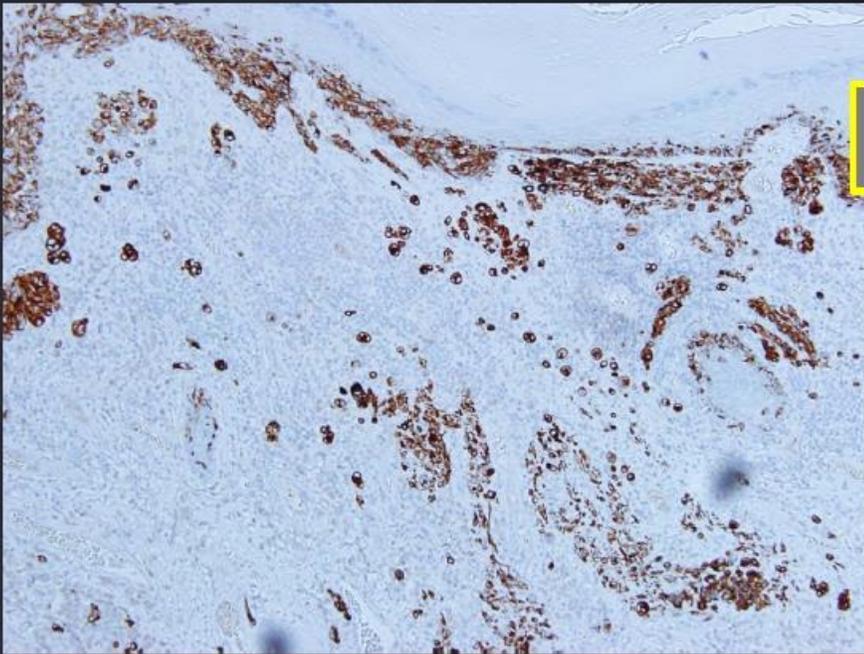
MUJER DE 86 AÑOS CON MELANOMA IN SITU,
LECHO UNGUEAL, PULGAR DERECHO



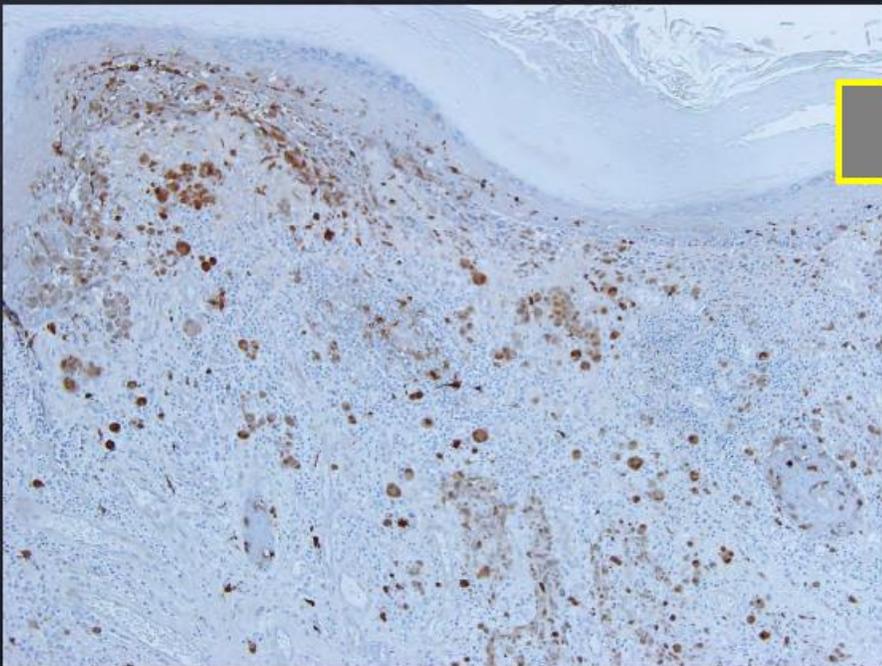
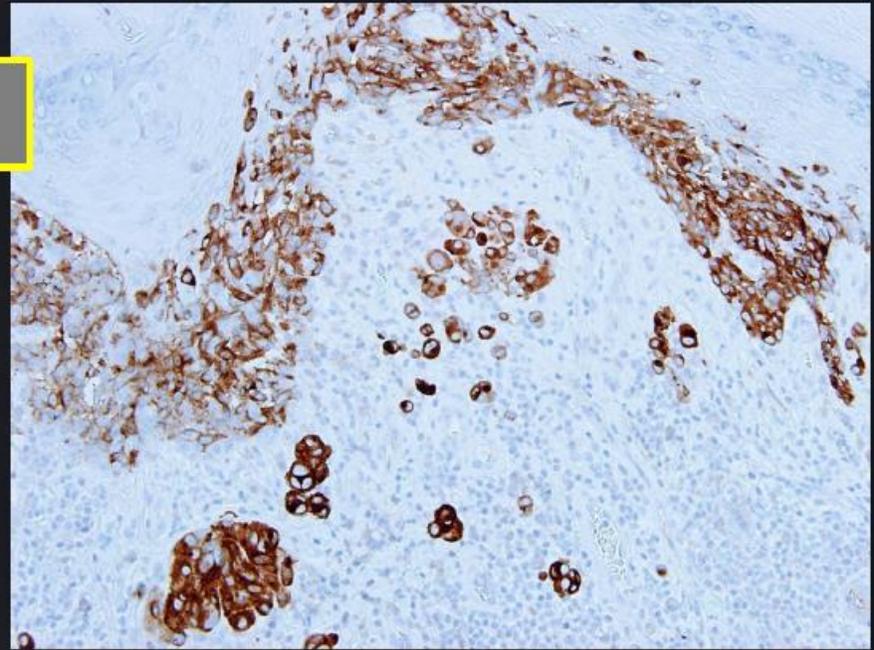




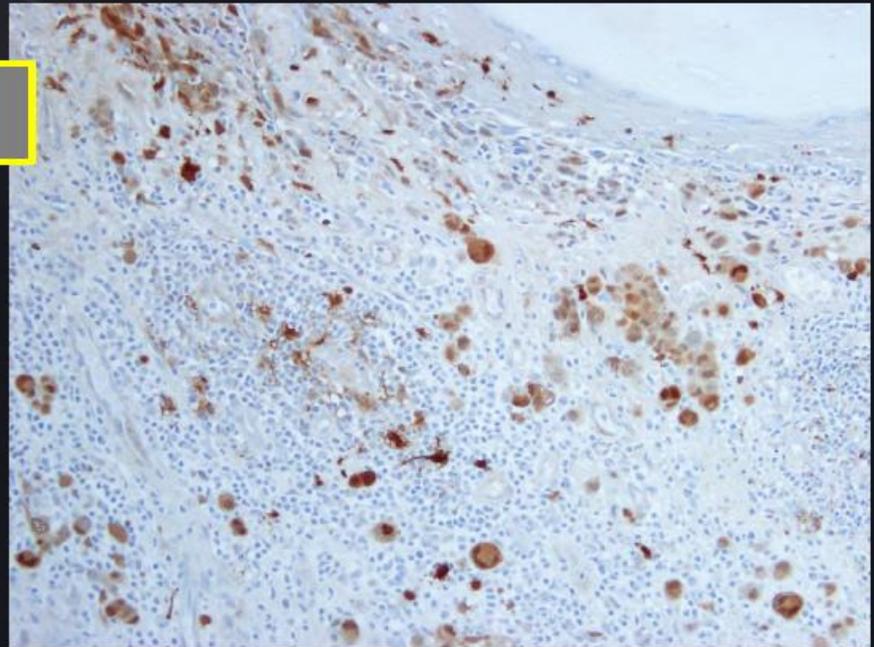
TALON DERECHO, HOMBRE DE 70 AÑOS CON LESION LENTIGINOSA ACRAL



Melan A



S100

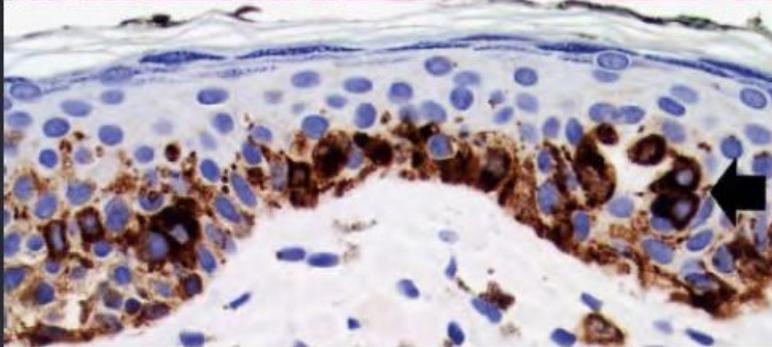
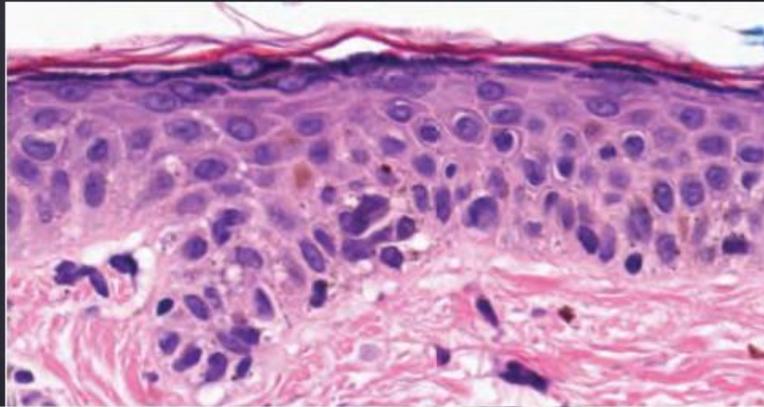


MELAN-A

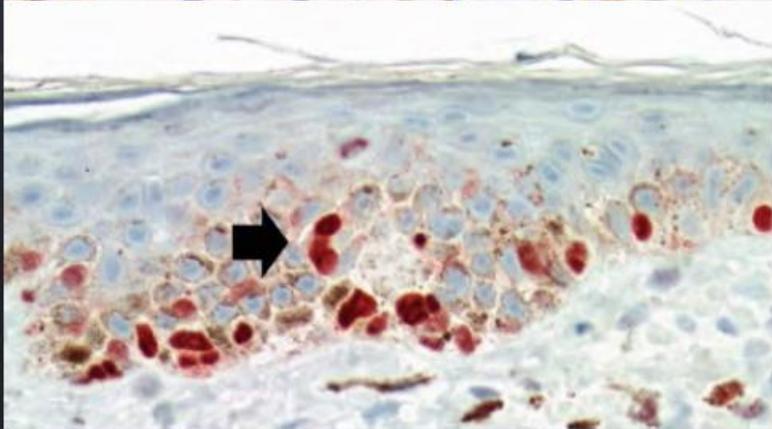
- **Pitfall 1**

- Cautela en la evaluación de proliferaciones melanocíticas de la unión con MELAN A-MART-1 en **piel con daño solar**.
- Melan-A se observa como un aumento de los melanocitos, simulando confluencia.
- Fácil sobrediagnosticar erróneamente un melanoma in situ en una queratosis actínica pigmentada o en piel dañada por el sol.
- **Marcadores melanocíticos nucleares son más útiles en este contexto.**

Melanoma in situ

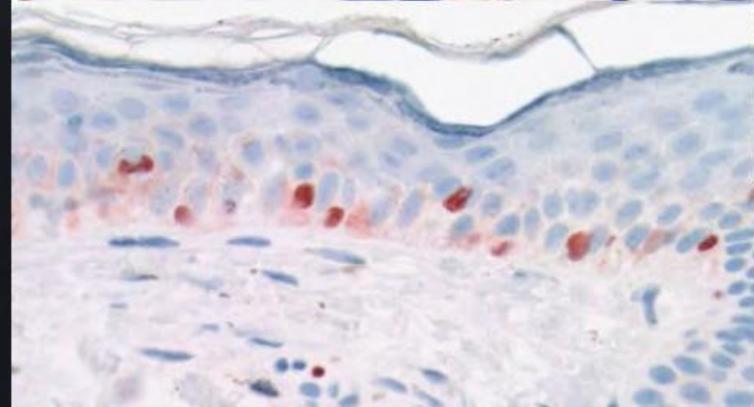
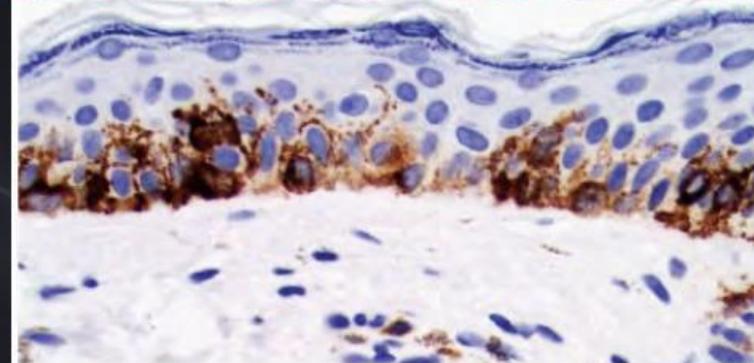
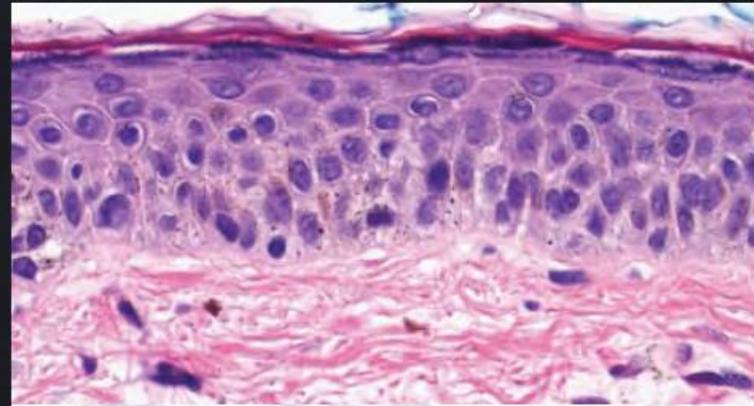


Melan A
(cocktail)

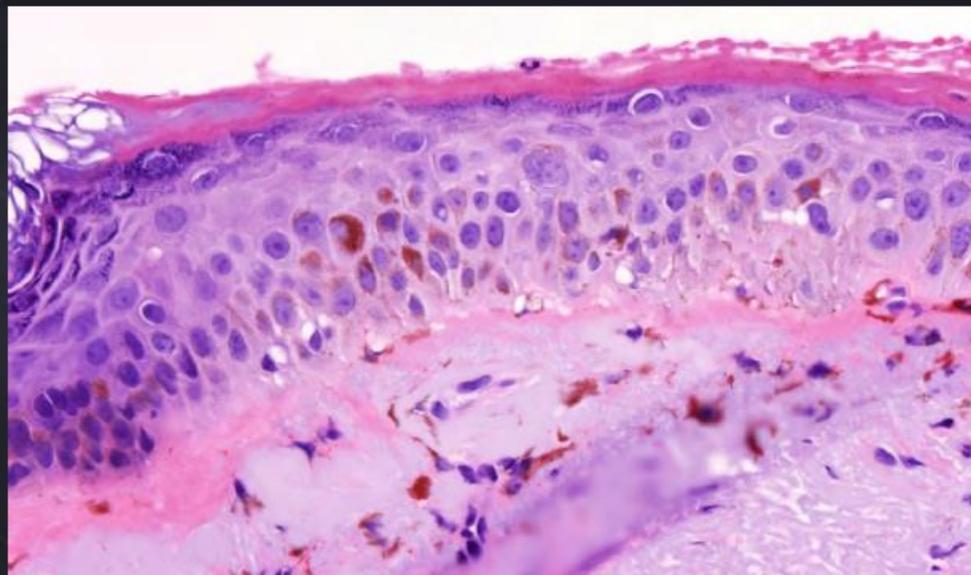


MiTF

QUERATOSIS ACTINICA PIGMENTADA



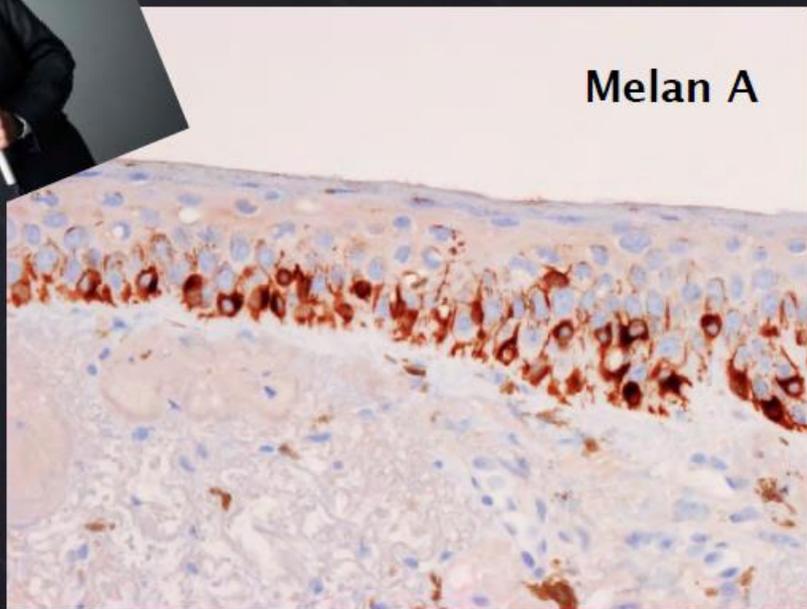
QUERATOSIS ACTINICA PIGMENTADA



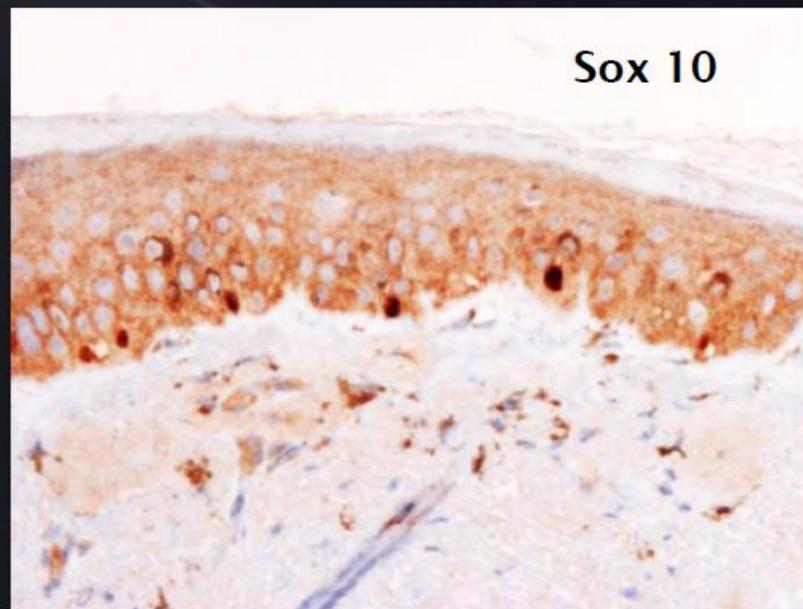
CAUTION



Melan A

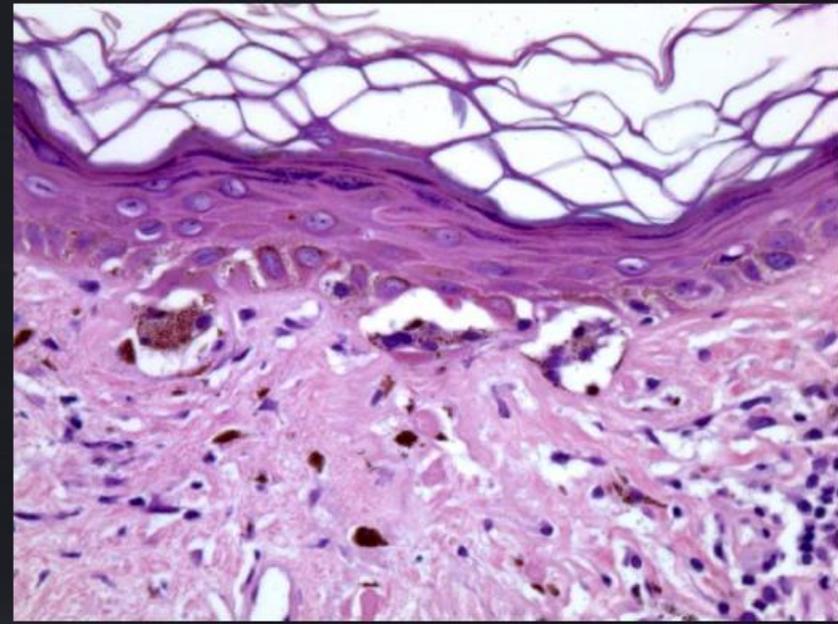
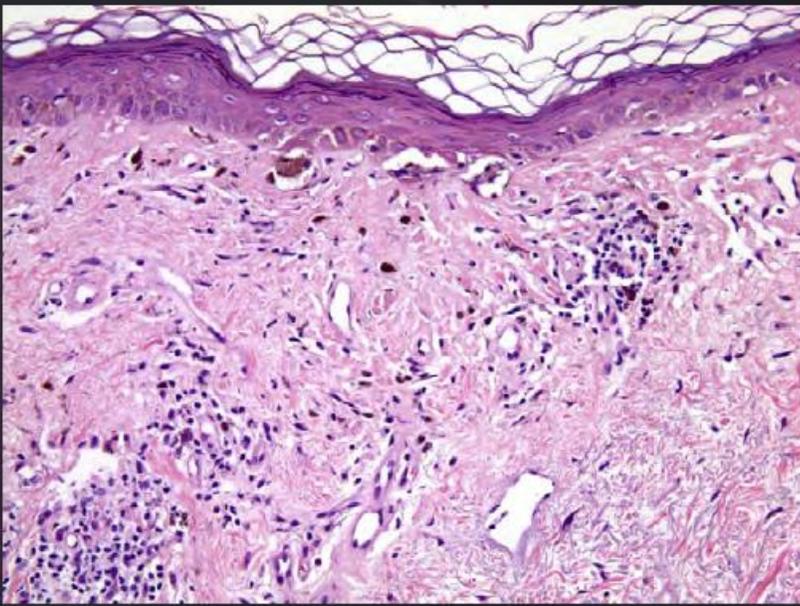


Sox 10

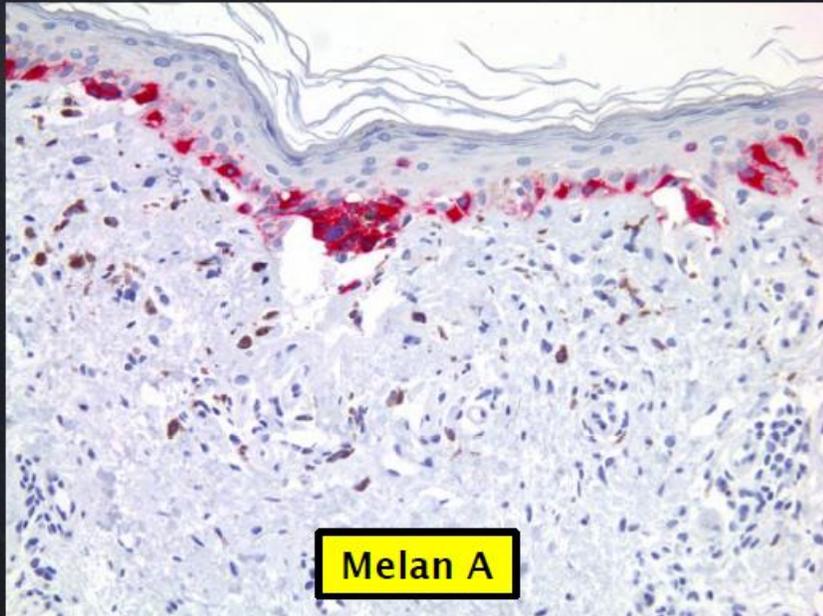


MELAN-A

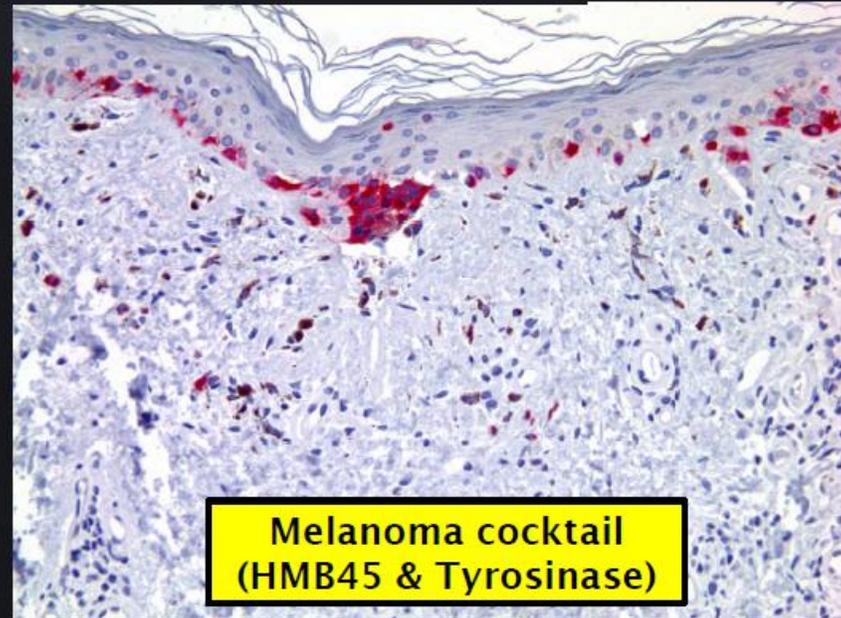
- **Pitfall 2**
- En dermatitis liquenoides puede existir falsa tinción positiva con Melan-A.
- Simulan una proliferación melanocítica de la unión.
- Fácil diagnosticar erróneamente un melanoma in situ
- Nota: Pueden observarse falsos nidos pseudomelanocíticos con SOX-10 y MITF.



