The Haunting Question: Nevus or Melanoma?

Ürkütücü Soru: Nevüs mü? Melanom mu?

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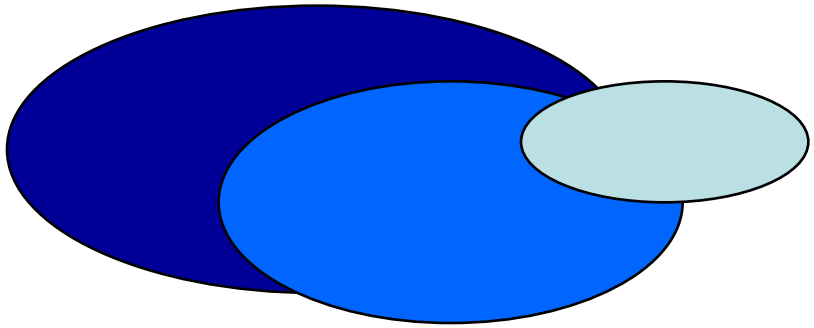


Melanocytic lesion in a female patient.

Histopathology will come first !

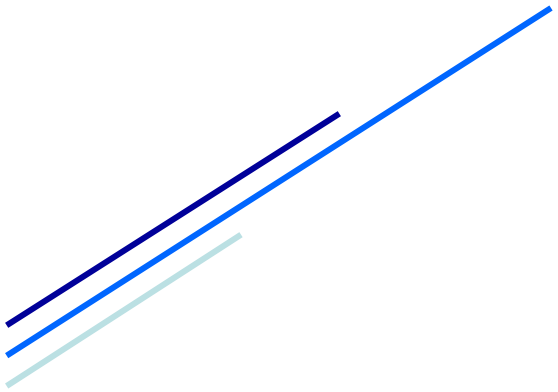
Other information like:

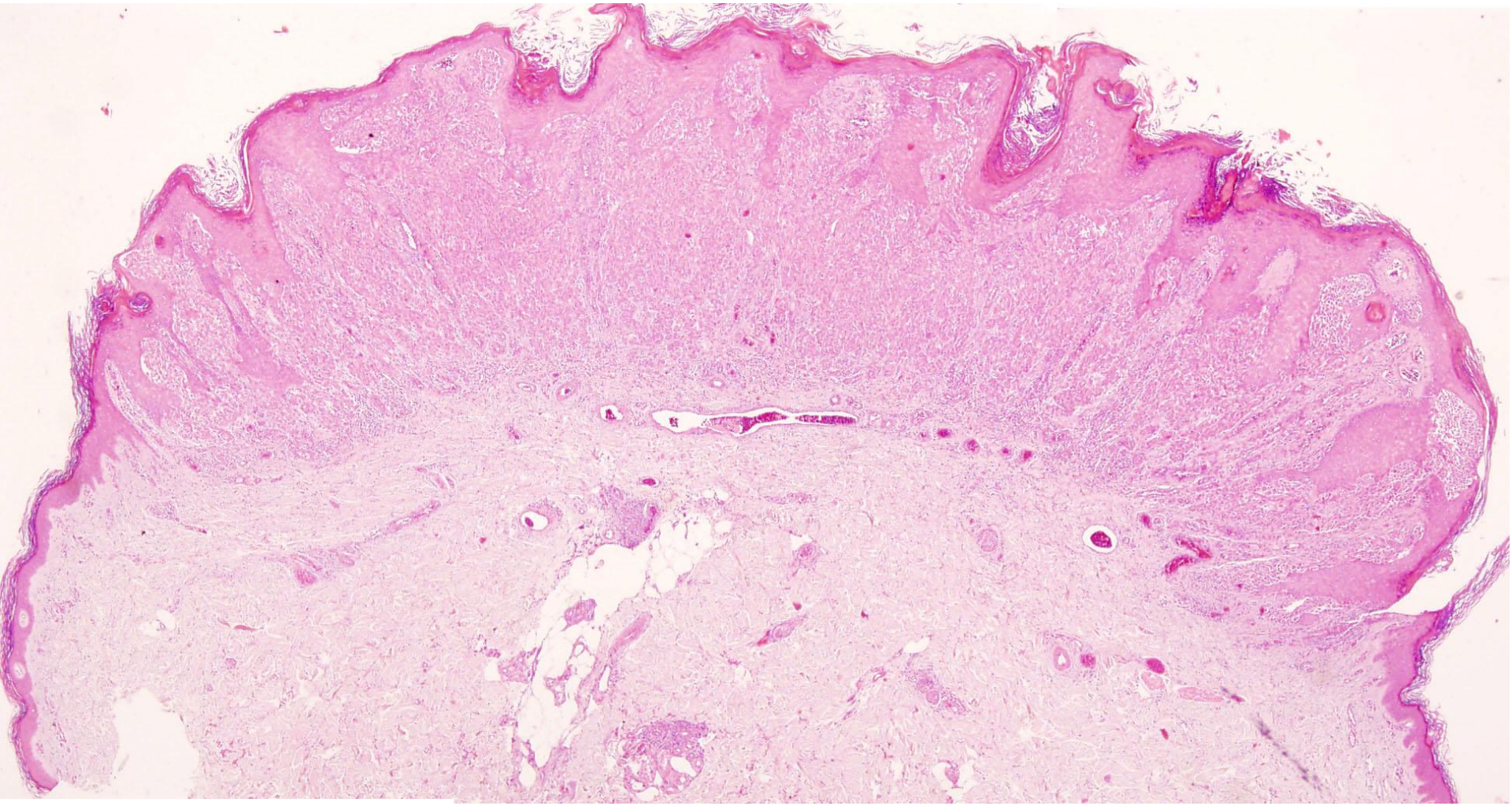
Age, localization, clinical appearance

will be disclosed later !

What is the order of importance of these the factors when making a diagnosis ?

Can we always be consistent while reasoning in such a case ?





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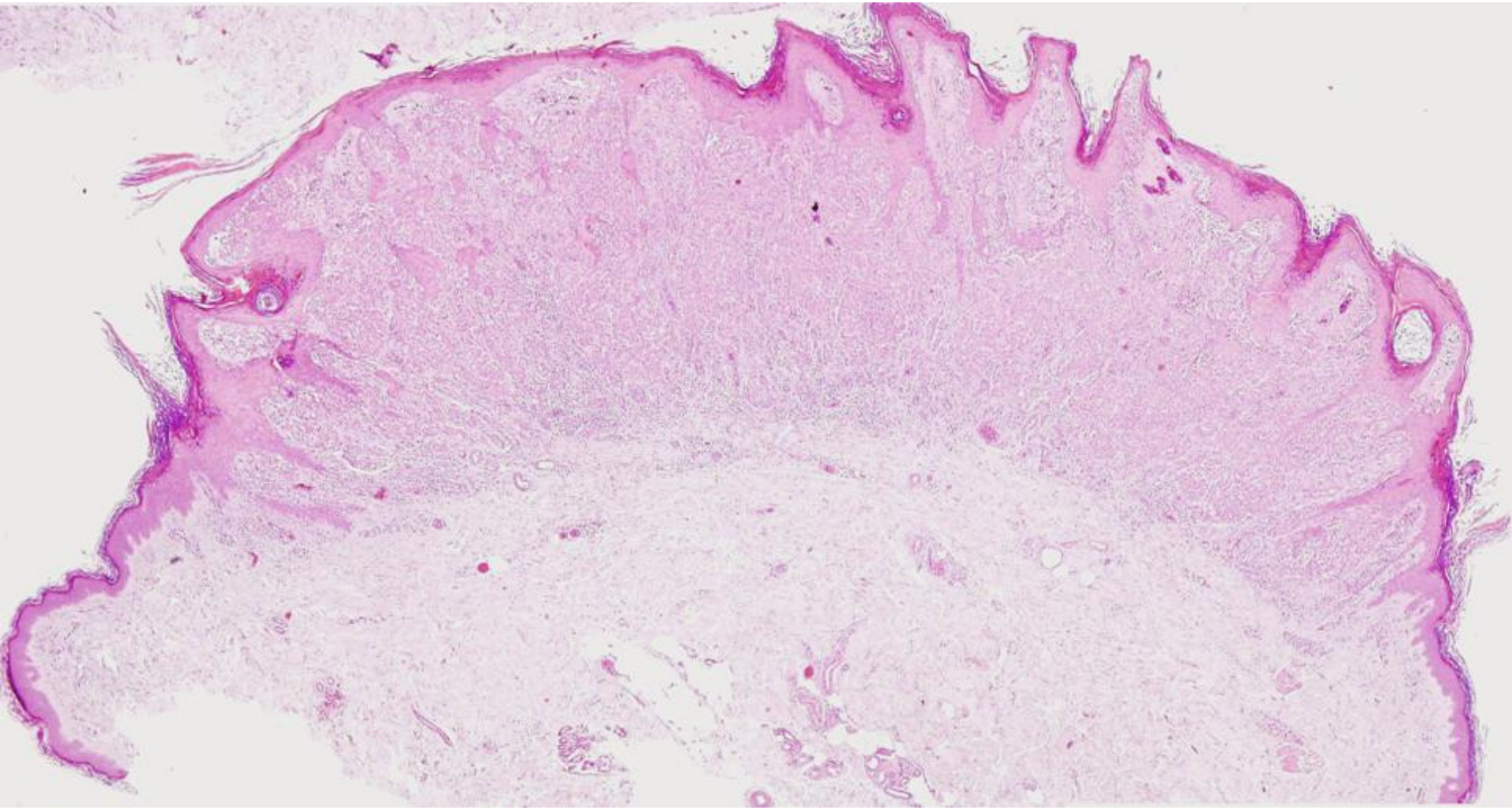

