# Diagnosis, biology and meaning of melanocytic dysplasia

SALVADOR J. DIAZ-CANO

ORCID 0000-0003-1245-2859

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# Melanocytic Dysplasia

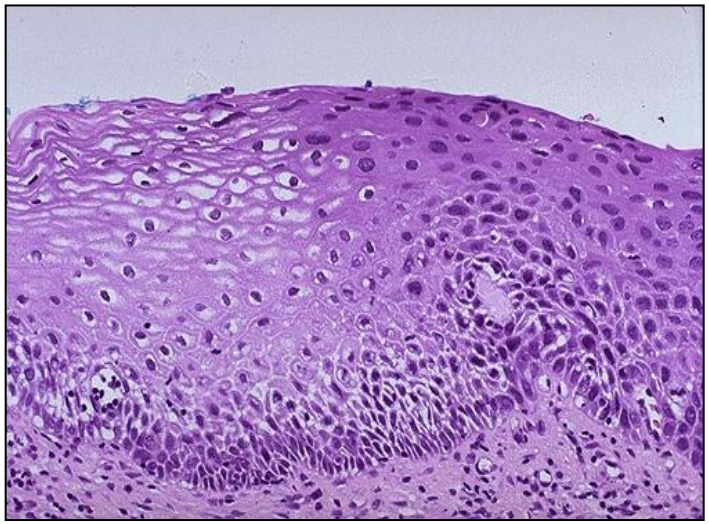
- **Concept and criteria. Grading**
- **Pathologic conditions**
- **Differential diagnosis**
  - **Atypia and regenerative changes**
  - **Inflammation and regression**
- **Is melanocytic dysplasia a progressive lesion?**

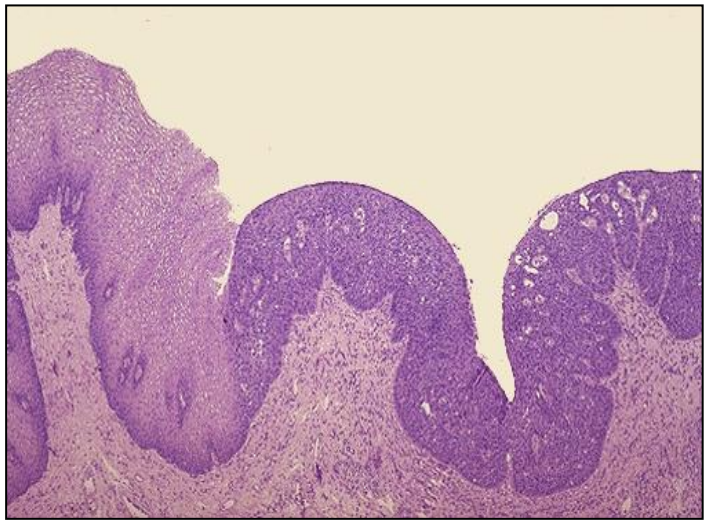
# MELANOCYTIC DYSPLASIA

## Concept and criteria. Grading

# Dysplasia

**Alterations in cell size and morphology (nuclear), with or without disorganized growth pattern (architecture)**





# AMN Histopathologic Diagnosis

**MAJOR CRITERIA**

- Basilar proliferation of atypical melanocytes (three rete ridges beyond the dermal component)
- Lentiginous or epithelioid growth pattern

**MINOR CRITERIA**

- Fibrosis
- Neovascularization
- Inflammatory response
- Fusion of rete ridges

**Diagnosis requires both major + 2 minor criteria**

Clemente et al. Hum Pathol 1991;22:313-9

# AMN. Histologic Criteria

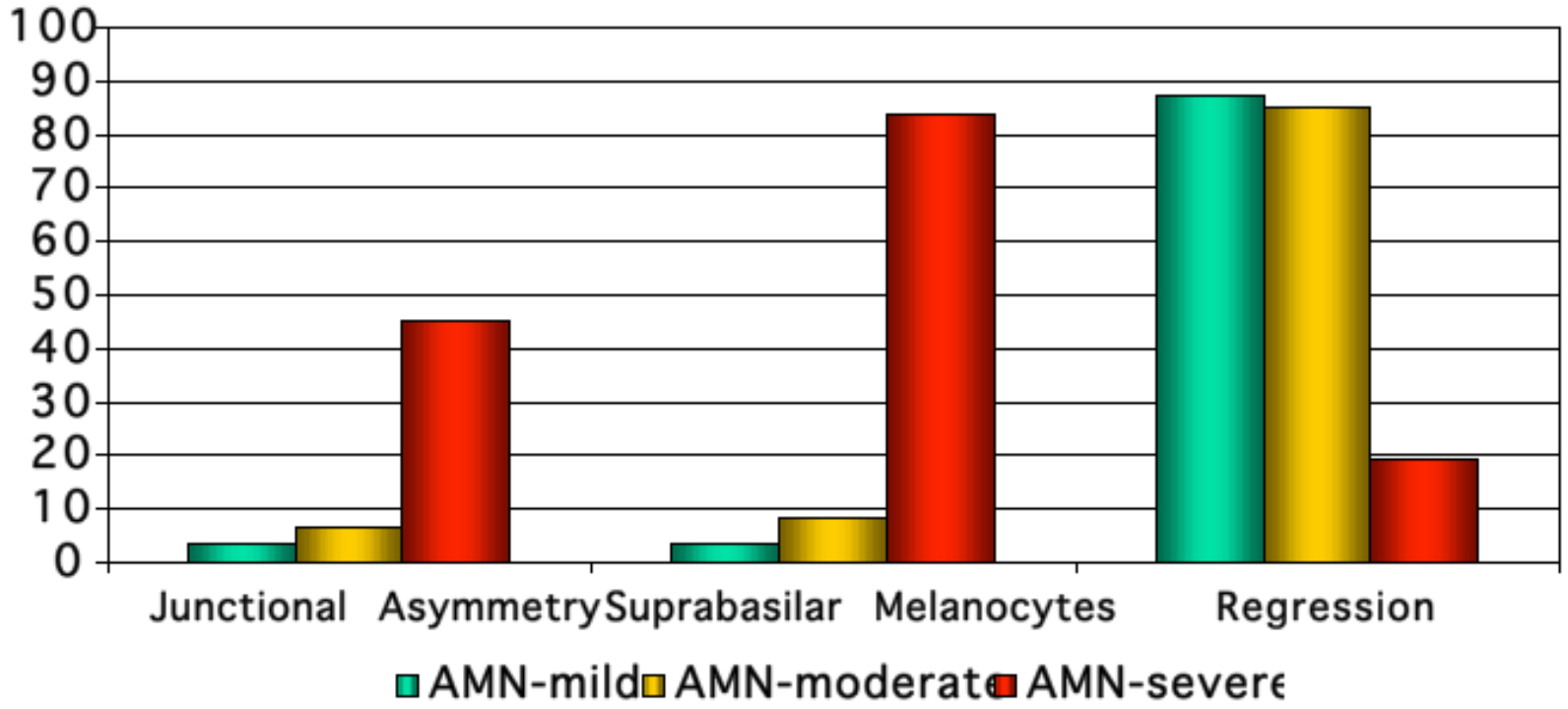
## Architectural disorder

- Lentiginous melanocytic hyperplasia
- Upward melanocyte migration
- Nesting variation and bridging

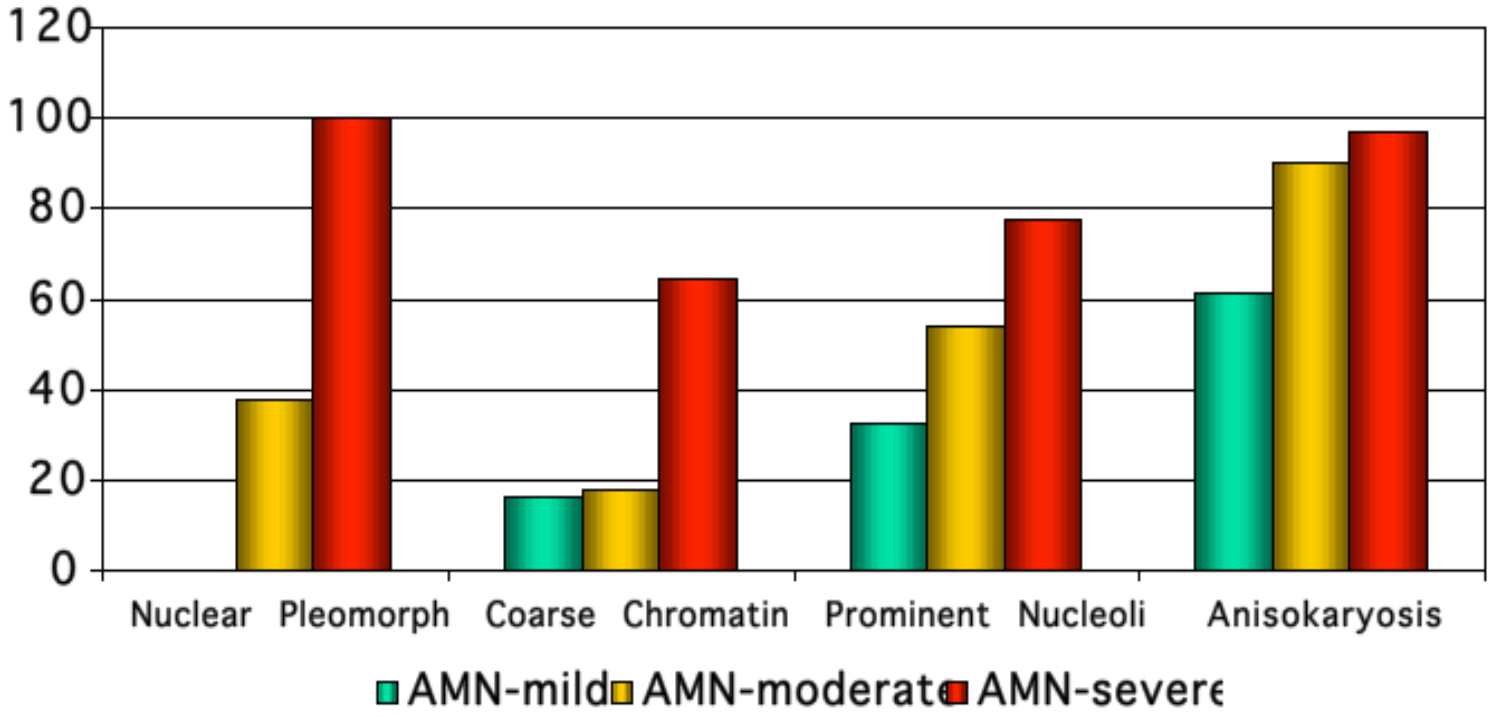
## Cytological atypia

- Nuclear enlargement (basal keratinocyte)
- Prominent nucleolus
- Pleomorphism
- Hyperchromatism

# Architectural Features in AMN



# Nuclear Features in AMN



# Grading Dysplasia

**60 melanocytic lesions, 10 from each group, including:**

- **common MN, Clark nevus, AMN-mild, AMN-moderate, AMN-severe, primary MM**

**Concordance for diagnosing dysplastic nevi was 77% (kappa statistic 0.55-0.84)**

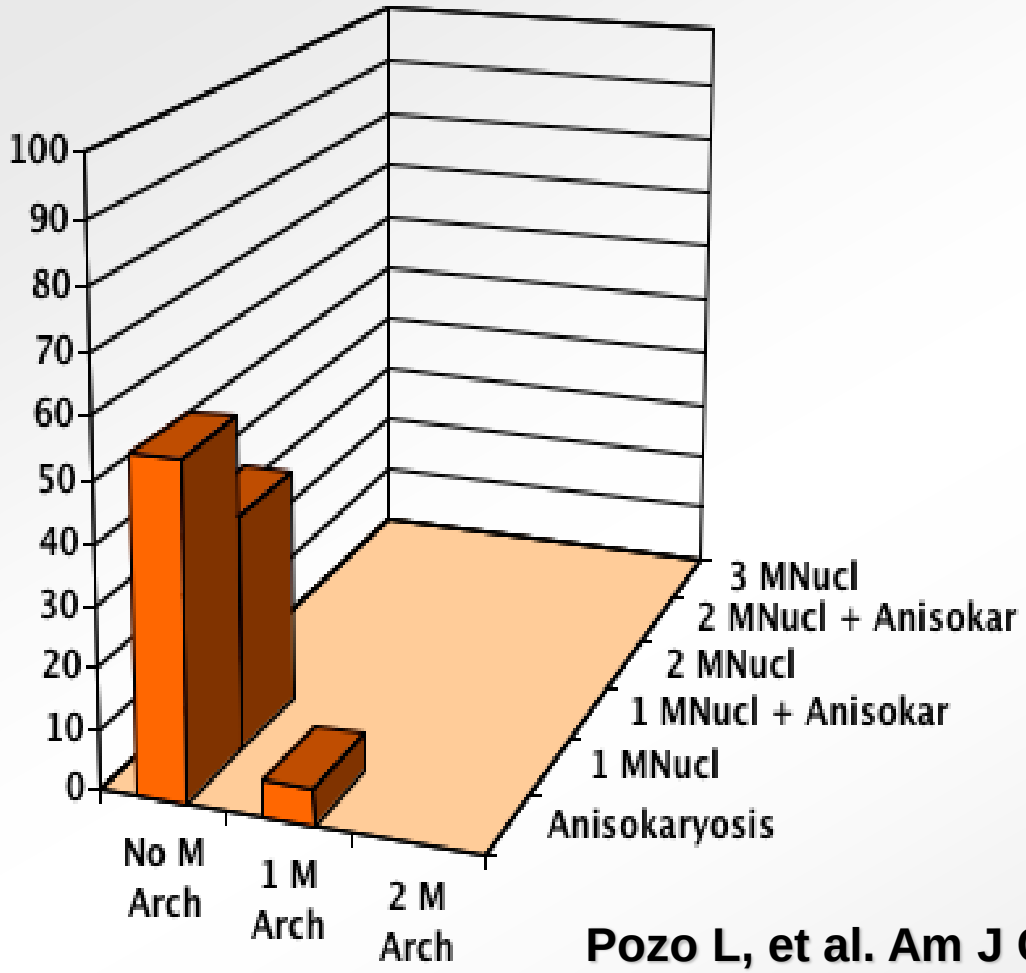
**Reliable distinction of dysplastic nevi from conventional nevi and MM**

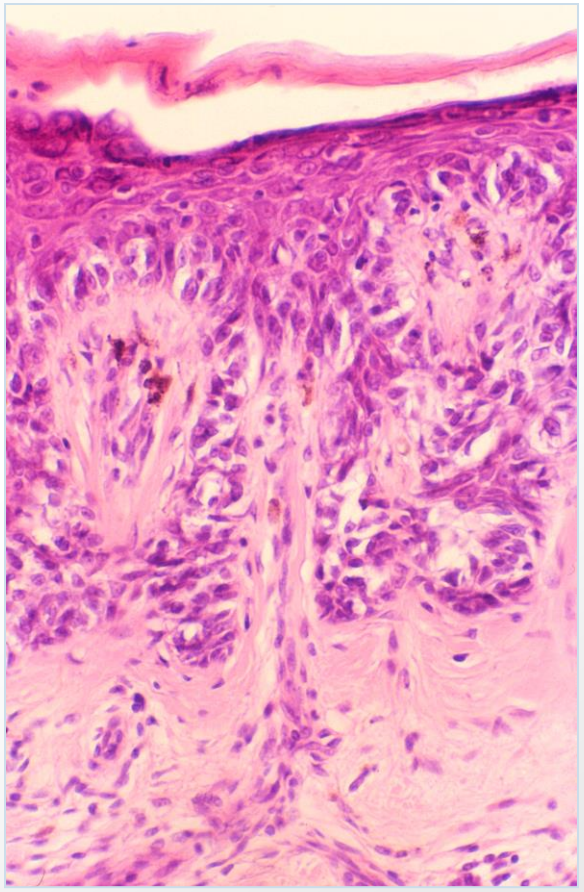
**Concordance in grading**

- **35% to 58% (kappa value 0.38-0.47)**
- **16% to 65% (kappa value 0.05-0.24)**