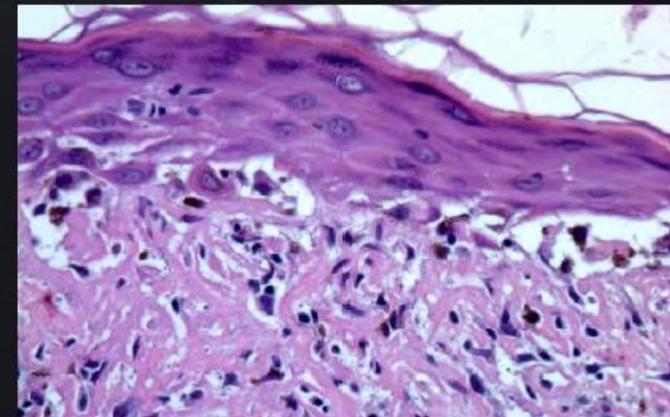
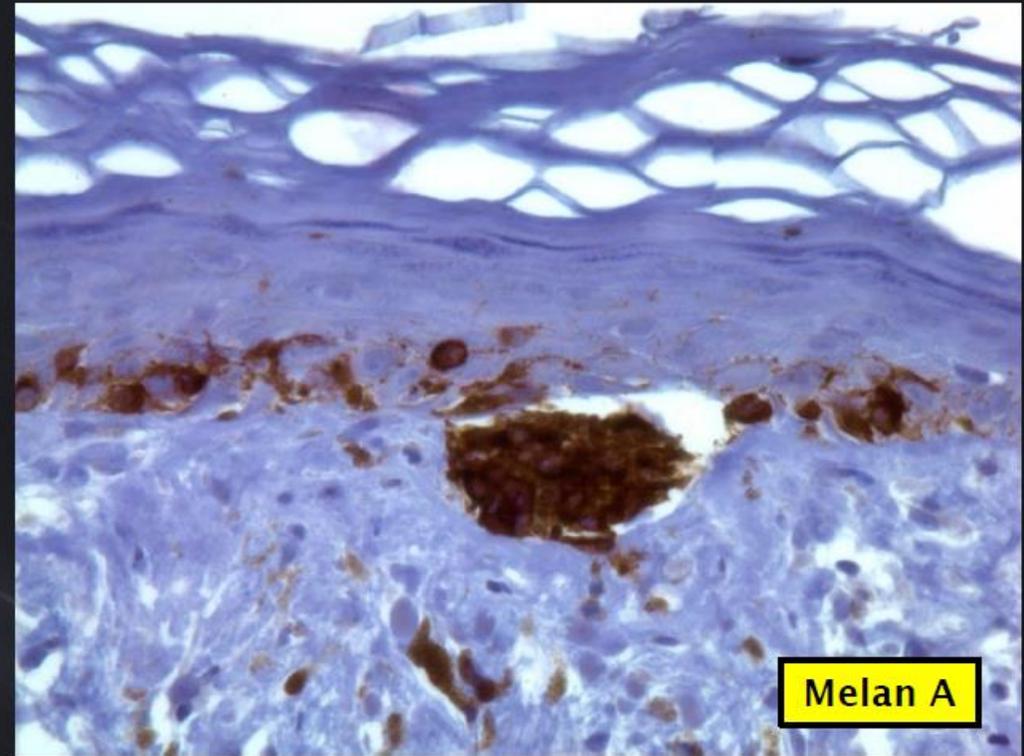
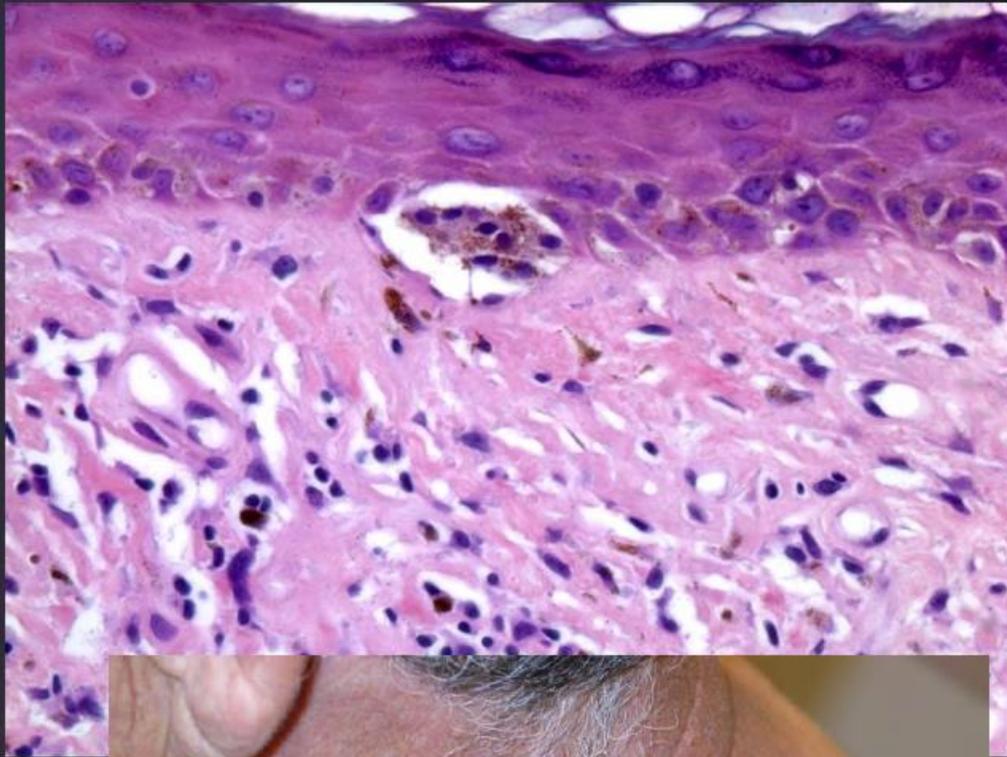
DERMATITIS LIQUENOIDE CON NIDOS DE PSEUDOMELANOCITOS



Melan A

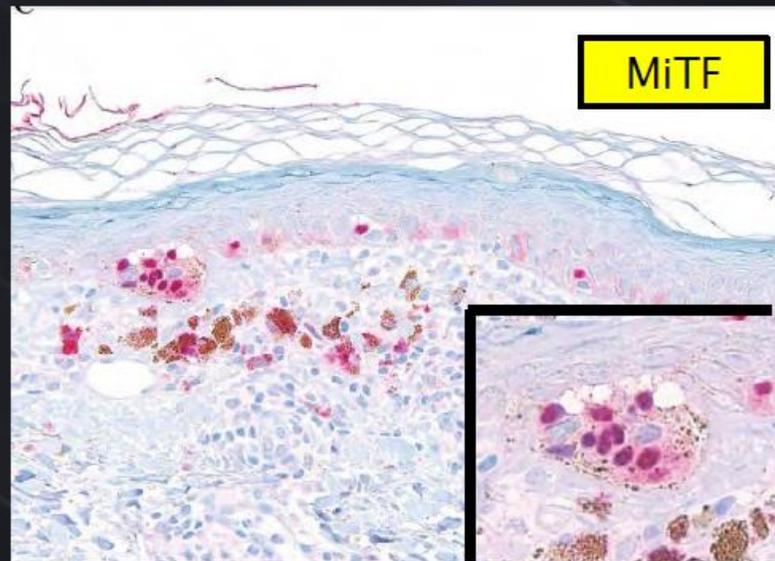
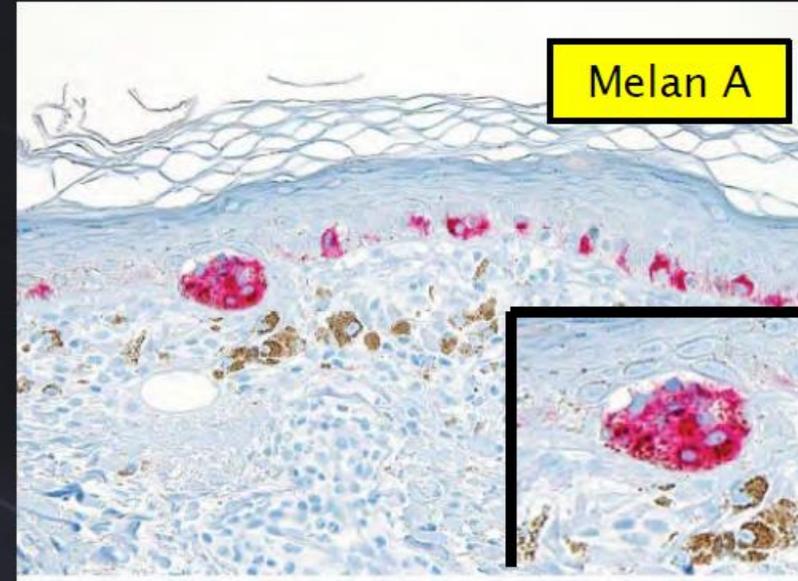
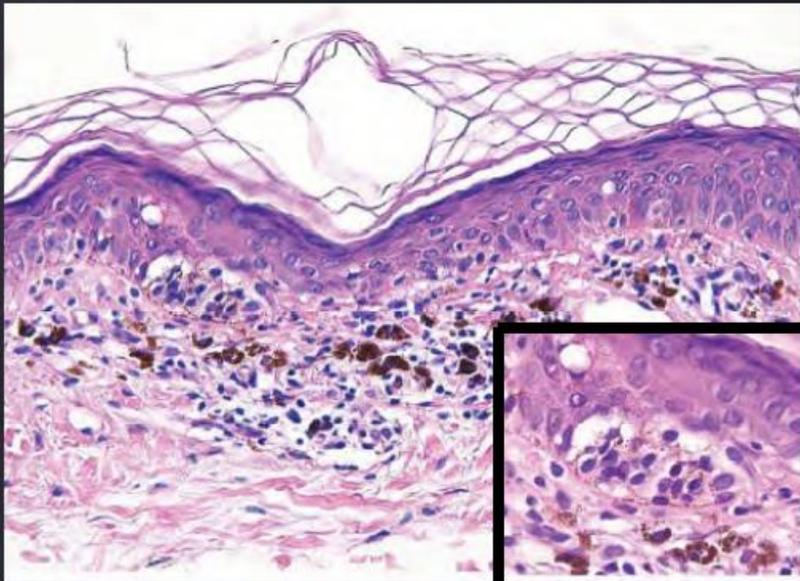


Melanoma cocktail
(HMB45 & Tyrosinase)



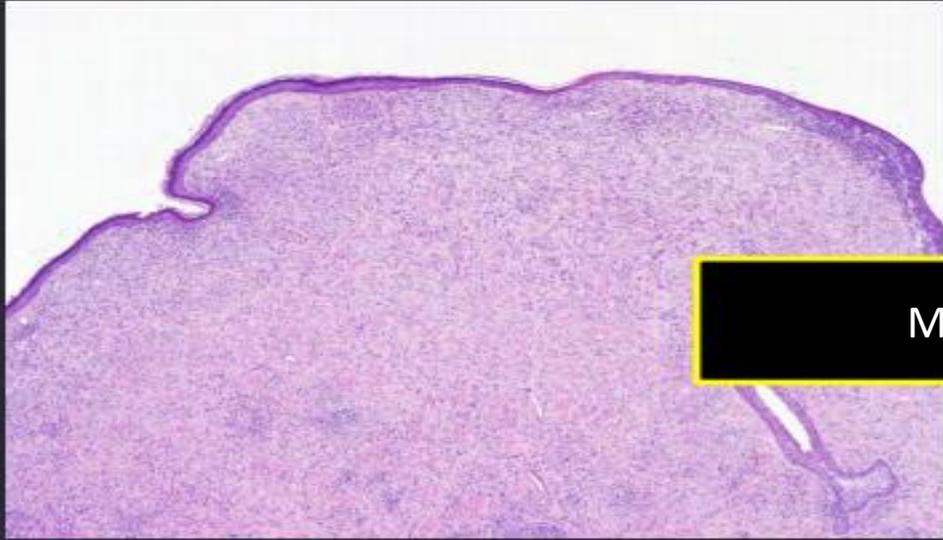
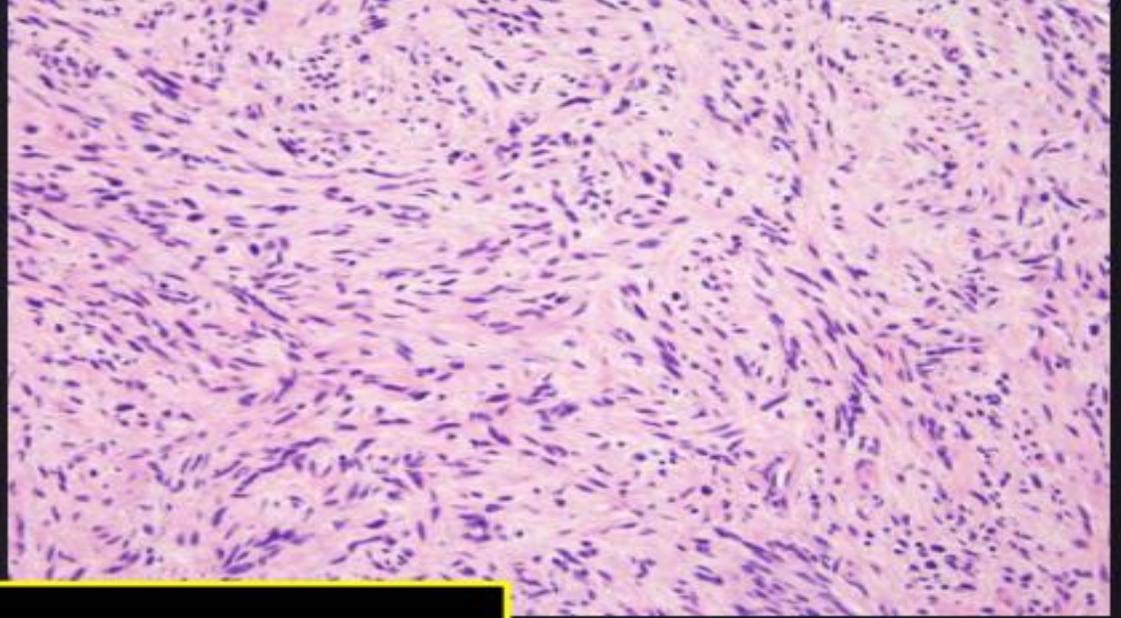
DIAGNOSTICO: ERUPCION LIQUENOIDE POR DROGAS (FOTOINDUCIDA) CON NIDOS DE PSEUDOMELANOCITOS

LUPUS ERITEMATOSO CON REACCION LIQUENOIDE Y NIDOS DE PSEUDOMELANOCITOS

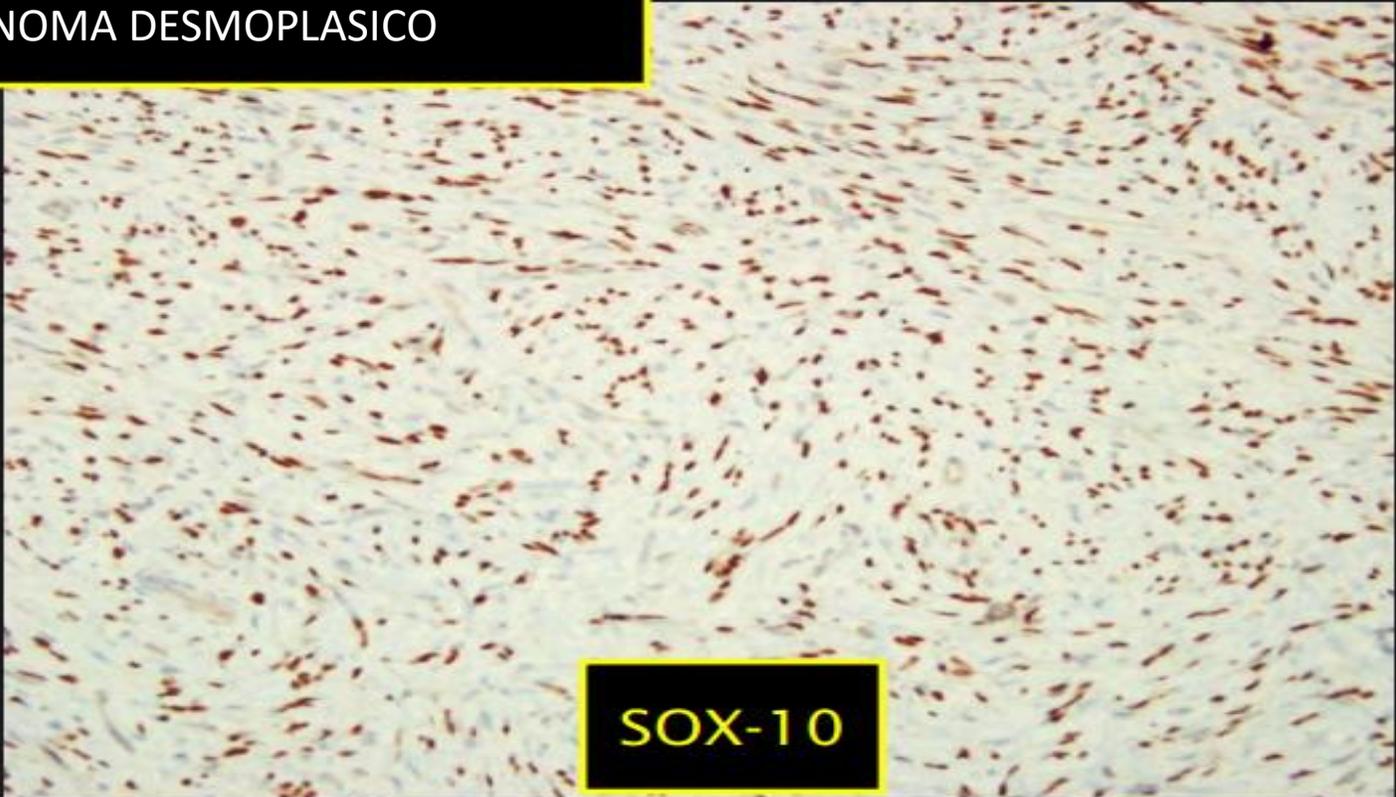
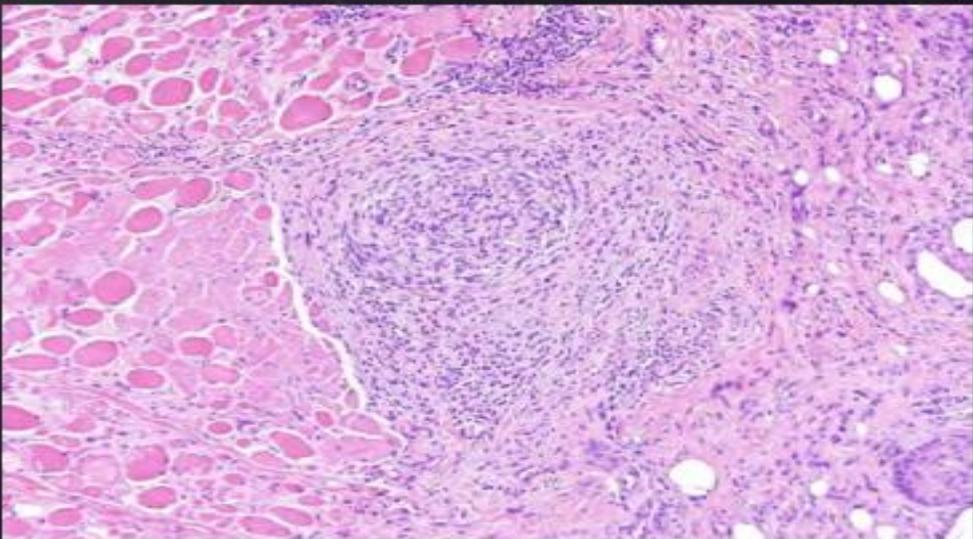


SOX-10

- Factor de transcripción de la cresta neural
- Importante en la diferenciación melanocítica y de células de Schwann.
- **Tinción nuclear**
 - Melanocitos
 - Células de Schwann
 - Ductos ecrinos células secretoras
 - Células mioepiteliales
- Mas sensible y específico que S100



MELANOMA DESMOPLASICO

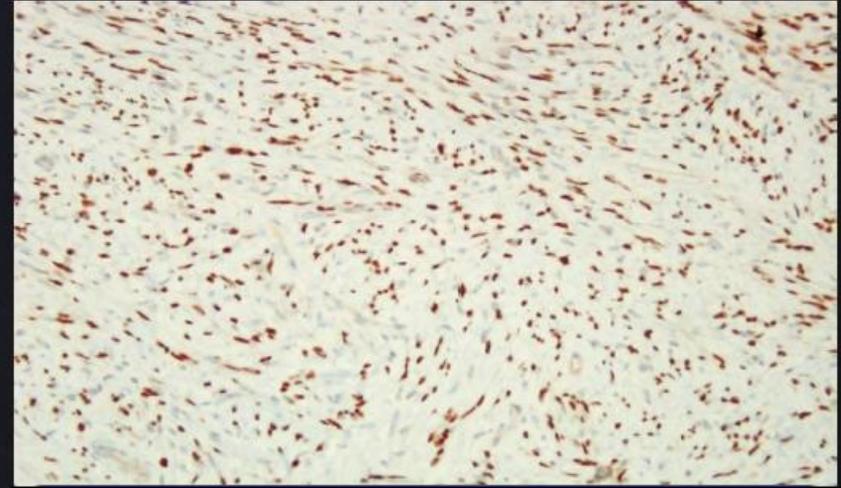


SOX-10

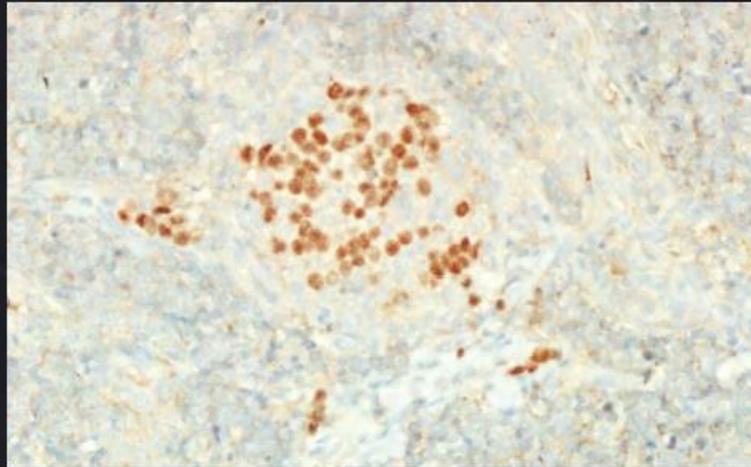
SOX-10



PROLIFERACIONES MELANOCITICAS DE LA UNION

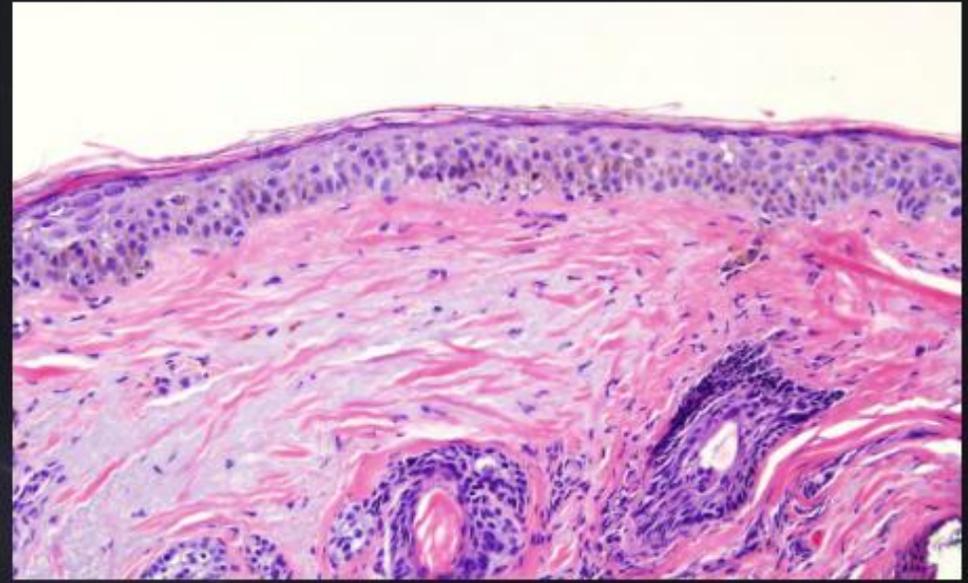
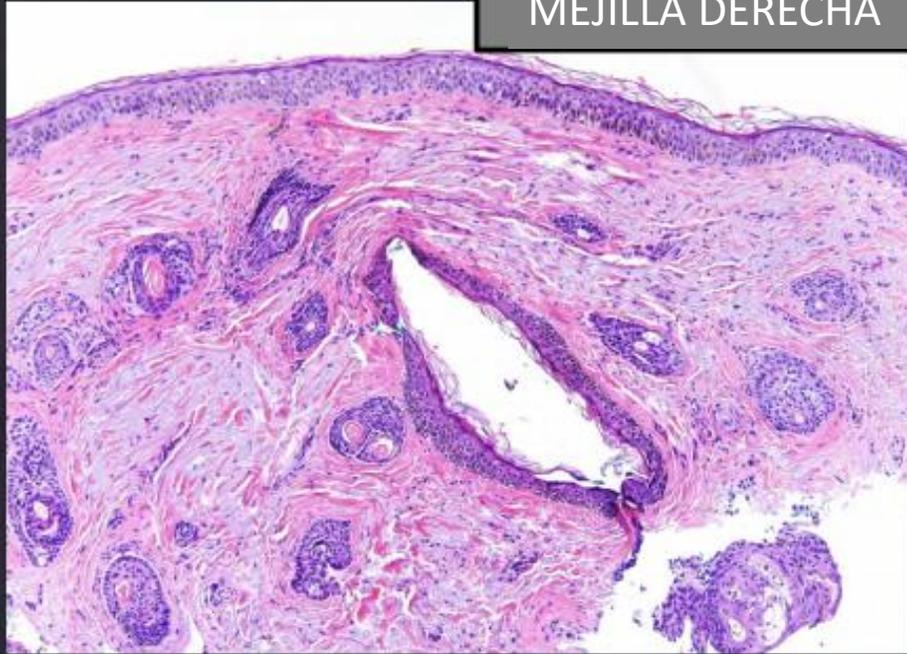