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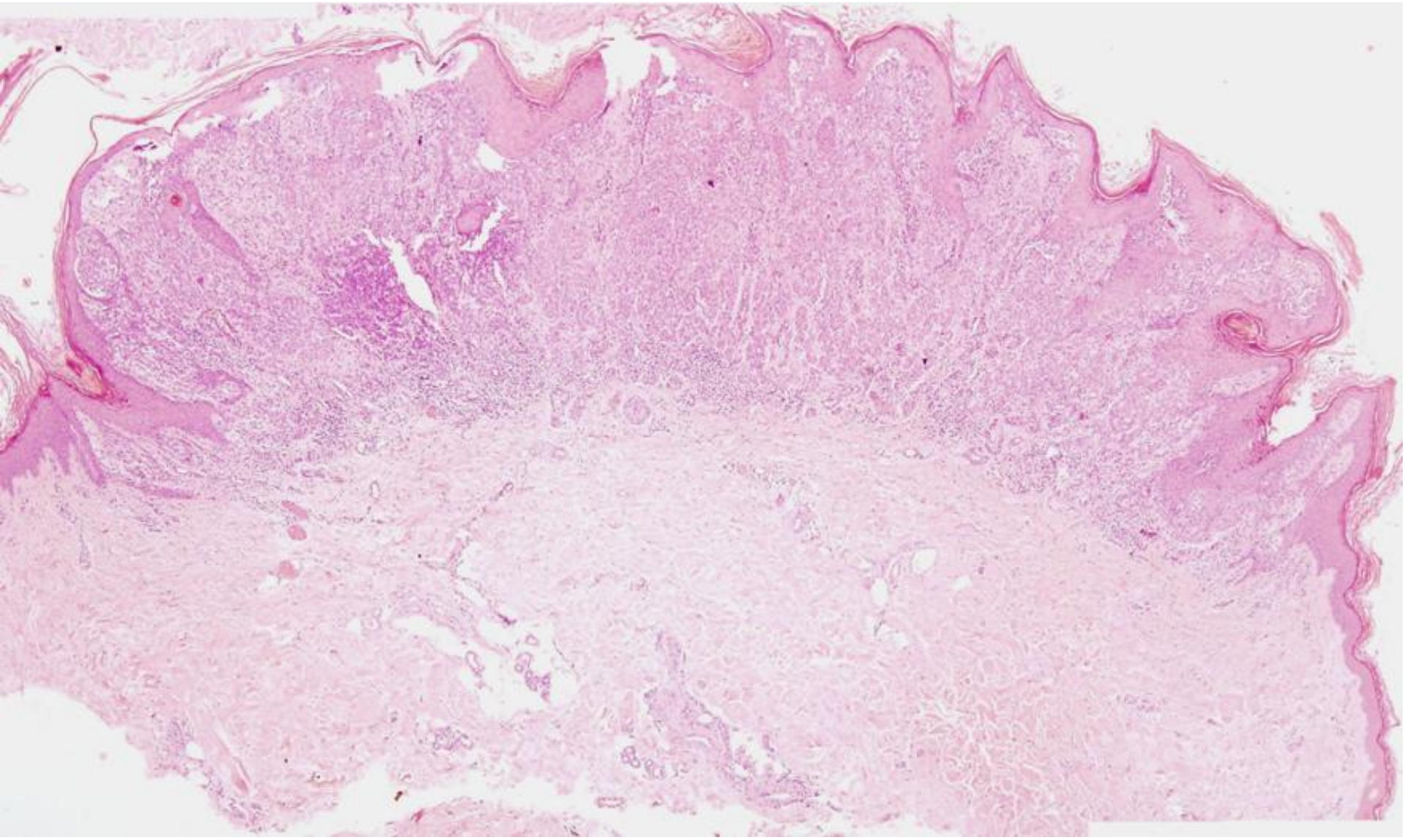

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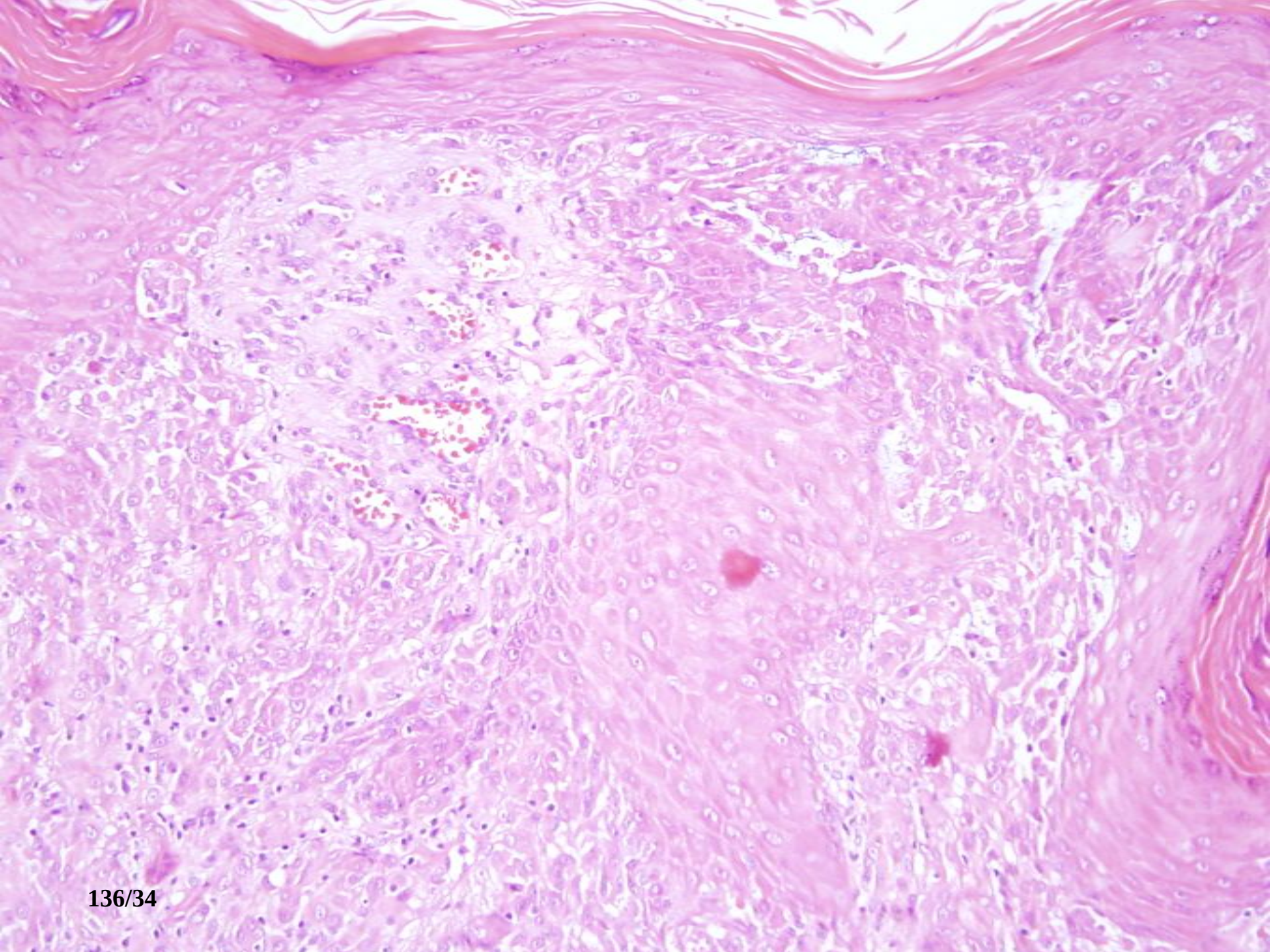

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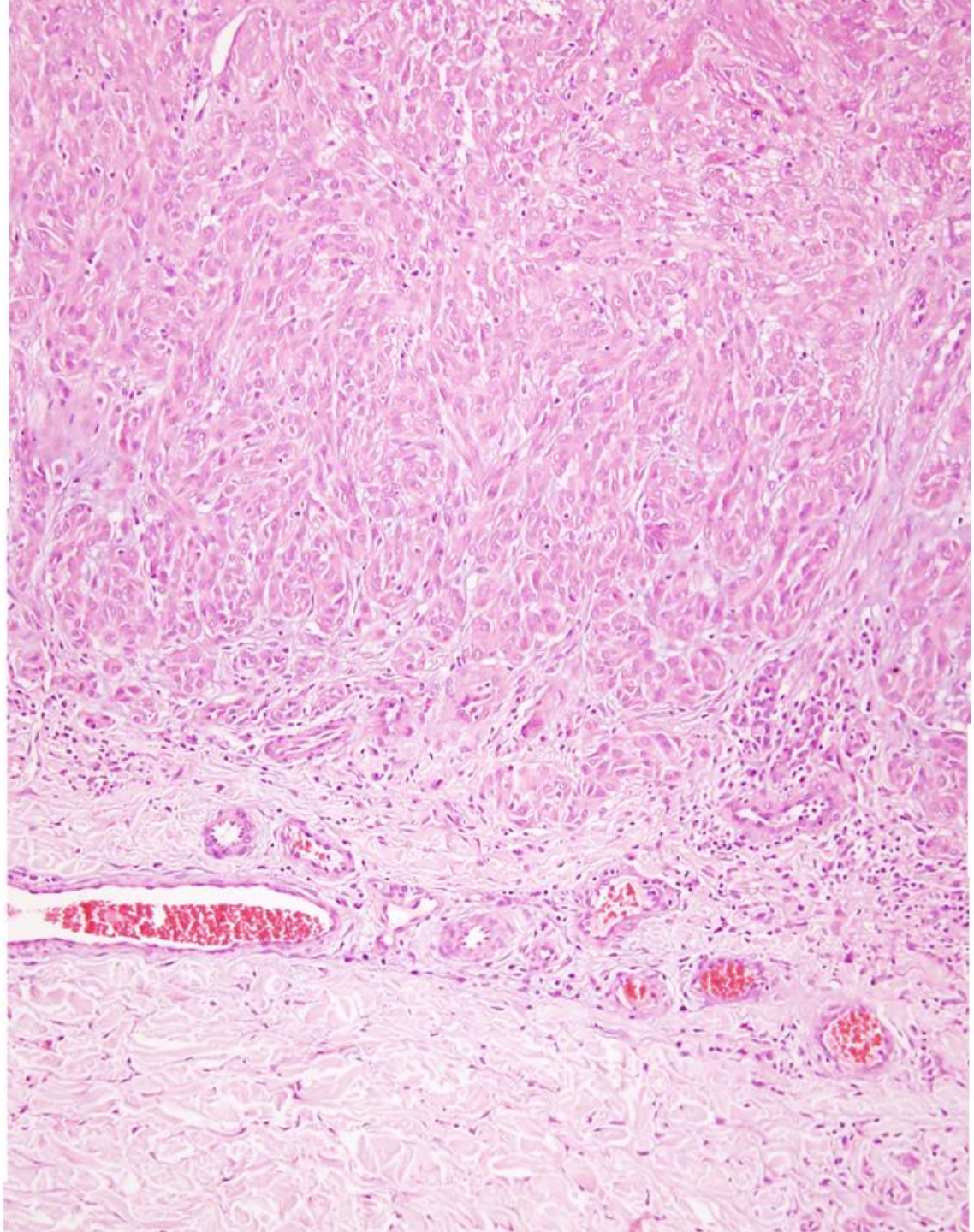