**Duncan et al. J Invest Dermatol 1993;100:318S-321S**

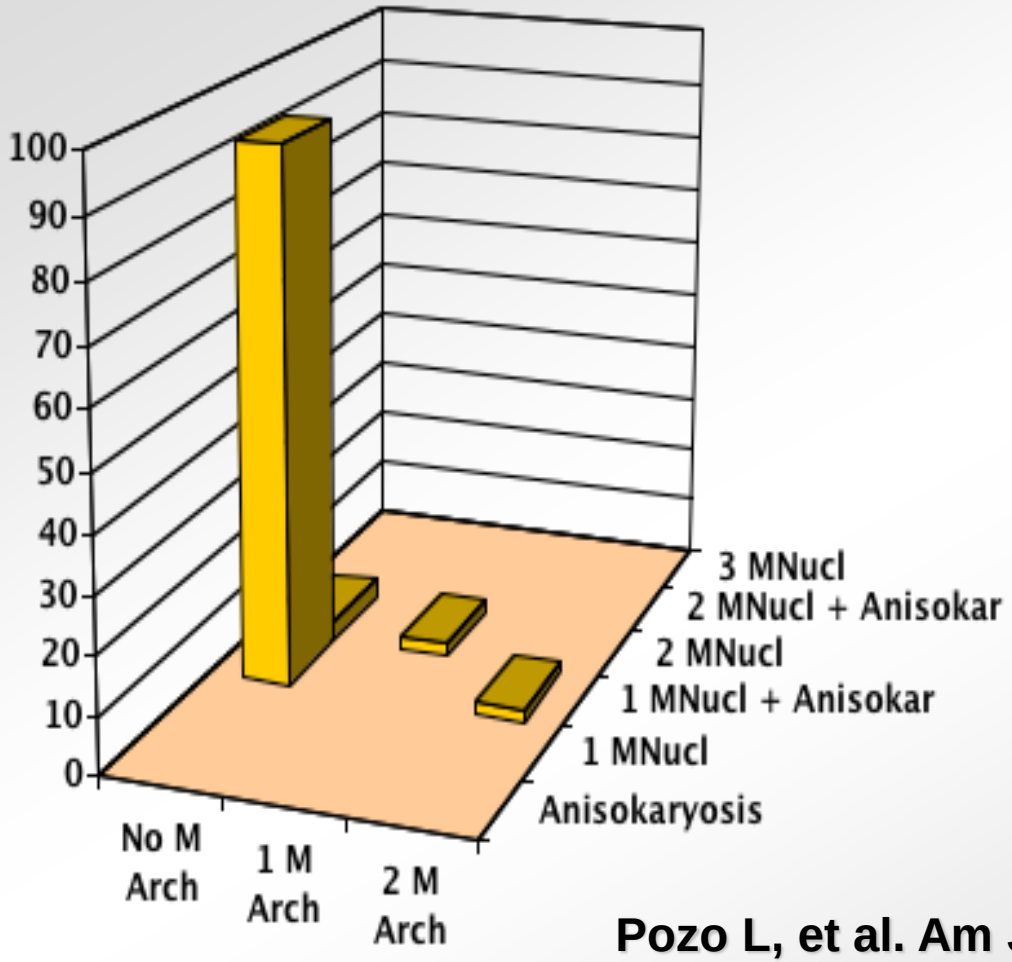
# AMN–mild

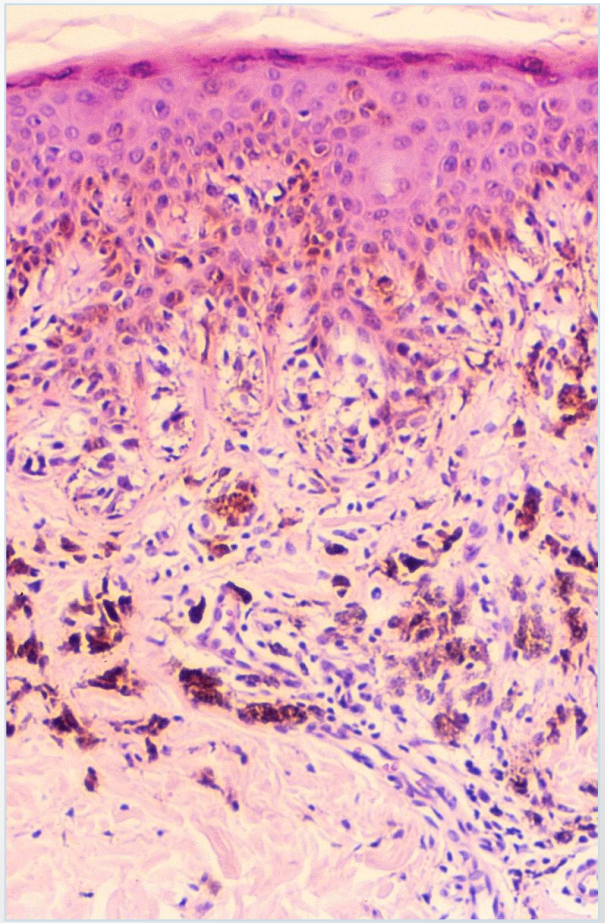


Pozo L, et al. Am J Clin Pathol 2001;115:194-204

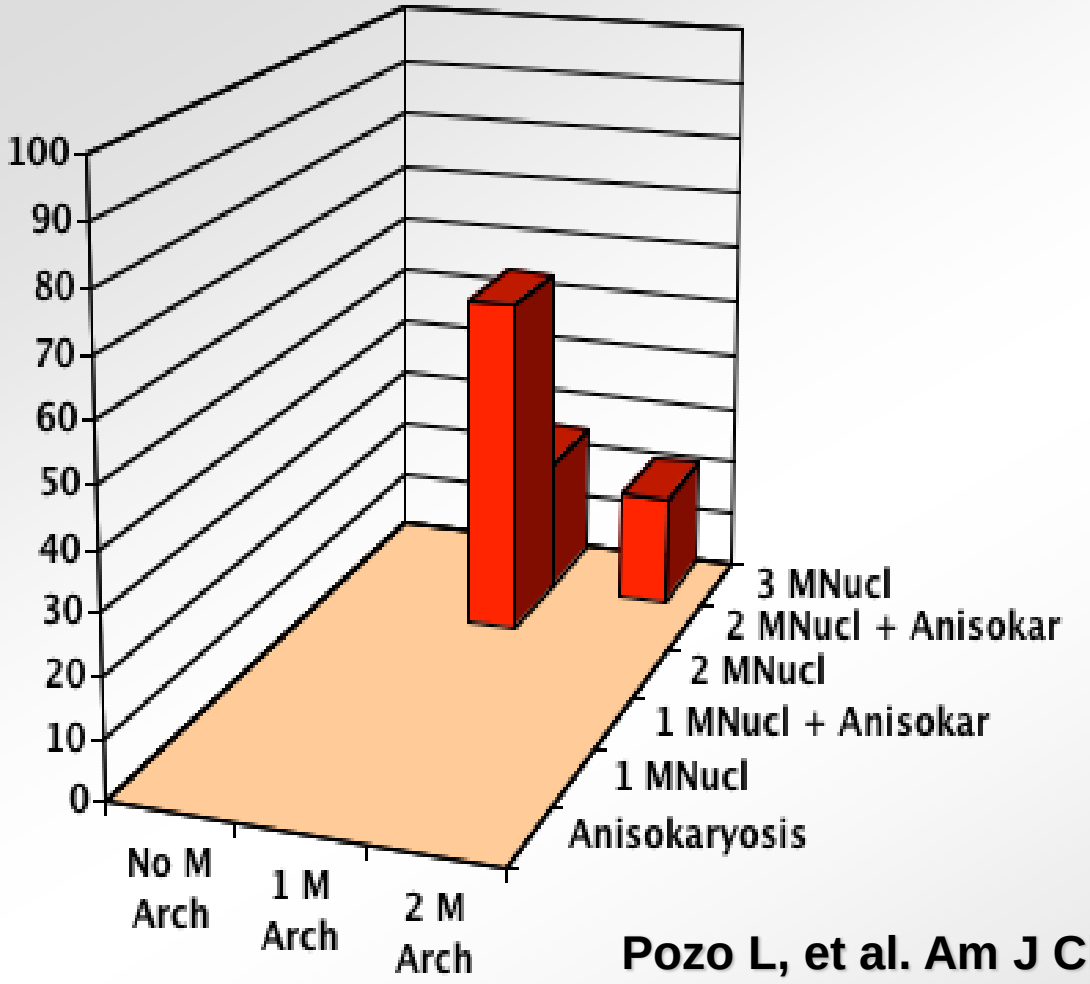
# AMN–moderate

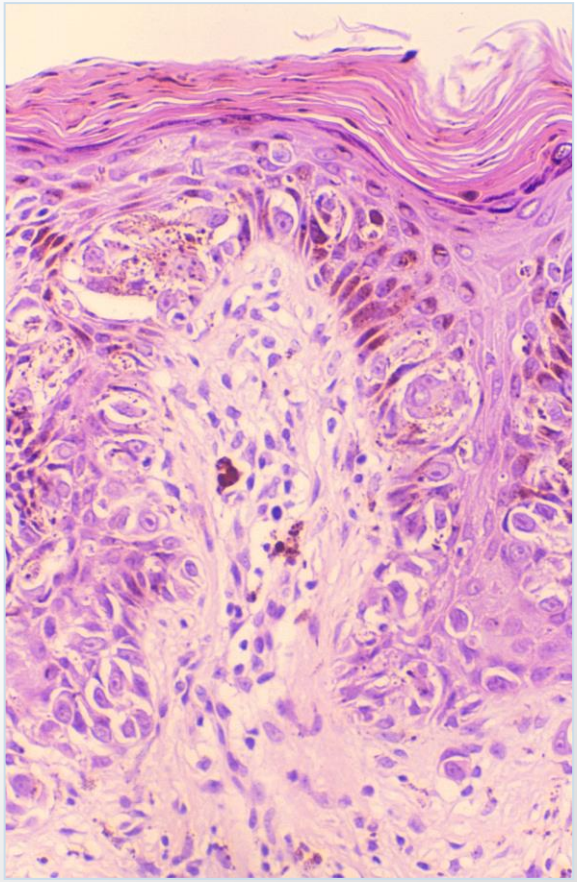


Pozo L, et al. Am J Clin Pathol 2001;115:194-204

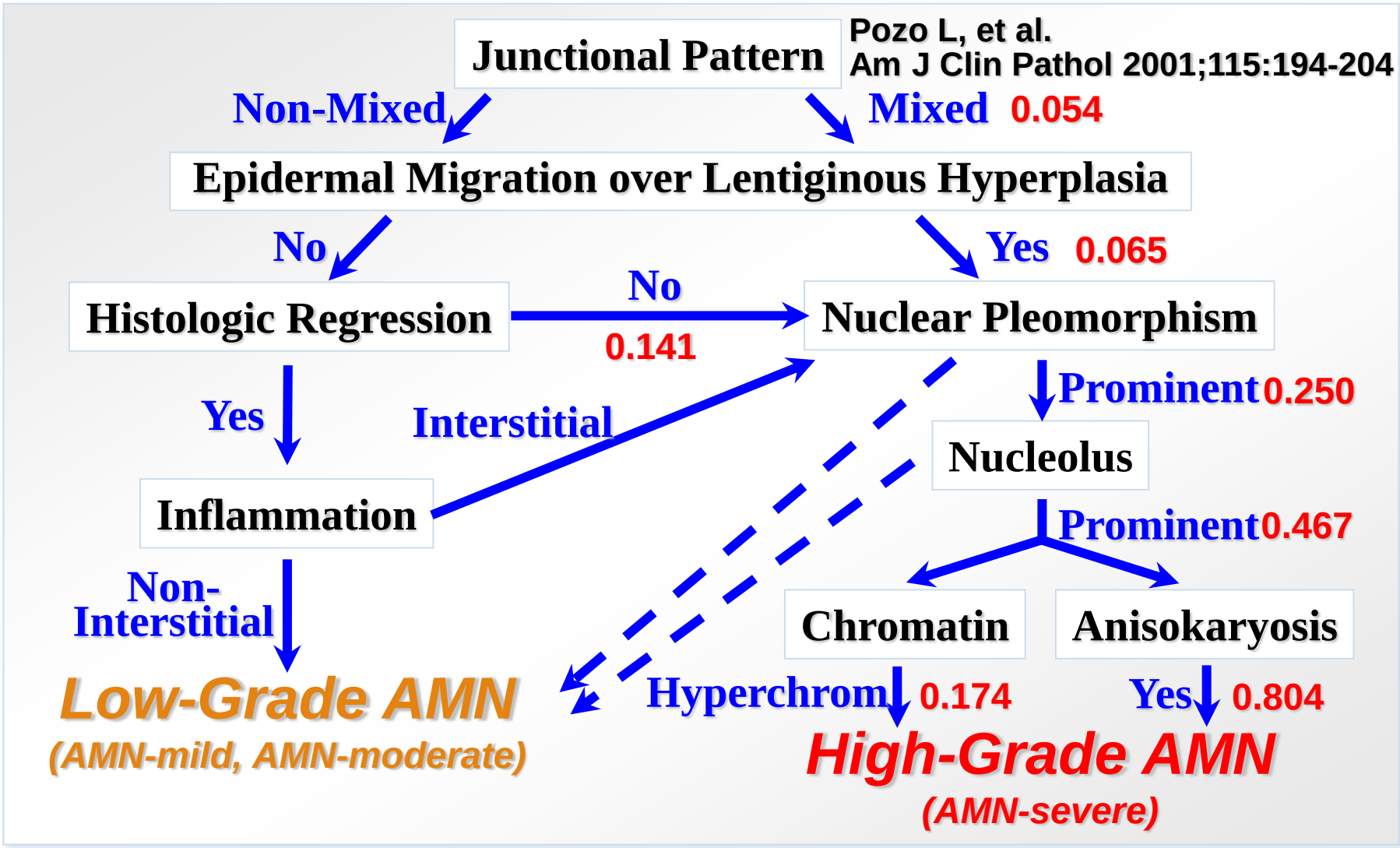
# AMN–severe

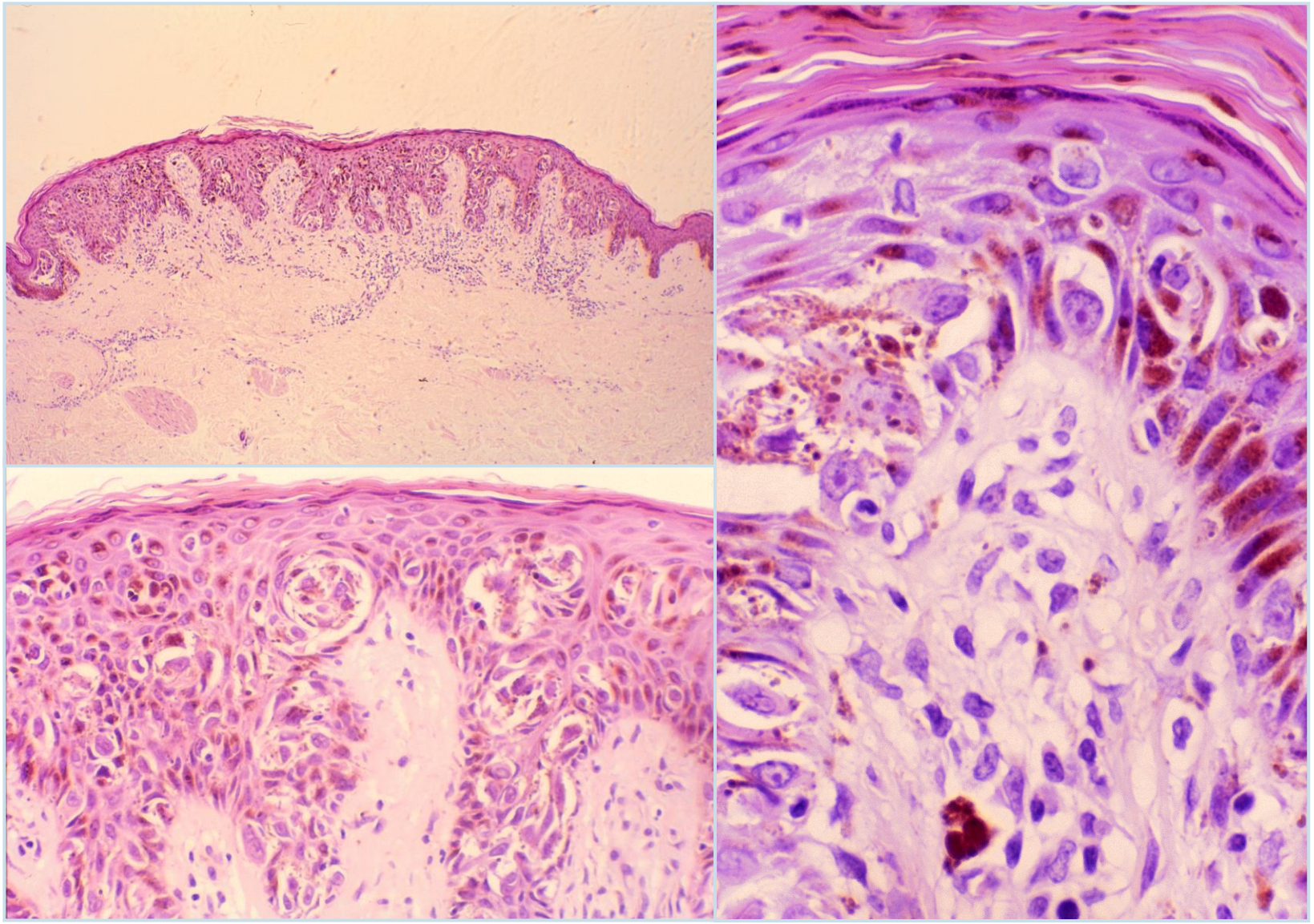


Pozo L, et al. Am J Clin Pathol 2001;115:194-204

# Grading Dysplasia in AMN





# Grading Dysplasia in AMN

**Histologic criteria reliably distinguish high-grade AMN (severe dysplasia) from low-grade AMN (mild-moderate dysplasia) only, based on the application of major features (3 nuclear and 2 architectural)**