MELANOMA DESMOPLASICO

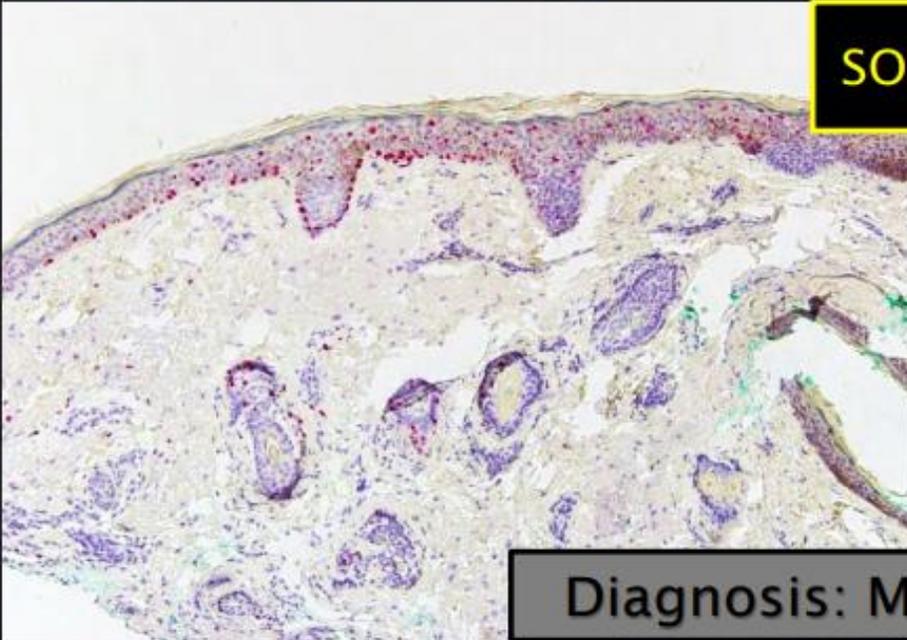


LINFONODO CENTINELA

69 AÑOS, MUJER CON UNA MACULA CAFÉ EN LA MEJILLA DERECHA

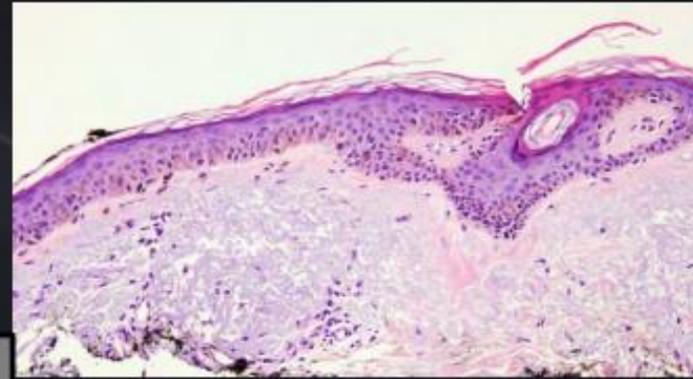


SOX-10

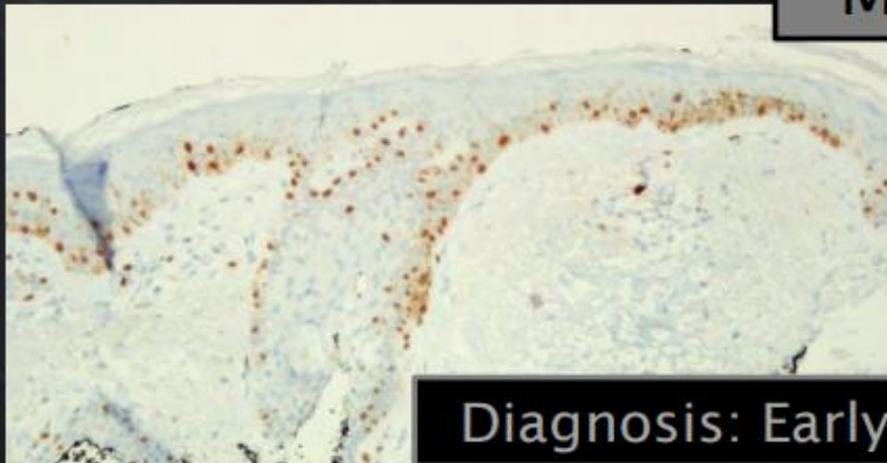


Diagnosis: Melanoma in situ

69 AÑOS, MUJER CON UNA MACULA CAFÉ EN LA MEJILLA DERECHA



MiTF

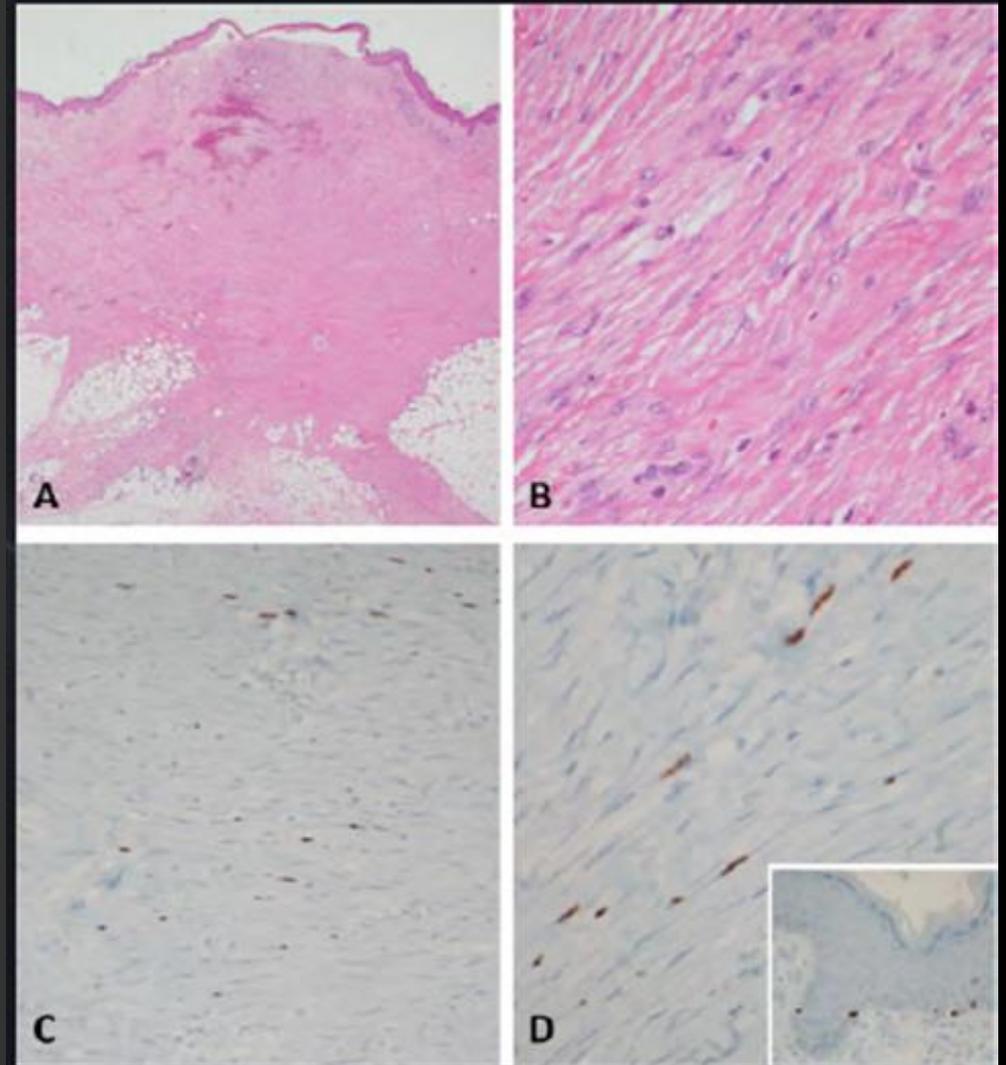


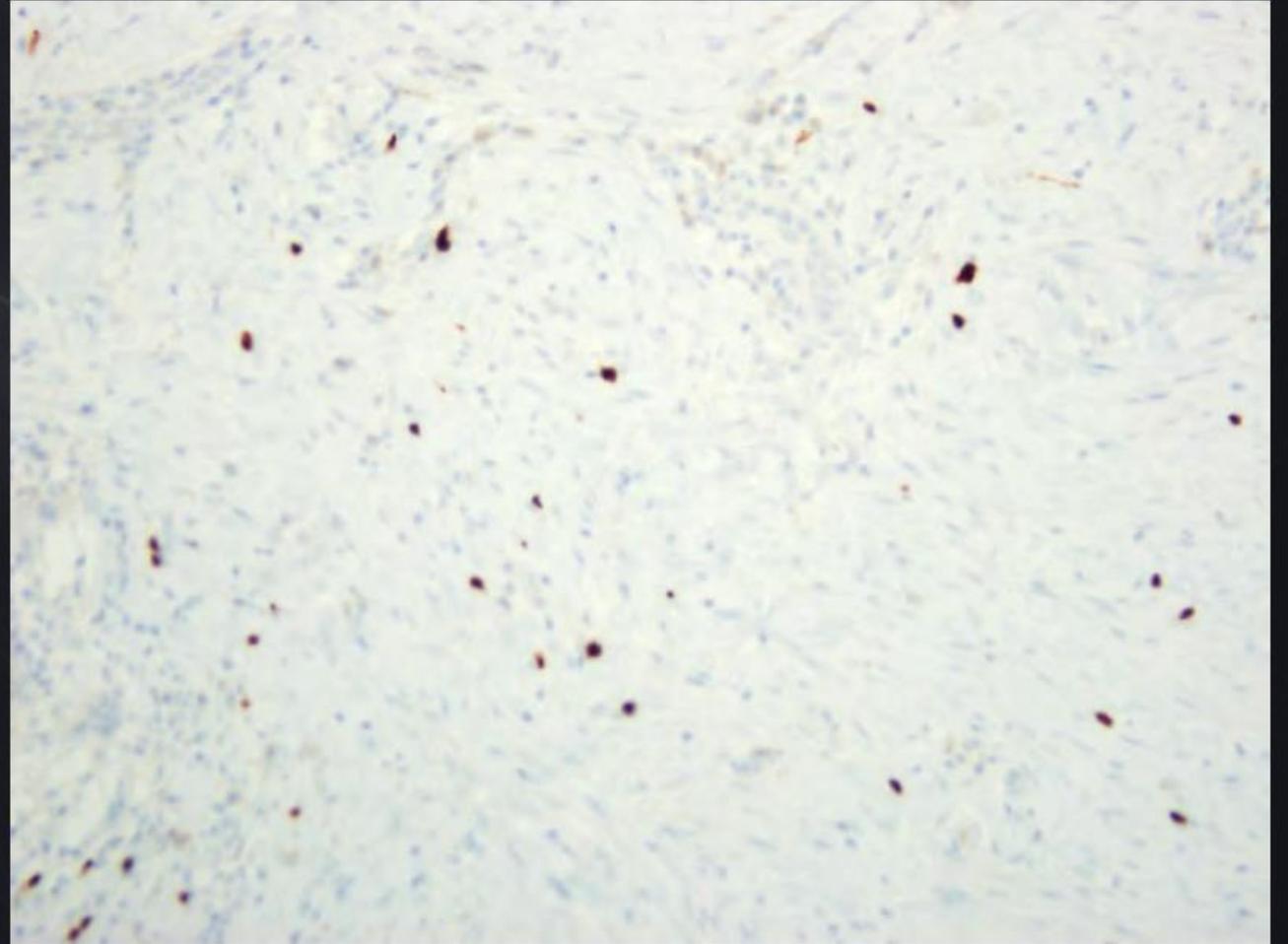
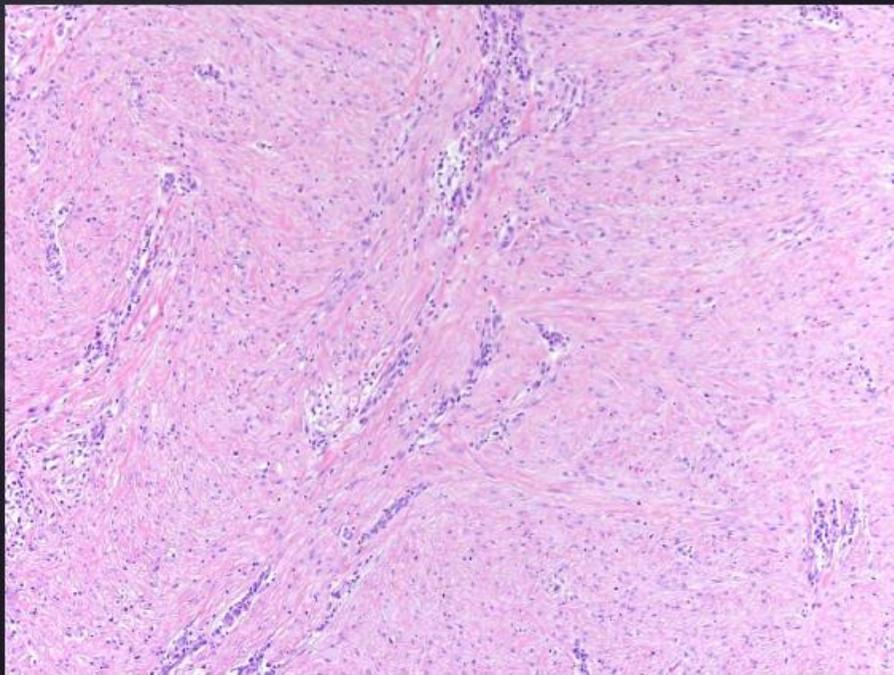
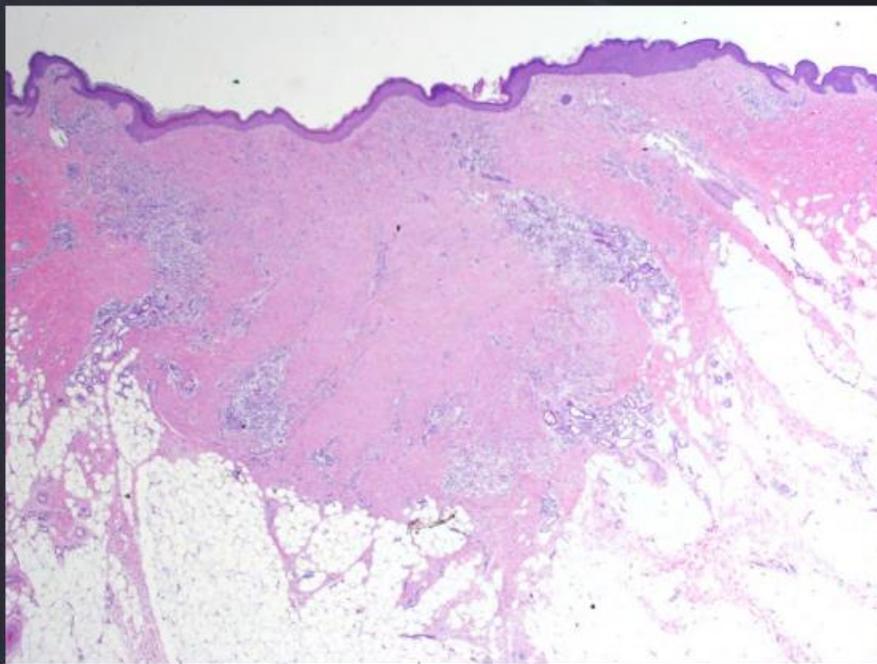
Diagnosis: Early melanoma in situ

SOX-10

- PITFALL: CICATRICES PUEDEN SER POSITIVAS

- Tambien se ha descrito para S100 y MITF



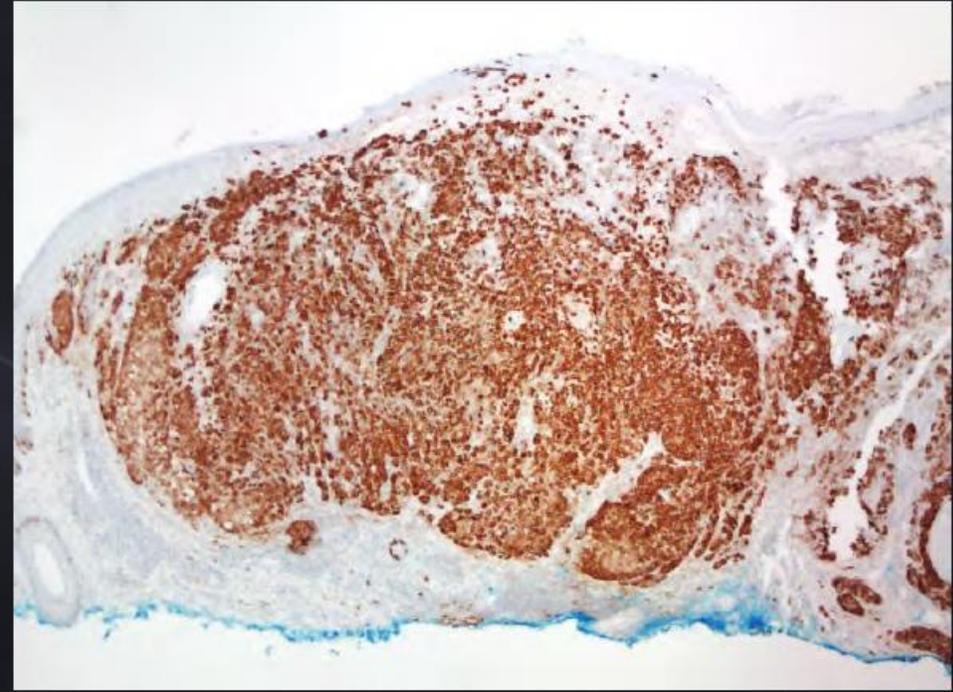
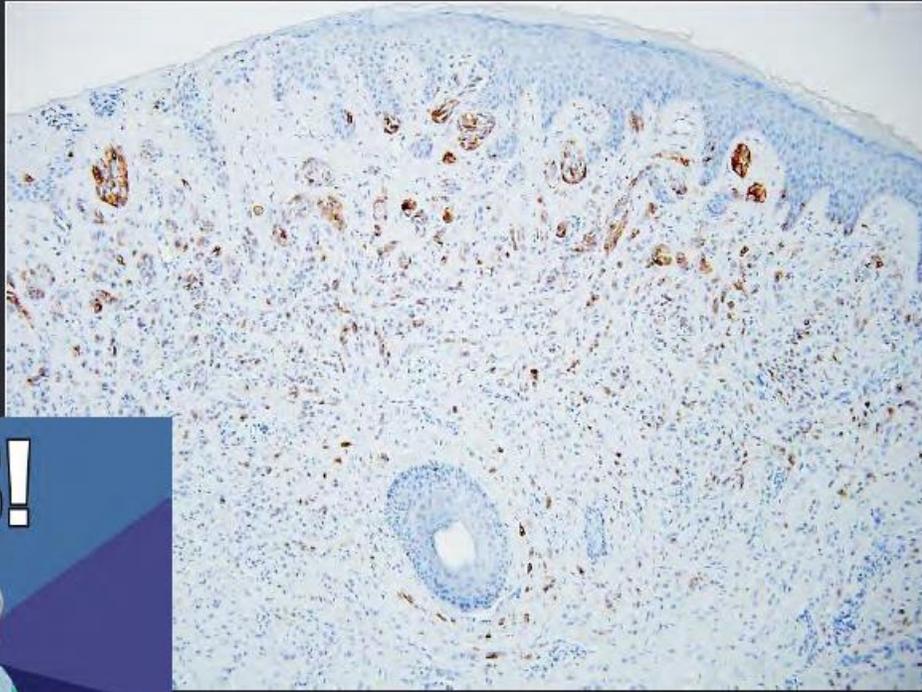


Sox-10 en cicatrices

HMB-45

- gp100 es muy específico de diferenciación melanocítica;
- Rara vez otras lesiones expresan este marcador (Angiomiolipoma y el Pecoma).
- El HMB-45 es particularmente útil para detectar el patrón de "maduración" de los nevos. (proporcional a capac de síntesis)
- Tipo A superficiales (células epitelioides, intraepidérmicas o cercanas al epitelio, y en su mayoría pigmentados) expresan marcadores neuronales y gp100,
- Tipo C localizados profundidad (células fusiformes) expresan marcadores de células de Schwann.

HMB-45



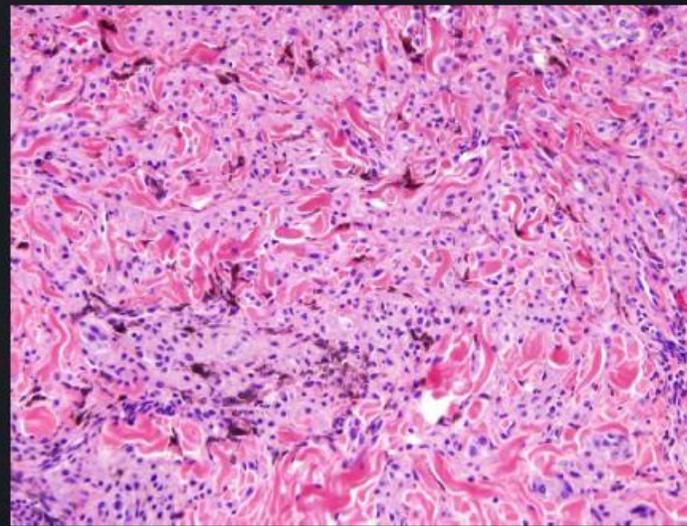
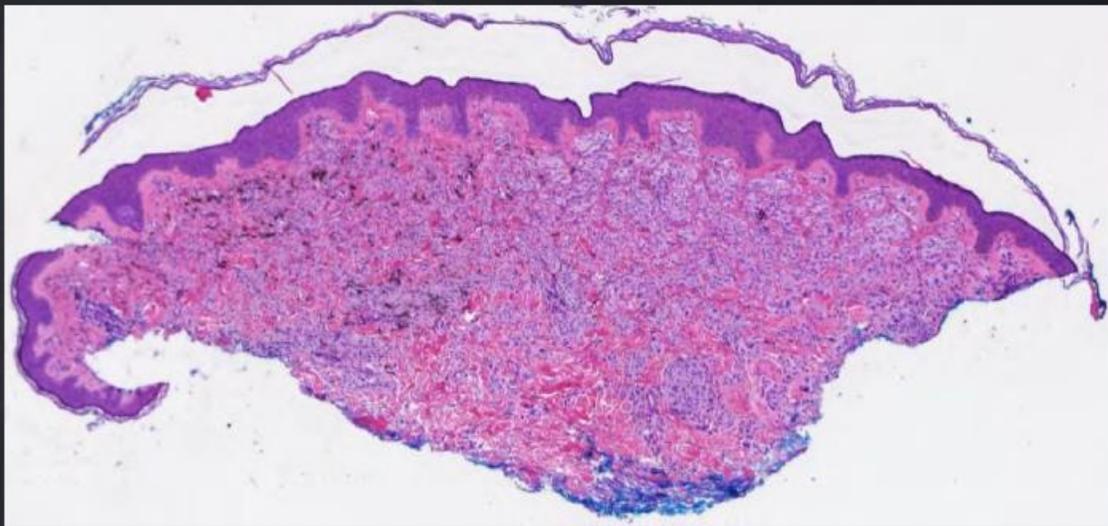
Nevus

Melanoma

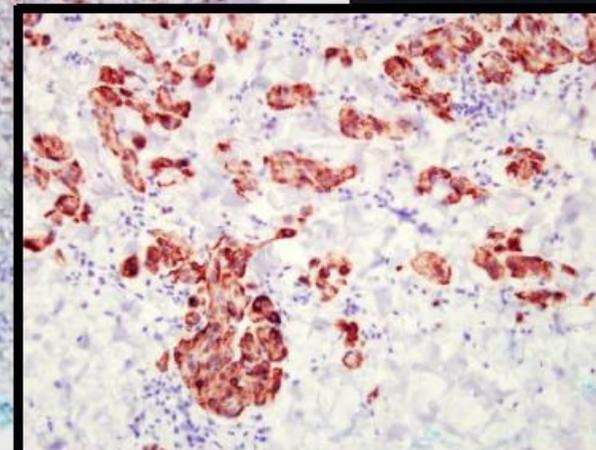
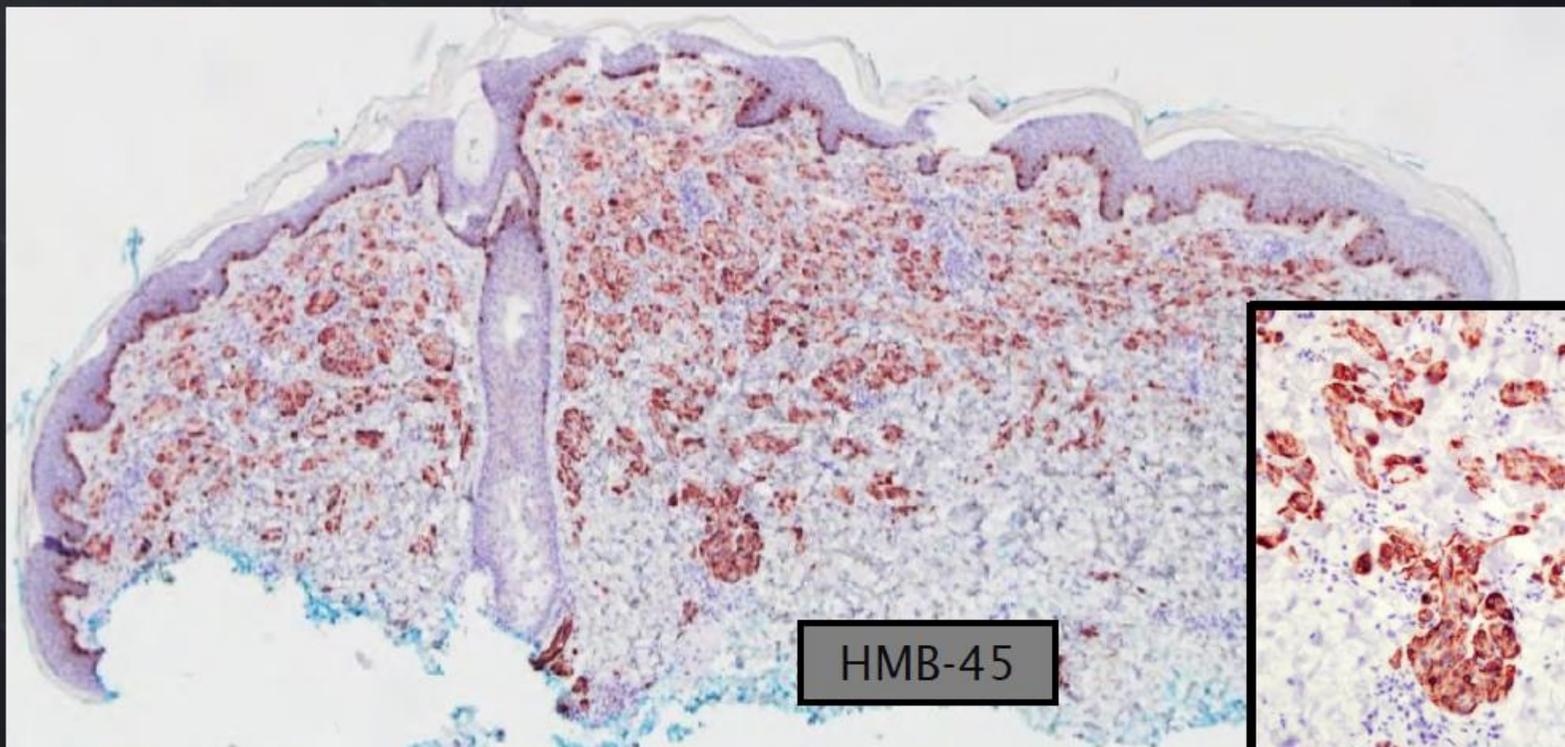
HMB-45

- Pitfalls

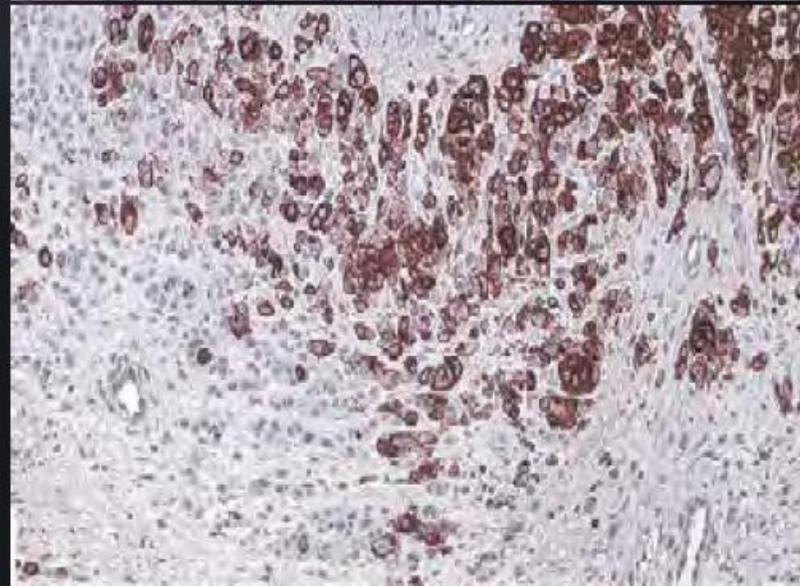
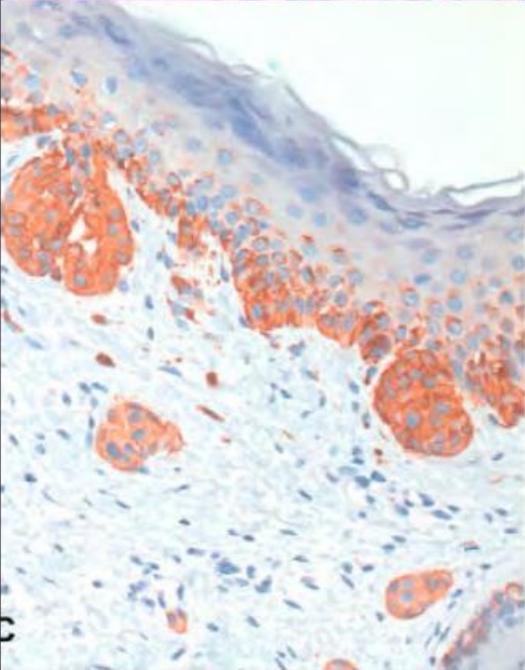
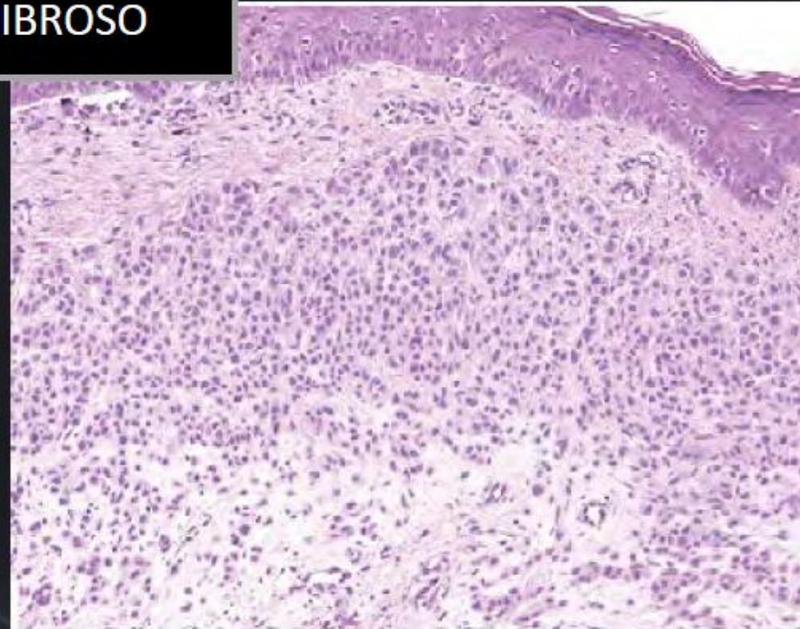
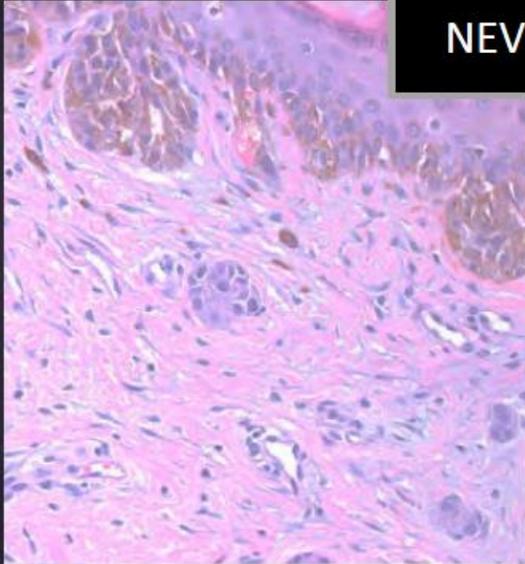
- Excepciones
- NEVO PENETRANTE PROFUNDO
- NEVO DISPLASICO TRAUMATIZADO/FIBROSO
- NEVOS BENIGNOS
 - No es necesario estratificación para ser un nevus.
 - No es necesario tener tinción completa para ser melanoma.