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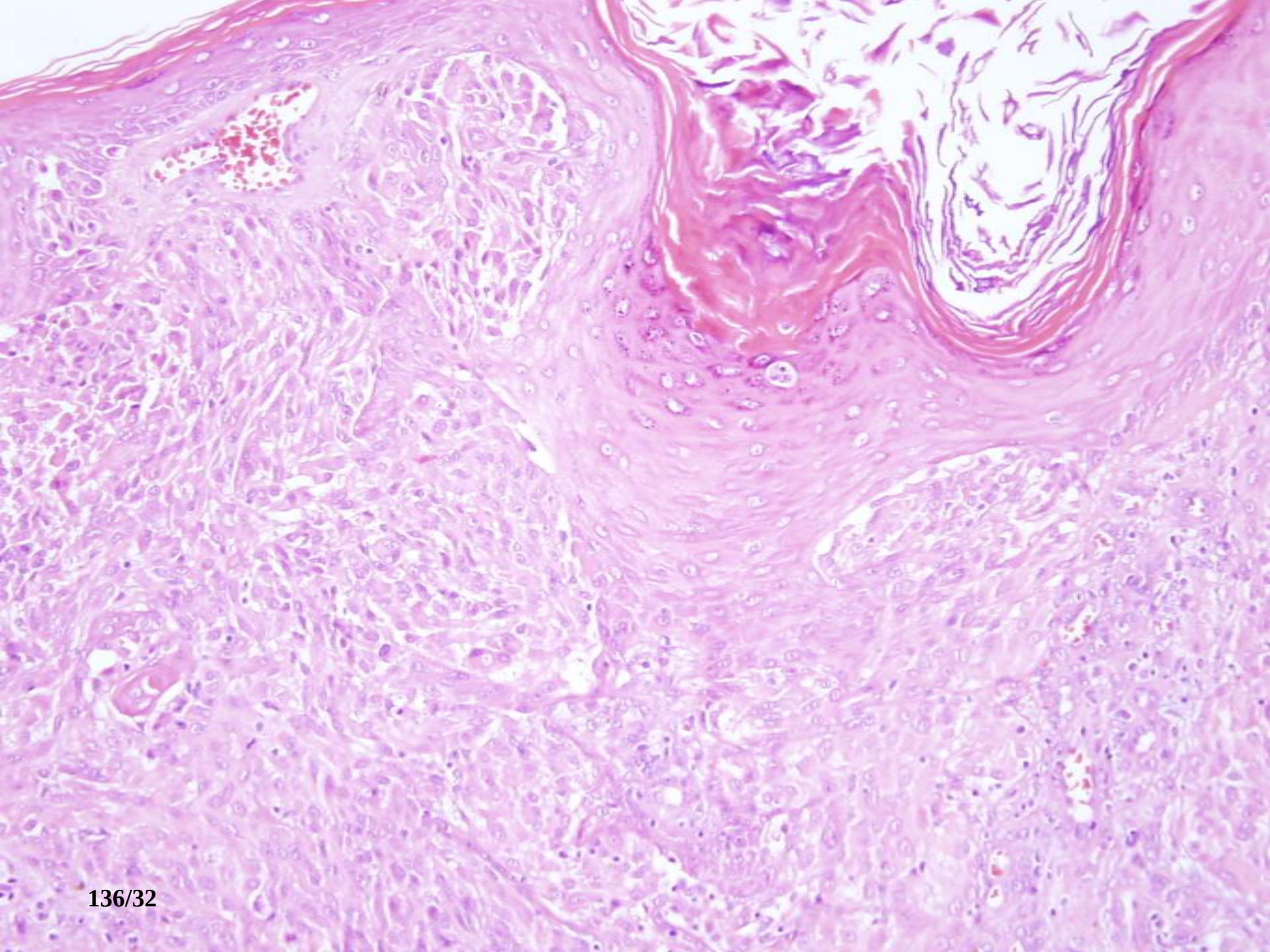

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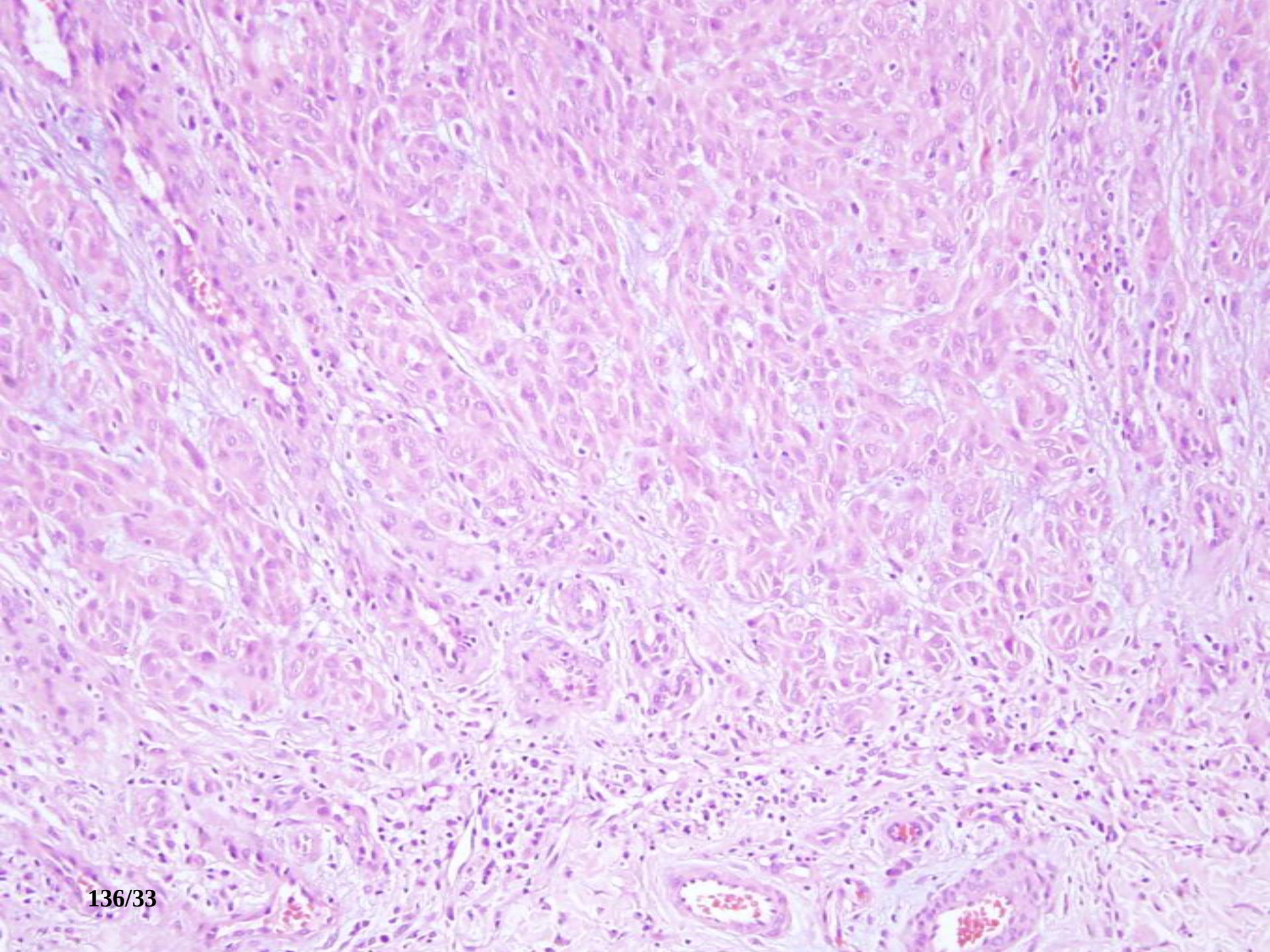
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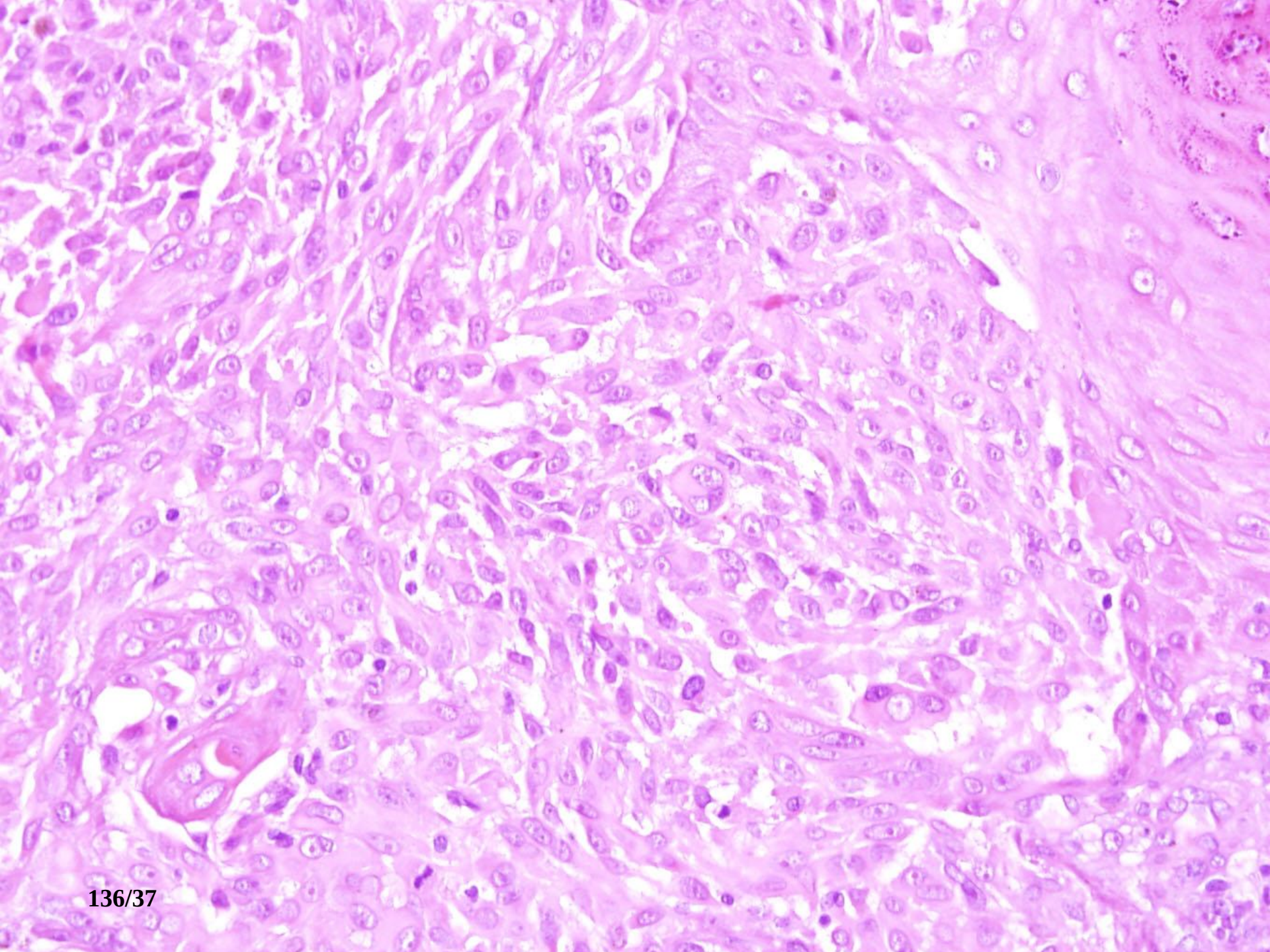
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-Symmetrical melanocytic lesion.