**Low-grade AMN are significantly associated with histologic regression. Its meaning needs further analyses**

**Pozo L, et al. Am J Clin Pathol 2001;115:194-204**

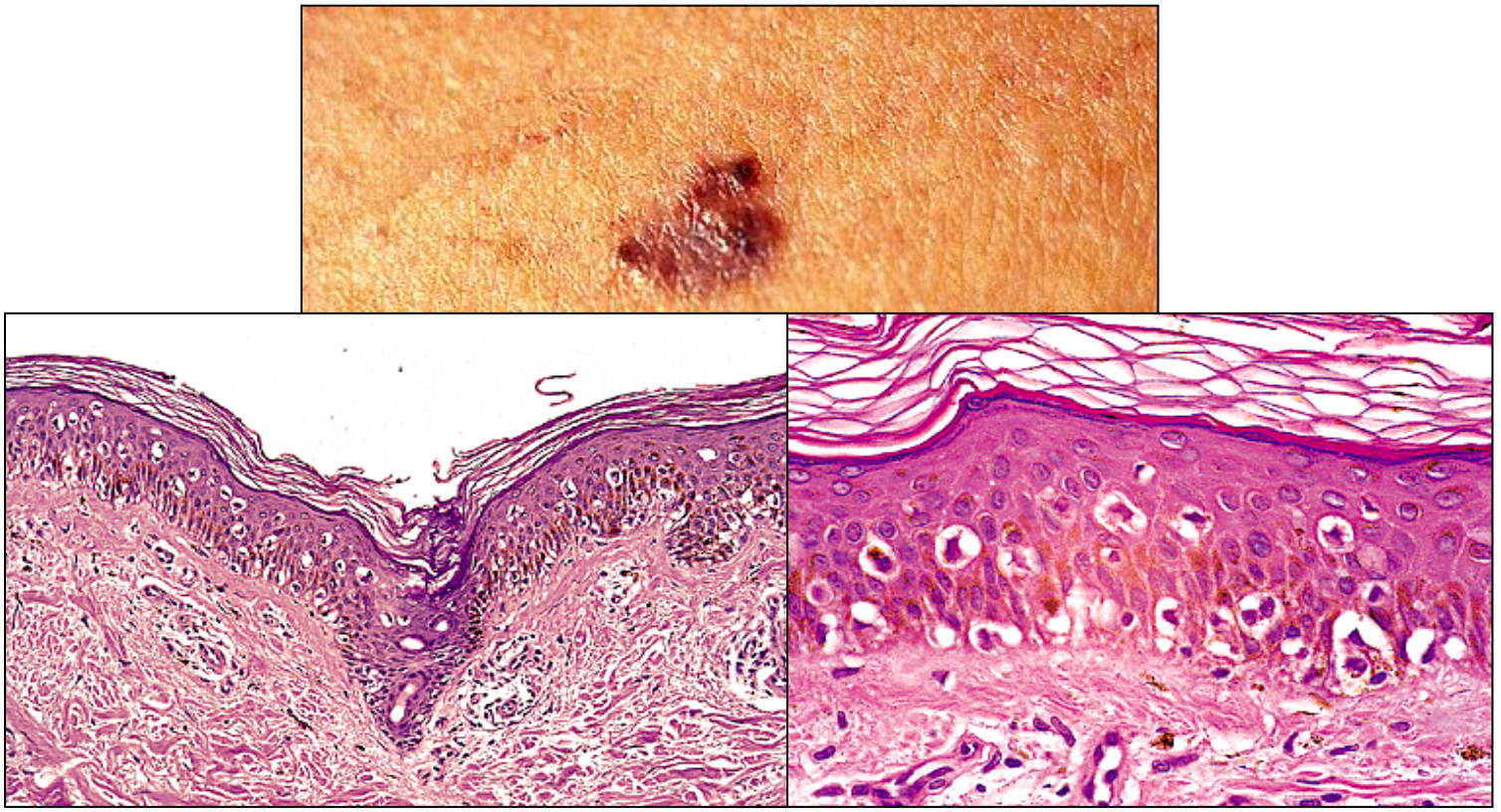
# Grading Dysplasia in AMN

**The accuracy of clinical diagnosis of moderate dysplasia was low (20%); however, all cases of severe dysplasia with or without in situ melanoma were diagnosed correctly.**

**Increasing darkness and confluence of pigmentation in these dysplastic melanocytic nevi correlated with increasing severity of dysplasia.**

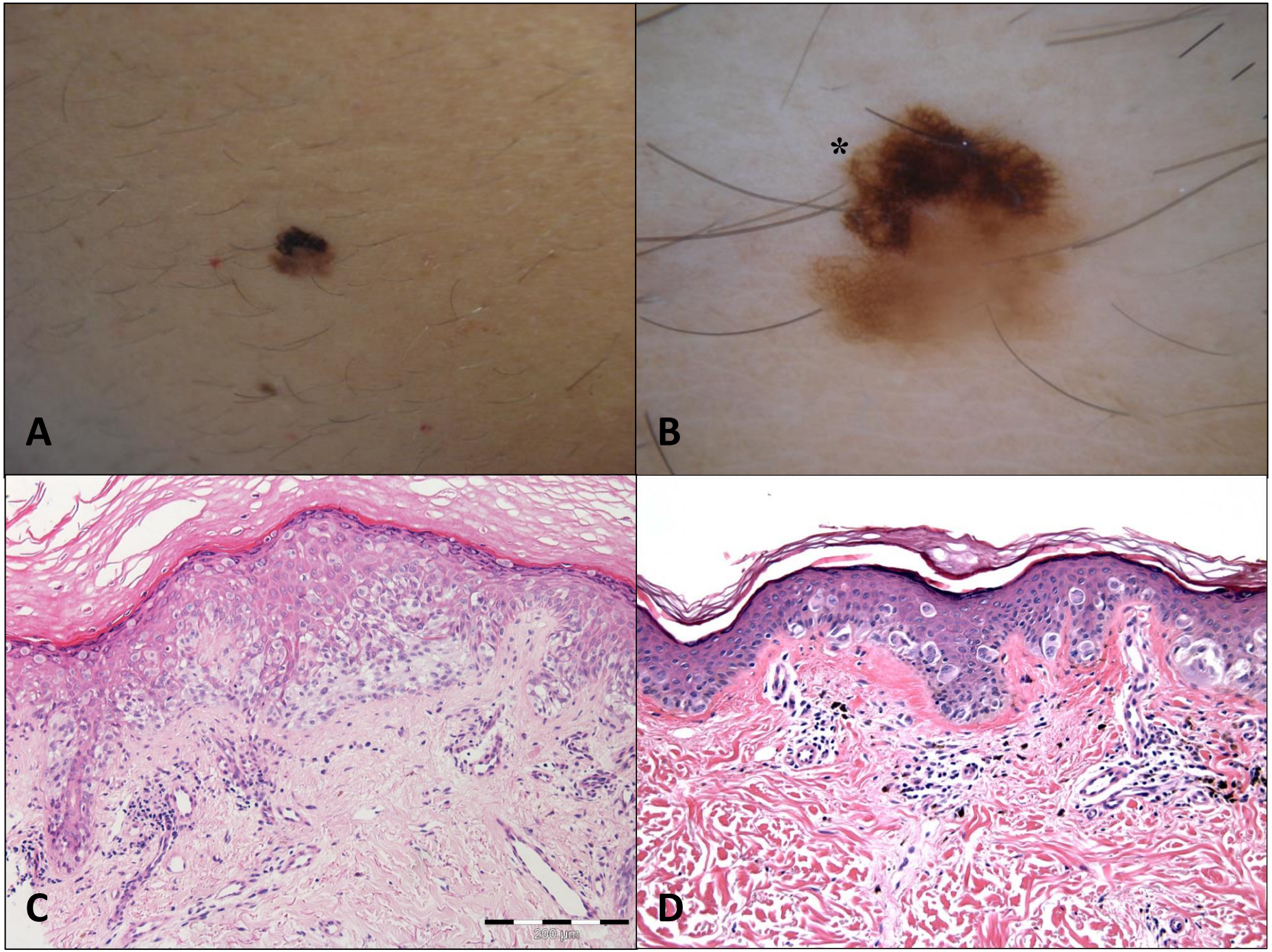
**Kelly et al. J Am Acad Dermatol 1986; 14:1044-52**

# High-Grade AMN *vs.* Melanoma *In Situ* (MIS)



# MELANOCYTIC DYSPLASIA

## Pathologic conditions


A
B
*
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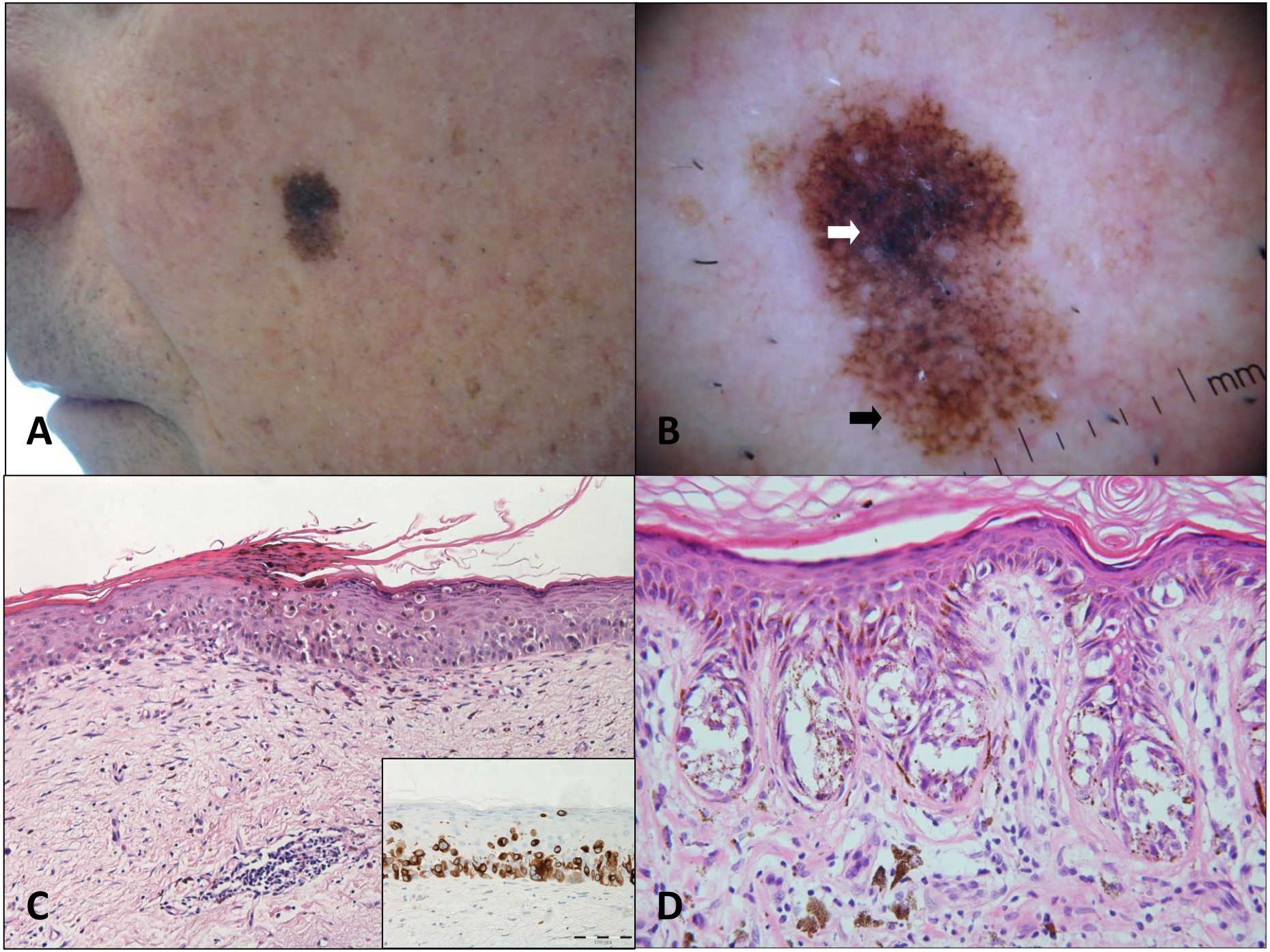
200 µm
D