NEVO PENETRANTE PROFUNDO

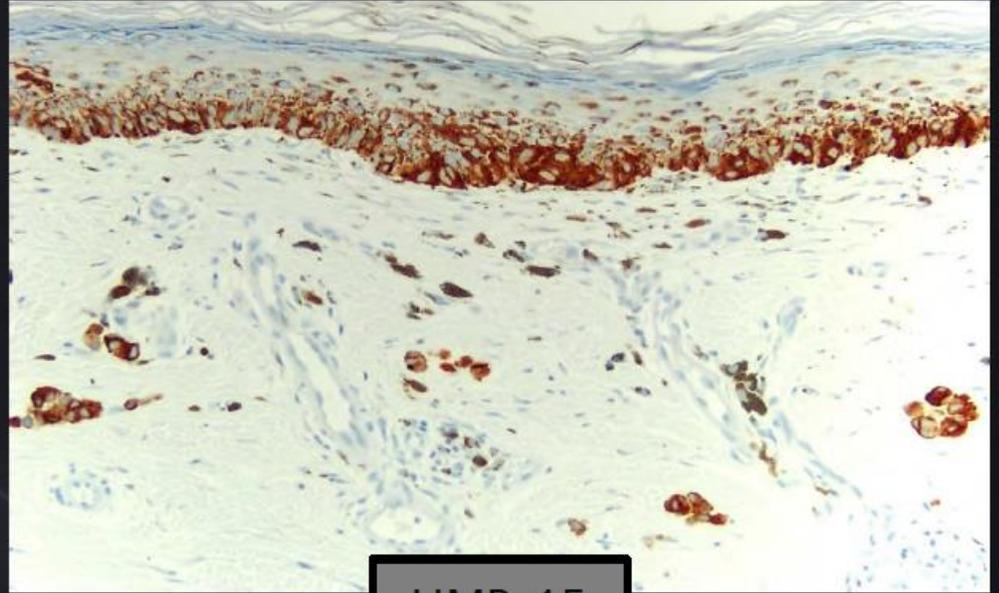
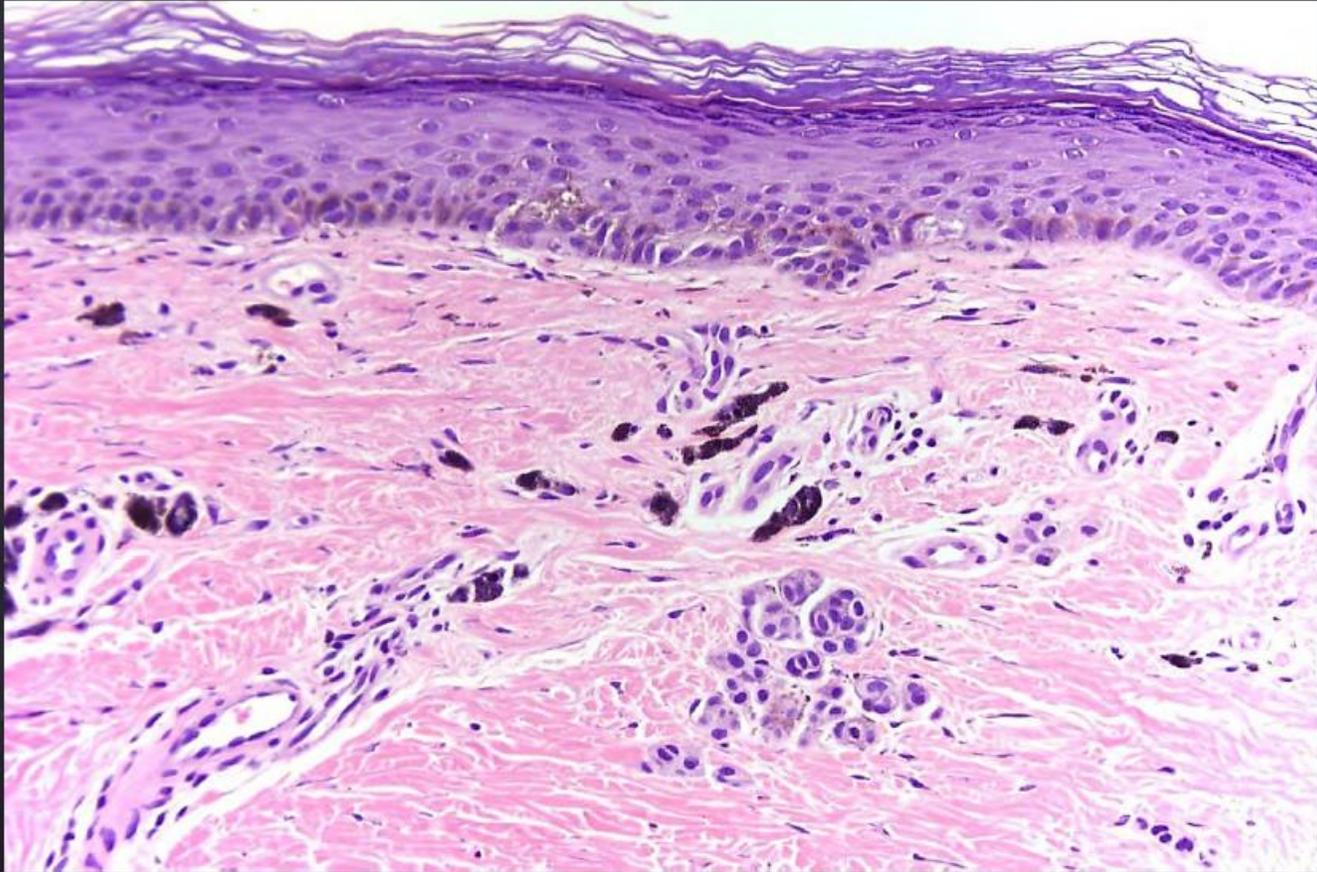


NEVO TRAUMATIZADO/FIBROSO

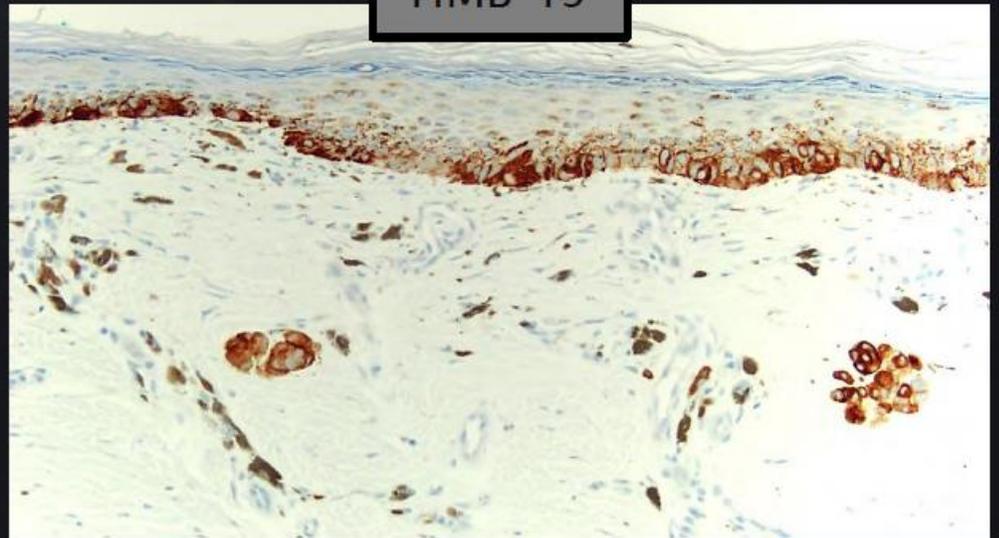


HMB-45

NEVO RECURRENTE/PERSISTENTE



HMB-45



HMB 45

		Nevi (74)	Melanoma (156)
HMB 45 Gradient	Yes	44.6%	10.3%
	Doubtful	24.3%	14.7%
	No	31.1%	75%

Modified from Uguen A et al.

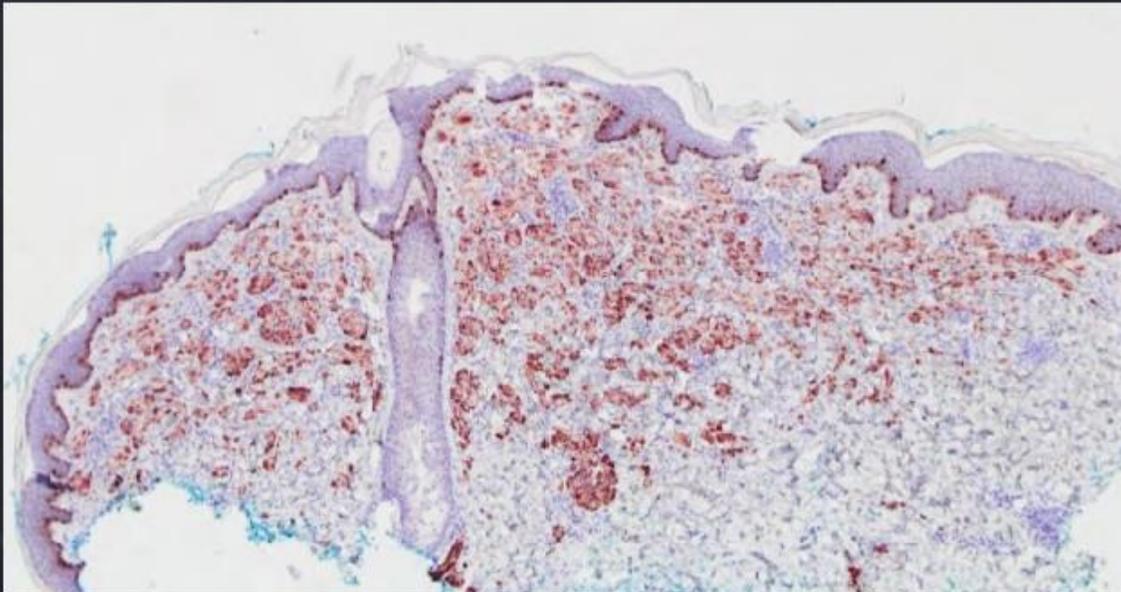




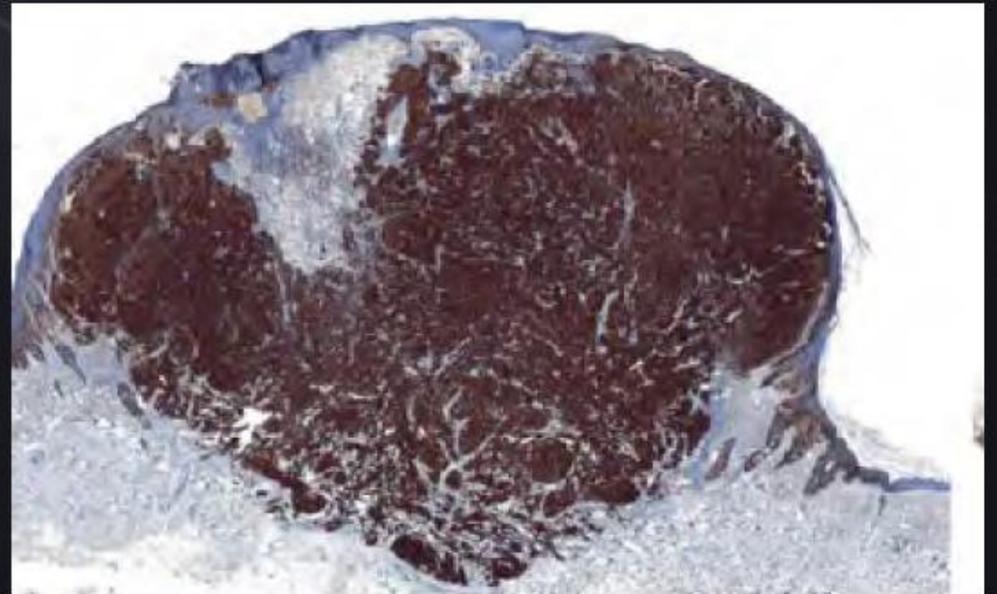
HMB-45



Deep Penetrating Nevus



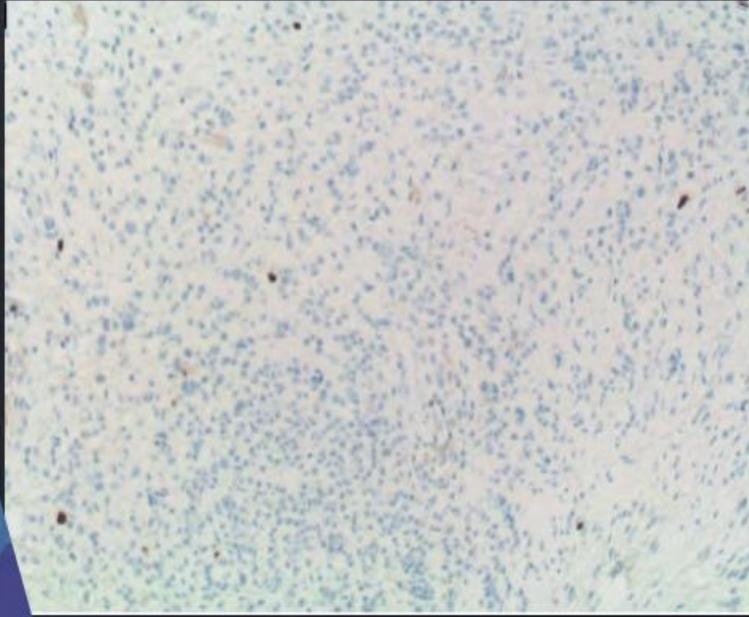
Nodular Melanoma



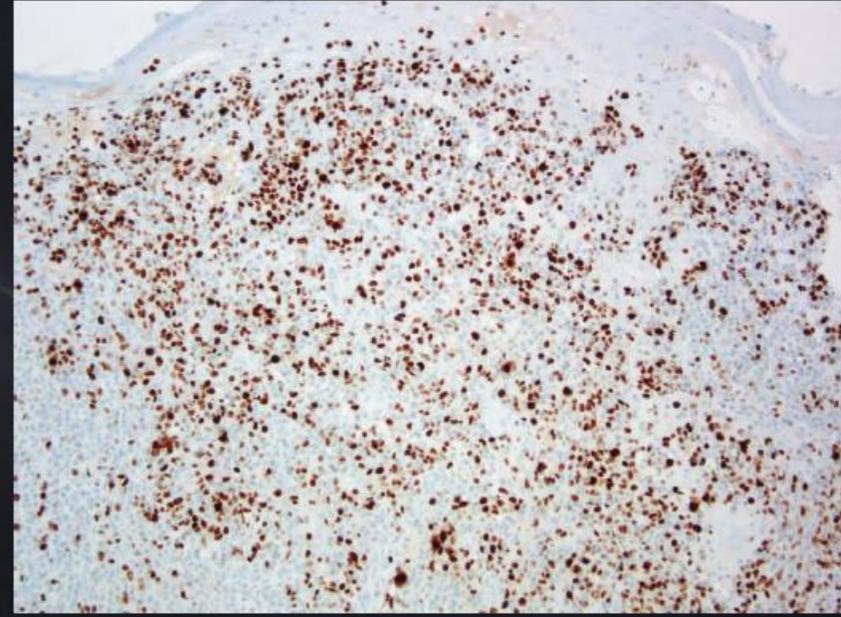
KI-67

- Marcador nuclear de proliferacion.
- Indice de proliferacion es mayor en melanoma que en nevus.
- Benignas: menor a 5%, unión y dermis superficial.
- Malignas: 5-50% positivas, al azar por toda la lesion.

Ki-67



Benign Nevus



Melanoma

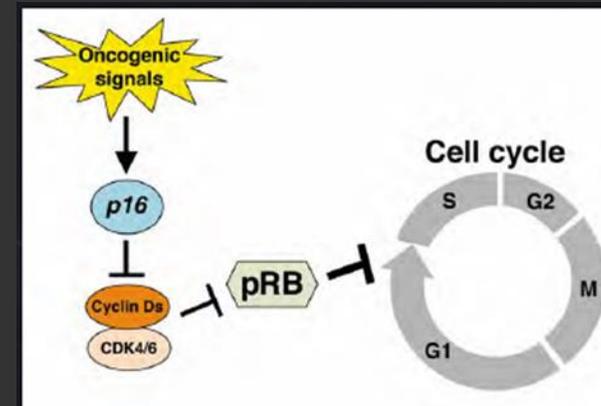


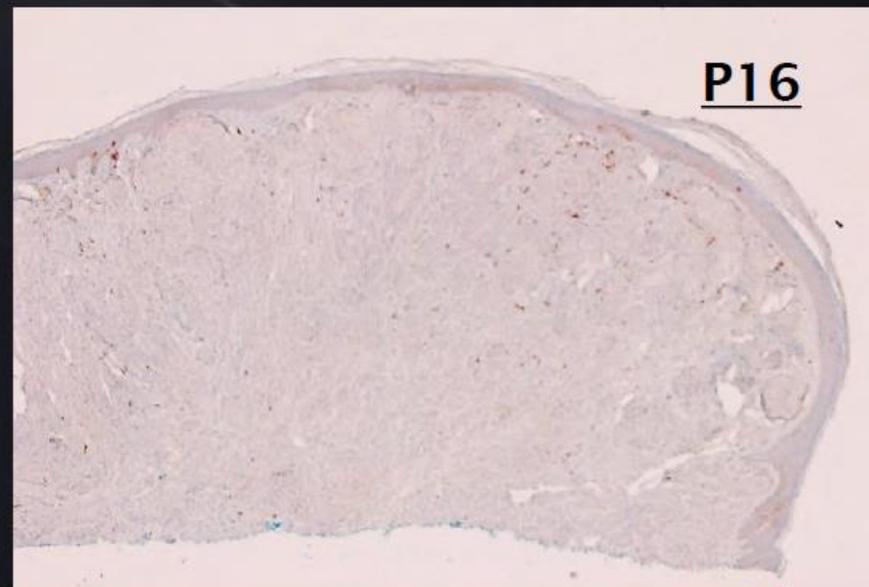
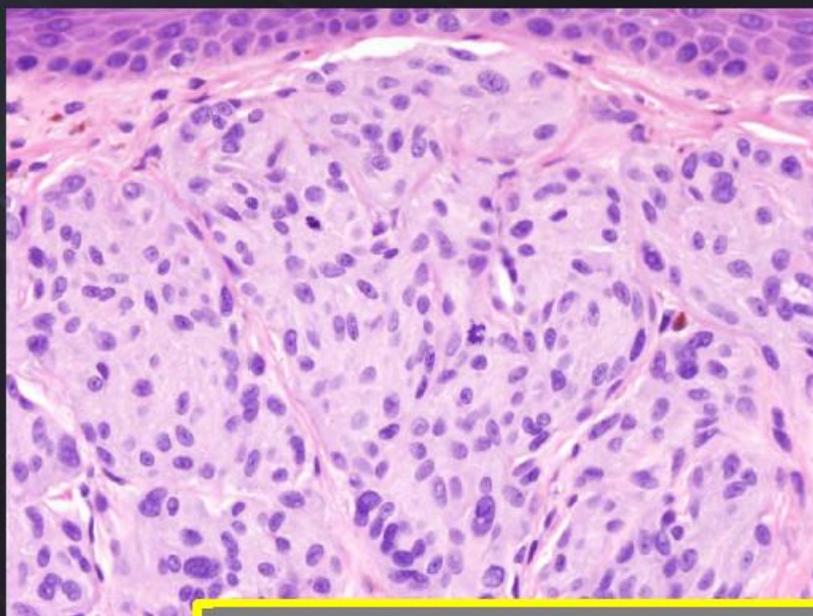
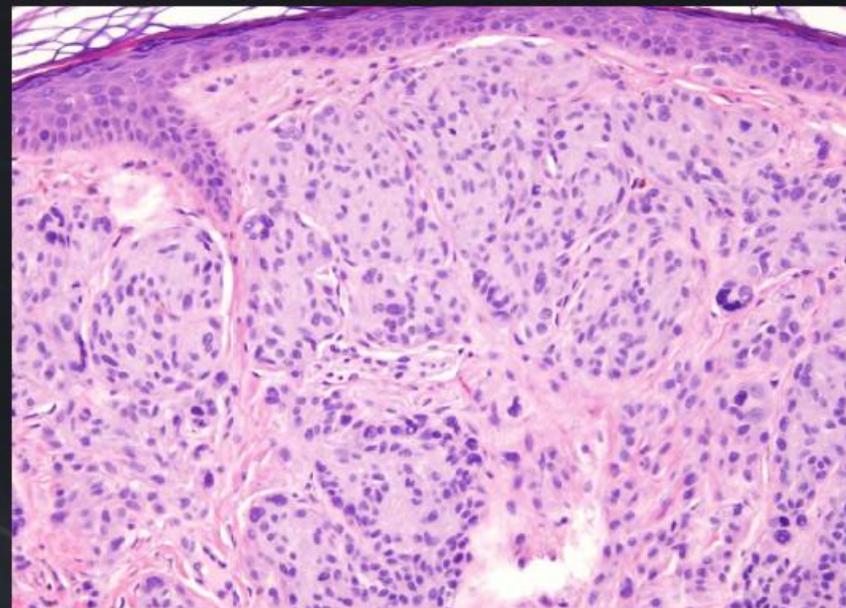
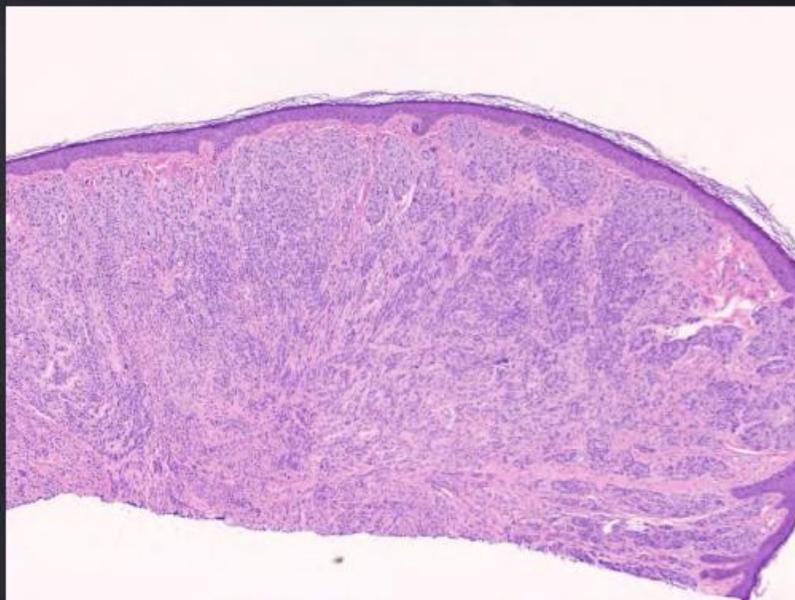
KI-67

- HECHO
- Aunque un índice de proliferación alto es un argumento para favorecer malignidad, pero uno bajo no lo descarta (múltiples reportes en la literatura).

p16

- Proteína con función reguladora del ciclo celular.
- Es un hecho, que p16 esta conservada en nevus y frecuentemente se pierde en casos de melanoma.





DIAGNOSTICO: MELANOMA, BRESLOW DE AL MENOS 2.05 MM

P16

- HECHOS
- Muchos melanomas todavía expresan p16.
- Nevos benignos pueden no expresar p16.
- P16 +/- no confirma ni descarta malignidad.
- P16 no refleja el estado del gen.

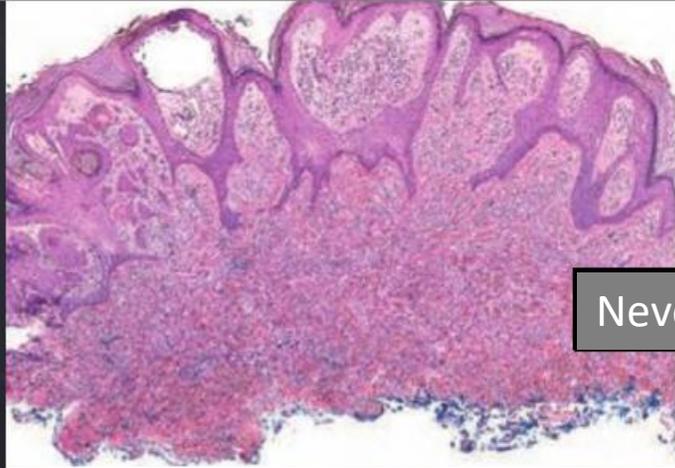
Expression of p16 alone does not differentiate between Spitz nevi and Spitzoid melanoma

Mason A, Wititsuwannakul J, Klump VR, Lott J, Laszova R. *J Cutan Pathol* 2012; 39: 1062-1074.

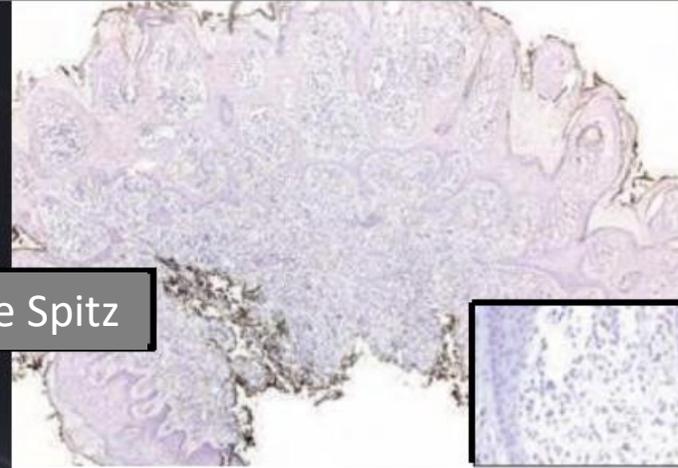
p16

- ❑ 83% (15/18) Spitz nevi positive
- ❑ 17% (3/18) Spitz nevi negative
- ❑ 79% (15/19) Spitzoid melanomas positive
- ❑ Caveat: All 19 patients with melanoma had poor outcome with death (6) or metastases (13)

7 años edad, pierna, márgenes positivos, sin Rx, > de 4 años de seguimiento

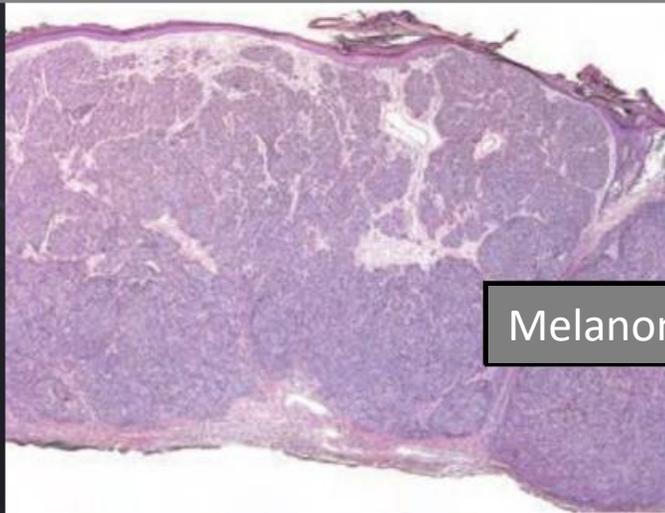


Nevo de Spitz



p16

86 años de edad, hombre, muere por su enfermedad (recurrencia local y metástasis)



Melanoma Spitzoide



p16

Comparative Analysis of Atypical Spitz Tumors With Heterozygous Versus Homozygous 9p21 Deletions for Clinical Outcomes, Histomorphology, BRAF Mutation, and p16 Expression

Pedram Yazdan, MD, Chelsea Cooper, BA,* Lauren Meldi Sholl, BA,* Klaus Busam, MD,† Alfred Rademaker, PhD,‡ Bing Bing Weitner, MS,‡ Roxana Obregon, BA,* Joan Guitart, MD,*§ and Pedram Gerami, MD*§*

Am J Surg Pathol 2014; 38: 638-645.

p16 IHC profile of ASTs with heterozygous and homozygous deletions of 9p21 by FISH

Atypical Spitz Tumor	p16 Negative	p16 Positive
9p21 heterozygous deletion	33% (4/12)	67% (8/12)
9p21 homozygous deletion	85% (11/13)	15% (2/13)

P16

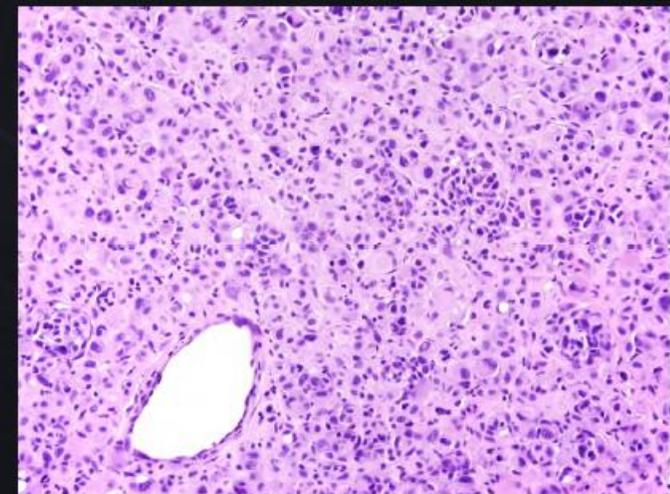
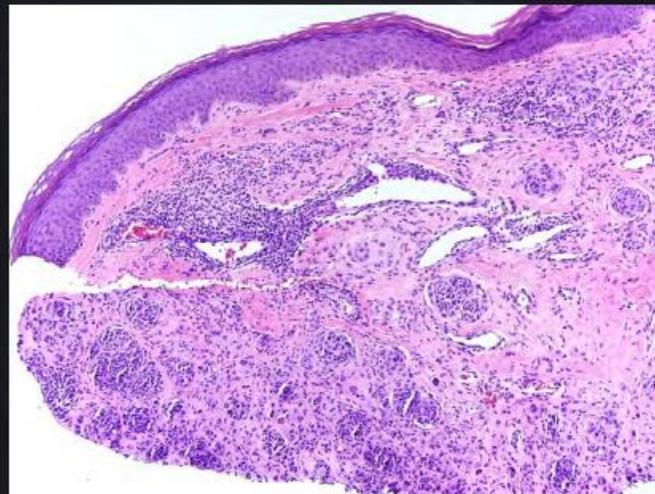
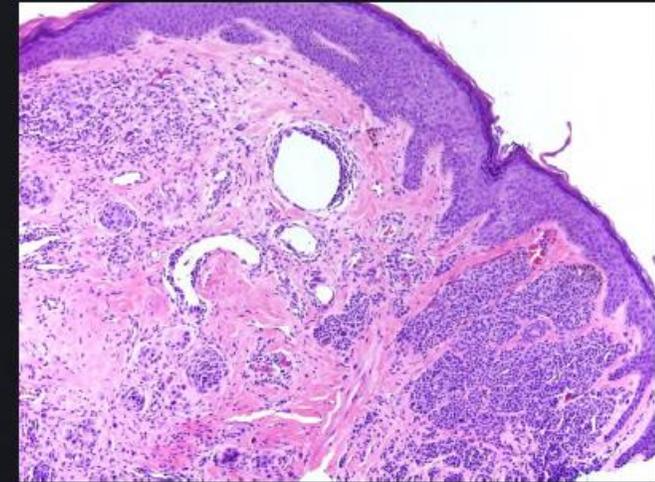
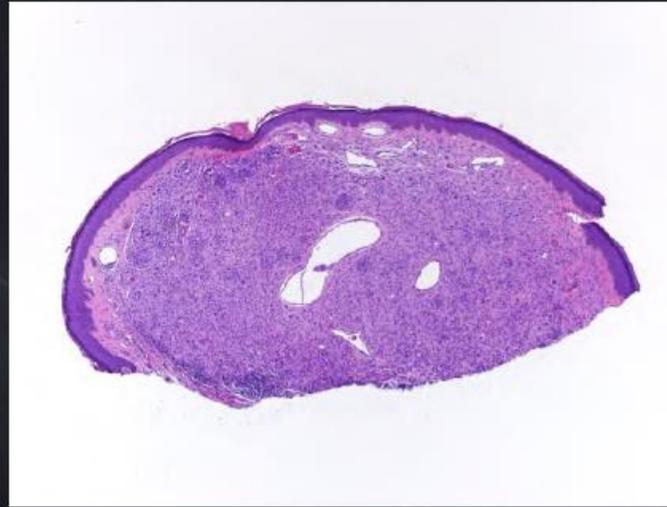
- Conclusión:
 - Positividad no concluye si es benigno o maligno.
 - Su pérdida no es equivalente a pérdida homocigota de 9p21 por FISH.