-Spindle and epitheloid melanocytic cells

-Quite uniform nuclei, small nucleoli, ground glass pink cytoplasm

-Size of junctional nests quite uniform, no intraepidermal pagetoid spread

-Uniform epidermal hyperplasia, no ulceration

-Prominent telengiectasias in papillary dermis, no Kamino bodies

-Slight reactive lymphocytic infiltration around deep dermal vessels

-Dermal component thickness 1.50 mm

-No involvement of subcutaneous tissue

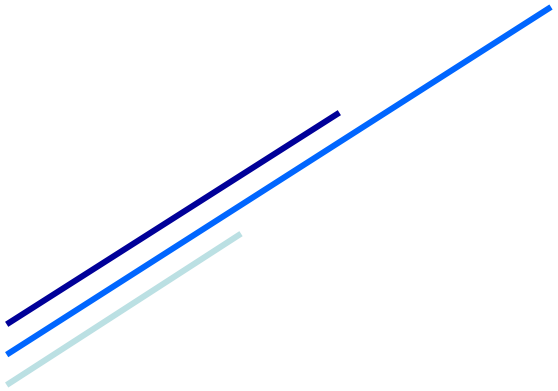
-No pushing border

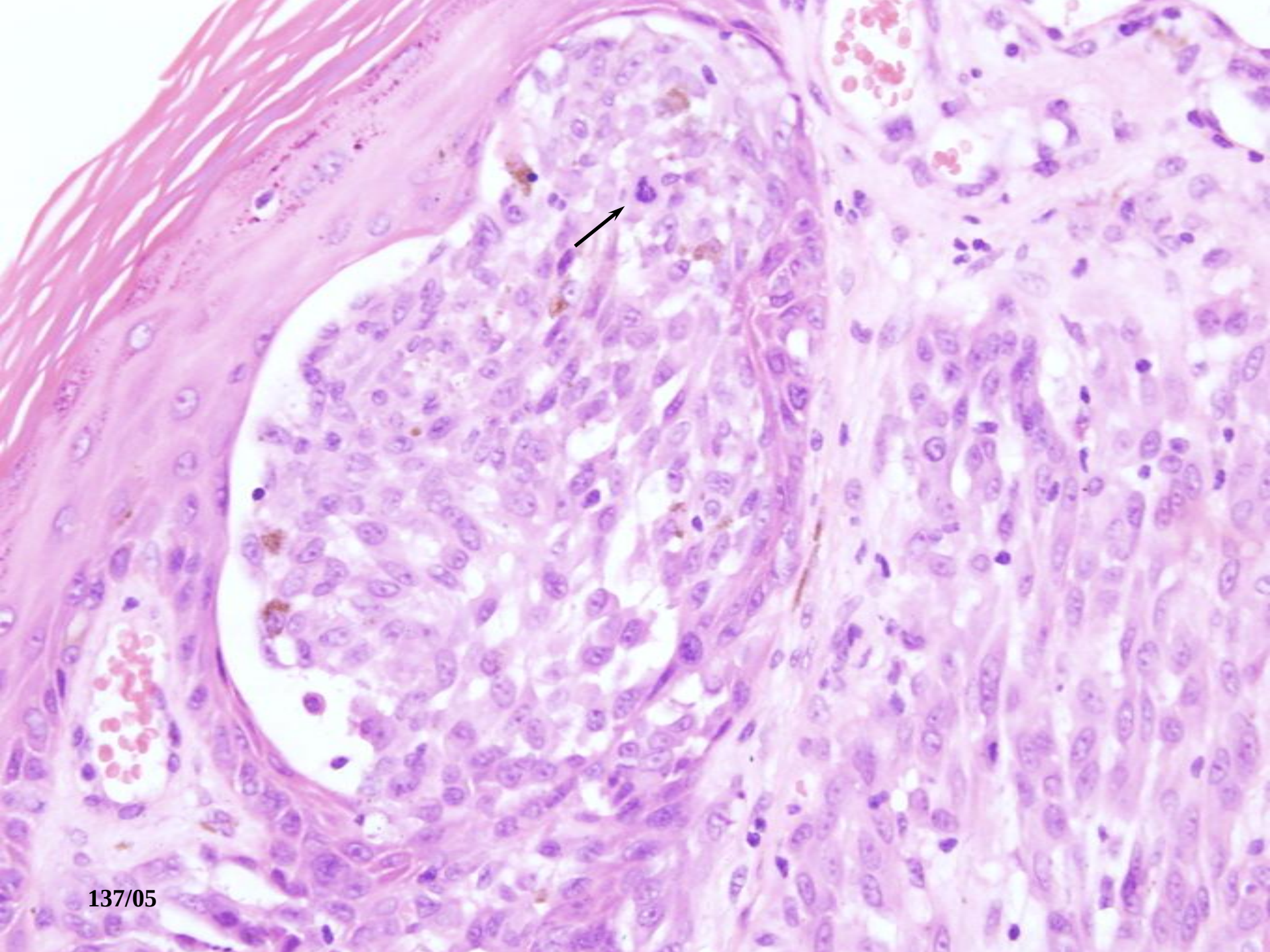
-Maturation in the deepest part questionable

What is your first impression diagnosis ?

Spitz nevus ?? Melanoma ?? or other ??

Which other missing information you want to have ??

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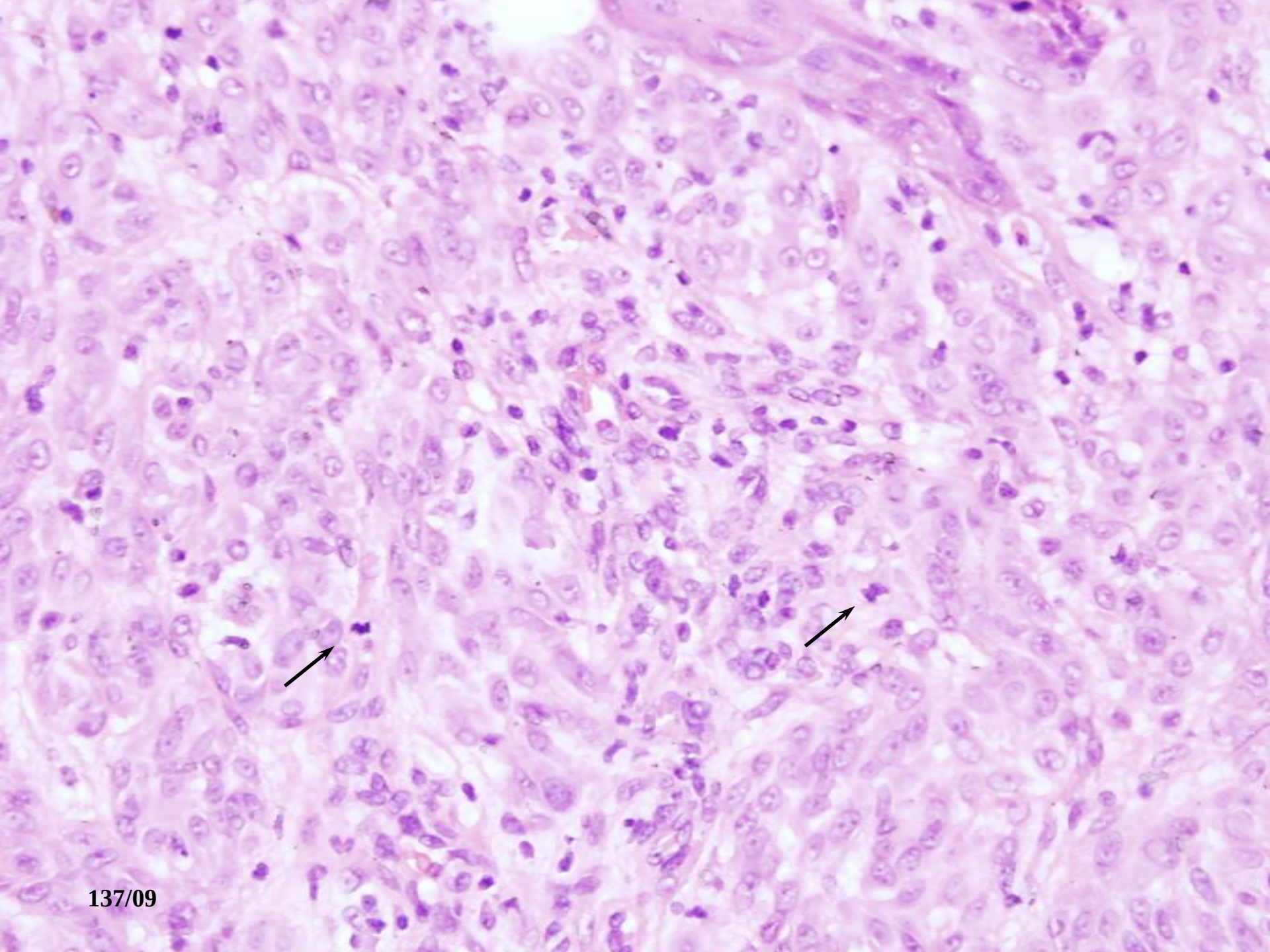
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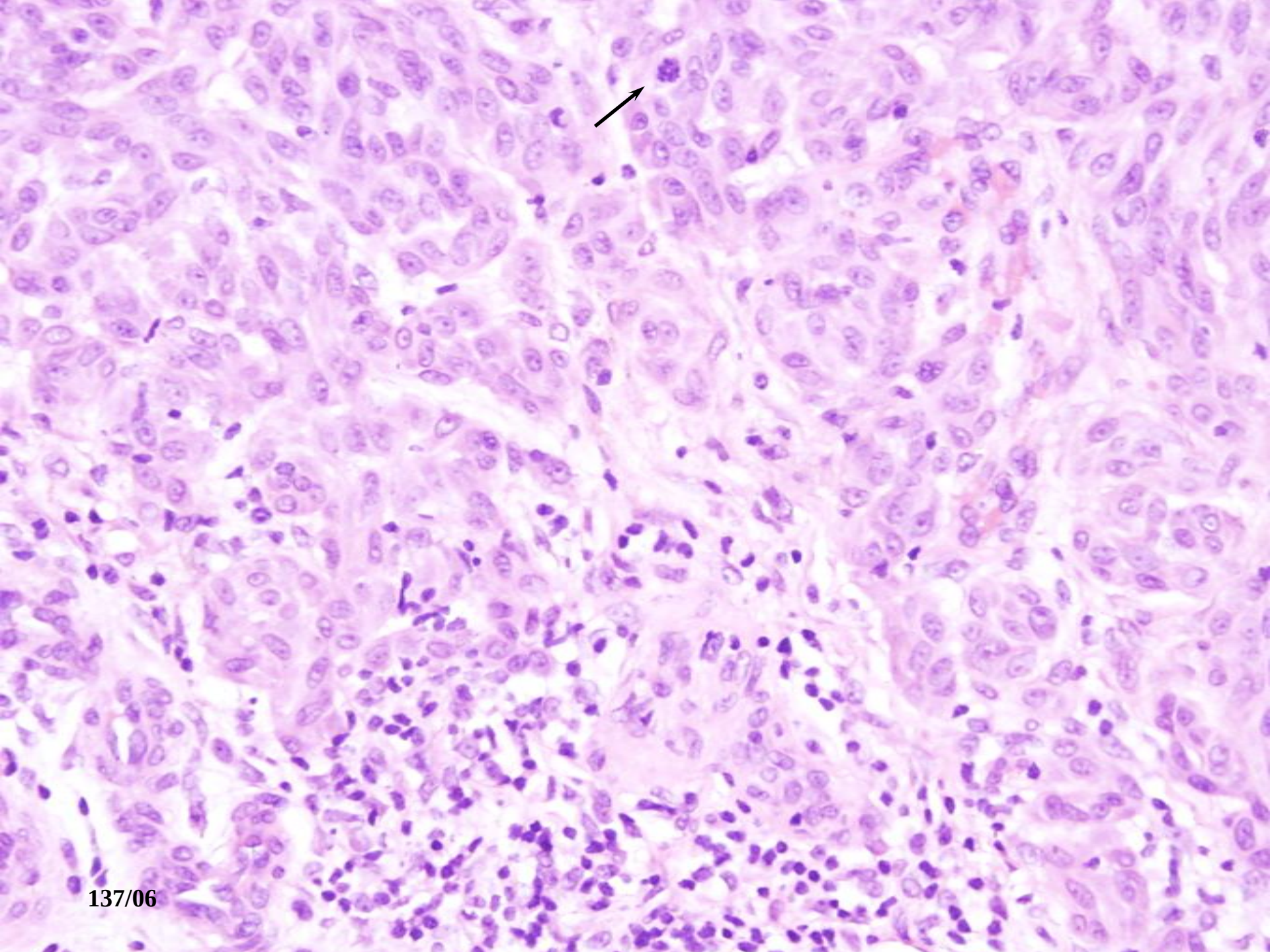