A
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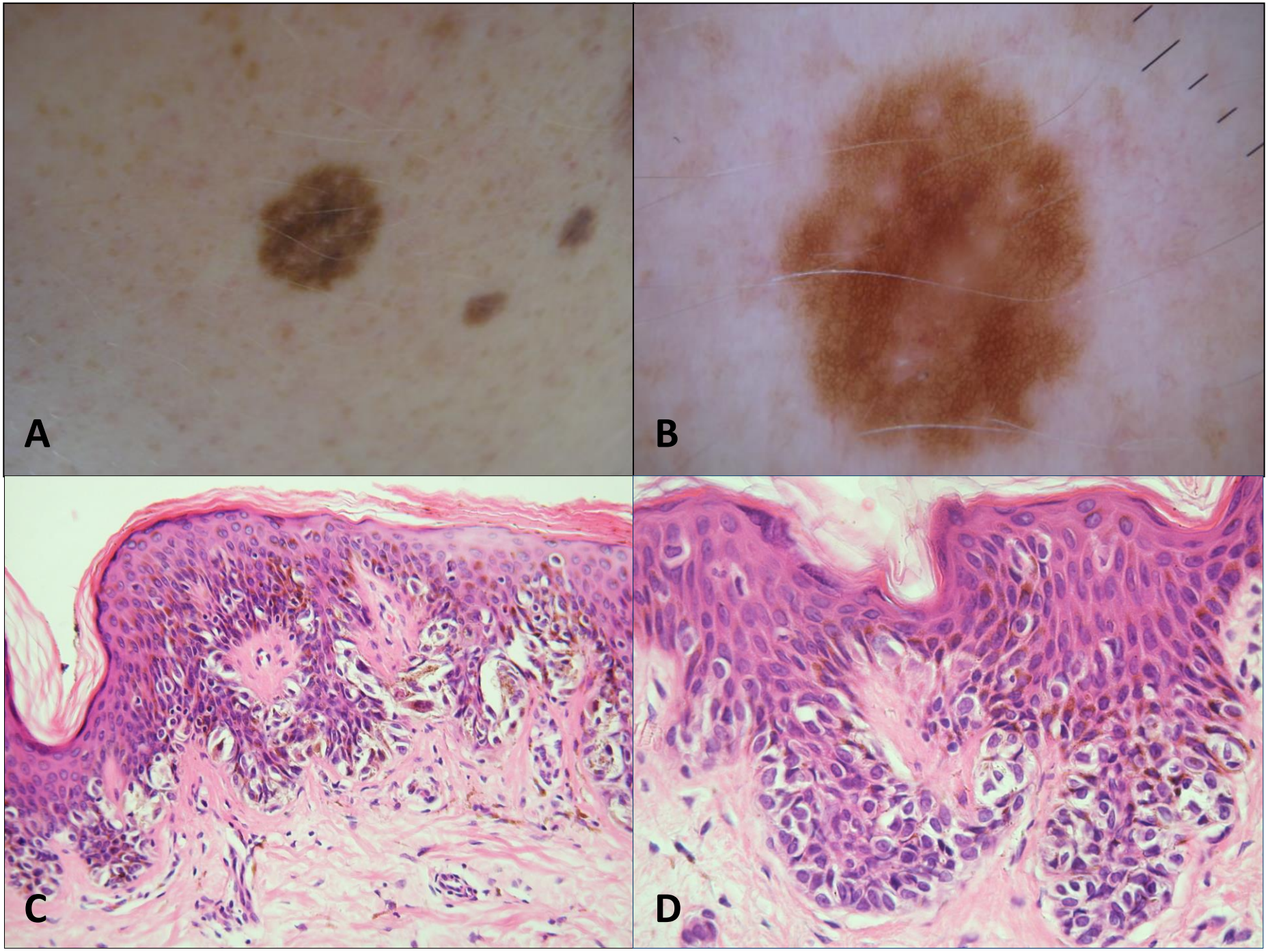
A
B
C
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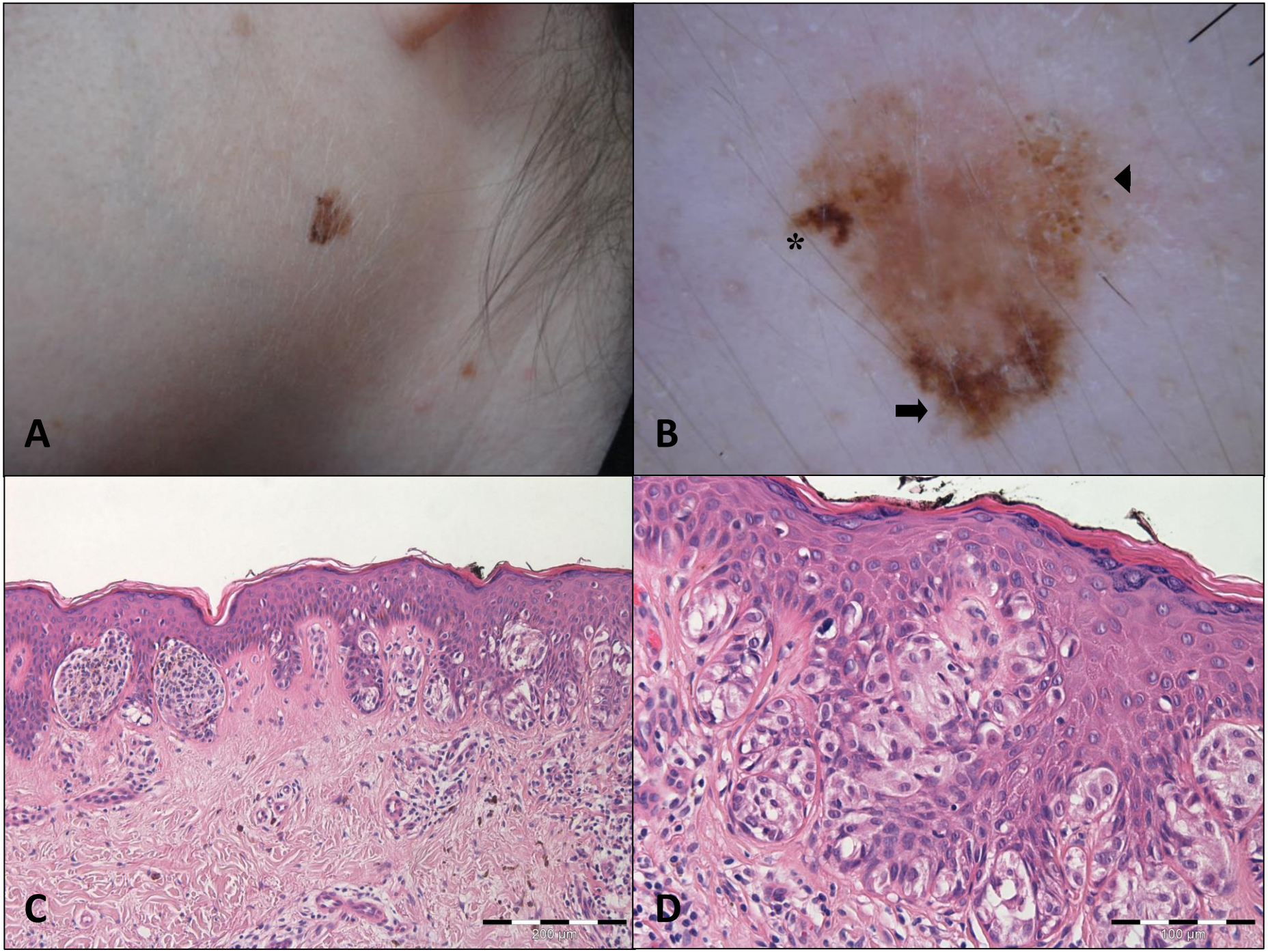
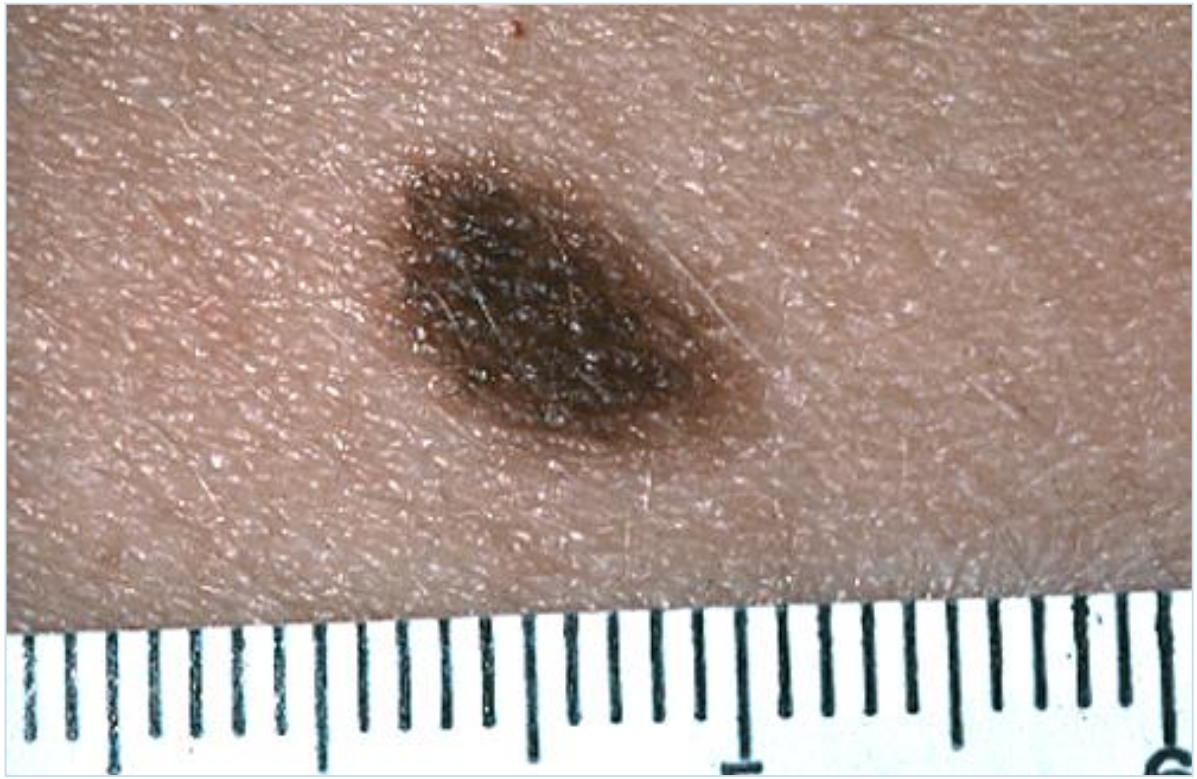

A
B
C
200 µm
D
100 µm

# Melanocytic Dysplasia

- **Atypical (dysplastic) melanocytic nevus**
- **De novo intraepidermal epithelioid melanocytic dysplasia**
- **Lentigo maligna**

# Atypical Melanocytic Nevus



# Does AMN Exist?

**Barnhill et al. Arch Dermatol 1990;126:463-5**

- **These findings confirm the existence of dysplastic nevi by histopathologic criteria as early as 1950…**

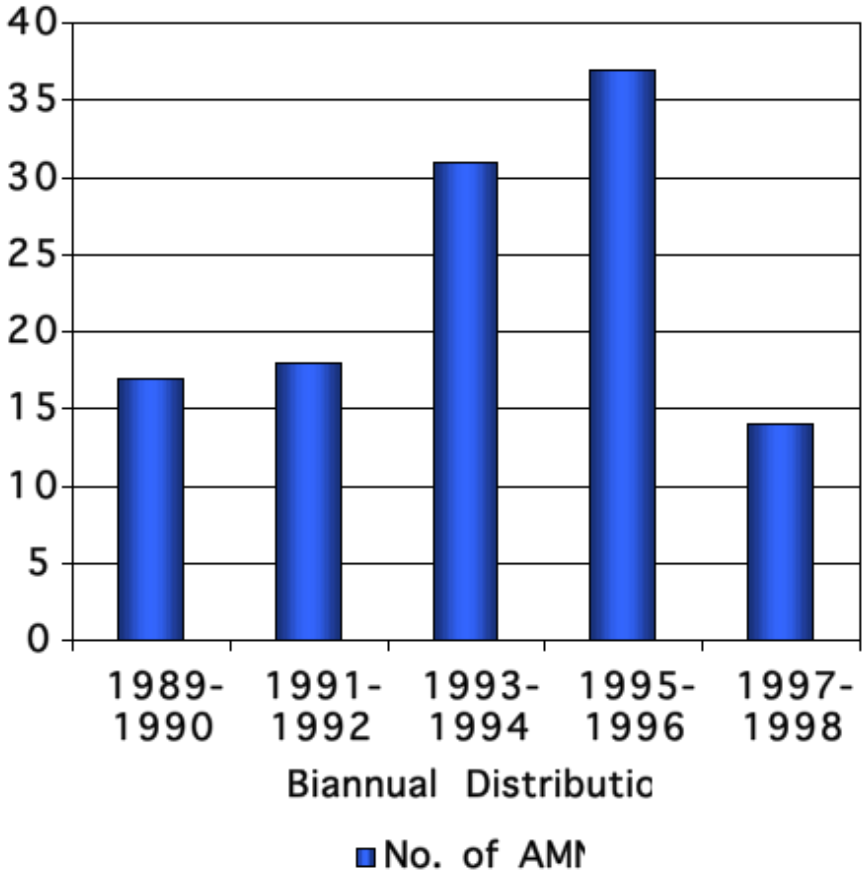
**Black and Hunt. Am J Surg Pathol 1990;14:44-52**

- **This study supports the validity of the dysplastic nevus as a clinical and pathologic entity**

**Cook, Fallowfield. Histopathology 1990;16:29-35**

- **The recognition of severely aberrant differentiation in the form of classic dysplastic nevus is worthwhile,… it confers a very high risk of developing melanoma**

# AMN Distribution 1989-1998




Pozo L, Diaz-Cano SJ.
Arch Dermatol 2000;136:934-935

# AMN. Histologic Criteria

## Architectural disorder

- Lentiginous melanocytic hyperplasia
- Upward melanocyte migration
- Nesting variation and bridging

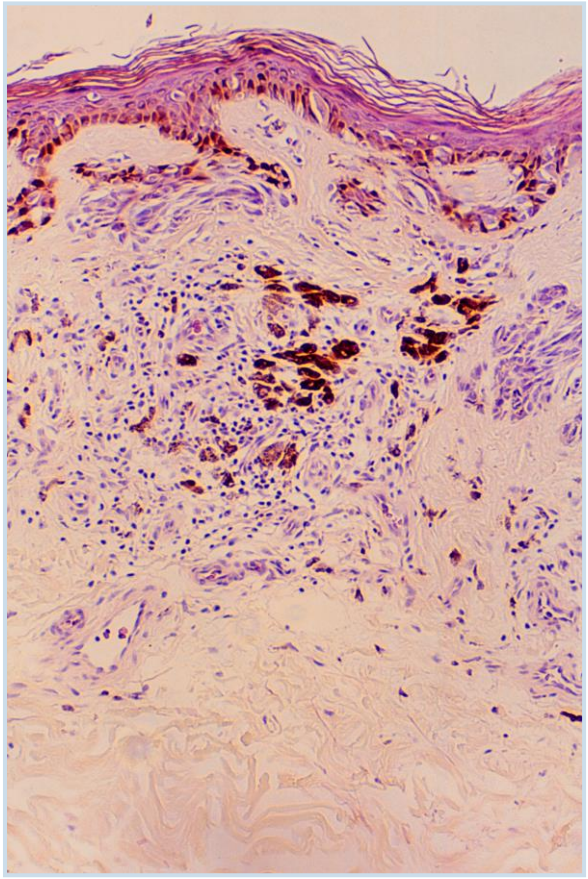
## Cytological atypia

- Nuclear enlargement (basal keratinocyte)
- Prominent nucleolus
- Pleomorphism
- Hyperchromatism

# AMN. Histologic Criteria

**Tissue response**

- **Lymphocytic infiltrate**
- **Fibroplasia (lamellar or not)**



# Significance and Controversy of AMN

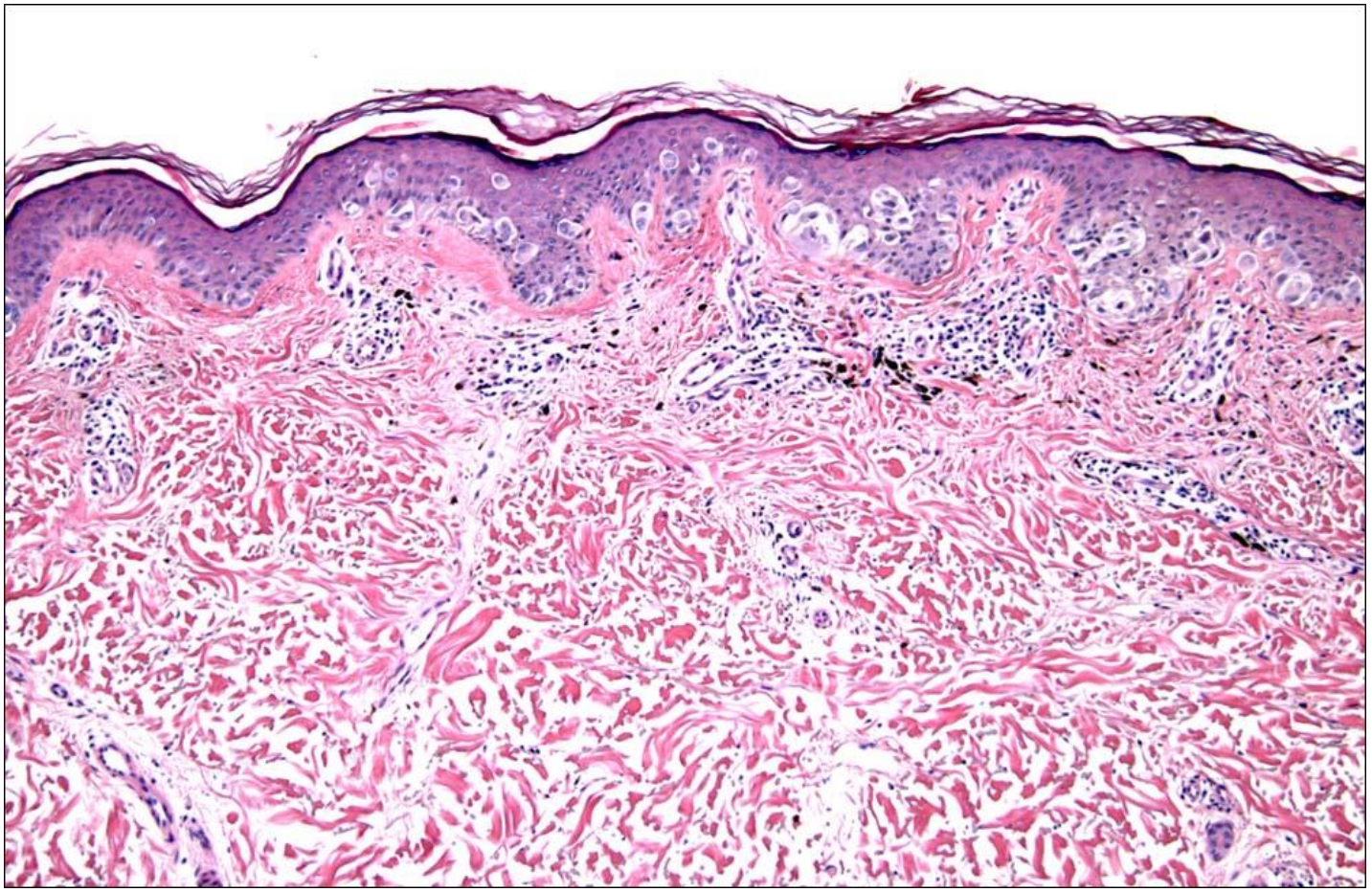
**AMN is an important marker of melanoma risk (≥ 8-fold increased risk of malignant melanoma)**