BAP-1

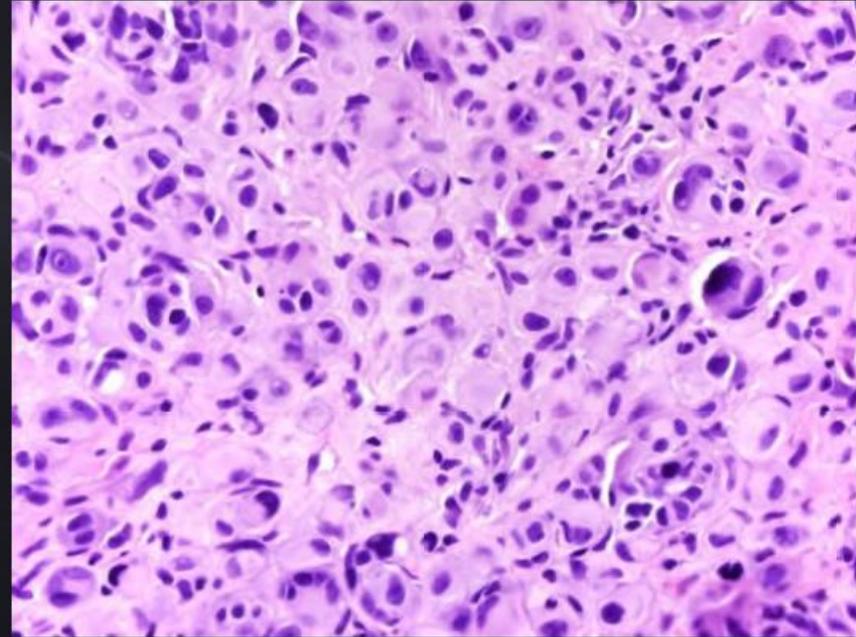
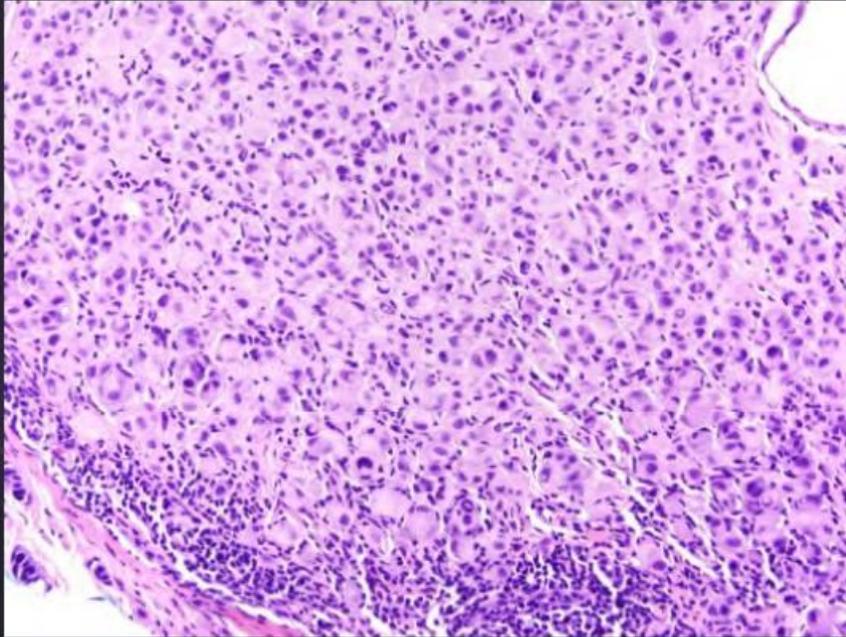
- Gen supresor de tumores que codifica la proteína 1-asociada a BRCA1.
- El estado de la mutación se correlaciona bien con la inmunohistoquímica.
- Tumor spitzoide con pérdida de BAP-1 se le ha llamado el tumor de Wiessner.

TUMOR SPITZOIDE CON BAP-1 MUTADO

- Tumor melanocítico cutáneo con células epiteloides distintivas.
- Lesión polipoide, mayormente dérmica, con células spitzoides, grandes, epiteloides.
- Pequeño componente de nevo común en la periferia.
- A menudo con componente inflamatorio asociado.
- Expresan BRAF V600E

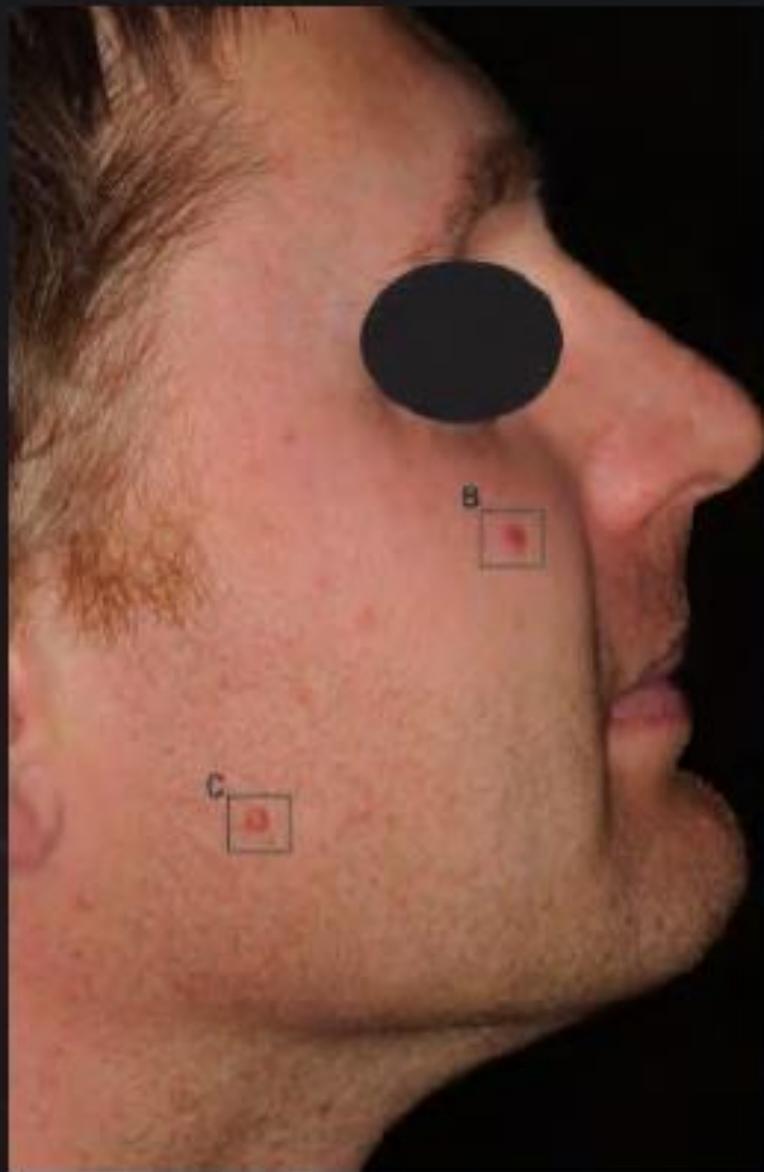


TUMOR SPITZOIDE CON BAP-1 MUTADO



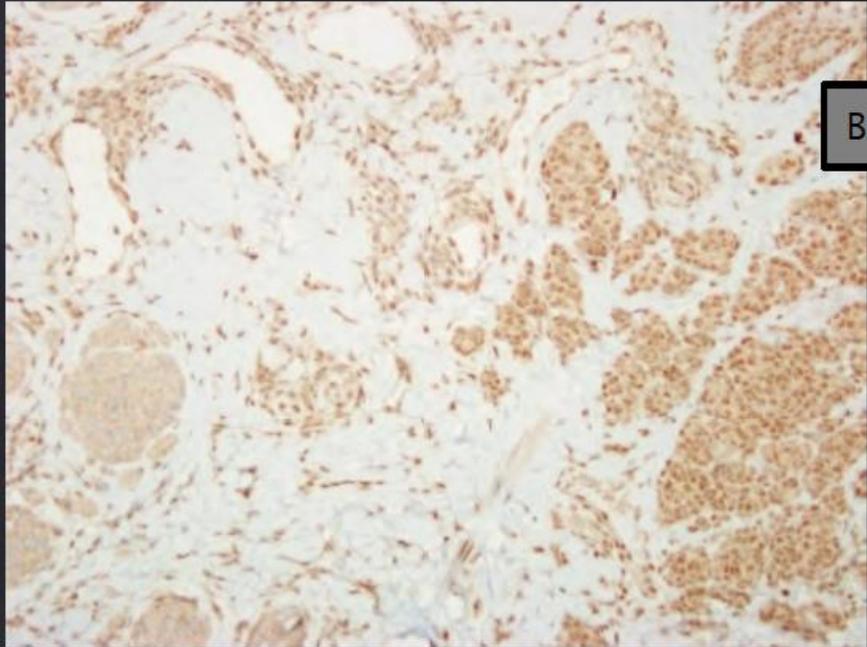
BAP-1

- MANIFESTACIONES DE MUTACION EN LINEA GERMINAL DE BAP-1
 - MELANOMA UVEAL Y CUTANEO
 - MESOTELIOMA
 - ADENOCARCINOMA DE PULMON
 - CARCINOMA DE CELULAS RENALES
 - MENINGIOMA
- PUEDEN EXISTIR MUTACIONES ESPORADICAS
 - APARIENCIA DE NEVUS COMUN

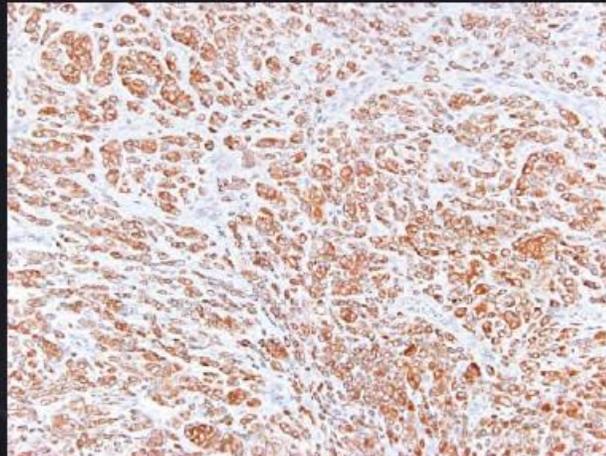
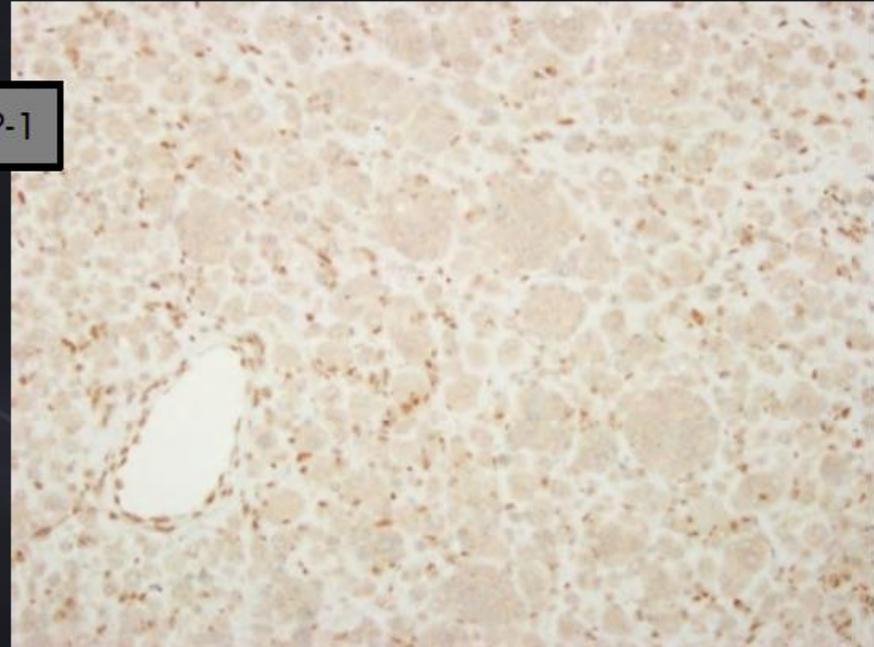


Wiesner T, et al. JDDG. 2013; 11(S4): 19.

TUMOR SPITZOIDE CON BAP-1 MUTADO

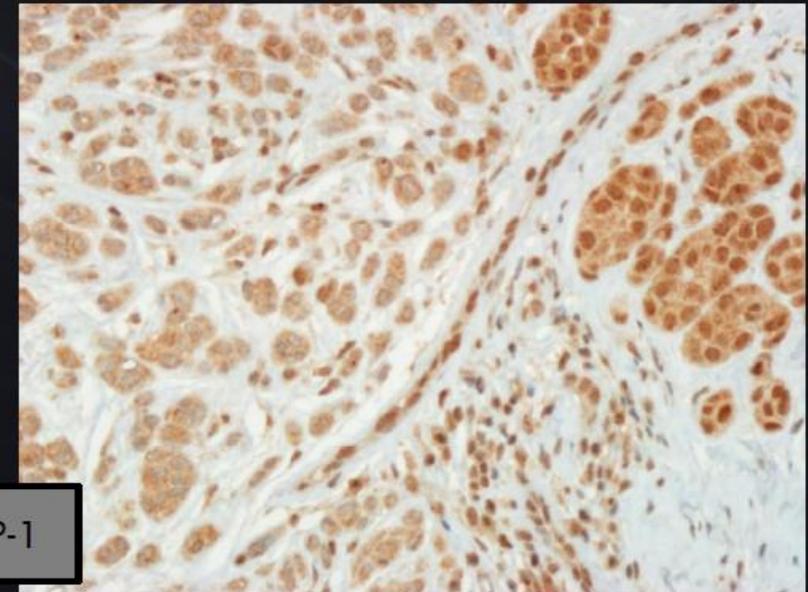
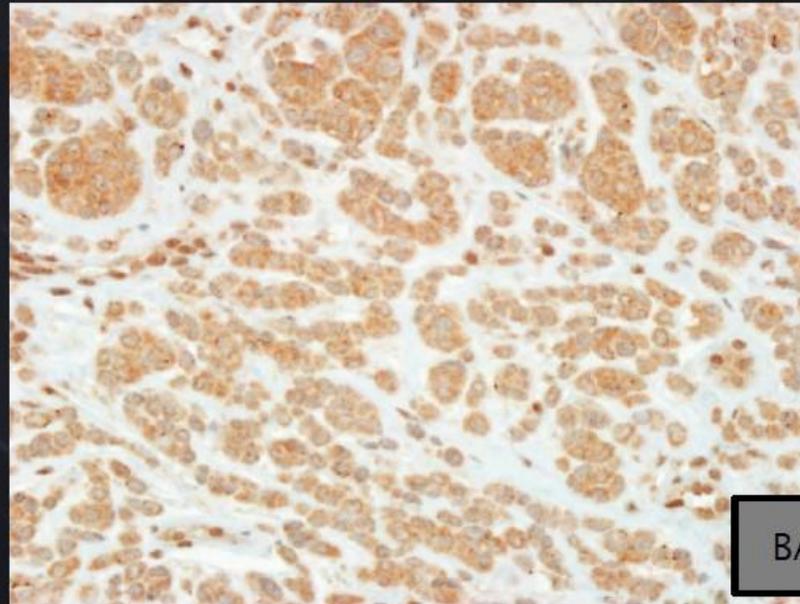
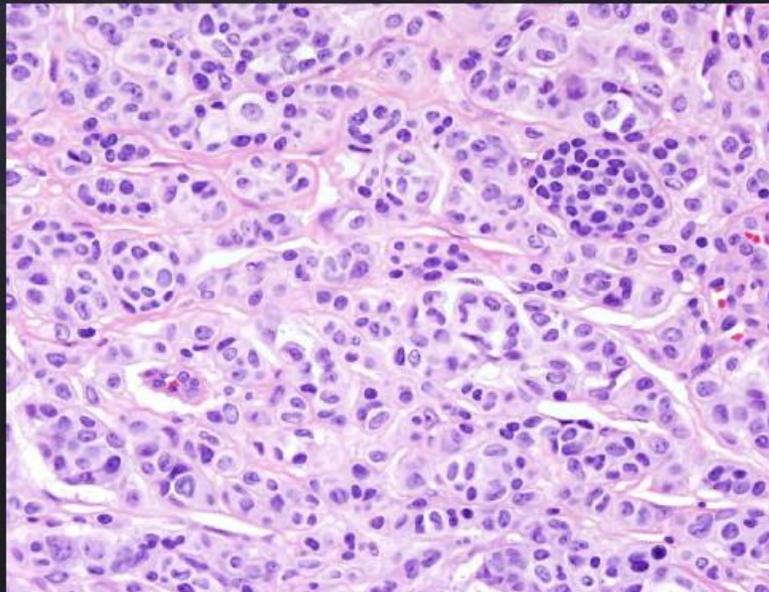
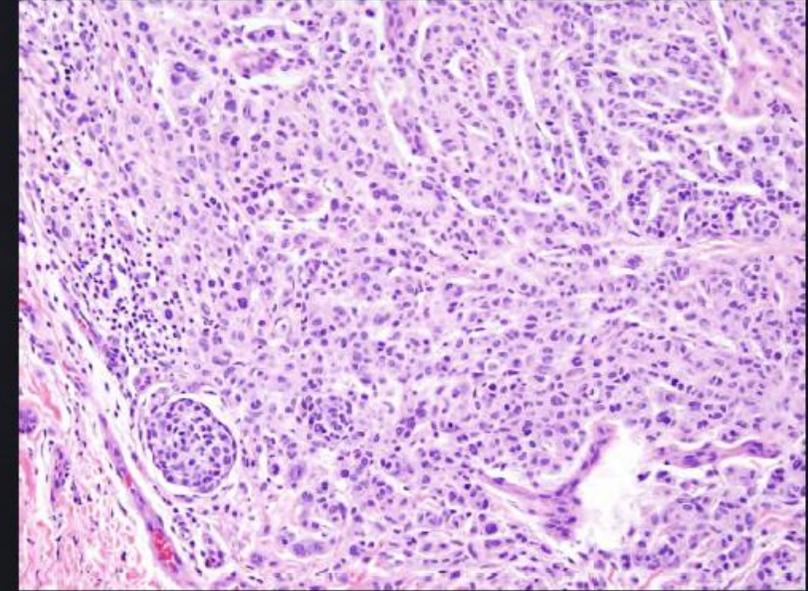
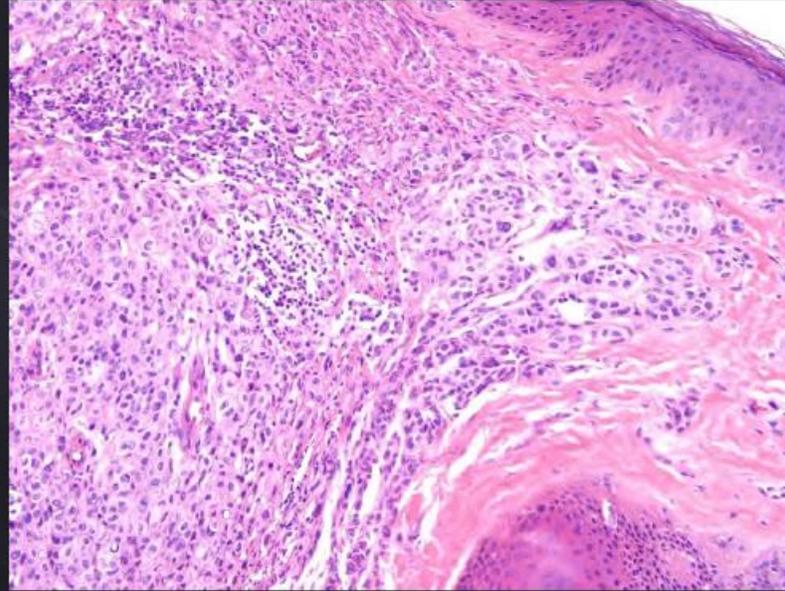
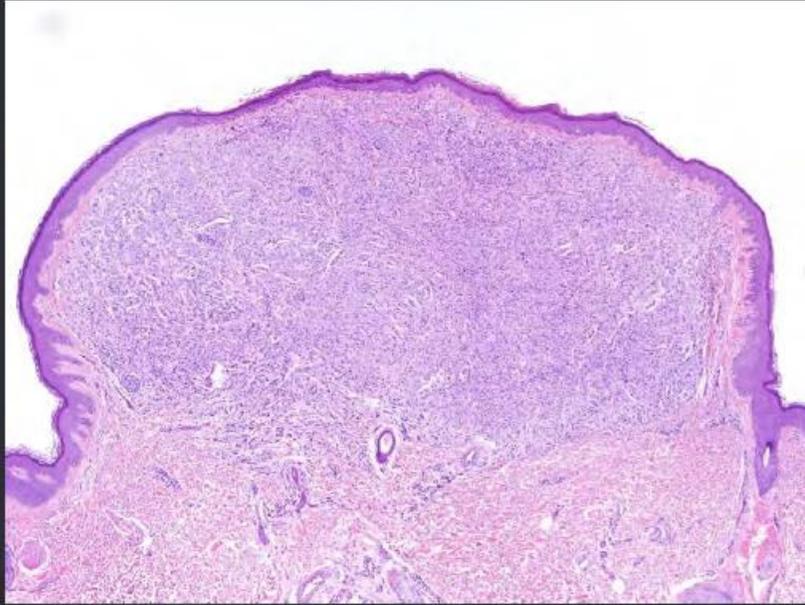


BAP-1



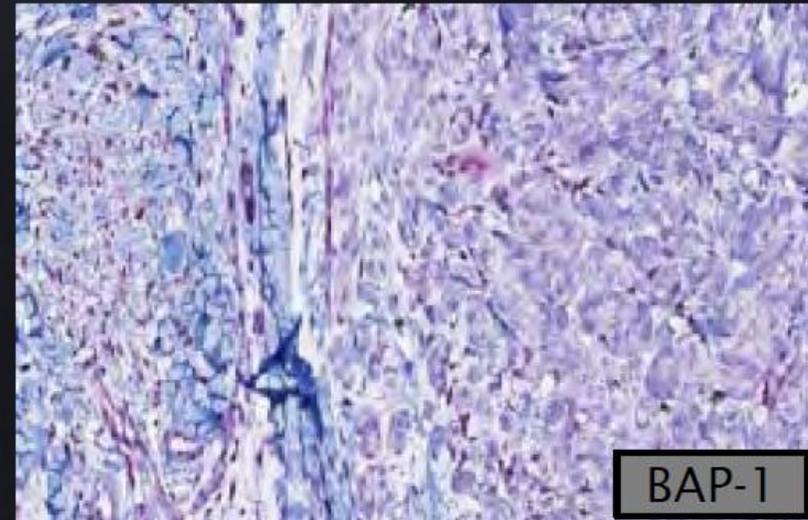
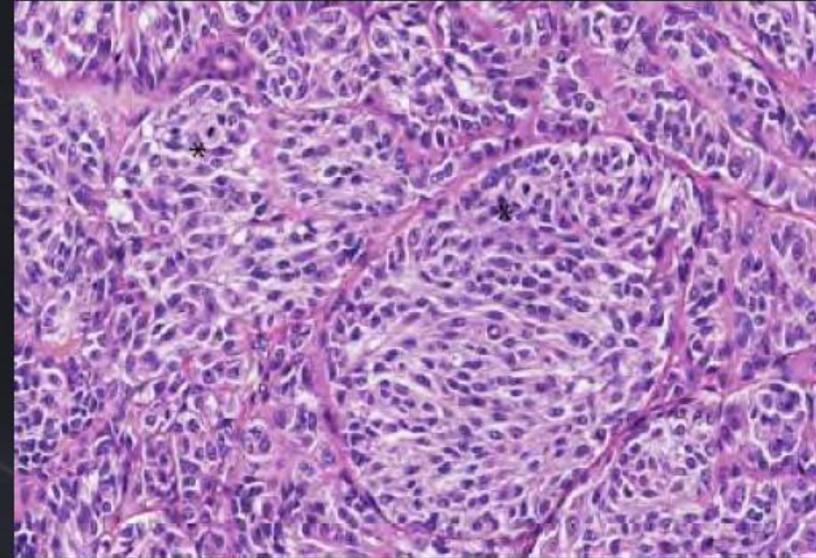
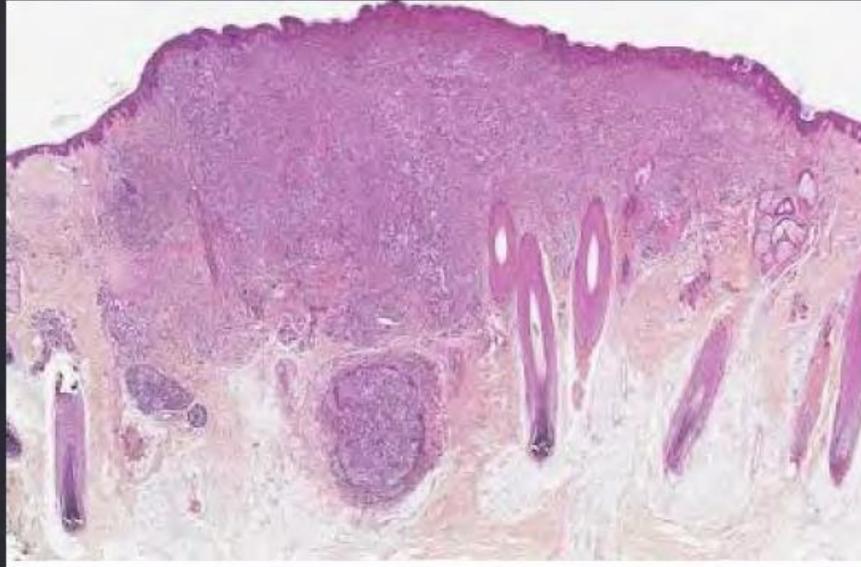
BRAF-V