137/06

5-6 mitosis in total were seen.

Mitotic count <2/mm2

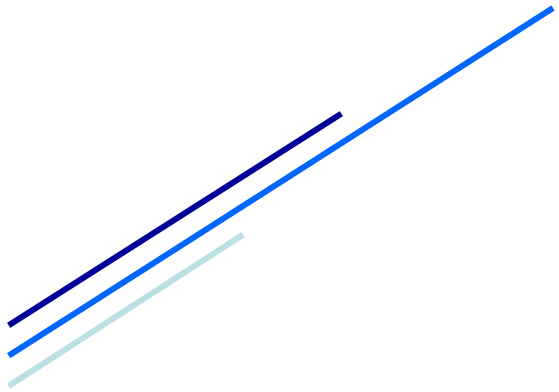
Some of them are situated at the deep part of the lesion.

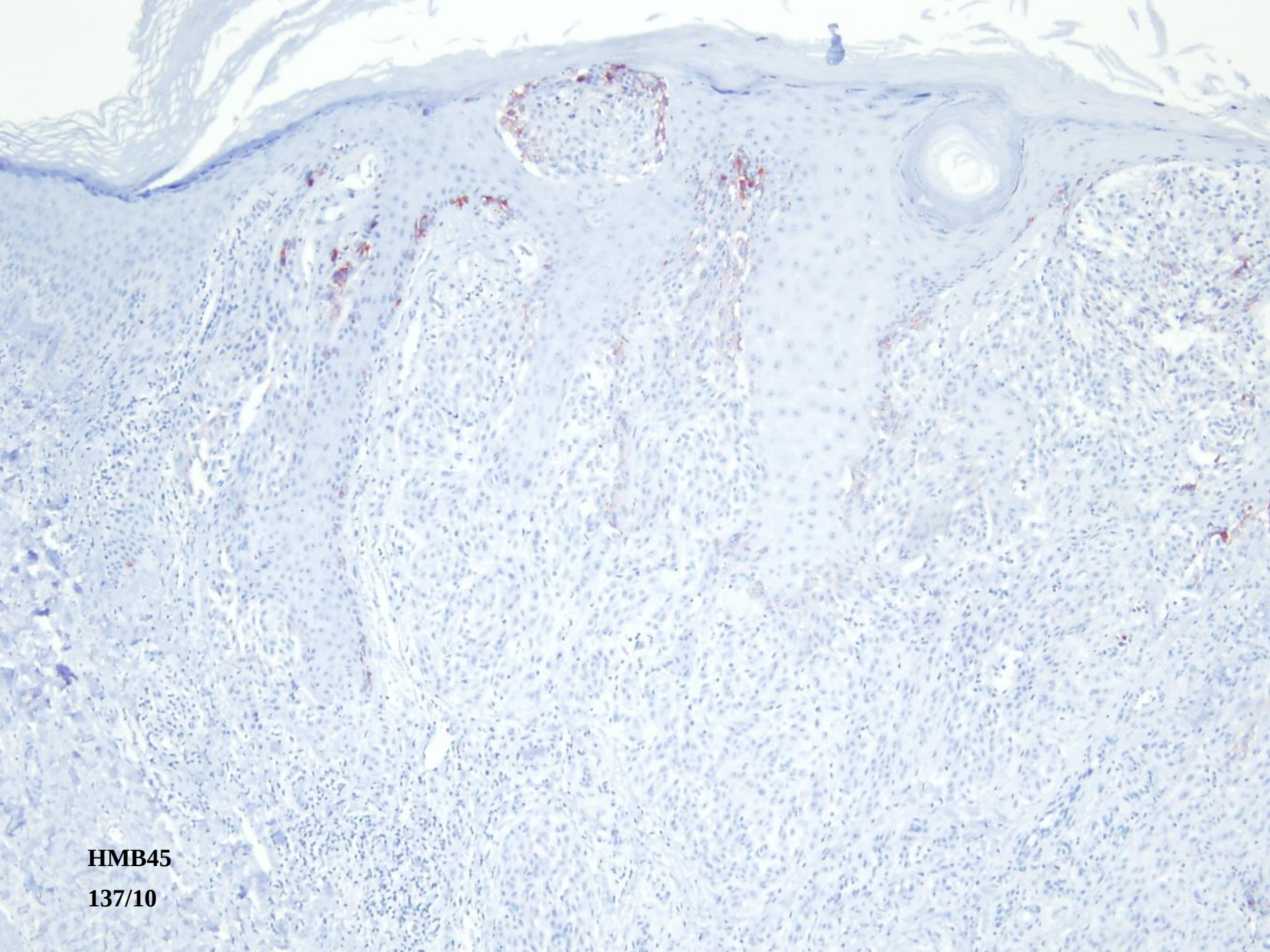
No atypical mitotic figure seen.

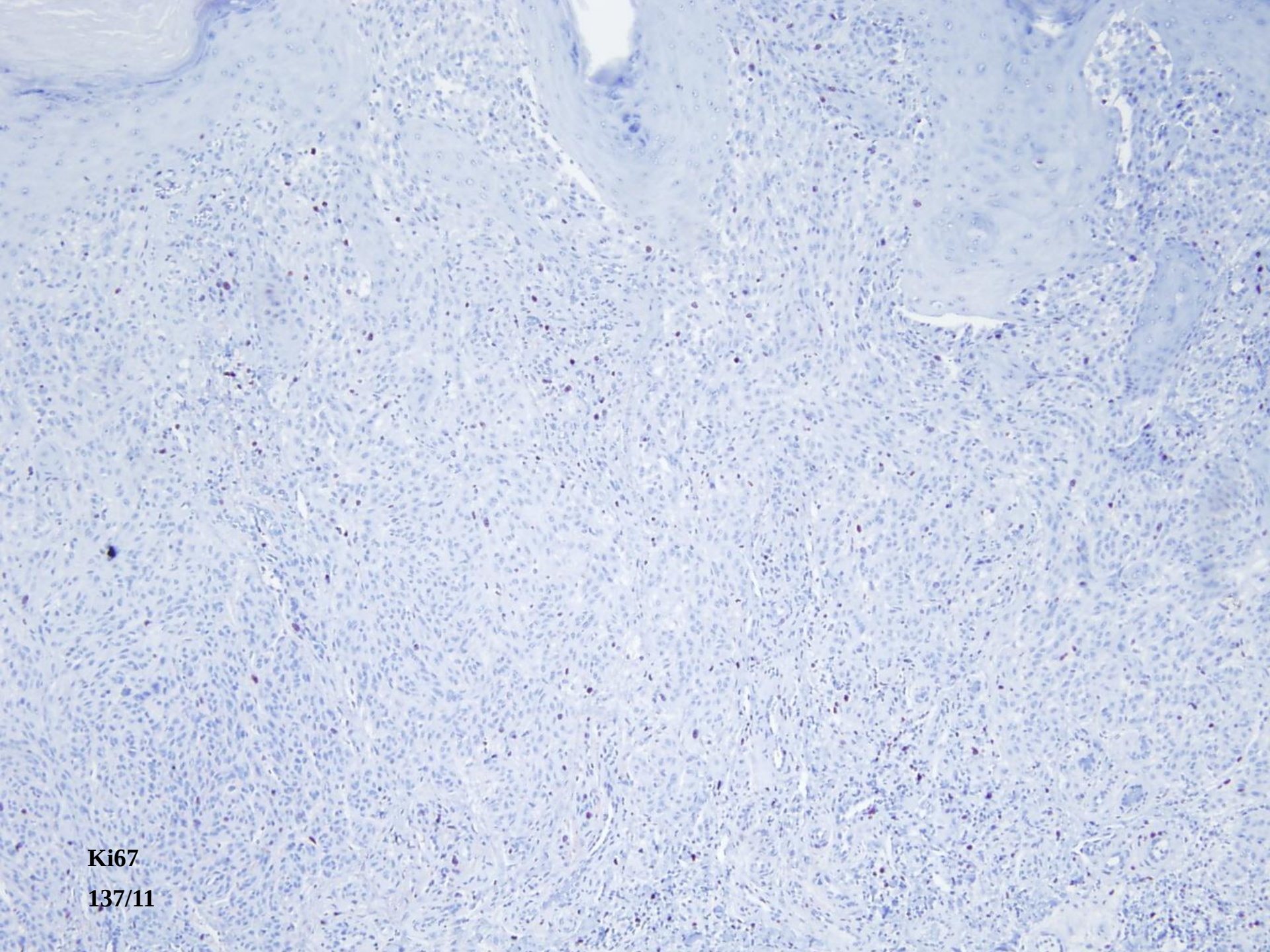
What is your diagnosis now ?