**Minimal criteria must be based on both nuclear atypia and architectural disorder**

**Subjective definition for grading AMN has resulted in no consensus on that matter**

**Systematic approach is needed**

# *De novo* Melanocytic Dysplasia



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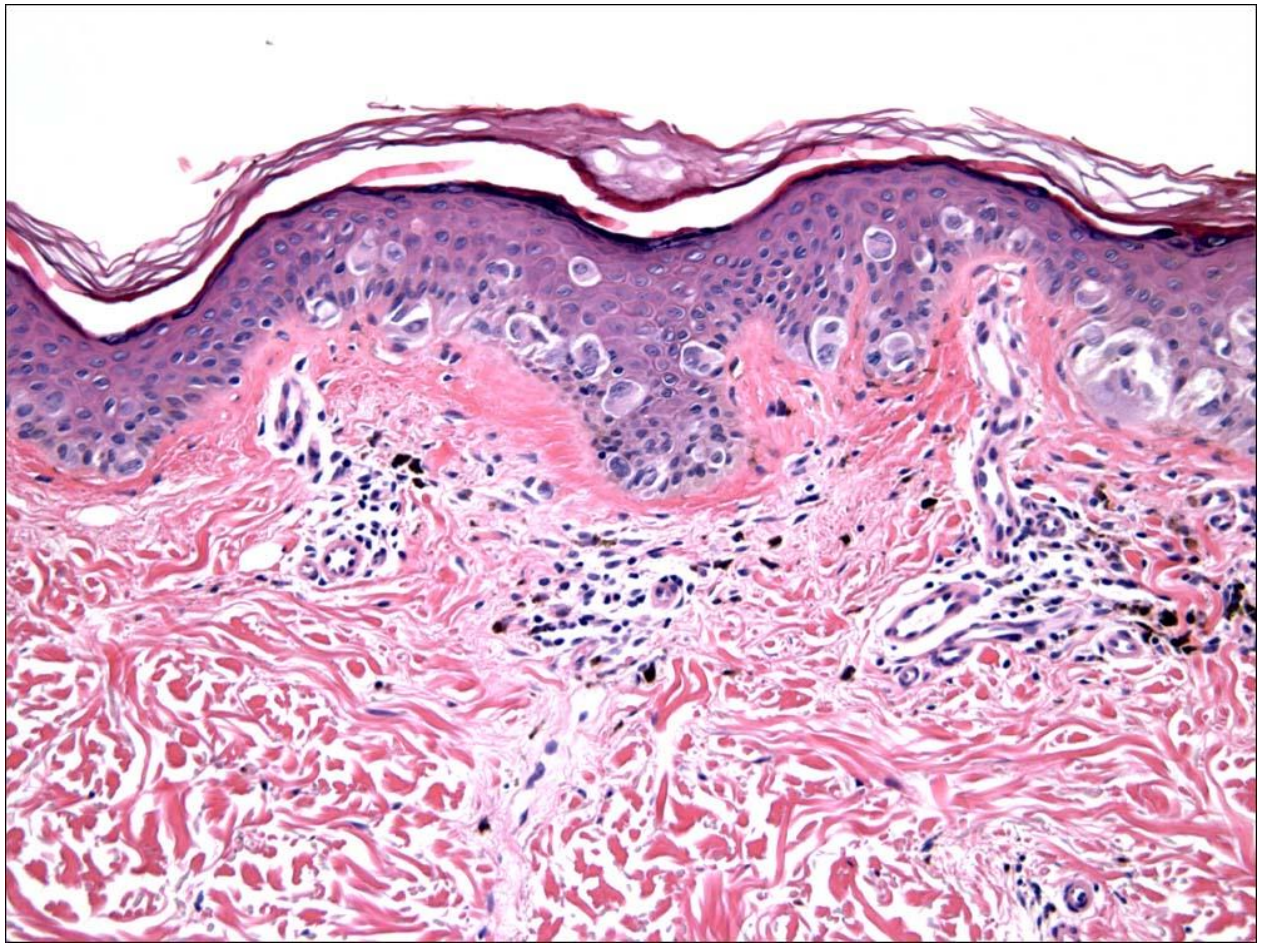

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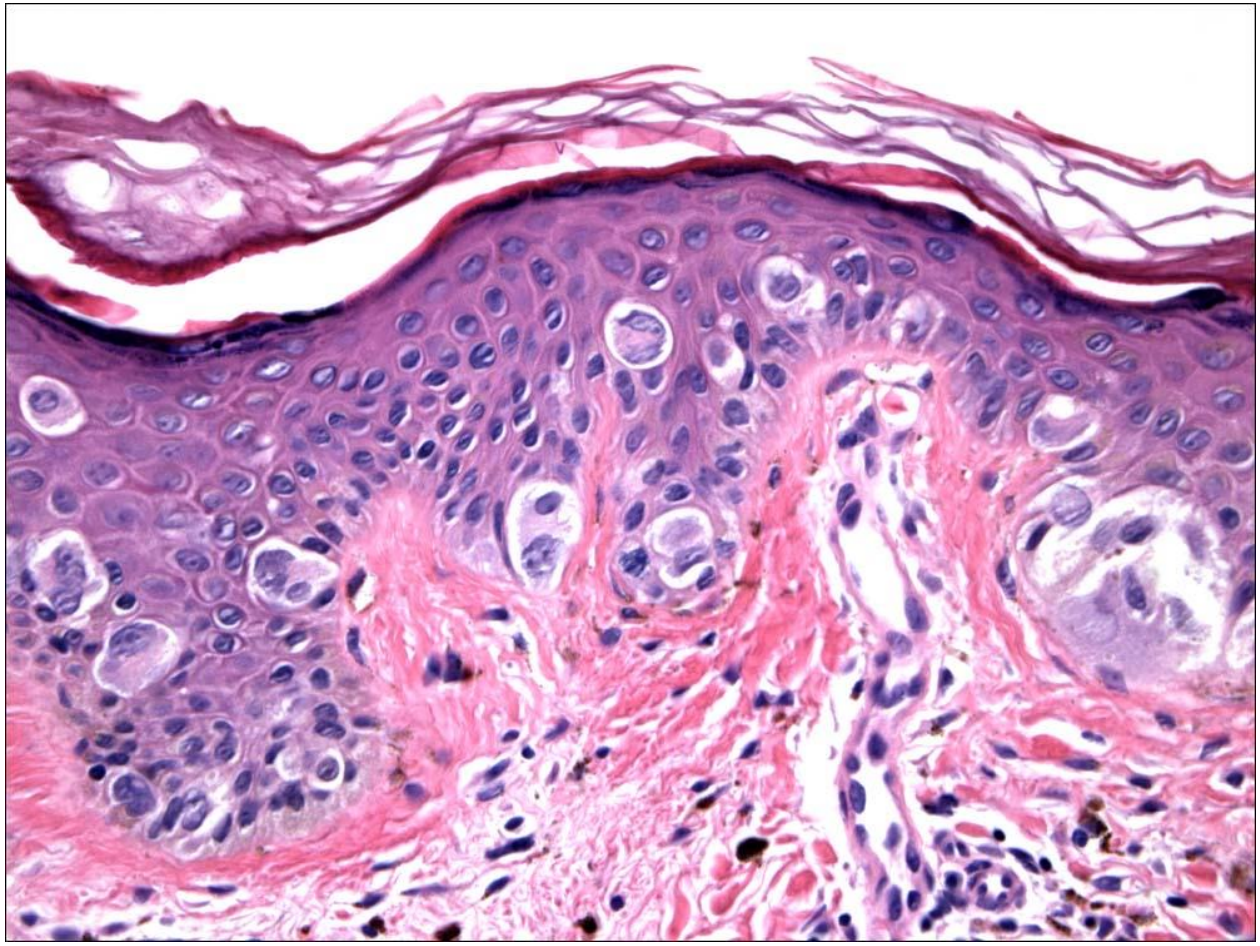
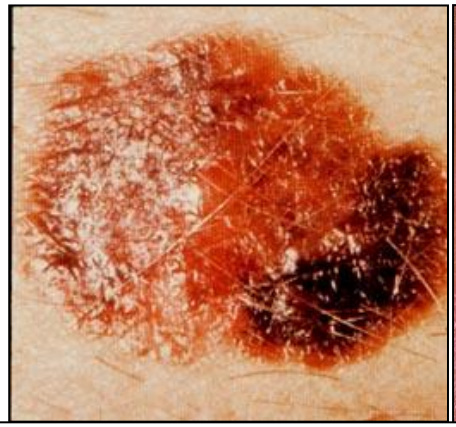
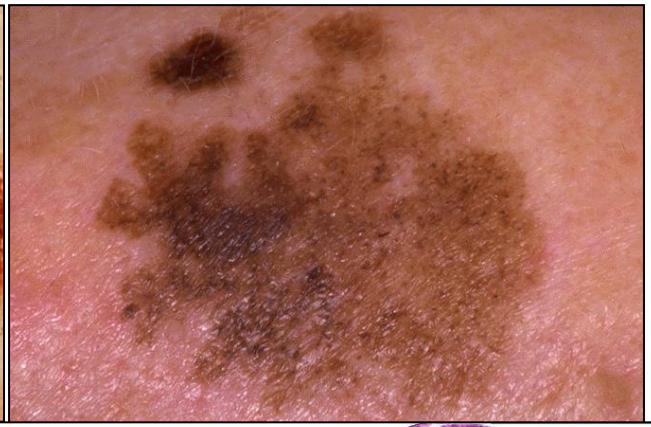


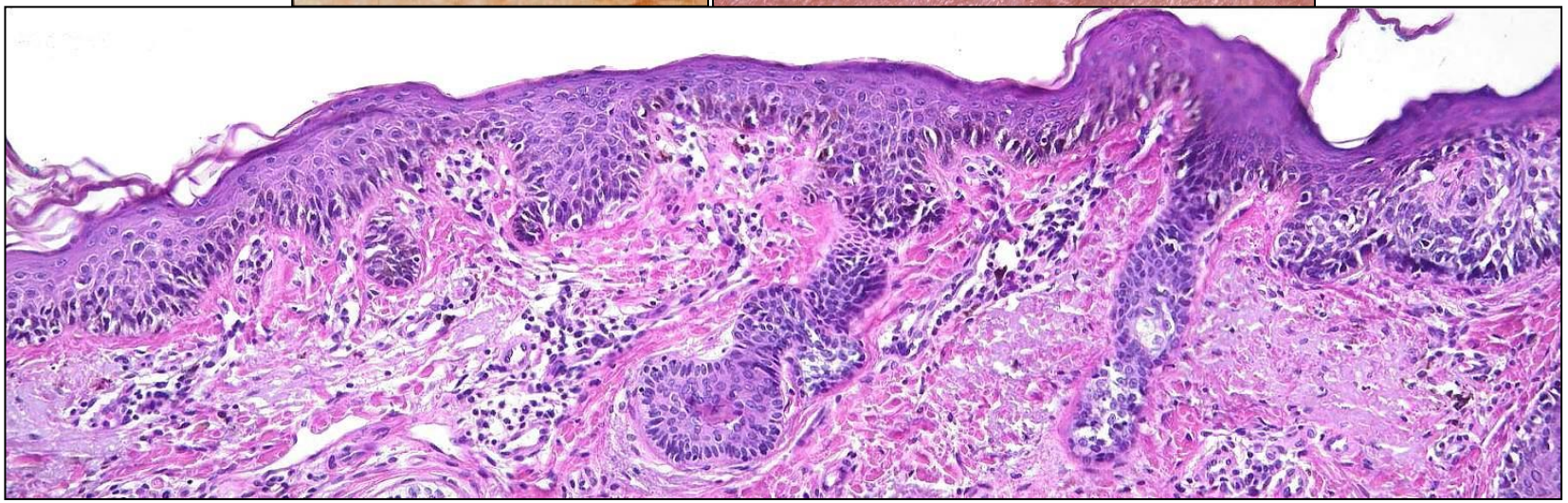
# *De novo* Melanocytic Dysplasia

- **Also known as pagetoid melanocytosis of pagetoid Spitz nevus**
- **Junctional, no tendency to nesting**
- **Epithelioid melanocytes**
- **Not enough atypia for MIS**
- **No dermal changes**