TUMOR SPITZOIDE CON BAP-1 MUTADO

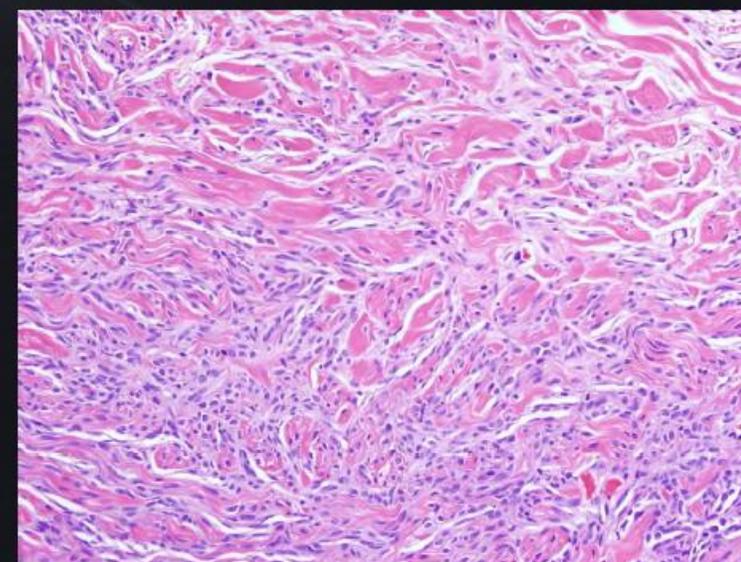
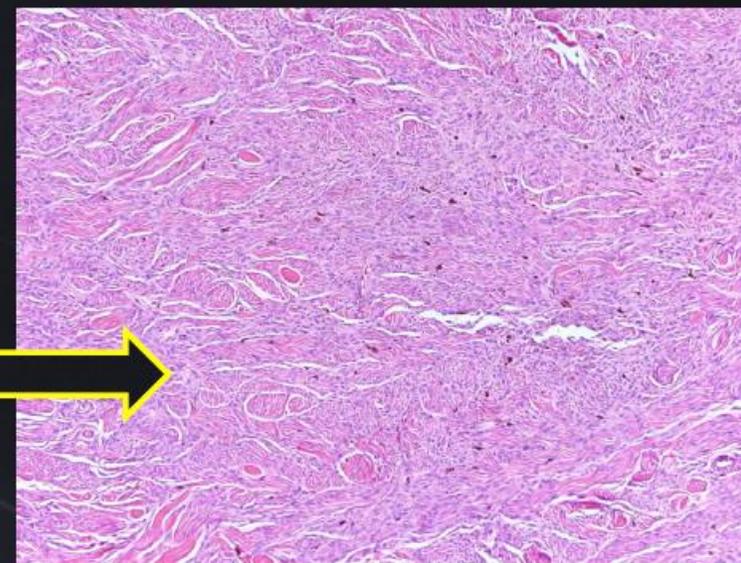
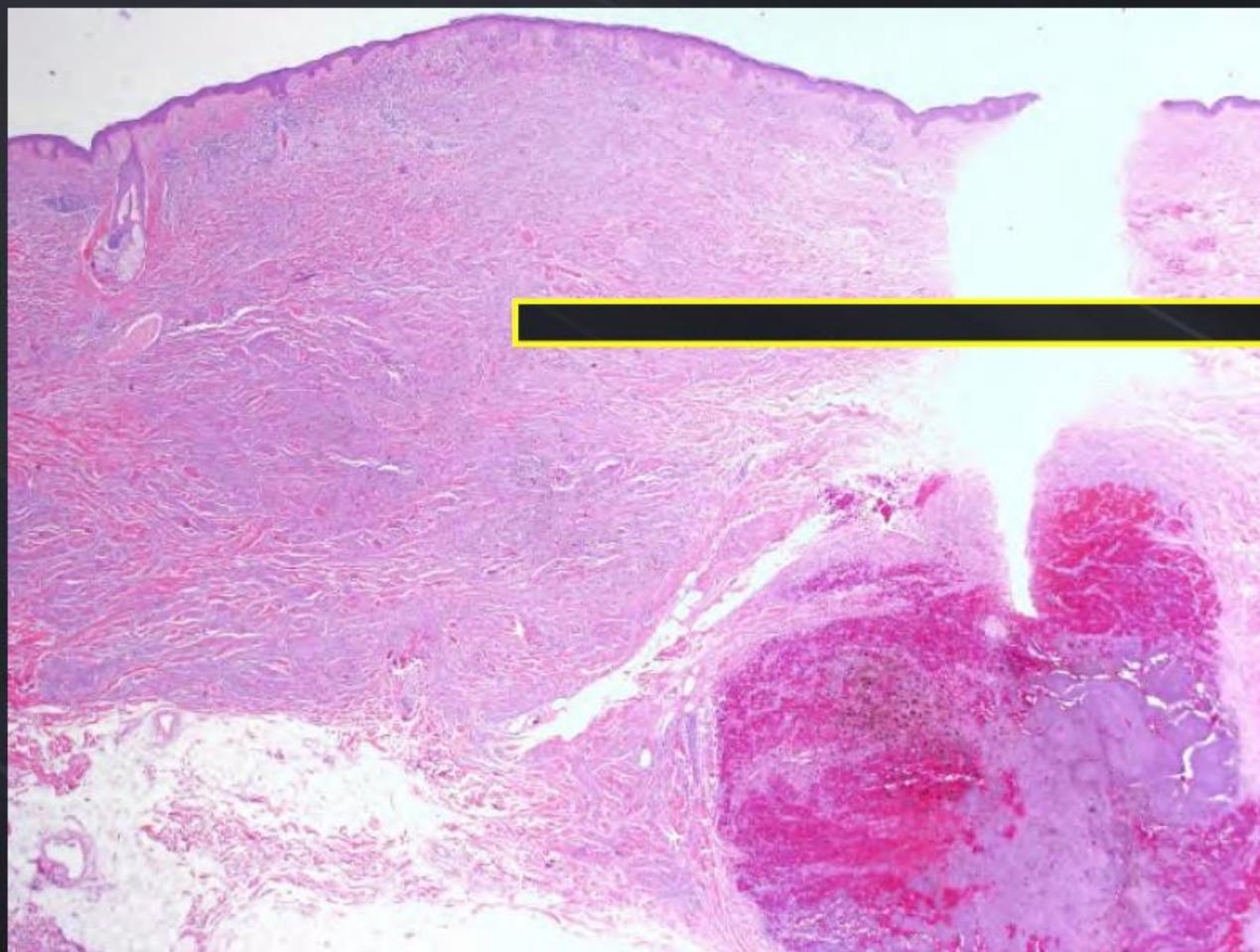


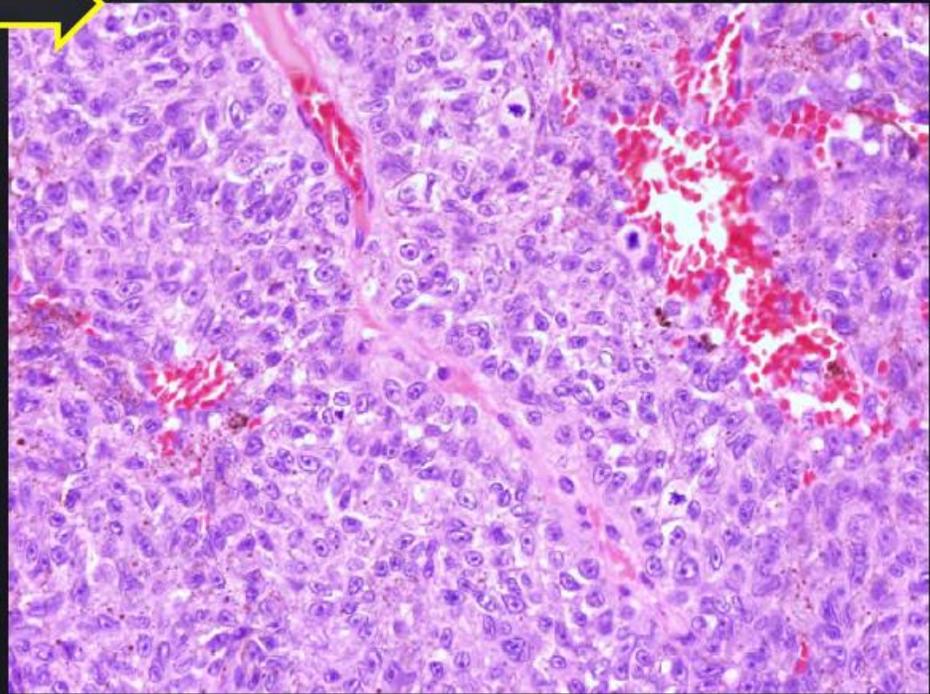
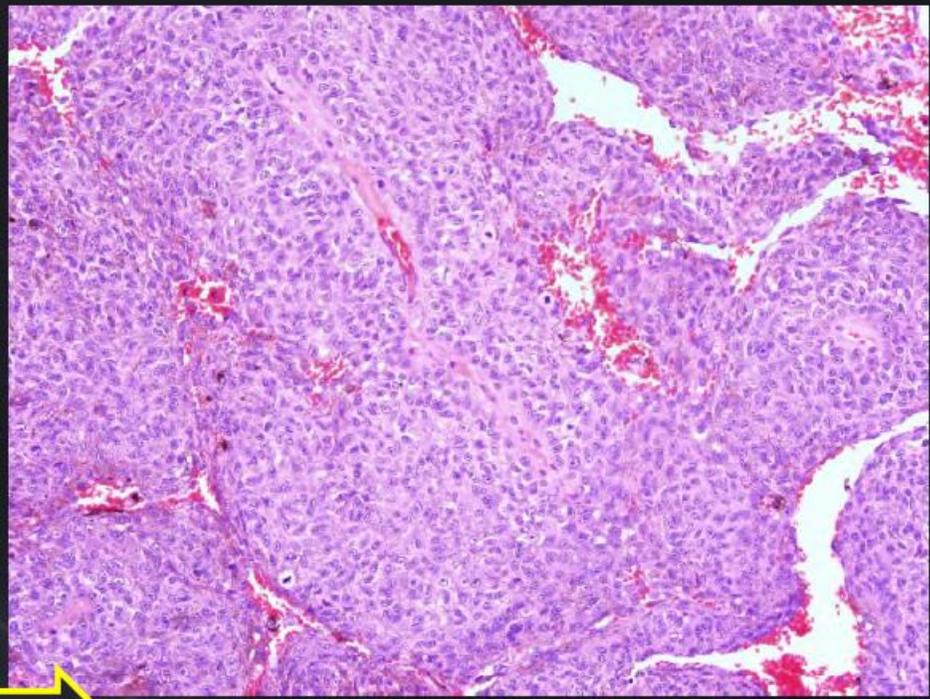
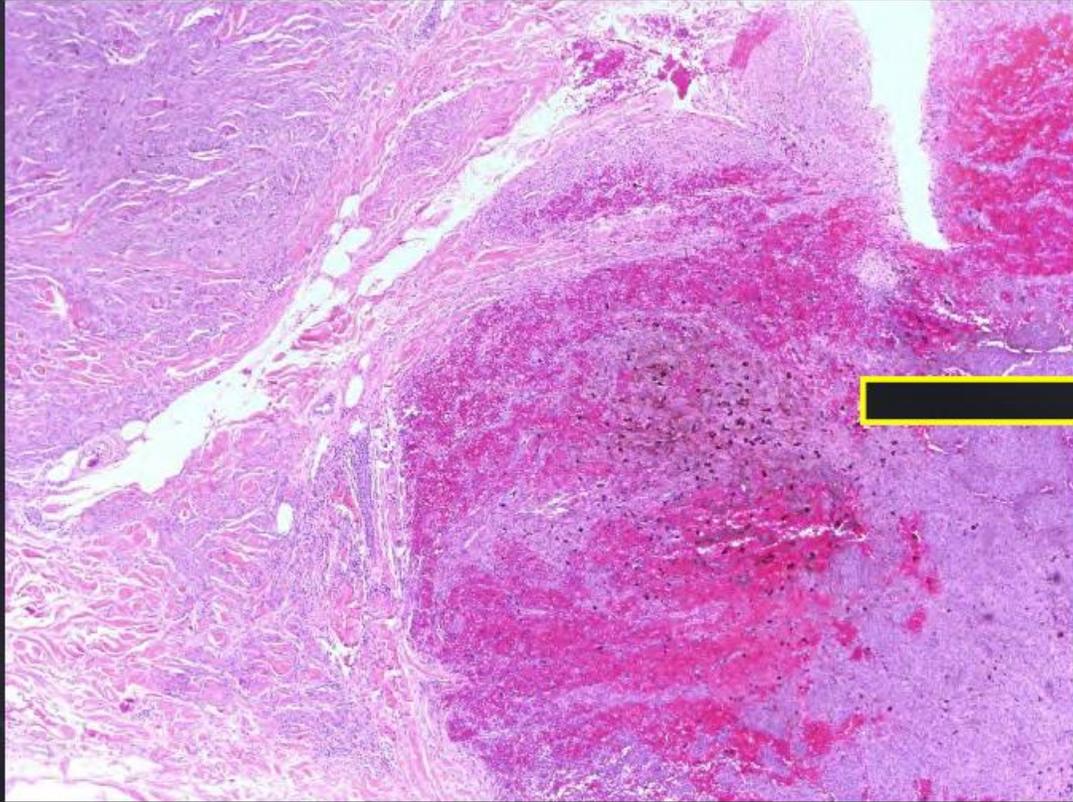
BAP-1

MELANOMA ORIGINANDOSE EN NEVO AZUL

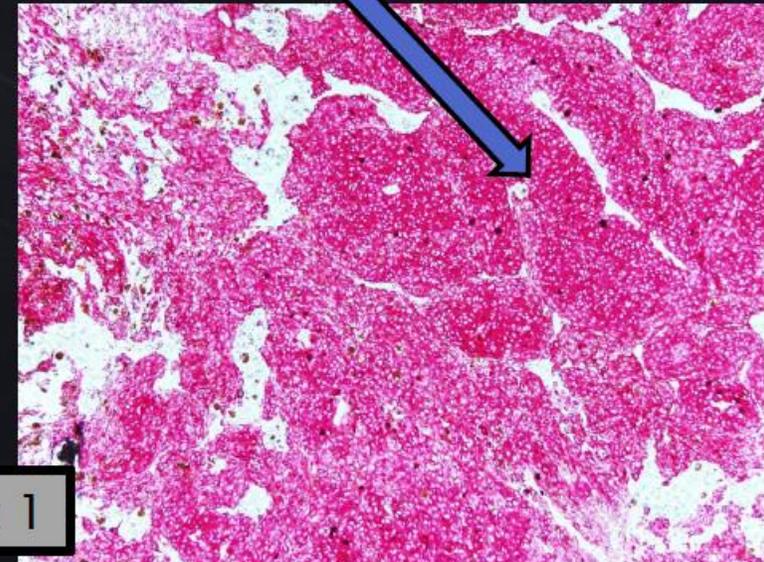
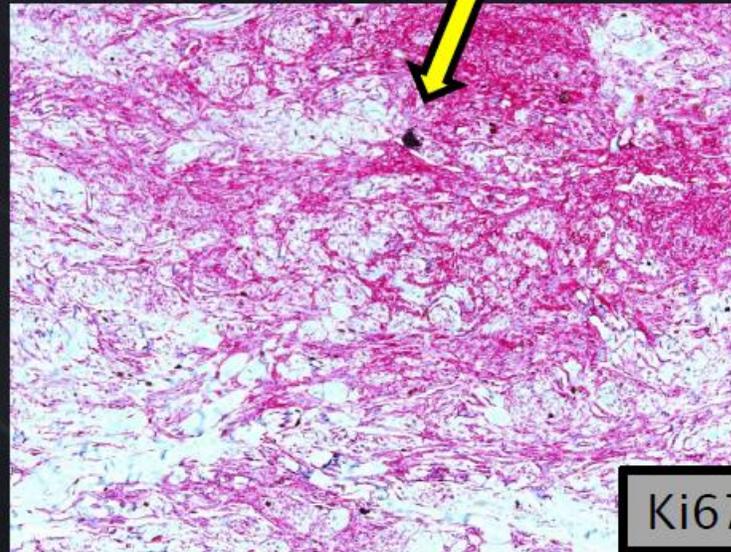
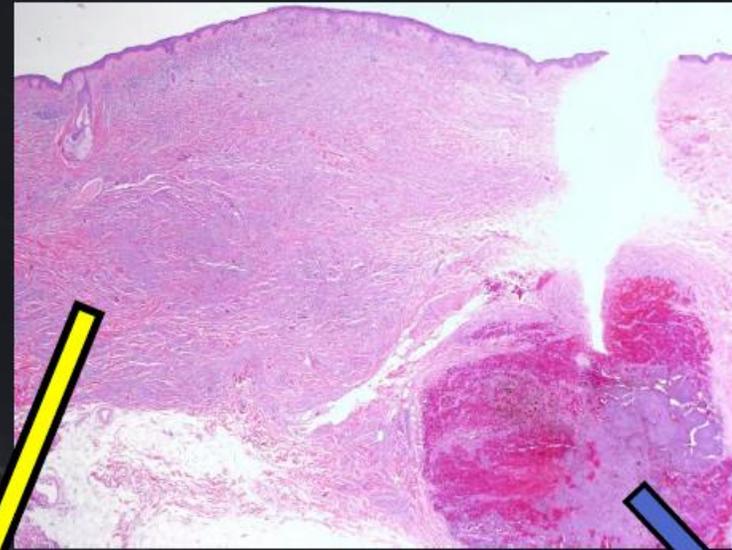
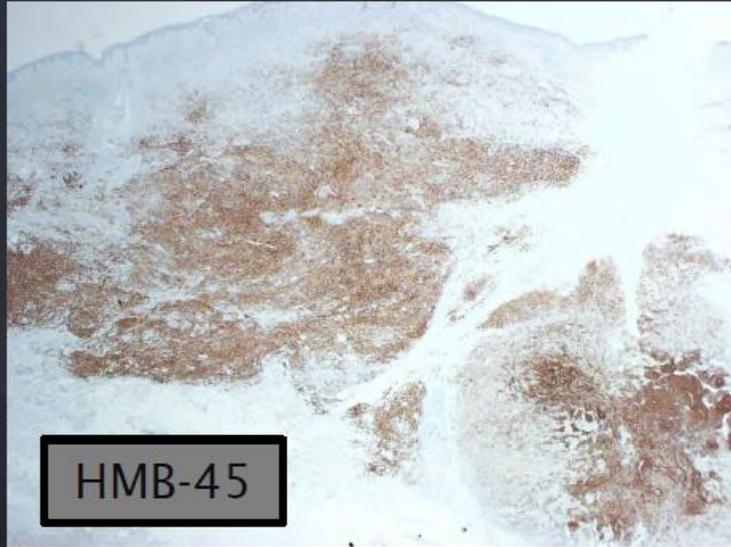


Melanoma Arising within Cellular Blue Nevus (Malignant Blue)



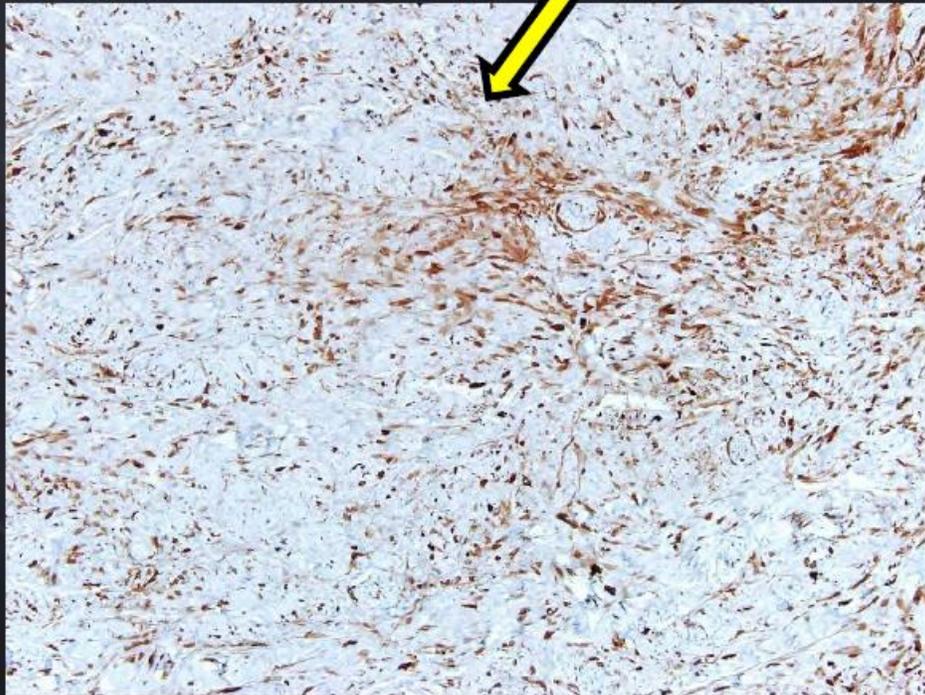
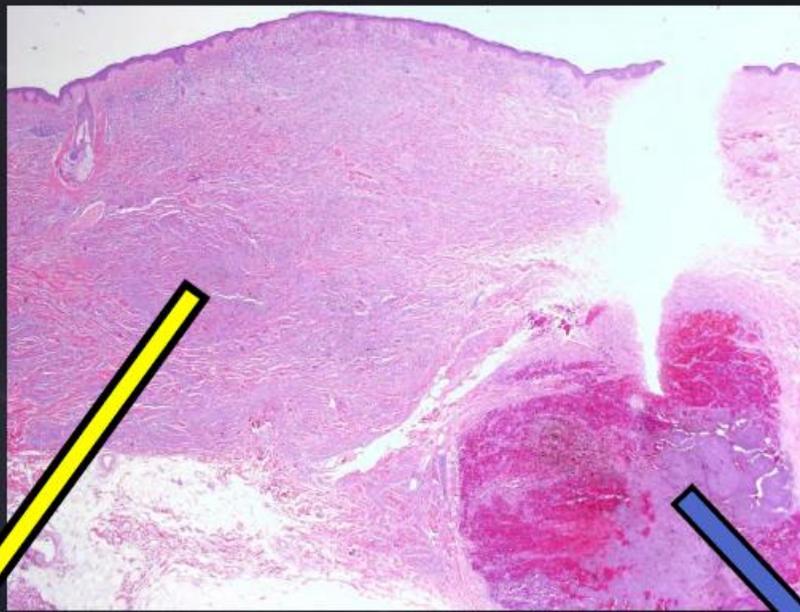


Melanoma Arising within Cellular Blue Nevus (Malignant Blue)

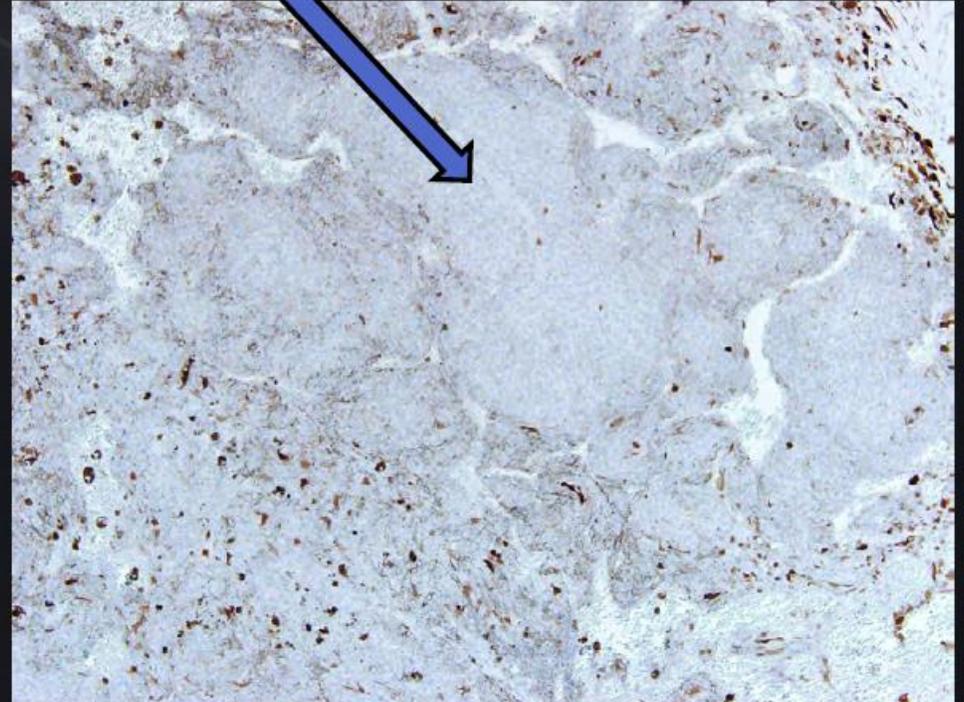


Ki67/Mart 1

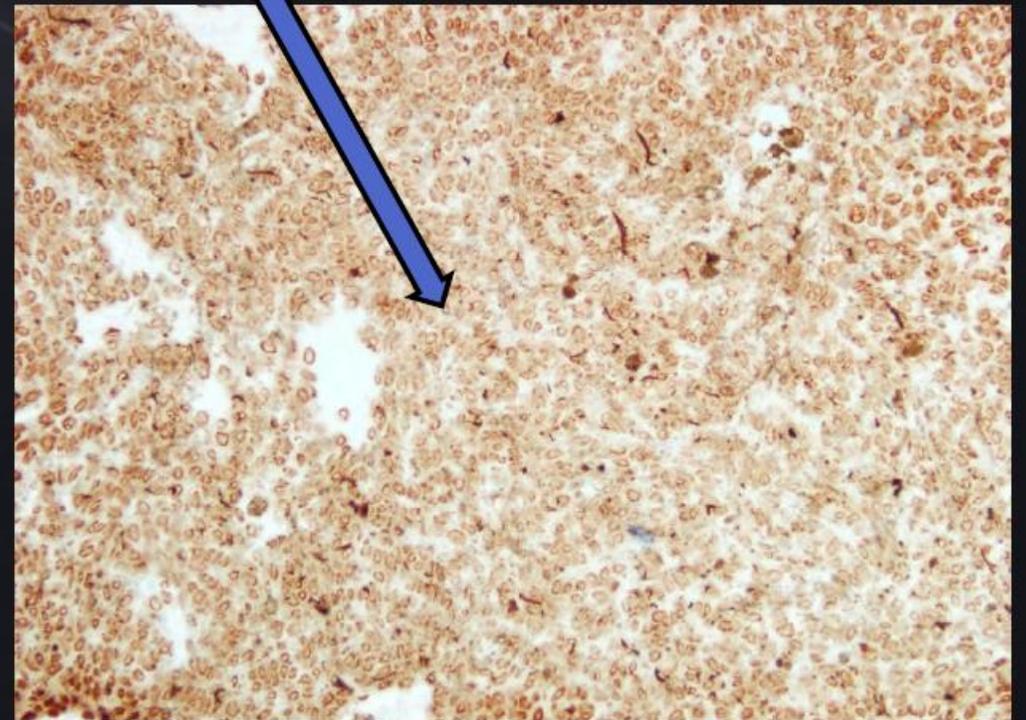
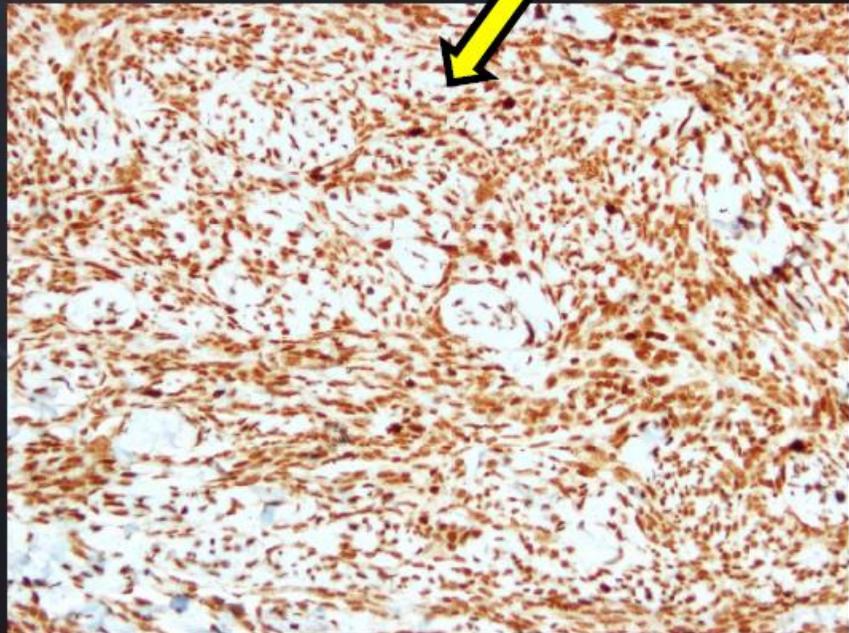
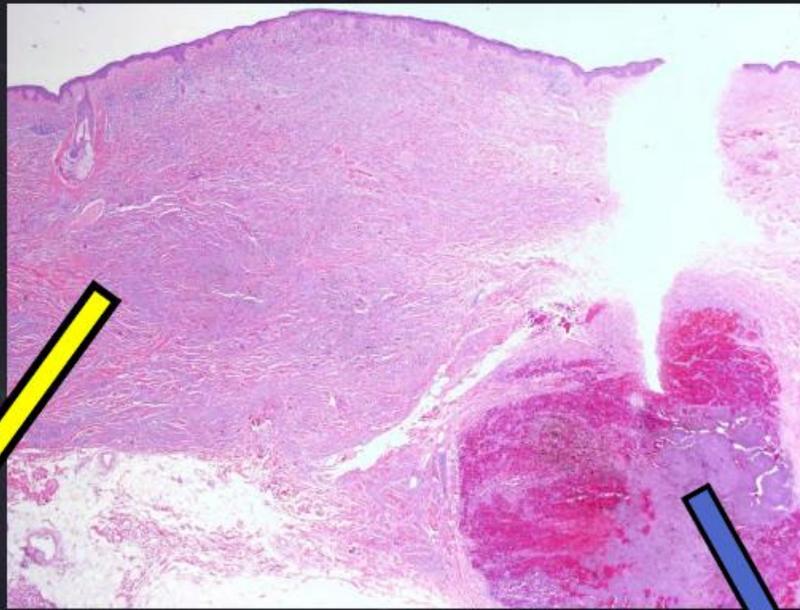
Melanoma Arising within
Cellular Blue Nevus
(Malignant Blue)



p16



Melanoma Arising within
Cellular Blue Nevus
(Malignant Blue)