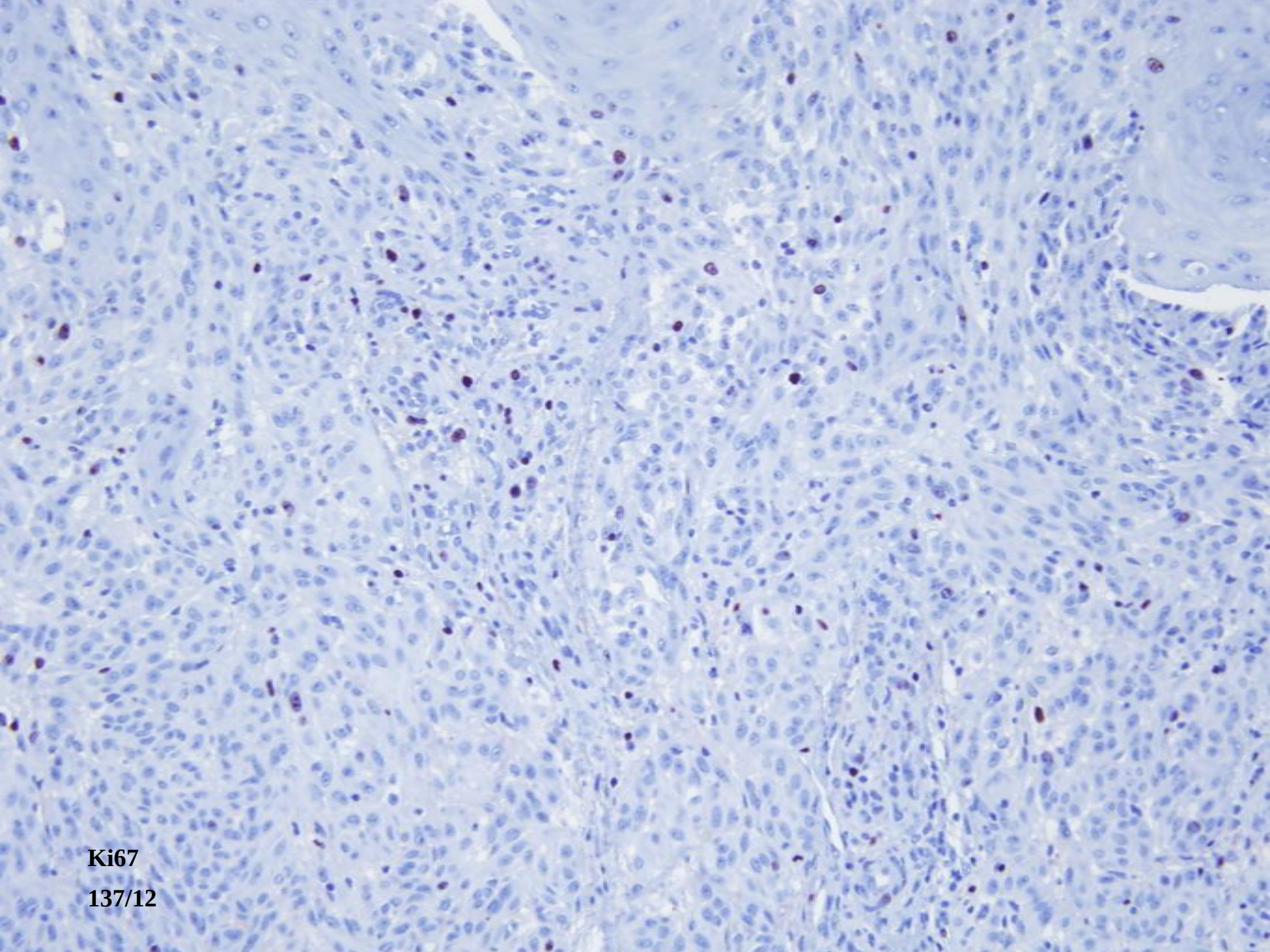
Spitz nevus ?? Melanoma ?? or other ??

Which other missing information you want to have ??




HMB45
137/10


Ki67
137/11


Ki67
137/12

HMB45 positive staining in just a few junctional cells. Dermal cells negative.

Ki67 evaluation difficult.

Intermingled keratinocytes and especially inflammatory cells.

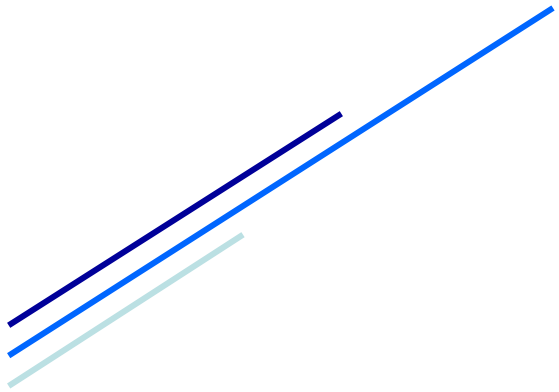
Sligtly higher index in superficial part, but <10%

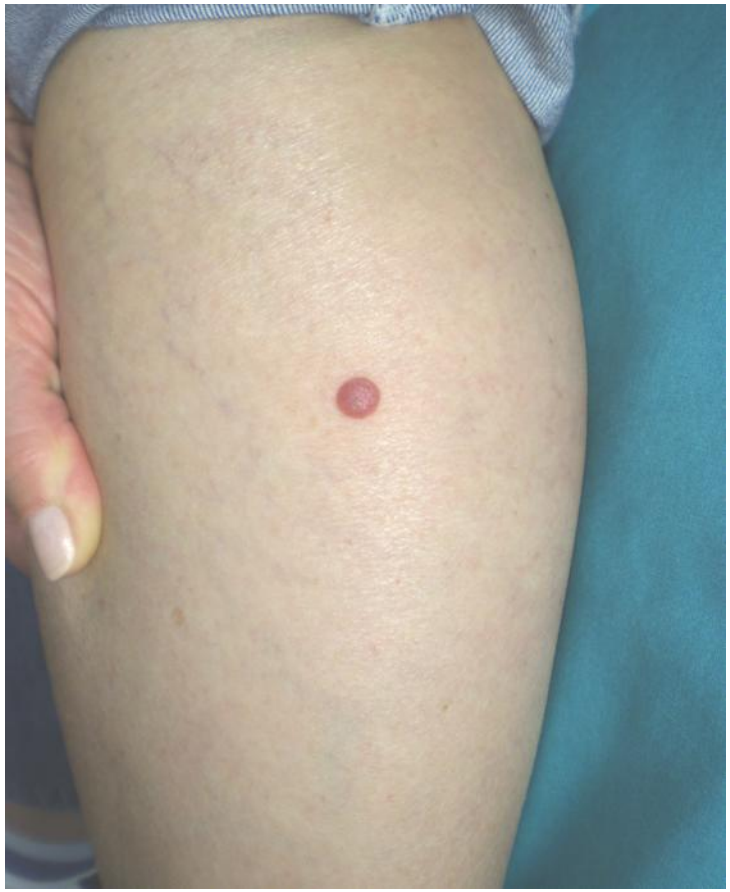
What is your diagnosis now ?

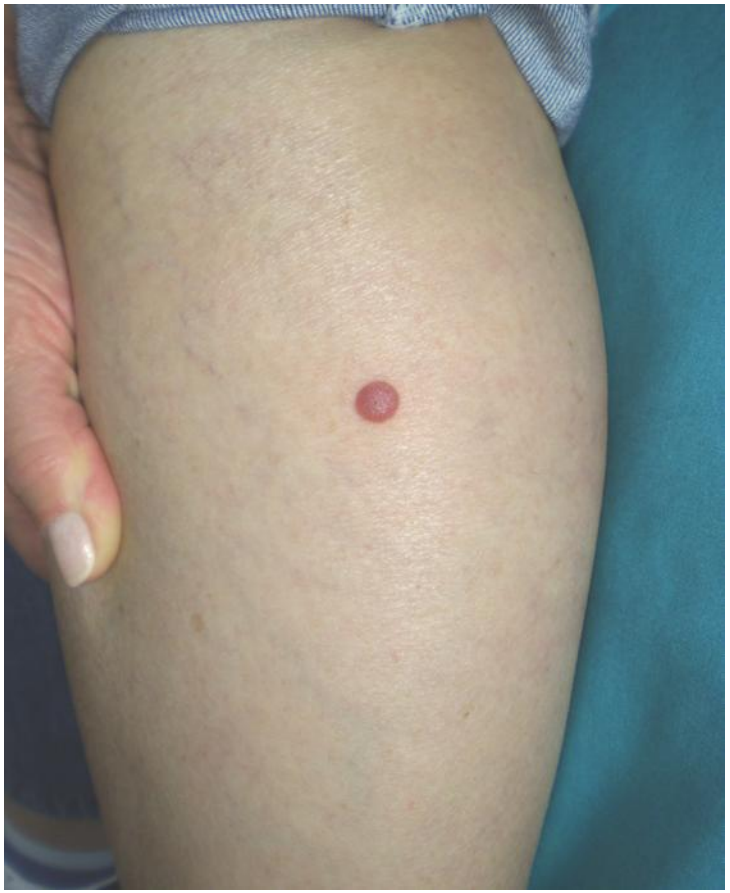
Spitz nevus ?? Melanoma ?? or other ??