# Lentigo Maligna







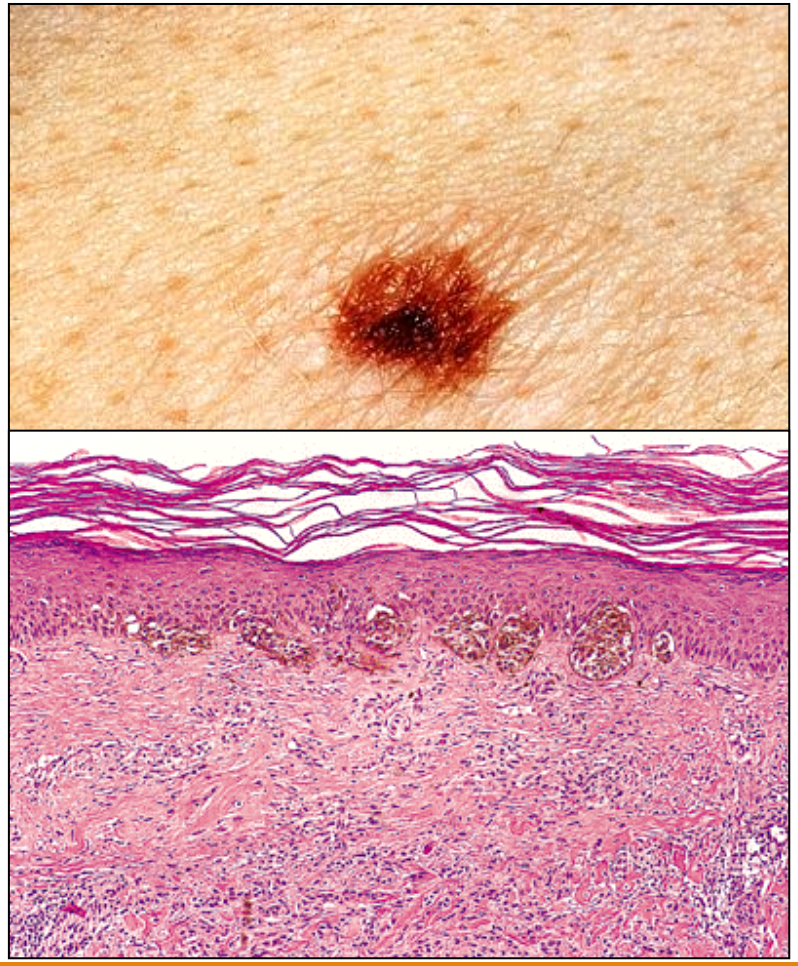
# MELANOCYTIC DYSPLASIA

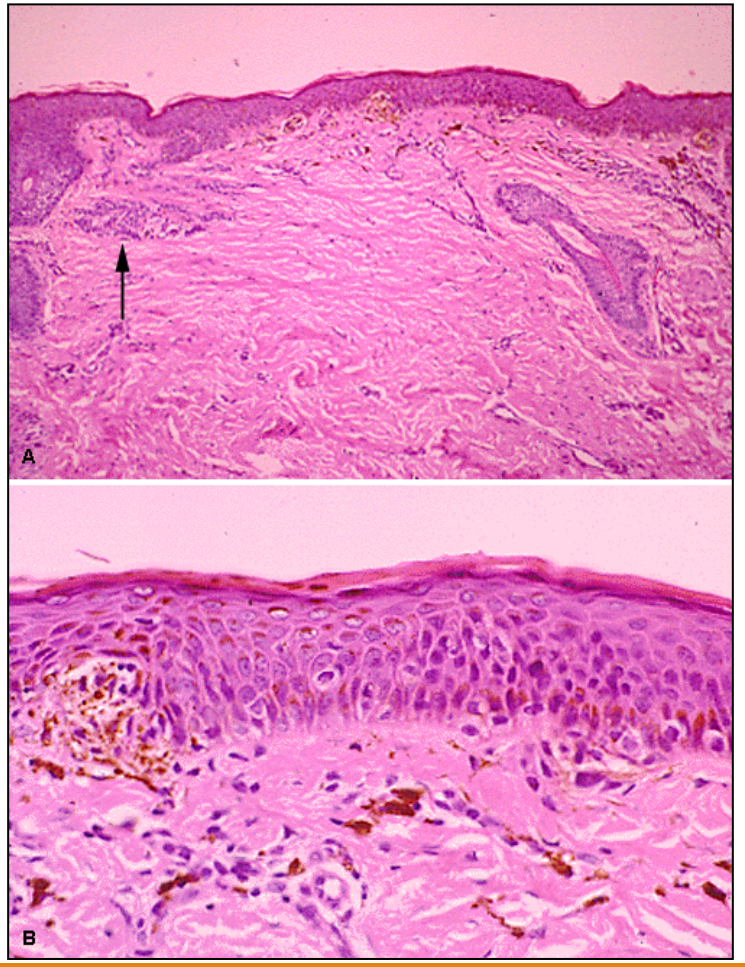
## Differential diagnosis

# Dysplasia and Regression in Melanocytic Lesions

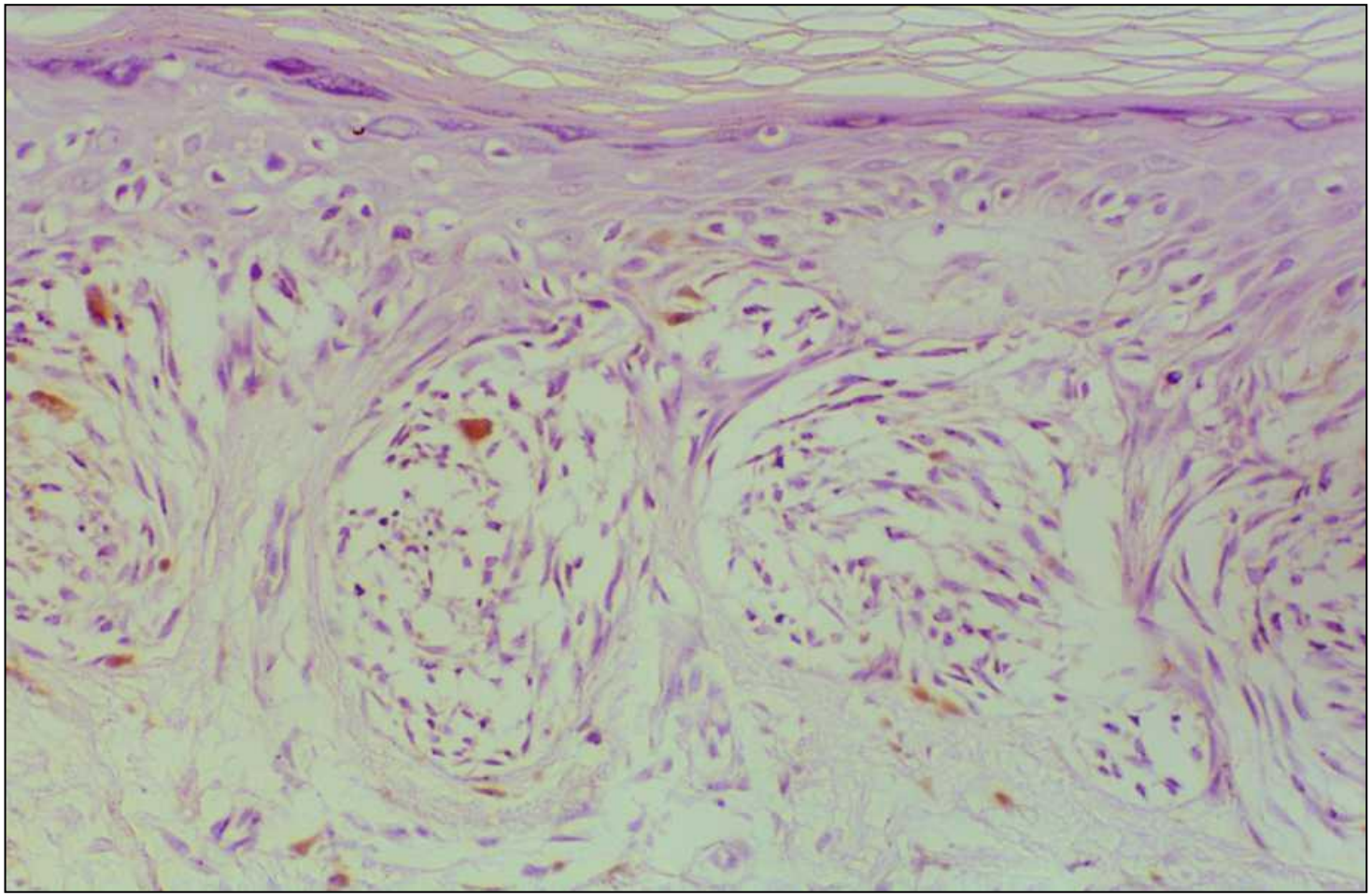
- **Dysplasia *vs*. atypia in melanocytic lesions**
  - **Atypical and non-dysplastic melanocytic lesions**
    - **Recurrent nevus**
    - **Nevus with architectural disorder**
    - **Genital skin nevus**
    - **Acral type nevus**
    - **Spitz tumor**
- **Regression and atypia in melanocytic lesions. What is first?**

# Recurrent Melanocytic Nevus

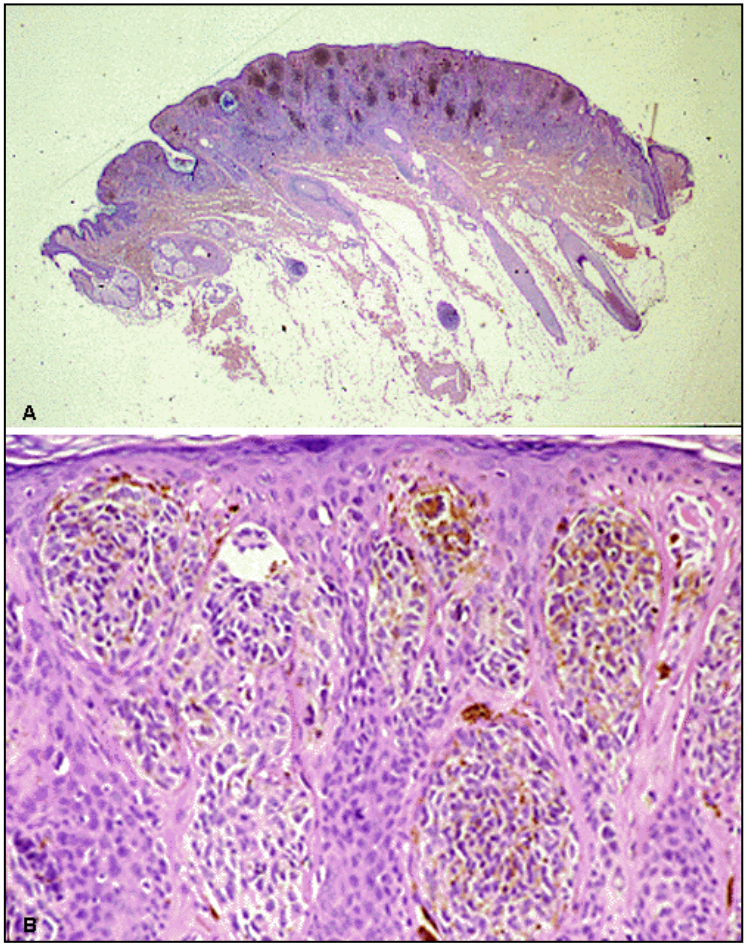




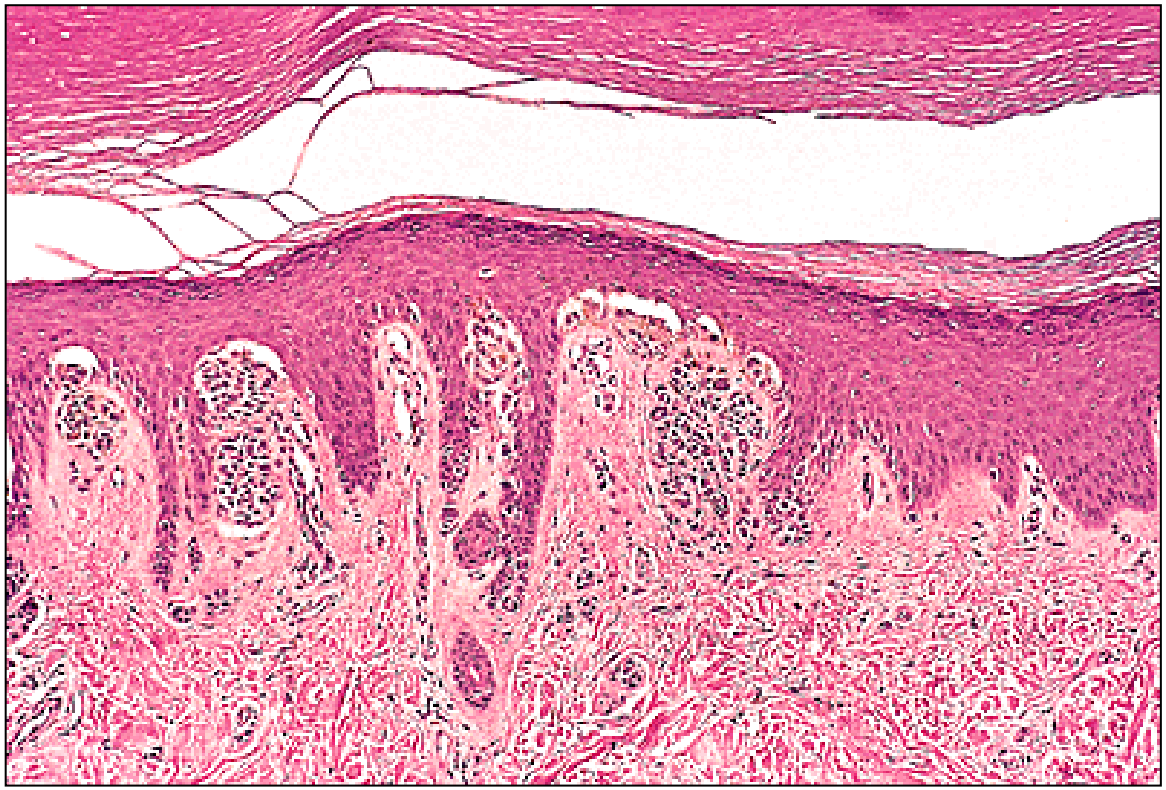
# Melanocytic Nevus with Architectural Disorder ONLY



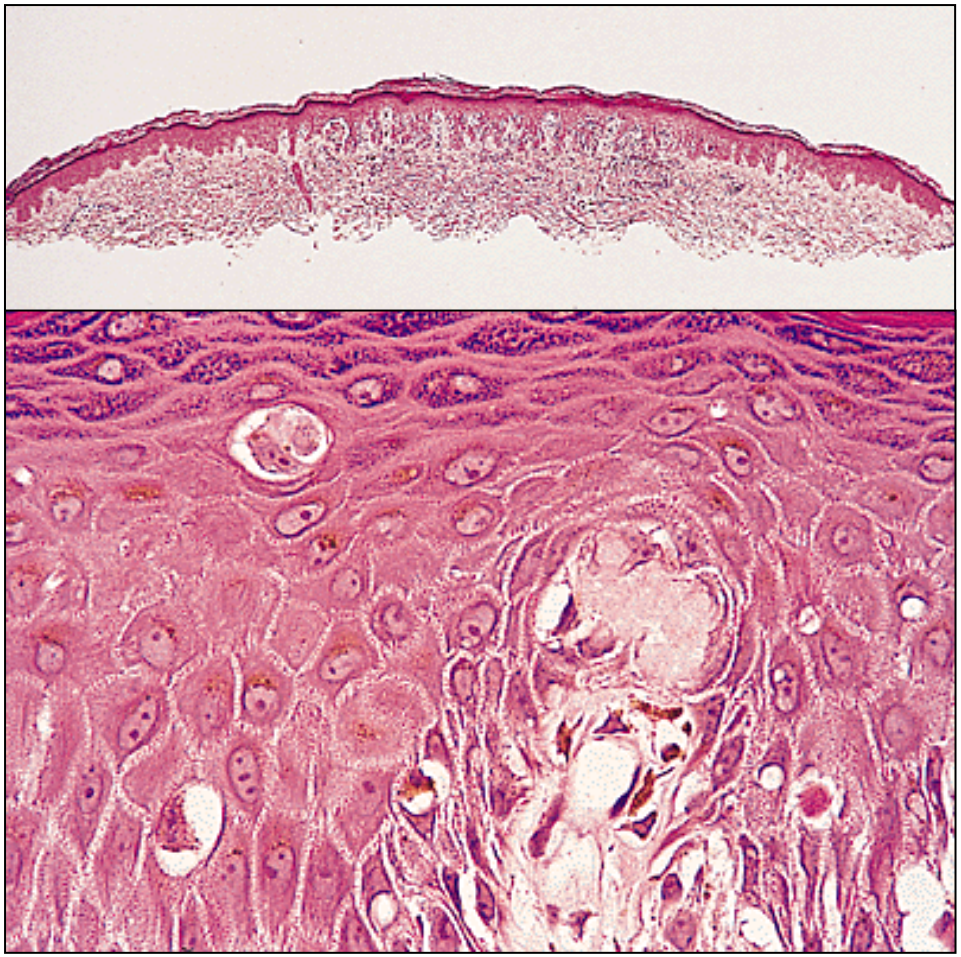
# Melanocytic Nevus, Genital Skin

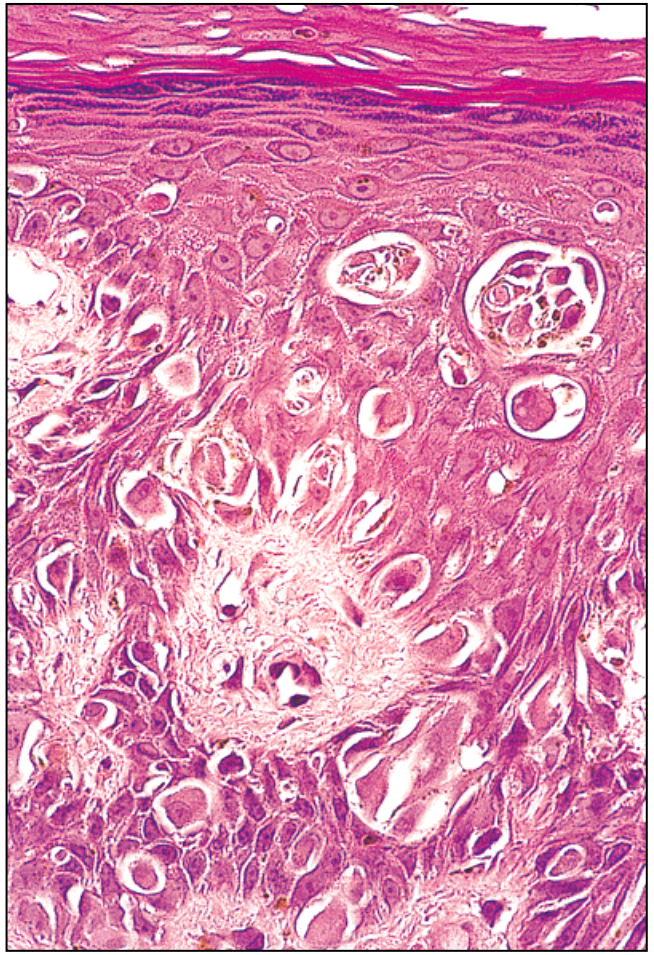


# Melanocytic Nevus, Acral Type

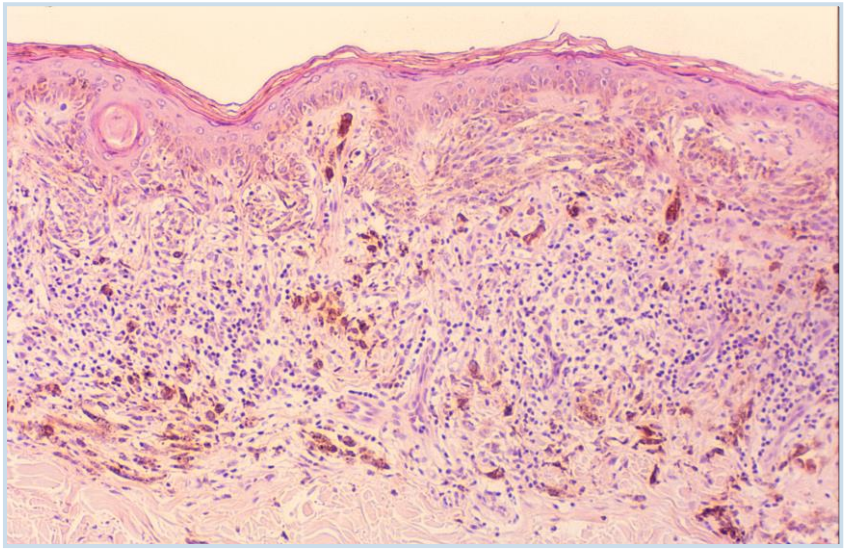


# Spitz Tumor

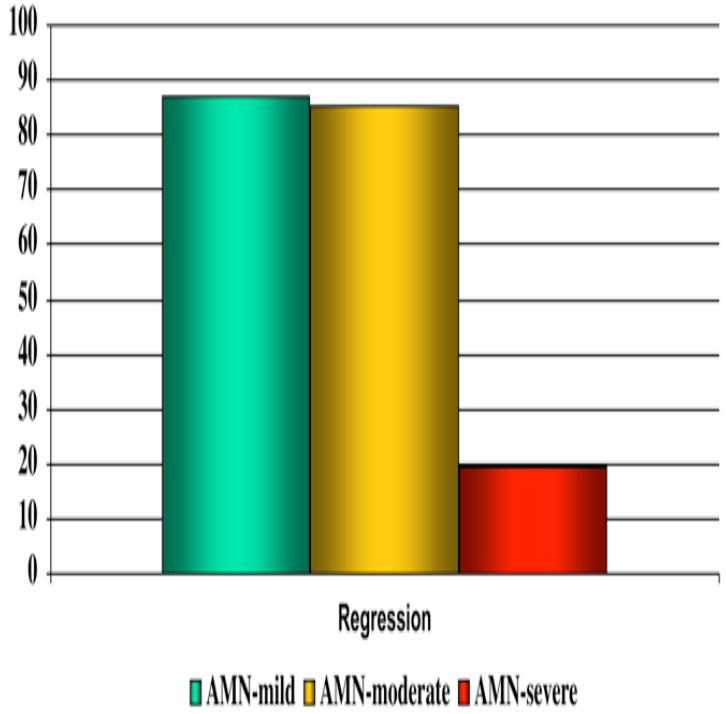




# Melanocyte Dysplasia in the Presence of Regression



- Melanocyte dropout with melanophages
- Prominent vascular reaction
- Fibrosis
- Lymphocyte infiltrate