BAP-1

RESEARCH

Open Access

A p16-Ki-67-HMB45 immunohistochemistry scoring system as an ancillary diagnostic tool in the diagnosis of melanoma



Arnaud Uguen^{1,2,3,4*}, Matthieu Talagas^{2,3,4}, Sebastian Costa², Sandrine Duigou², Stéphanie Bouvier², Marc De Bræekeleer^{1,3,5} and Pascale Marcorelles^{2,3,4}

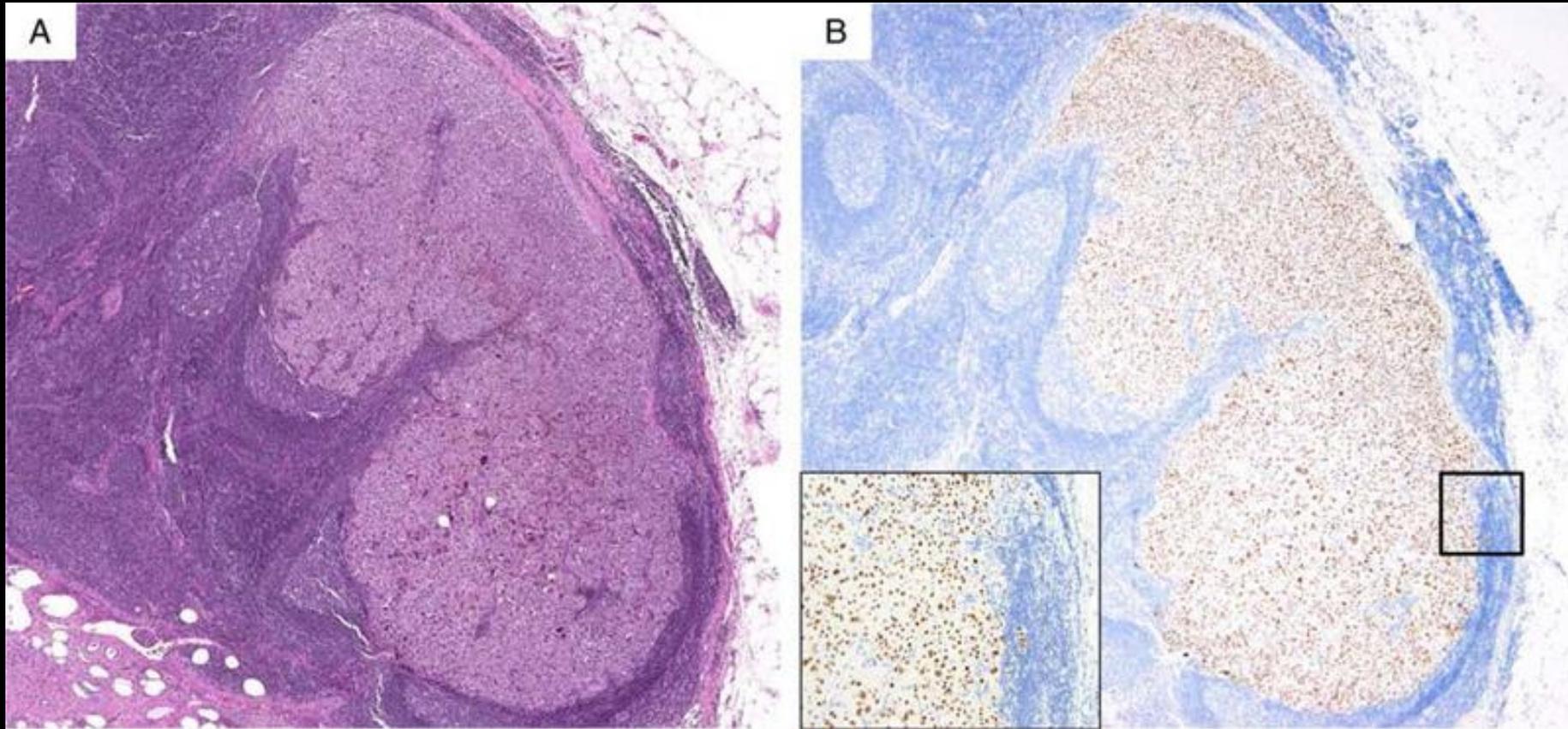
**HAY UN ROL PARA LA
INMUNOHISTOQUIMICA EN
MELANOMA O LESIONES
MELANOCITICAS AMBIGUAS**



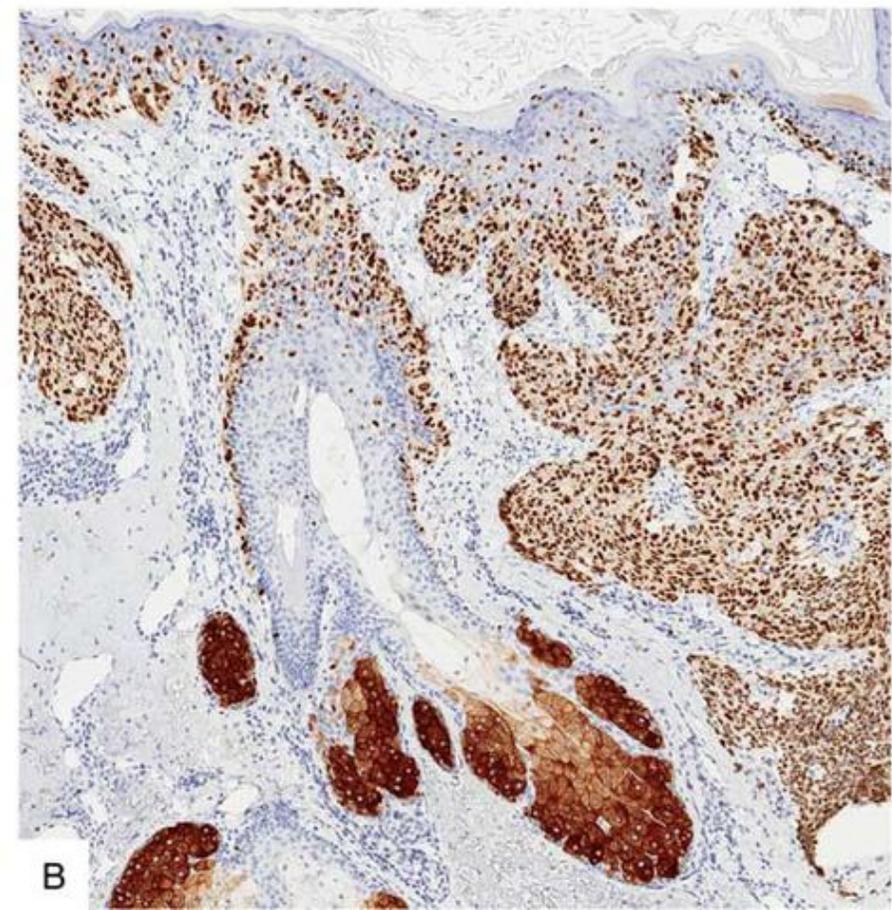
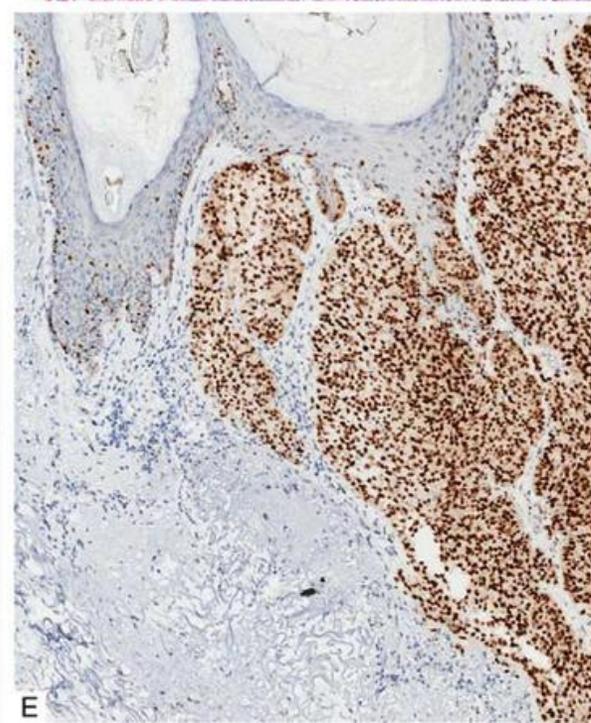
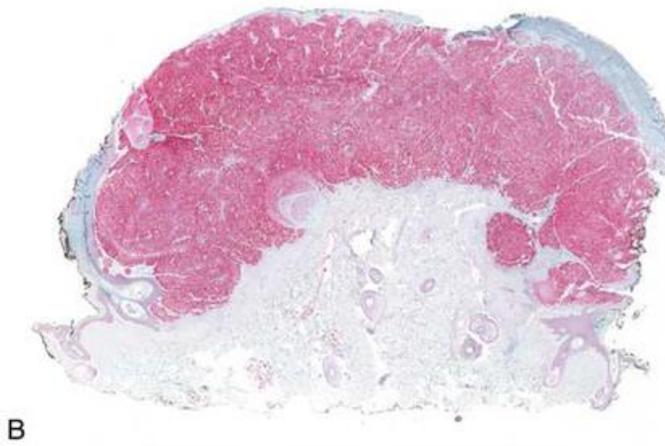
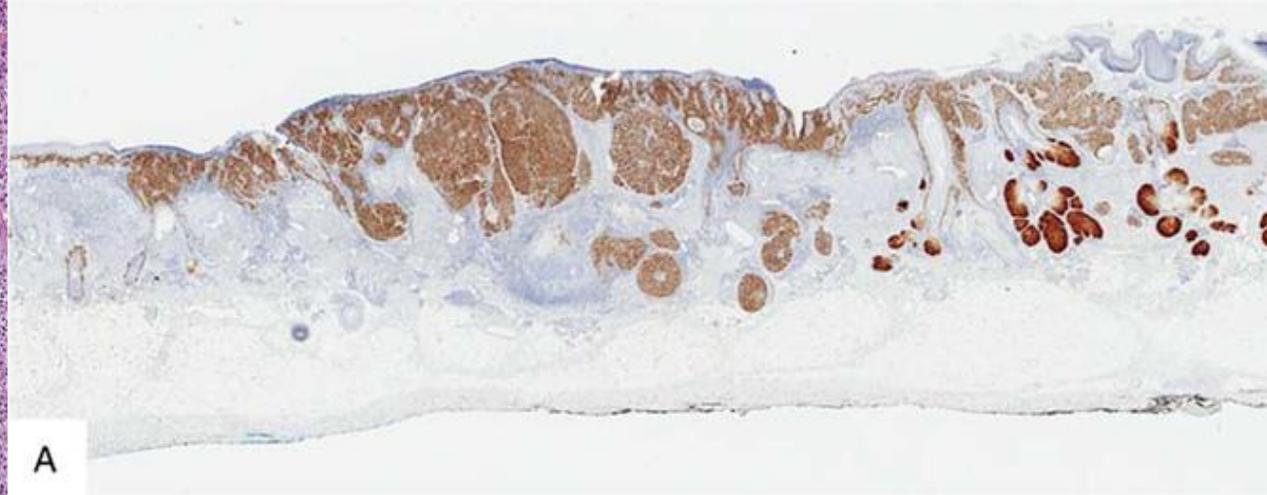
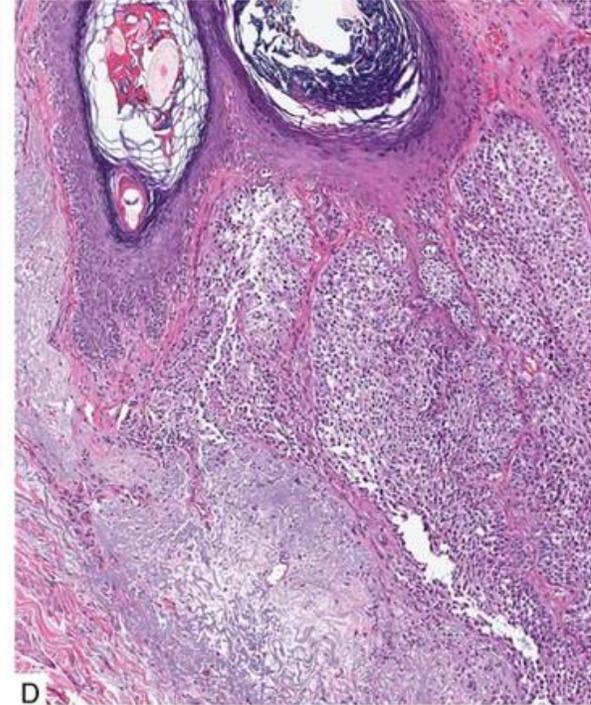
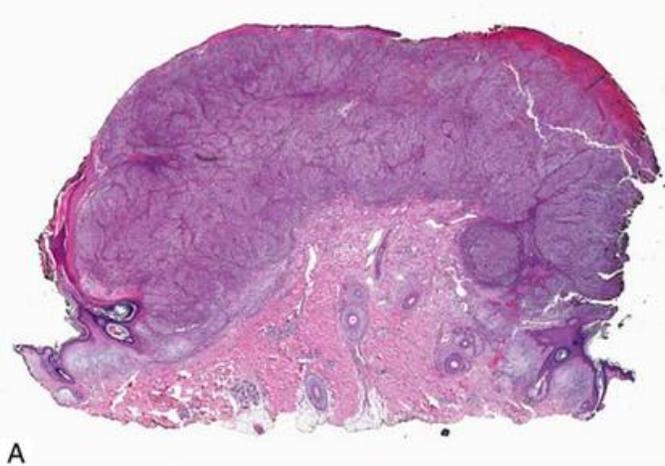
PRAME

- PRAME (PReferentially expressed Antigen in MElanoma).
- Descubierta como uno de los antígenos de linfocitos T reactivos.
- Tejidos normales no lo expresan, excepto: testículo, ovario, placenta, adrenales, and endometrio.
- Expresado en Melanomas, melanomas uveales y otros carcinomas y sarcomas.

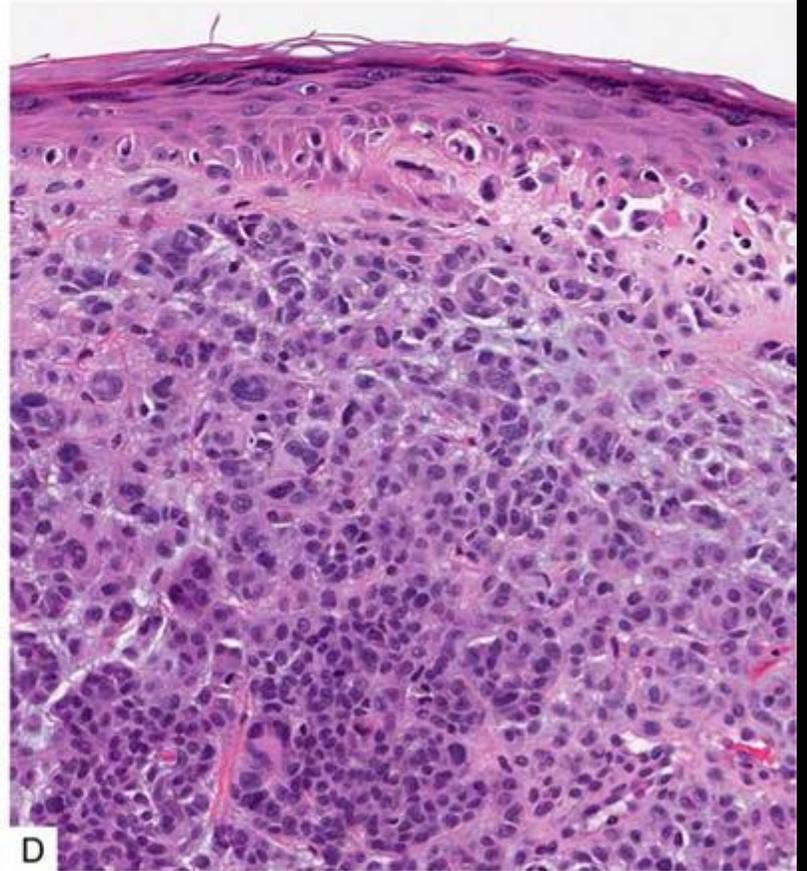
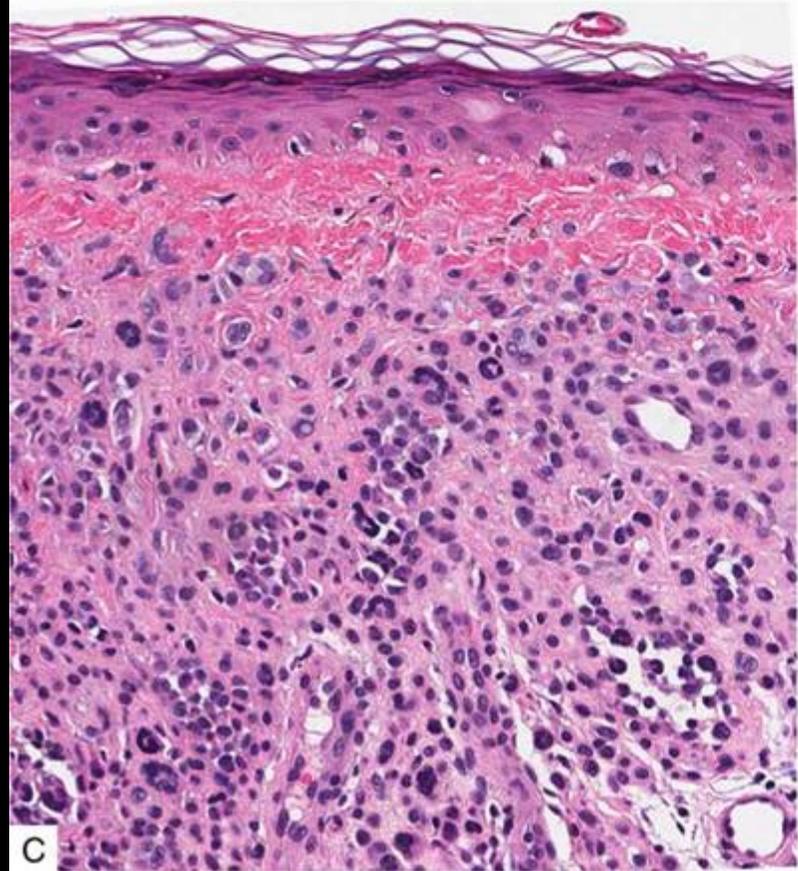
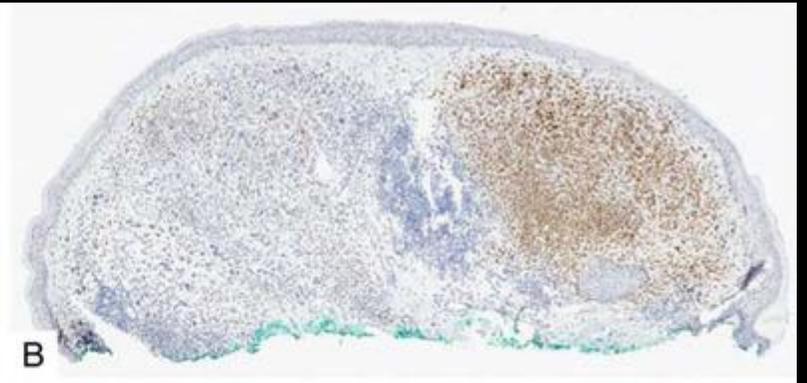
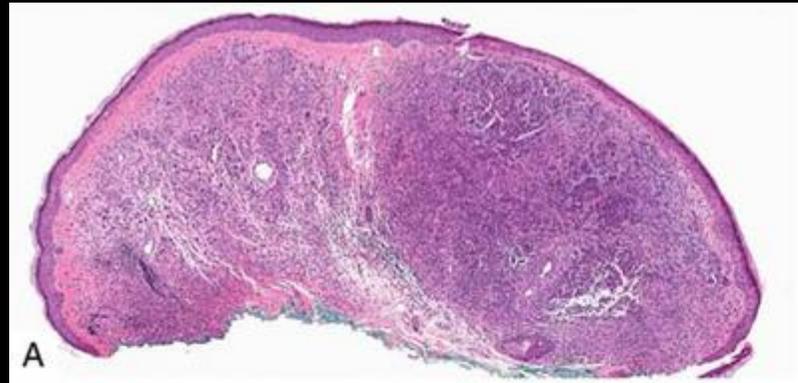
Utilidad: Reconocer el melanoma



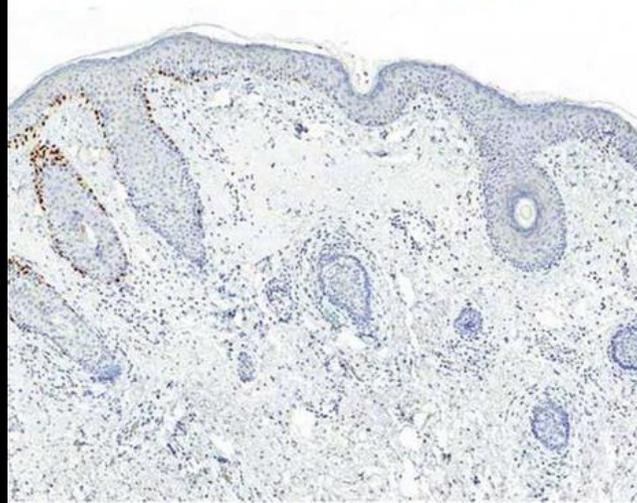
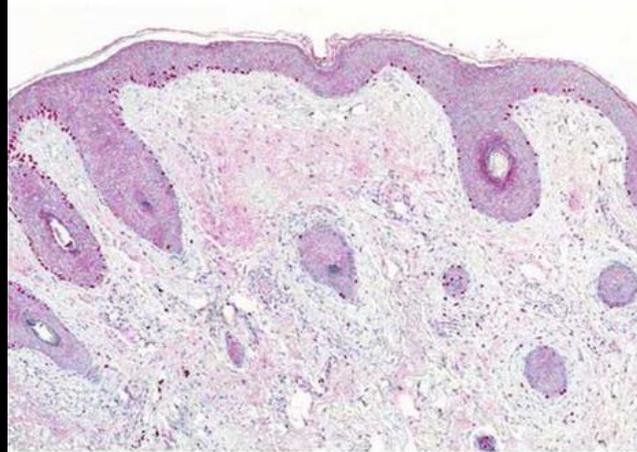
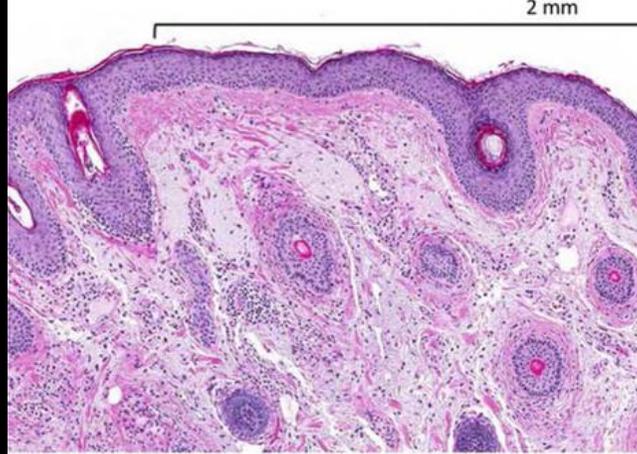
- 90% de los melanomas son difusamente positivos (sin desmoplasicos)
- 83% incluyendo los desmoplasicos.