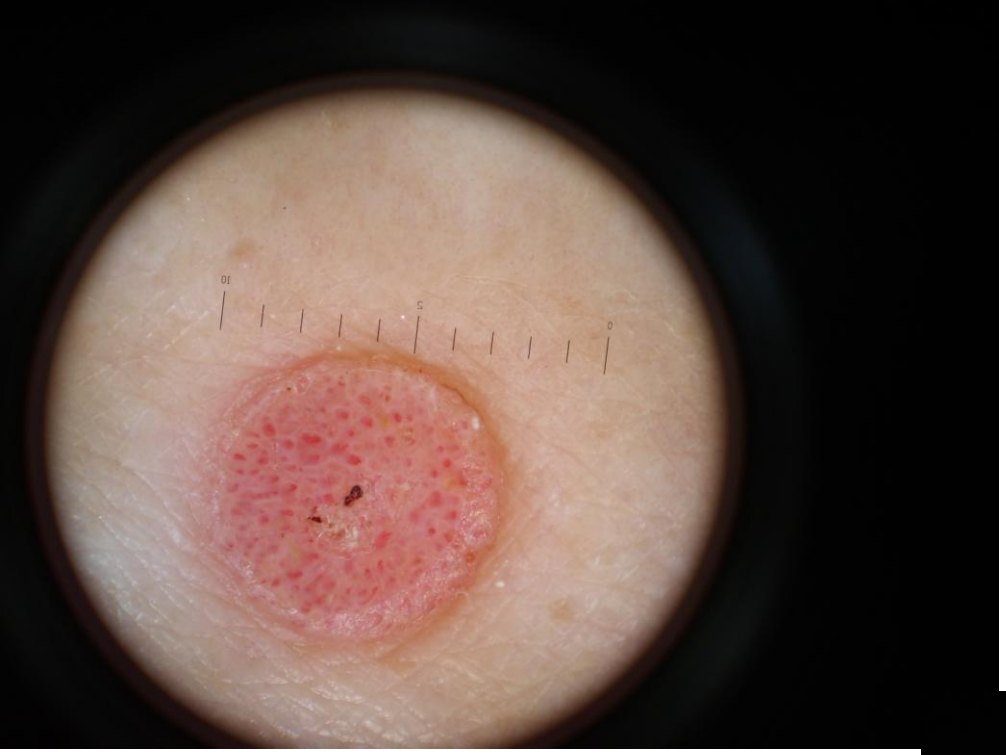
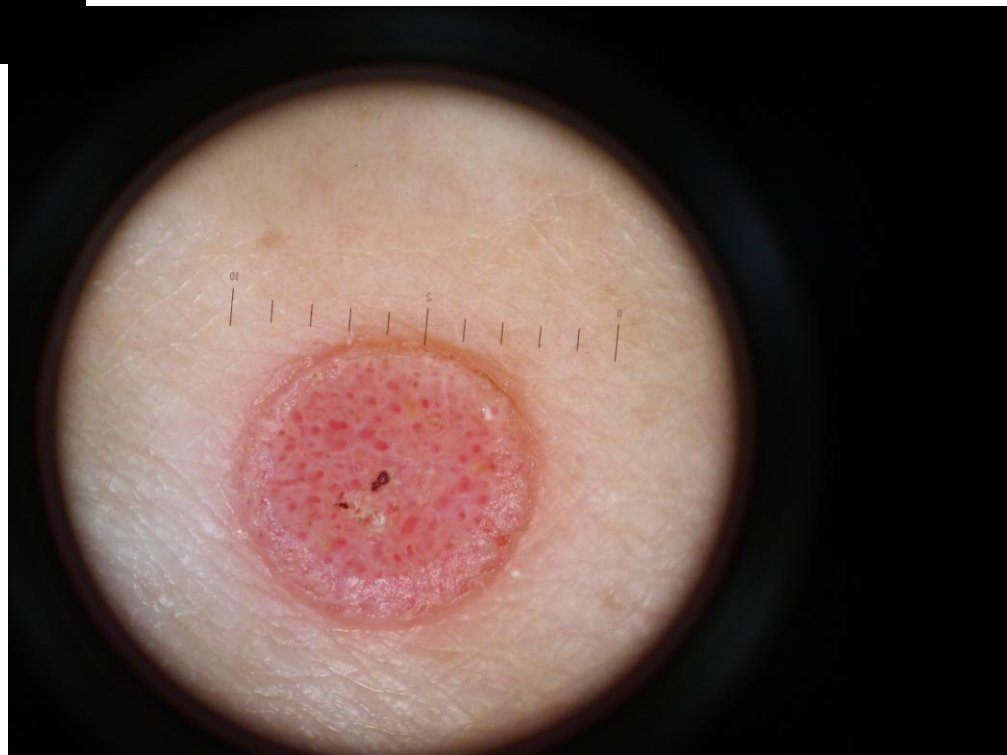
Did you change it ?

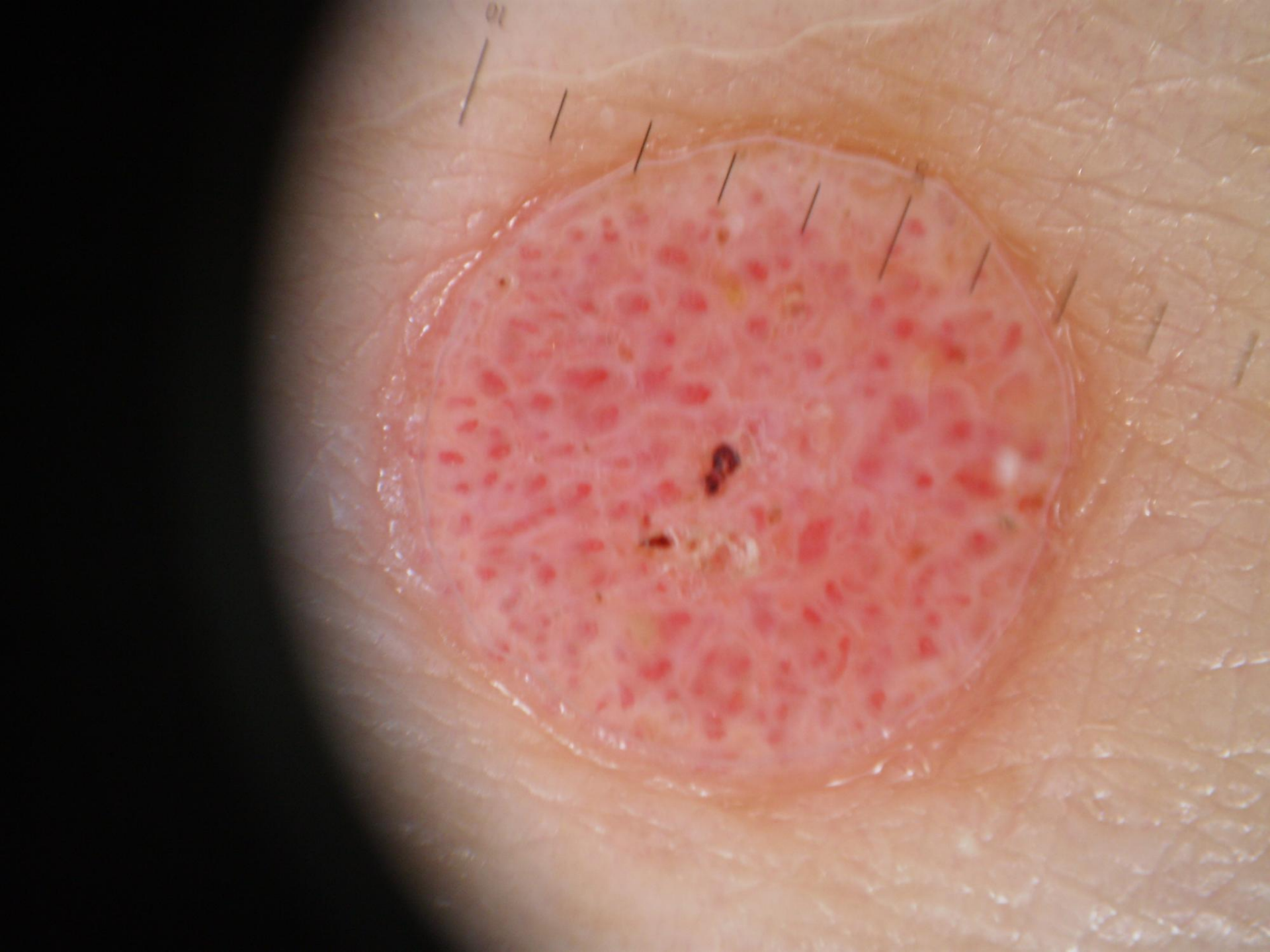
Which other missing information you want to have ??







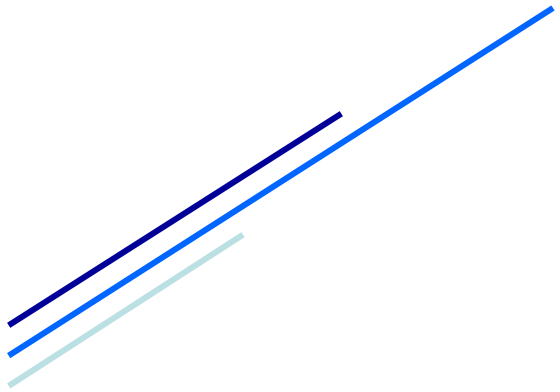


Which other missing information you want to have ??

Age of the patient: 74

Clinical information: Noticed by the patient 15-20 days before removal. Symmetrical, lightly coloured, slightly elevated lesion on the posterior aspect of the left thigh.

What is your final diagnosis ??



Final Diagnosis: Atypical Spitz Tumor

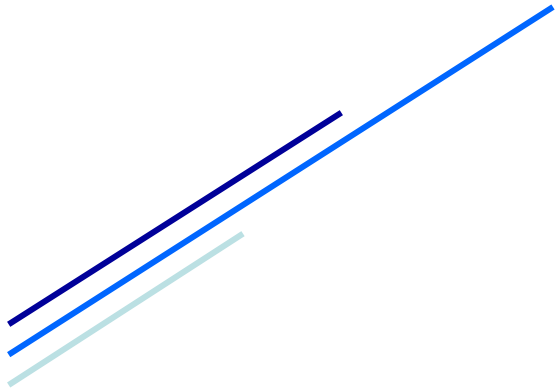
Management: Reexcision with 1 cm margins and SLNB

No melanocytic deposit.