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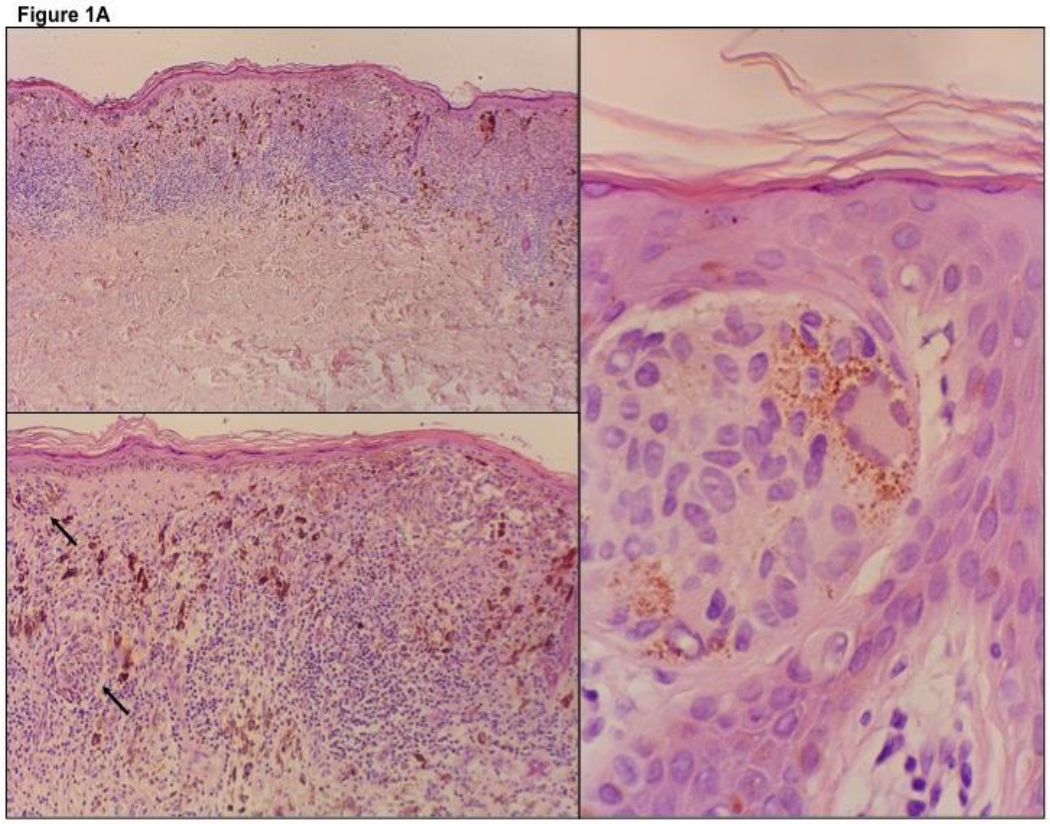
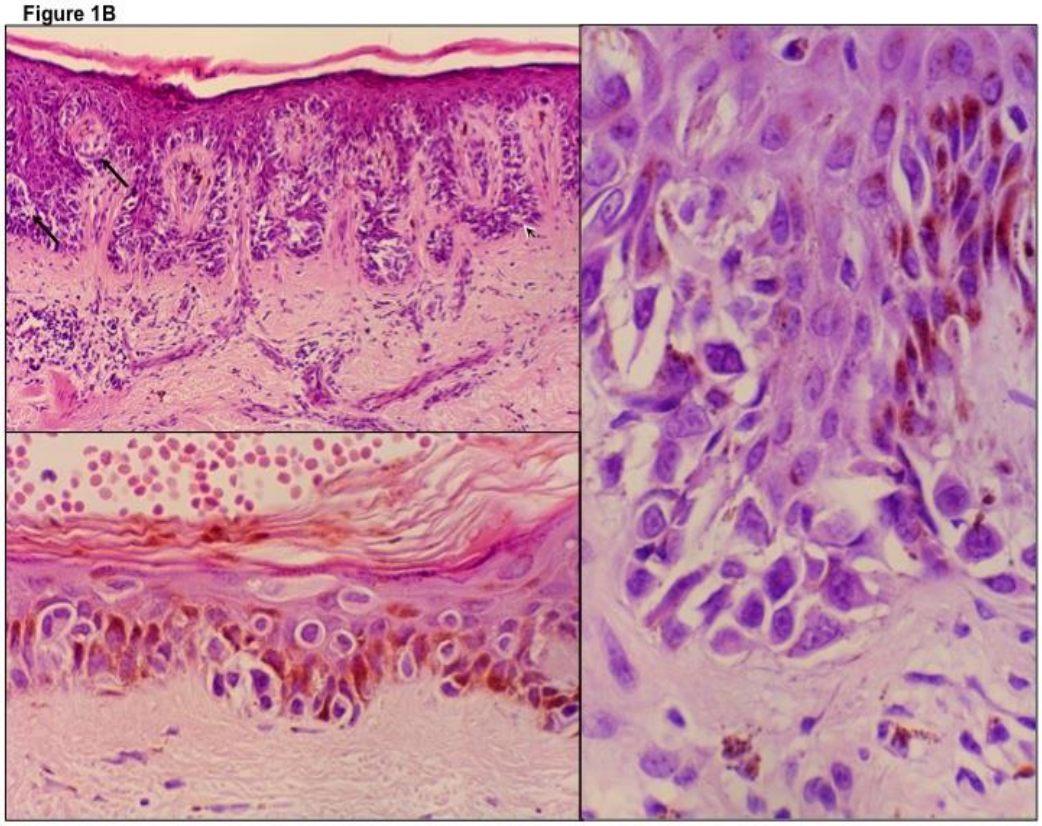



Pozo et al. Histopathology 2008, 52, 387–411

# Melanocyte Dysplasia in the Presence of Regression

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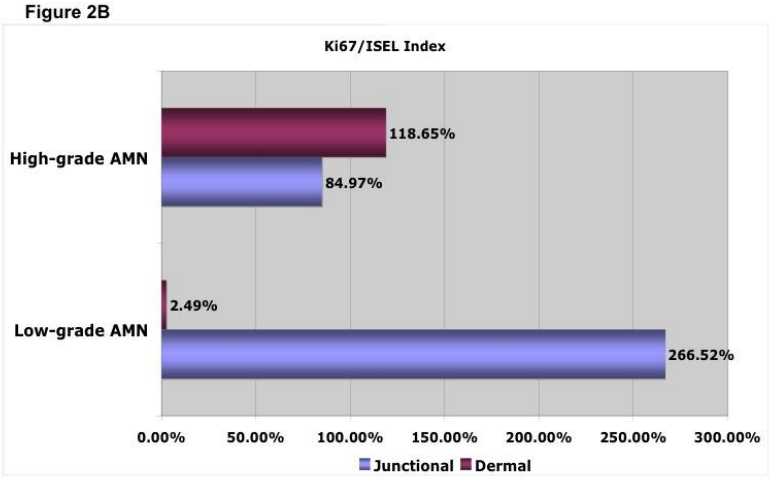
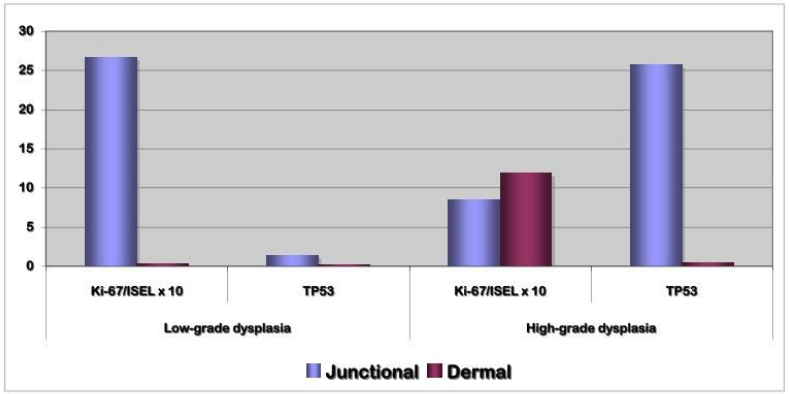
# Melanocyte Dysplasia in the Presence of Regression

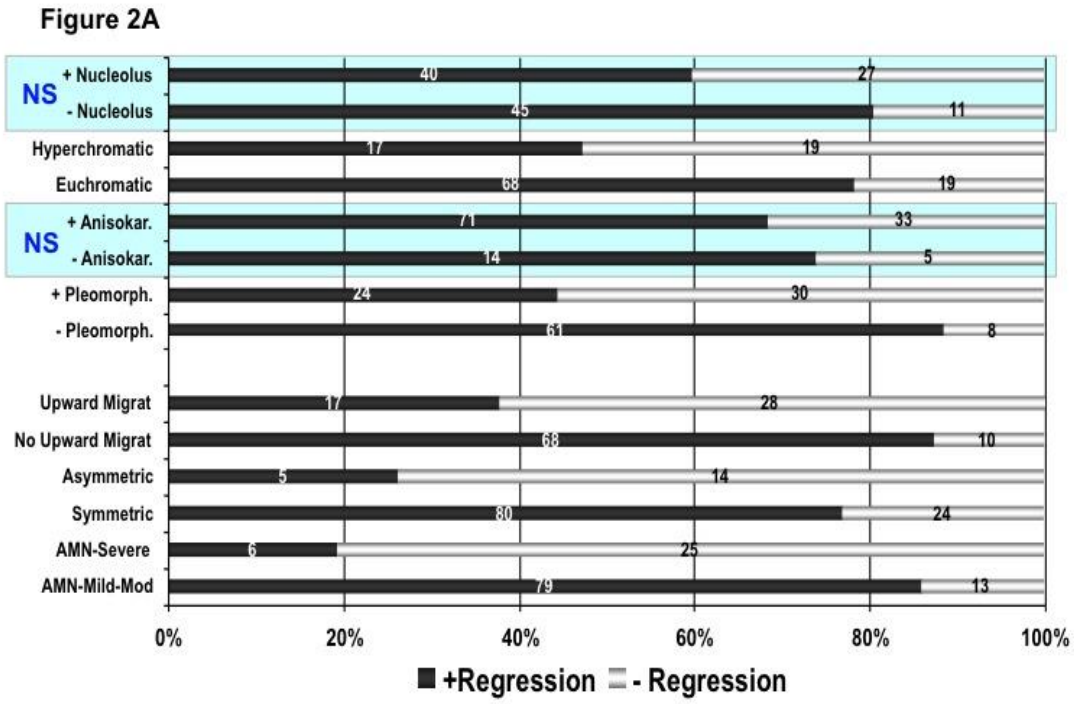
Pozo et al. Histopathology 2008; 52: 387–411




Diaz-Cano. N Engl J Med 2006; 355(13):1395

# Melanocyte Dysplasia in the Presence of Regression




Pozo et al. Histopathology 2008, 52, 387–411

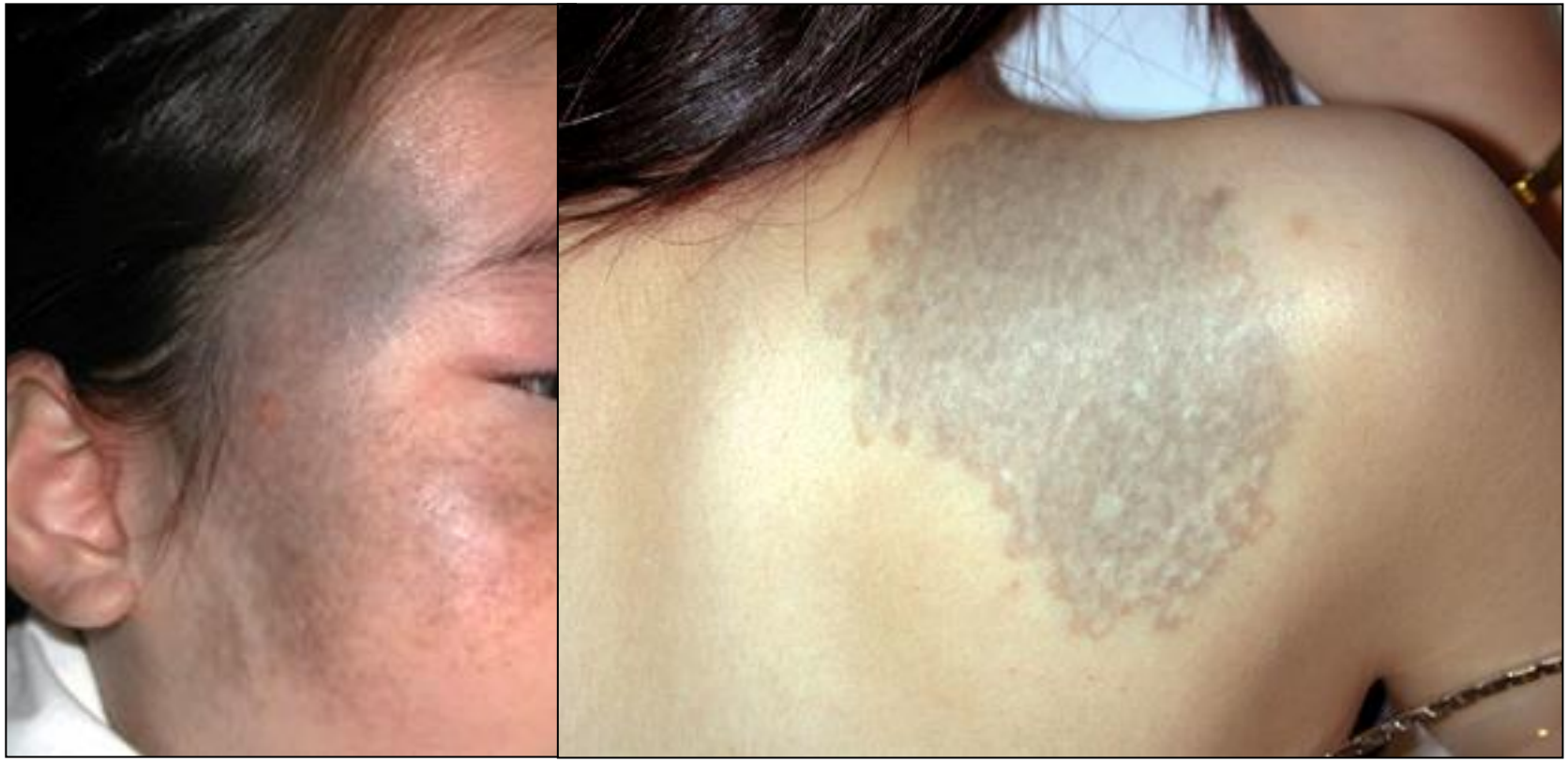
# It is NOT melanocytic dysplasia

**Atypical changes in primarily dermal melanocytic lesions**

- **Dermal melanocytosis**
- **Epithelioid blue nevus**
- **Neurocristic hamartoma**
- **Congenital melanocytic nevus**

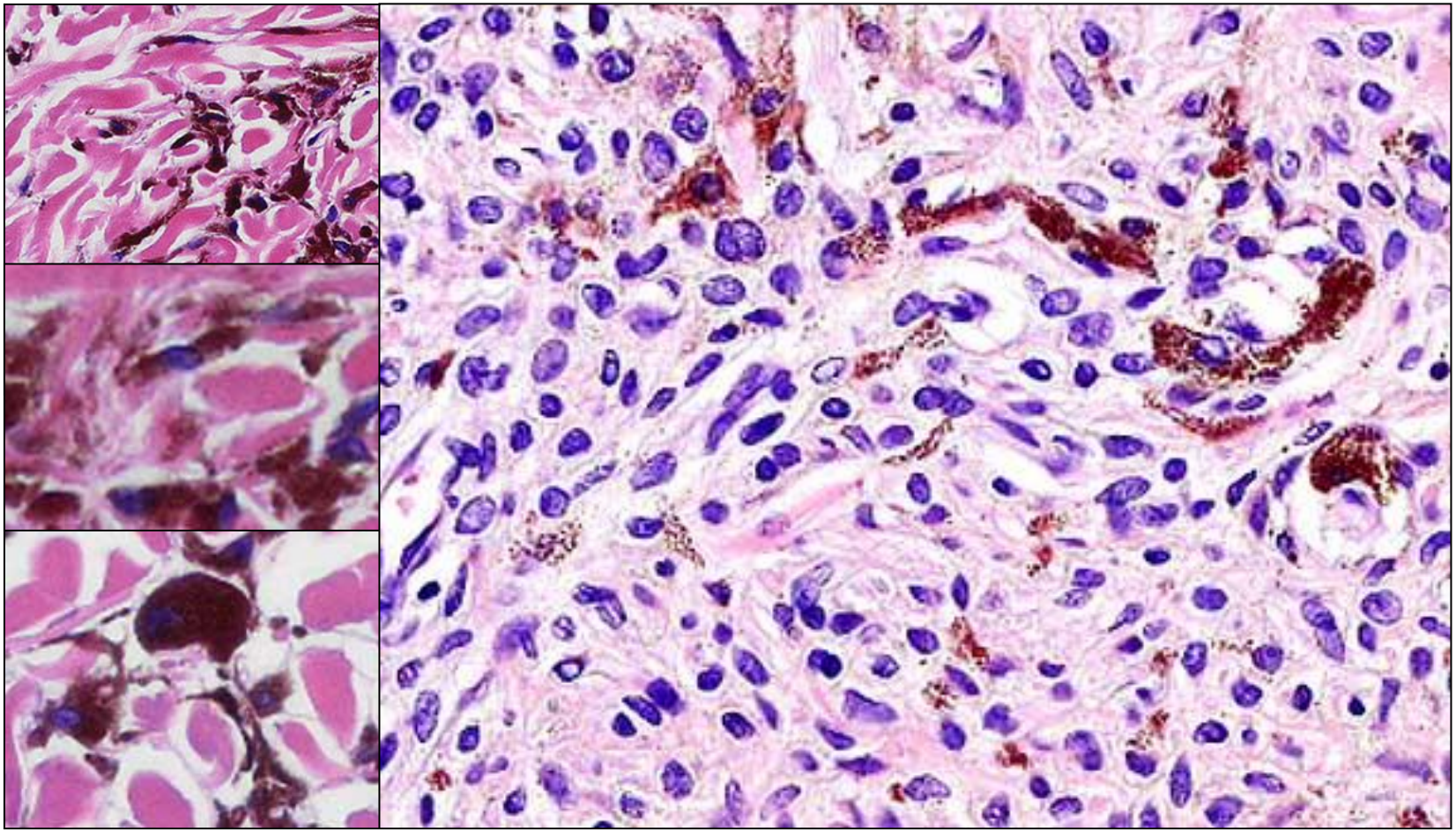
**Must be distinguished from malignancy!**