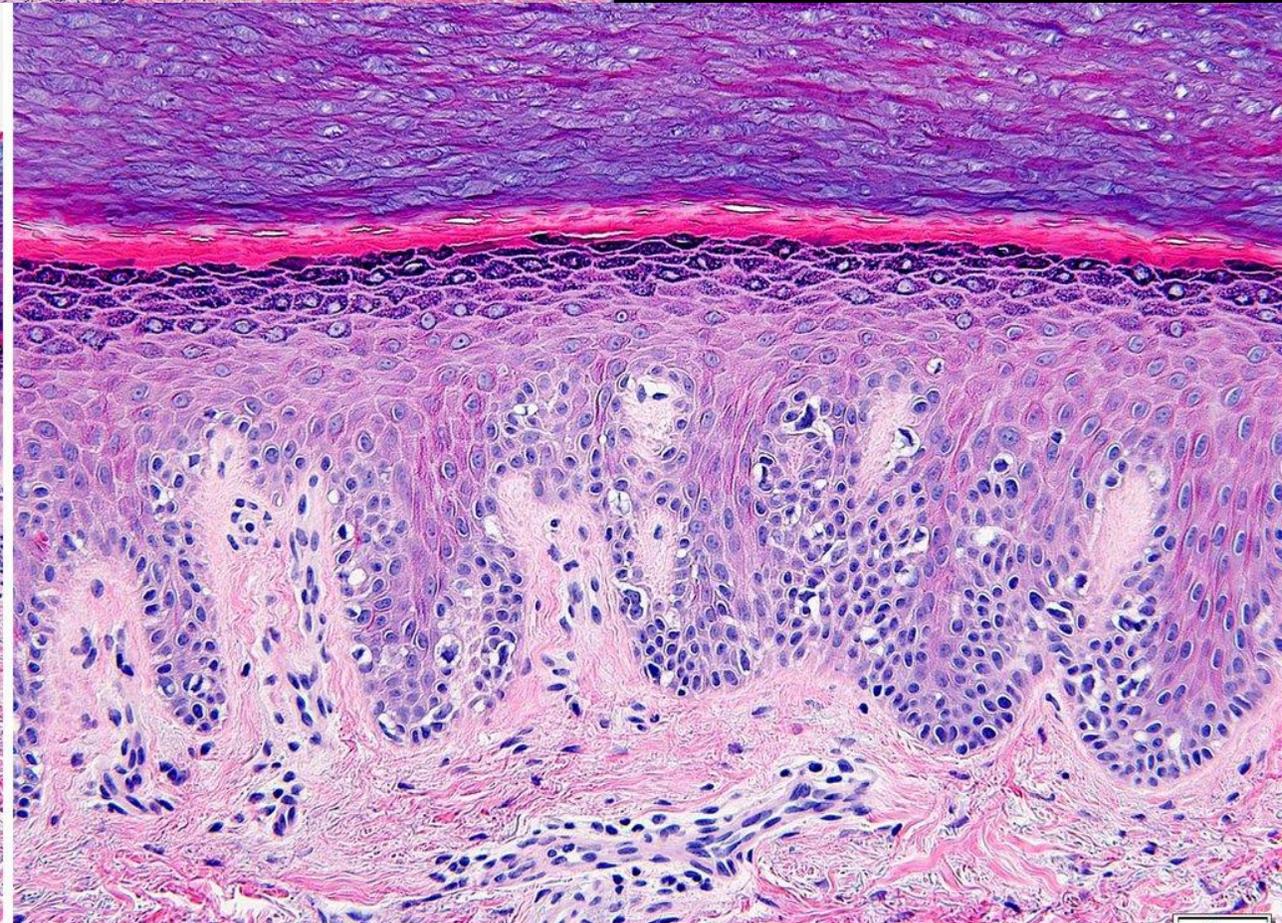
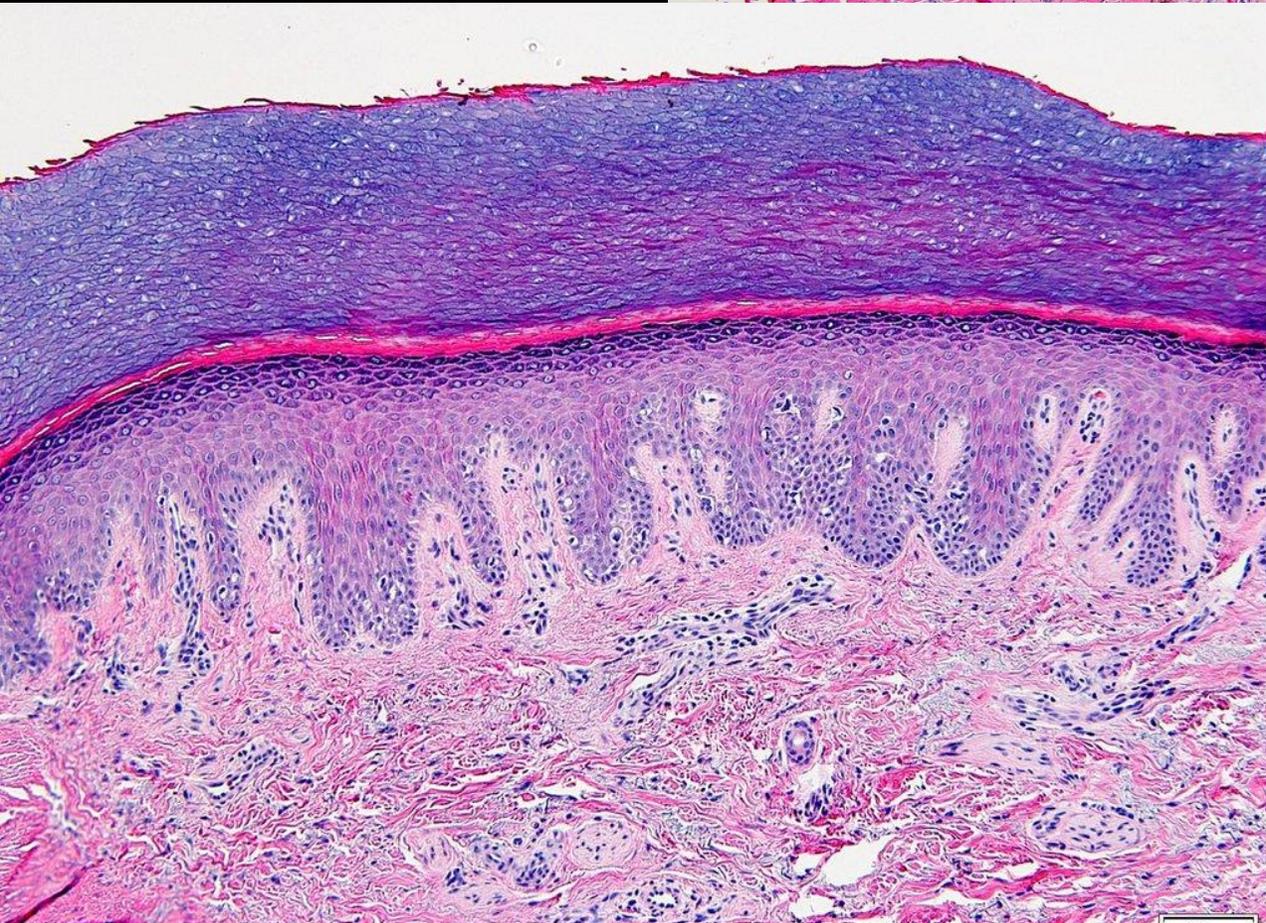
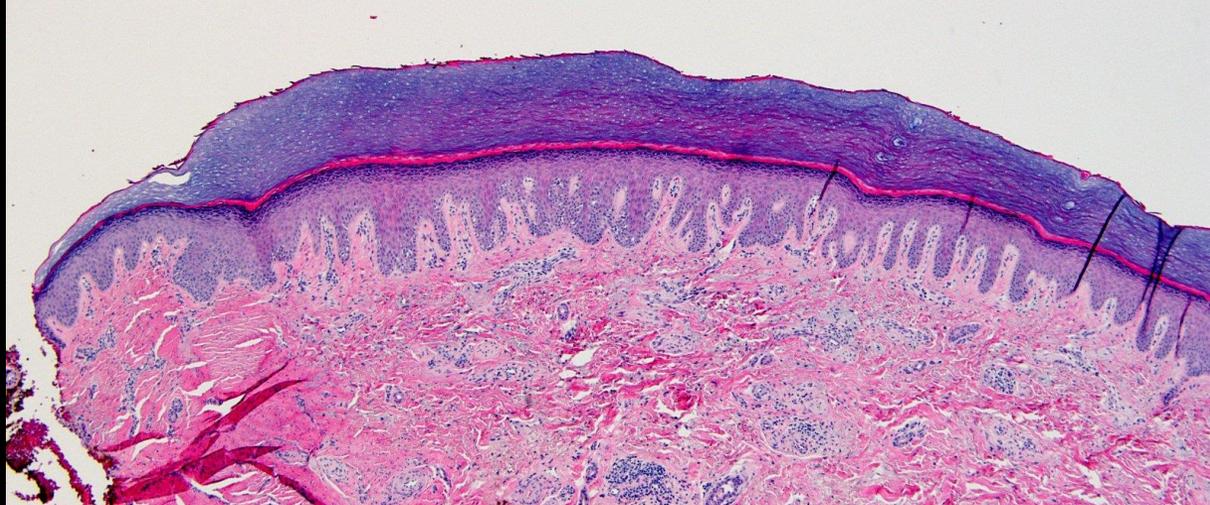


Benigno vs maligno

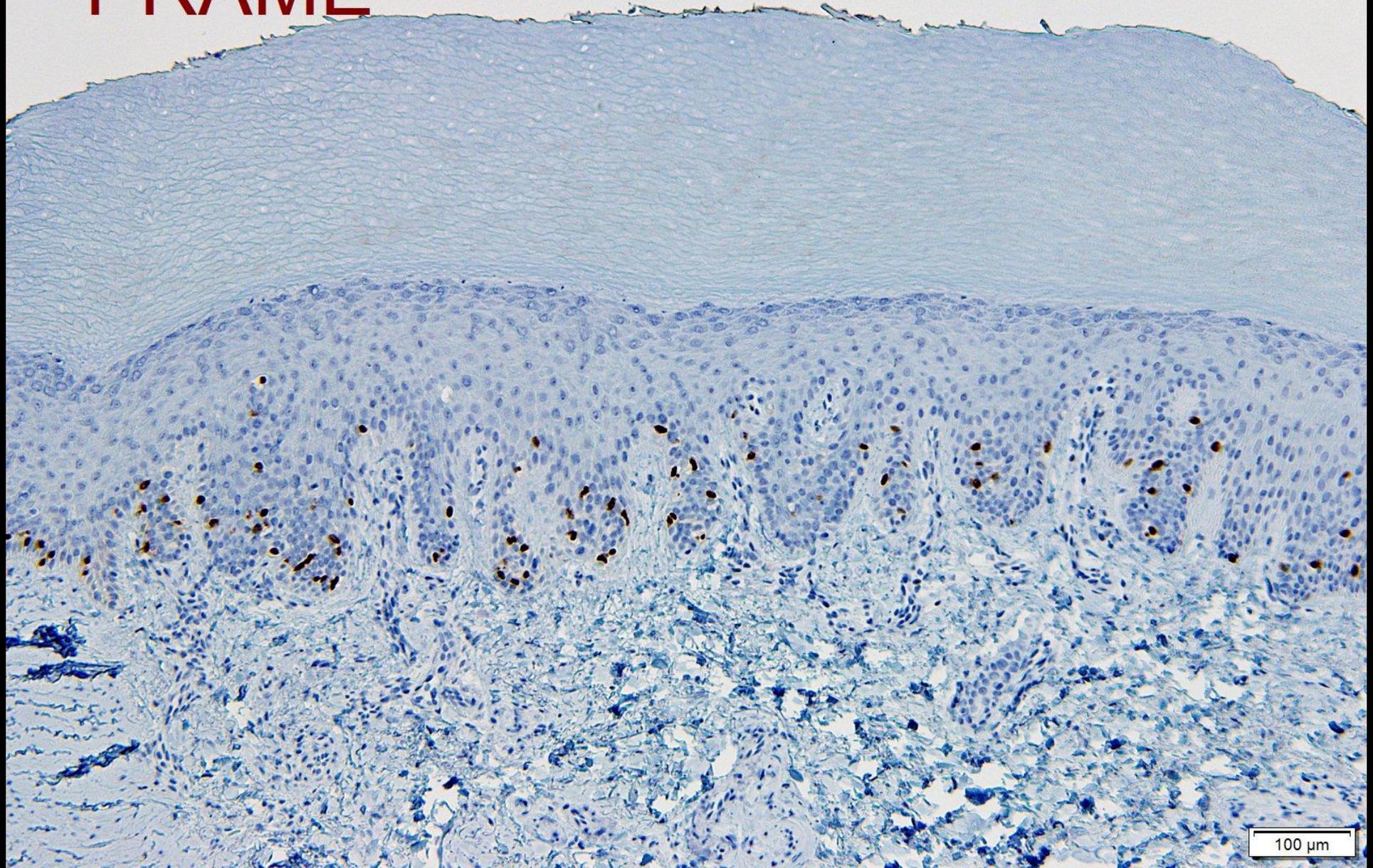


Determinar el
borde
quirúrgico



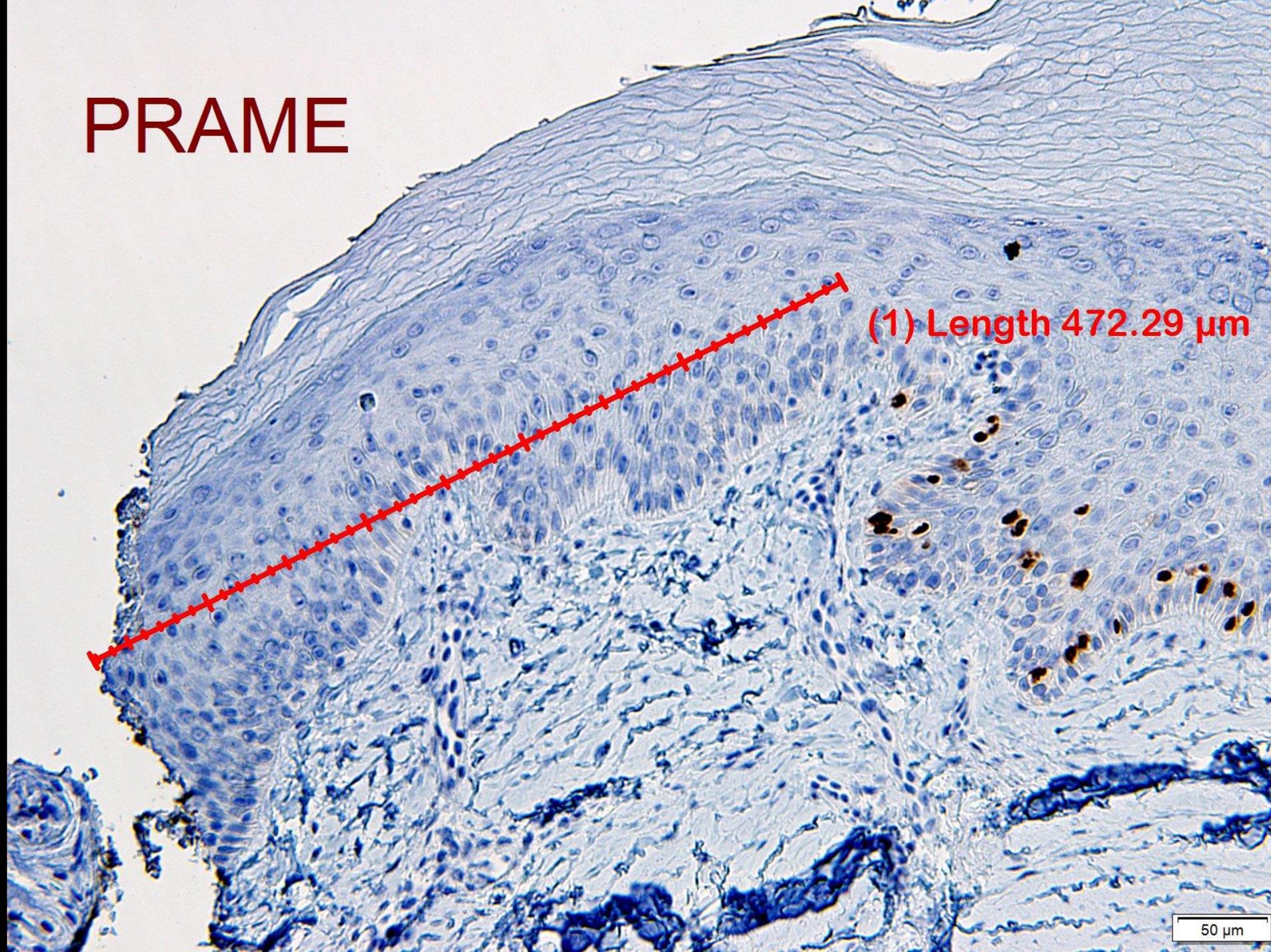


PRAME



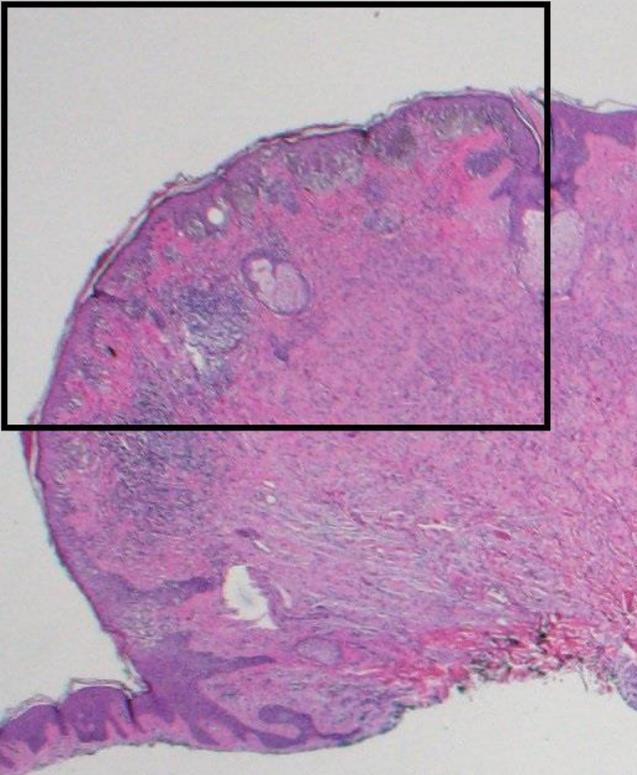
100 μm

PRAME

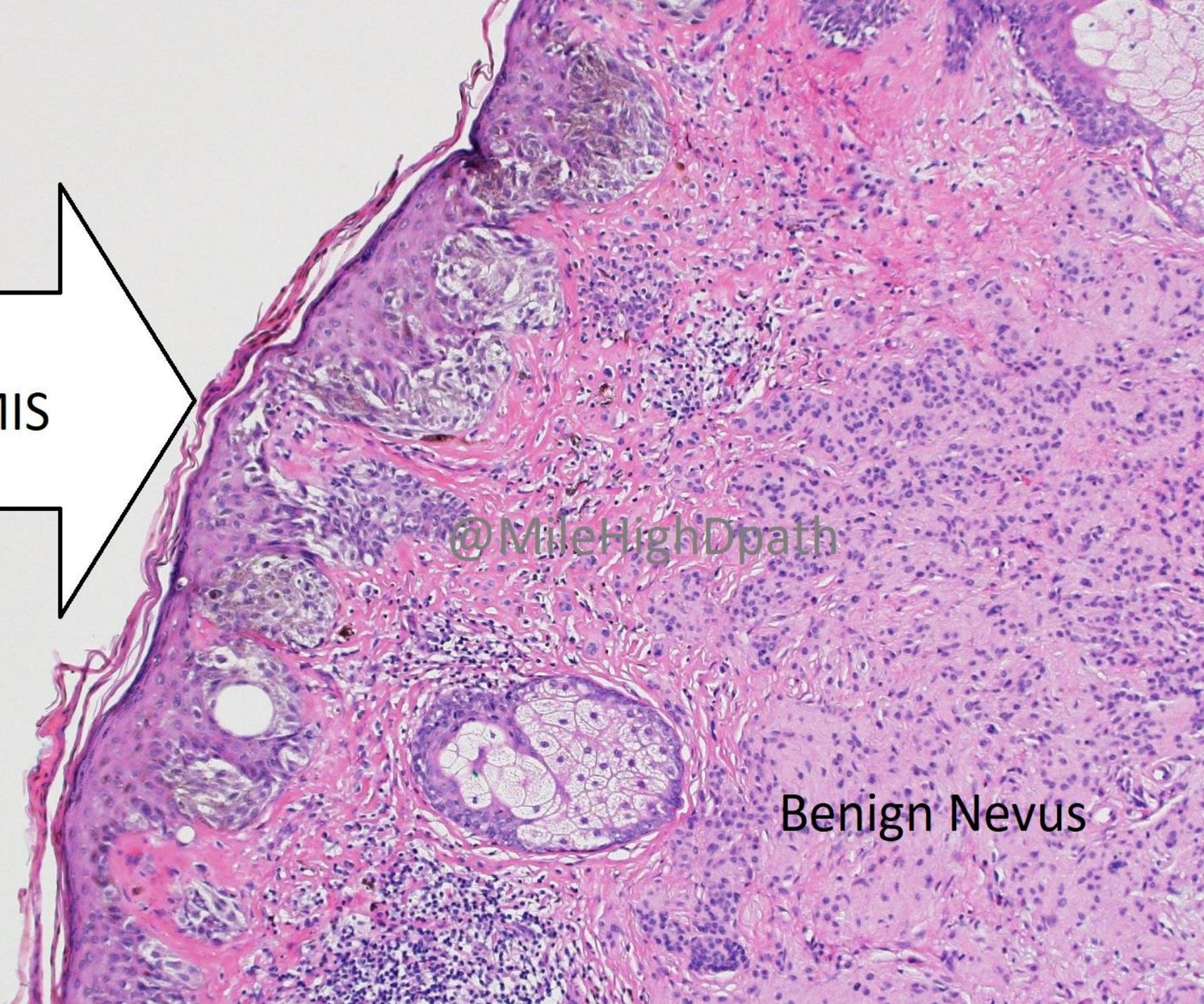


(1) Length 472.29 μm

50 μm

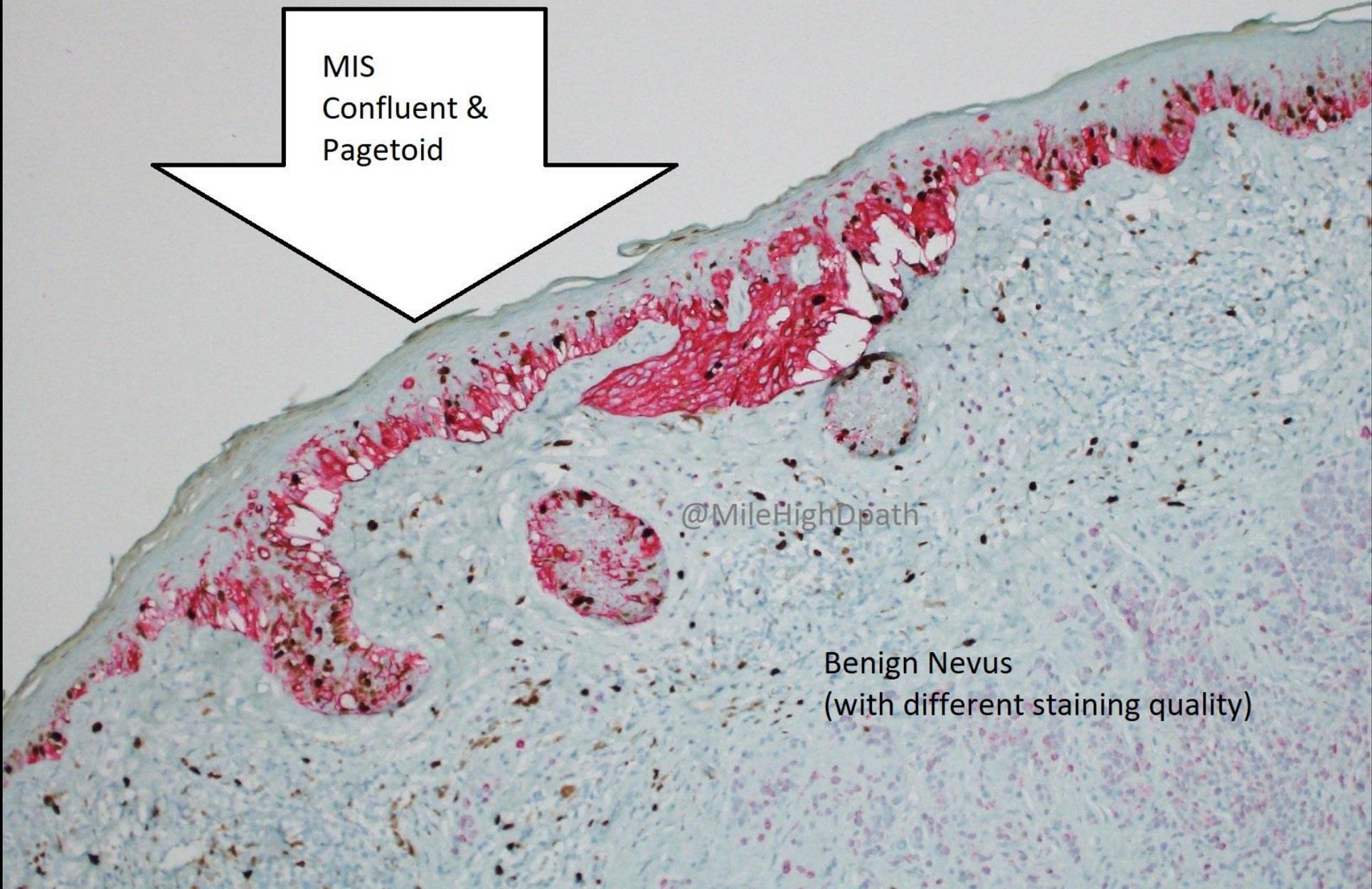


MIS



@MileHighDpath

Benign Nevus

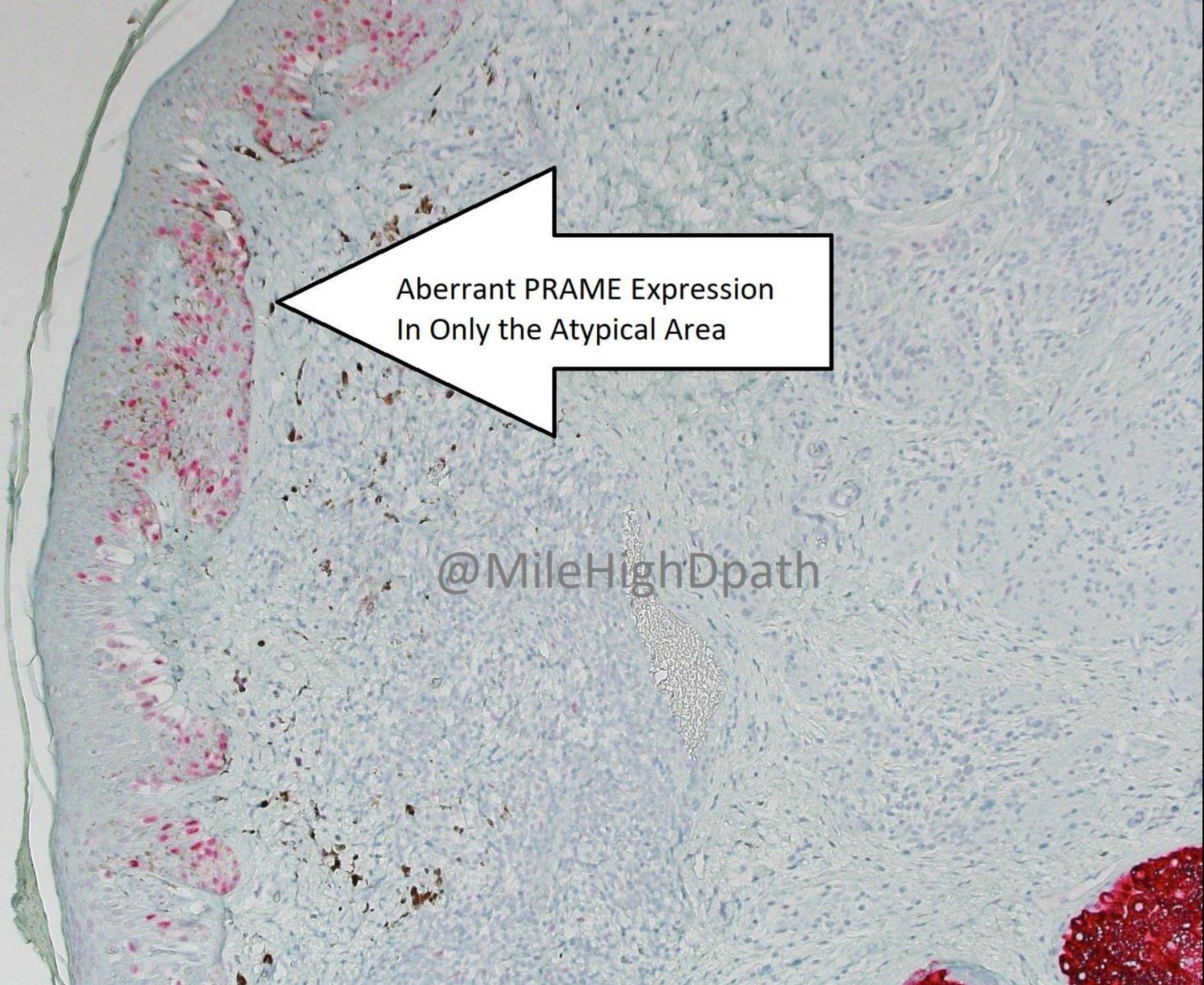


MIS
Confluent &
Pagetoid

This histological slide shows a cross-section of skin. The epidermis is stained with hematoxylin and eosin (H&E). A prominent feature is a thick, confluent layer of melanocytes along the dermal-epidermal junction, characteristic of melanocytic in situ (MIS). The melanocytes are arranged in a pagetoid pattern, with some cells extending upwards into the epidermal layers. The underlying dermis contains a benign nevus, which is a cluster of melanocytes with varying staining intensity. The overall appearance is consistent with a melanocytic lesion, possibly a melanoma in situ or a dysplastic nevus.

@MileHighDpath

Benign Nevus
(with different staining quality)



Aberrant PRAME Expression
In Only the Atypical Area

@MileHighDpath

PRAME

- UTILIDAD
 - DIAGNOSTICO DE MELANOMA CUTANEO
 - NEVO NODAL VS MELANOMA METASTASICO
 - MICROESTADIAJE DEL MELANOMA
 - MARGENES EN MELANOMA IN SITU

CONCLUSION

- NINGUN MARCADOR POR SI SOLO ES DIAGNOSTICO
- MAYORIA DE LAS LESIONES SE DIAGNOSTICAN POR HE.
- ROL:
 - LINEA MELANOCITICA
 - PROLIFERACIONES DE LA UNION
 - ESTRATIFICACION DE RIESGO
 - IDENTIFICACION DE SUBTIPOS DE LESIONES MELANOCITICAS.

GRACIAS