PET-CT: Without any particularity.

Follow-up information:

Regularly followed. 27 months. Last visit September 2011.



Spitzoid Melanocytic Lesions

Terminology

Dichotomous classification **Spitz Nevus – Melanoma**

Spitzoid lesions **→Different from banal nevi and melanoma (CGH, mutation analysis, behavior)**

Better categorisation of Spitzoid neoplasms

- **-Spitz tumor without significant abnormality (Spitz Nevi),**
- **-Spitz tumor with atypical features (atypical Spitz tumor[AST]), some with indeterminate biological potential, and**
- **-Malignant melanoma**

Barnhill RL. Mod Pathol. 2006 Feb;19 Suppl 2:S21-33.

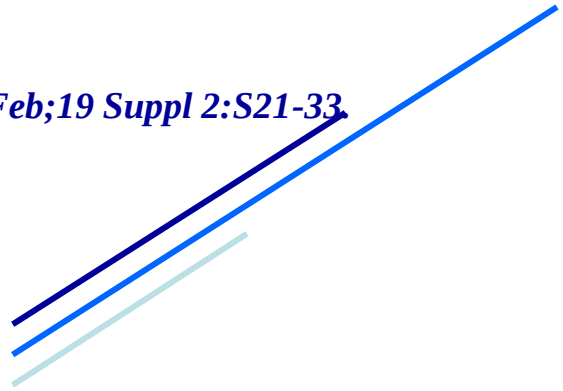


Table 5 Histopathological criteria for atypical Spitz tumors

Organizational criteria
- Diameter in mm (≥10 mm considered abnormal)
- Depth in mm (involvement of subcutaneous fat considered abnormal)
- Ulceration
- Poor circumscription
- Pagetoid melanocytosis over a large front
- → Prominent confluence of melanocytes
- → High cellular density
- → Lack of zonation and maturation
- Asymmetry
- Few or no dull pink (Kamino) bodies

Proliferational criteria
- → Significant mitotic rate—>2–6/mm²
- → Deep/marginal mitoses
- → Proliferation index, that is, Ki-67 expression
  - Between 2 and 10% (Vollmer)
  - ≥10% (Kapor *et al*[38])

Cytological criteria
- Granular *vs* ground glass cytoplasm
  - High nuclear to cytoplasmic ratios
  - Loss of delicate or dispersed chromatin patterns
  - Thickening of nuclear membranes
  - Hyperchromatism
  - Large nucleoli

Barnhill RL. Mod Pathol. 2006 Feb;19 Suppl 2:S21-33.

Differentiation of Spitz Tumor – Melanoma

Clinical Features

Age

349 Spitz nevi cases **40% ≤15 years old**

13/217 (6%) cases in females ≥45 years old

"... we believe that no changes should be made to a clear histopathological diagnosis of Spitz nevus or melanoma because of the patient's age."

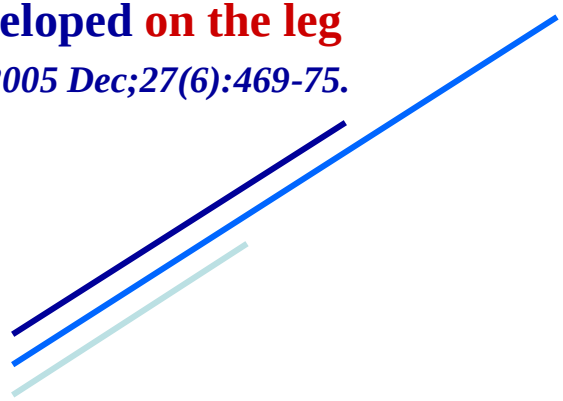
Requena C et al. Am J Dermatopathol. 2009 Apr;31(2):107-16.

247 Spitz nevi **66% ≥20 years old**

21/162 (13%) cases in females ≥40 years old

in 60% of women ≥40 the lesion developed on the leg

Cesinaro AM et al. Am J Dermatopathol. 2005 Dec;27(6):469-75.



Differentiation of Spitz Tumor – Melanoma

Clinical Features

Age

Yale group

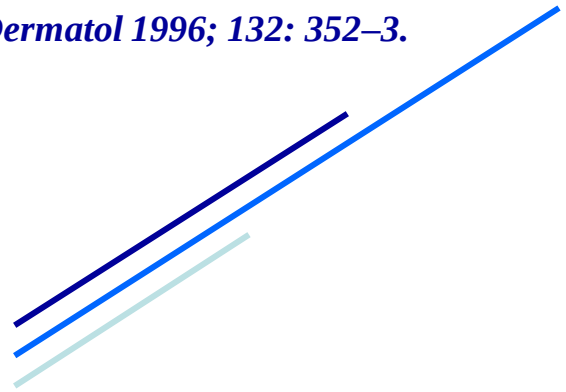
Spitz naevi age range **6 months-71 years**

average age 22, median age 19

Ratio of Spitz naevi/melanoma

age	**≤20 years**	**60:1**
	20-29 years	**3:2**
	30-39 years	**1:3**
	40-49 years	**1:7**
	>50 years	**1:60**

Herreid PA, Shapiro PE. Arch Dermatol 1996; 132: 352–3.



Differentiation of Spitz Tumor – Melanoma

Immunohistochemistry

29 compound Spitz nevi

8/29 (28%) negative; 5/29 (17%) epidermal component only; 16/29 (55%), including 10 deep SNs, both the epidermal and dermal components.

10 deep SNs 8/10 upper dermis only; 2/10 some cells in deep dermis.

Stratified pattern of HMB-45 staining

Bergman R et al. Am J Dermatopathol. 1995 Dec;17(6):542-6.

p27 expression was significantly higher in Spitz nevi

Stefanaki C et al. J Am Acad Dermatol. 2007 May;56(5):815-24.

"a high level of p21 expression makes a tumor more likely to be a typical or atypical Spitz nevus than a malignant melanoma"

Kapur P et al. Mod Pathol. 2005 Feb;18(2):197-204.

Differentiation of Spitz Tumor – Melanoma

Ancillary Techniques

Molecular Pathology

Early Studies

96 spitzoid melanocytic lesions **mutations in BRAF, NRAS, and HRAS**

BRAF or NRAS mutations **31/36 (86%) spitzoid melanomas**

0/14 Spitz nevi and 0/16 atypical Spitz nevi

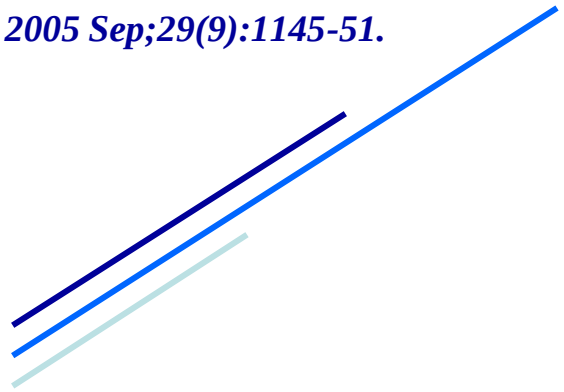
HRAS mutations

4/14 (29%) Spitz nevi and 3/22 (14%) atypical Spitz nevi

0/36 spitzoid melanomas

"Spitz nevi and spitzoid melanomas are genetically unrelated entities."

van Dijk MC et al. Am J Surg Pathol. 2005 Sep;29(9):1145-51.



Differentiation of Spitz Tumor – Melanoma

Ancillary Techniques

Molecular Pathology

HRAS mutation analysis

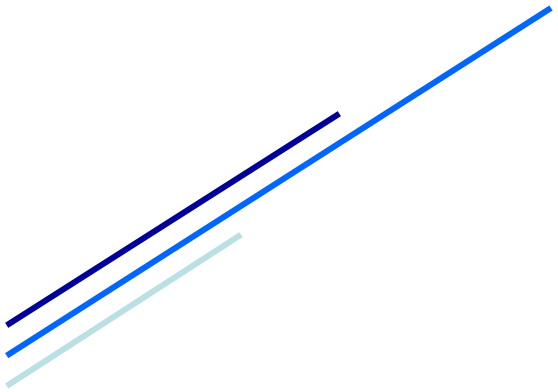
93 Spitz nevi and 77 STUMPs →24 lesions harbored HRAS mutation.

None of the HRAS mutated cases developed recurrences or metastases (10.5 years of follow-up).

HRAS mutations had not been reported in Spitzoid melanomas.

HRAS mutation analysis may be a useful diagnostic tool.

Blokx WA et al. Am J Surg Pathol. 2010 Oct;34(10):1436-41.



Differentiation of Spitz Tumor – Melanoma

Ancillary Techniques

Molecular Pathology

FISH

RREB1 (6p25)/MYB (6q23)/CCND1 (11q13)/CEP6 (6p11.1-q11 Alpha Satellite DNA)

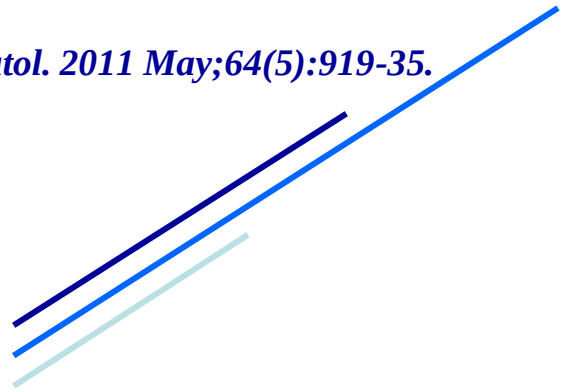
38 controversial, atypical Spitzoid lesions (≥ 1 mm in thickness)

4 lymph node deposits (SLNB), 4 bulky metastases (1 death).

FISH analysis → chromosomal alterations in 6/25 cases (incl. the fatal case)

"FISH assay may be of help in the prognostic evaluation of atypical Spitzoid tumors. But require validation in a larger series with longer follow-up information."

Massi D et al. J Am Acad Dermatol. 2011 May;64(5):919-35.



Conclusions

What to do in front of a "Spitzoid" melanocytic lesion?

Examination of the entire lesion →Is there a clearcut melanoma ??

→Is there a "Spitzoid tumor without atypicality" ??

If not →Try to obtain detailed clinical information including photographs

→Careful histopathological examination

immunohistochemistry (HMB45, Ki67),

other aditional means (CGH, HRAS mutation, FISH) if avilable

→Consultation

Risk assessement

Management

Reexcision, consideration of SLNB

Long term follow-up with regular intervals