# Dermal Melanocytosis

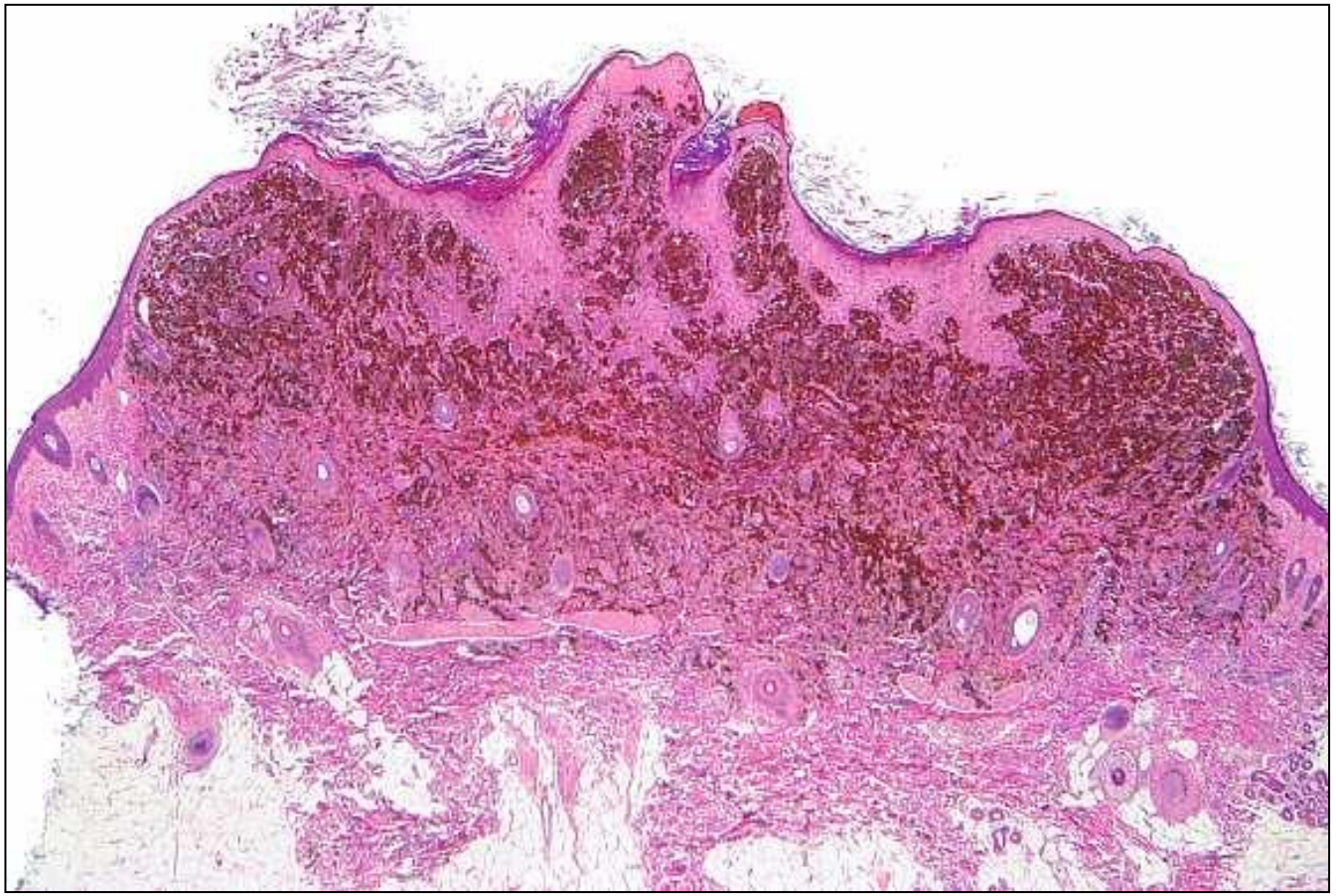


# Dermal Melanocytosis

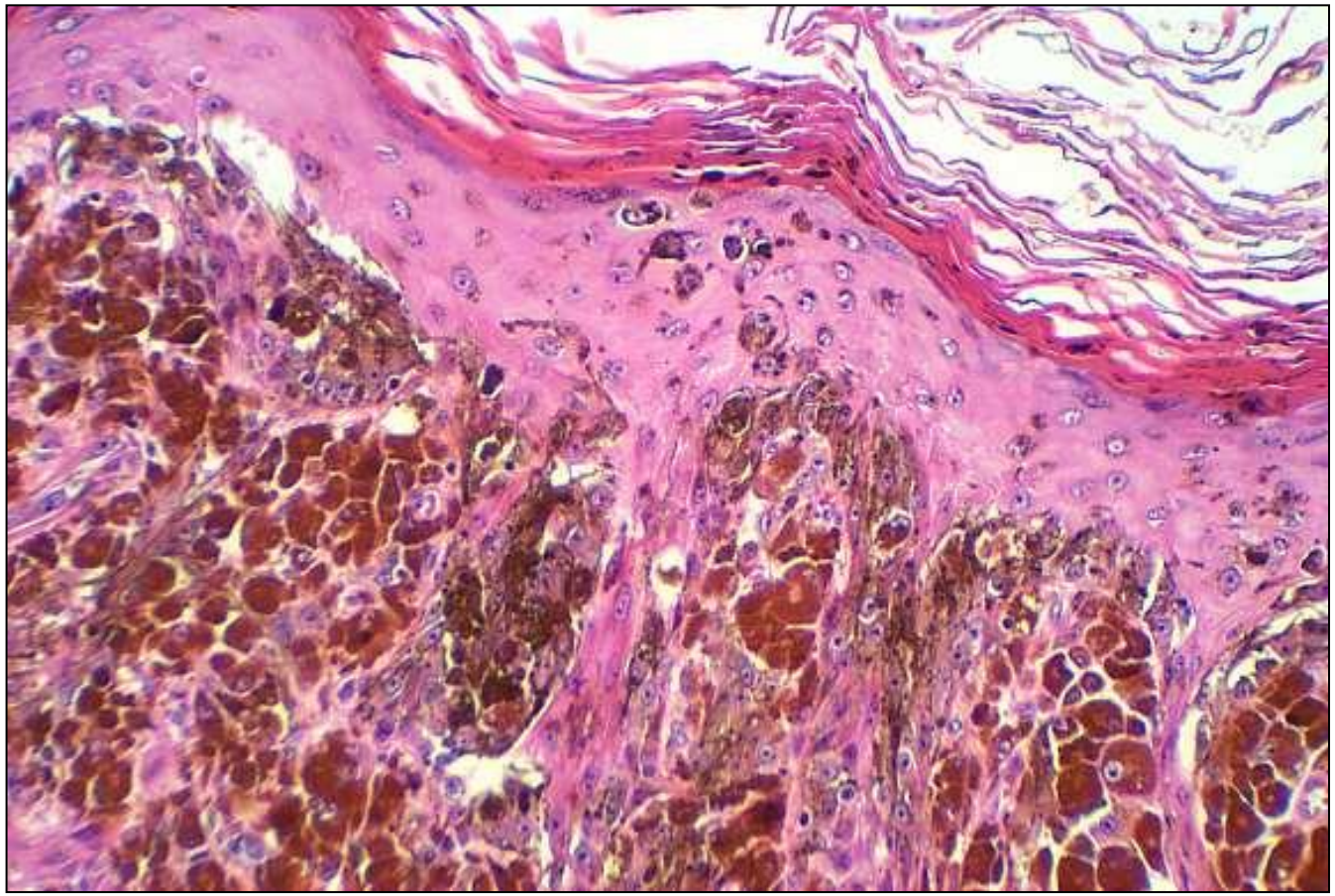
# Blue Nevus



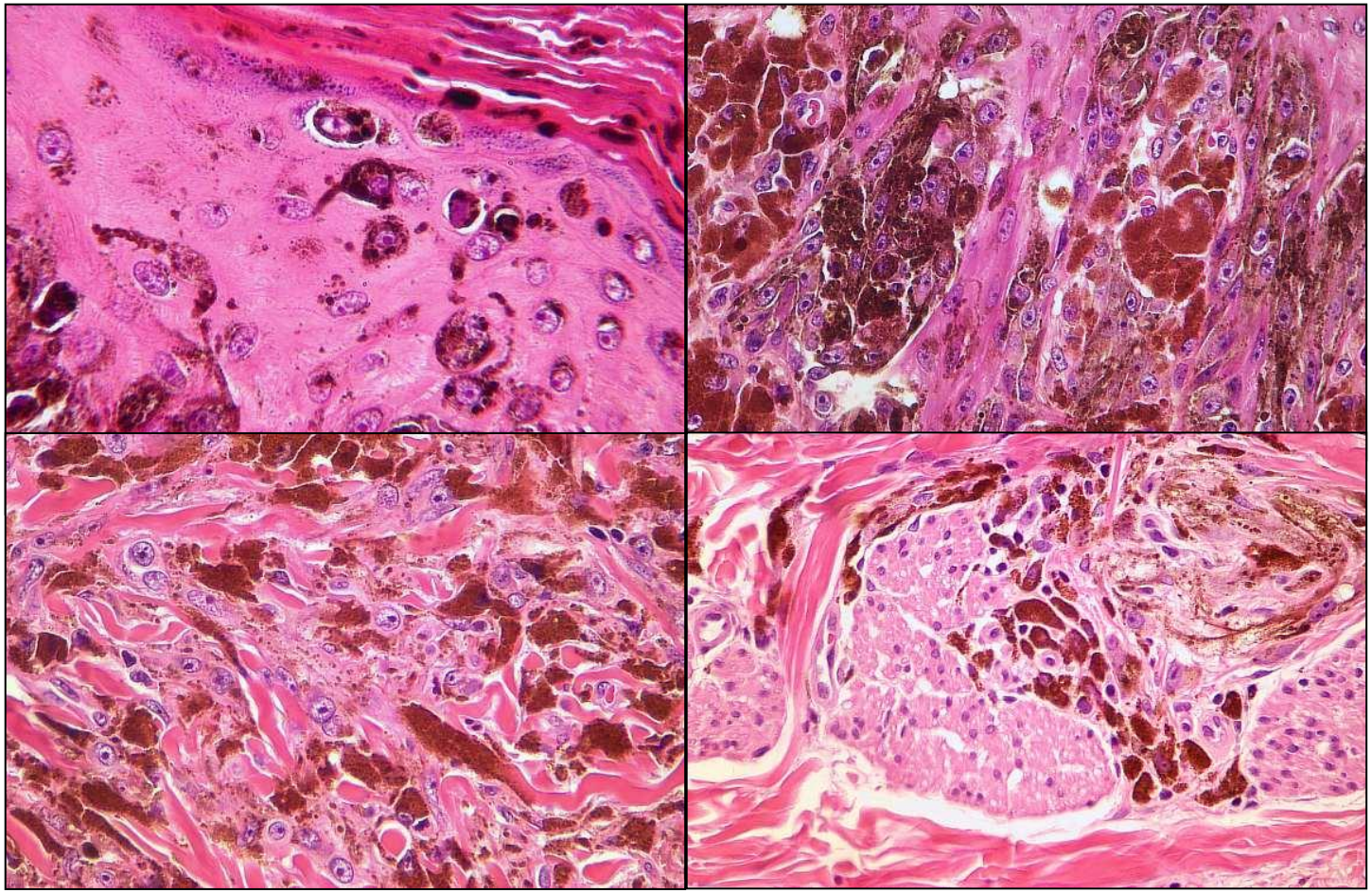
# Epithelioid Blue Nevus



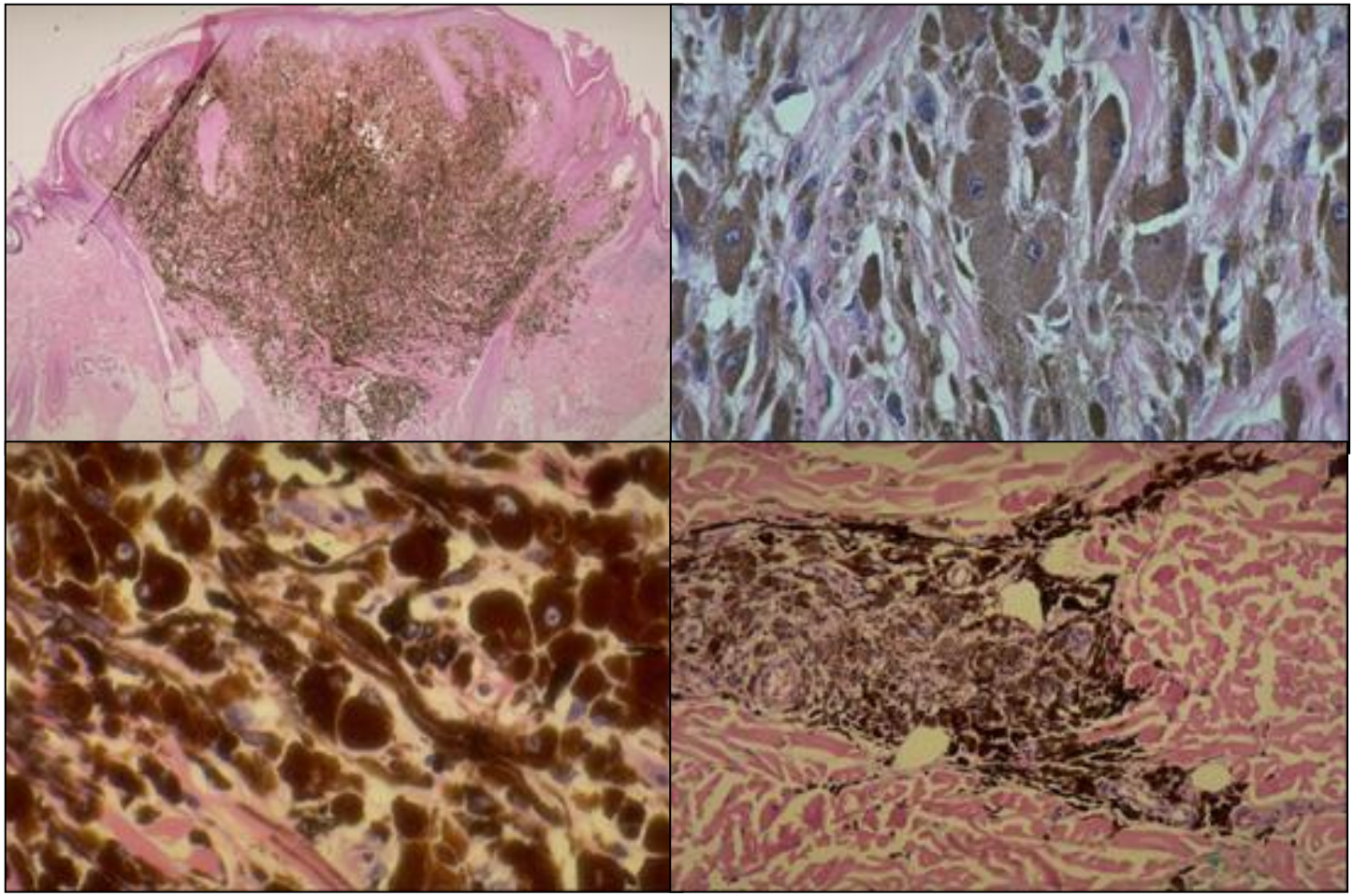
# Epithelioid Blue Nevus



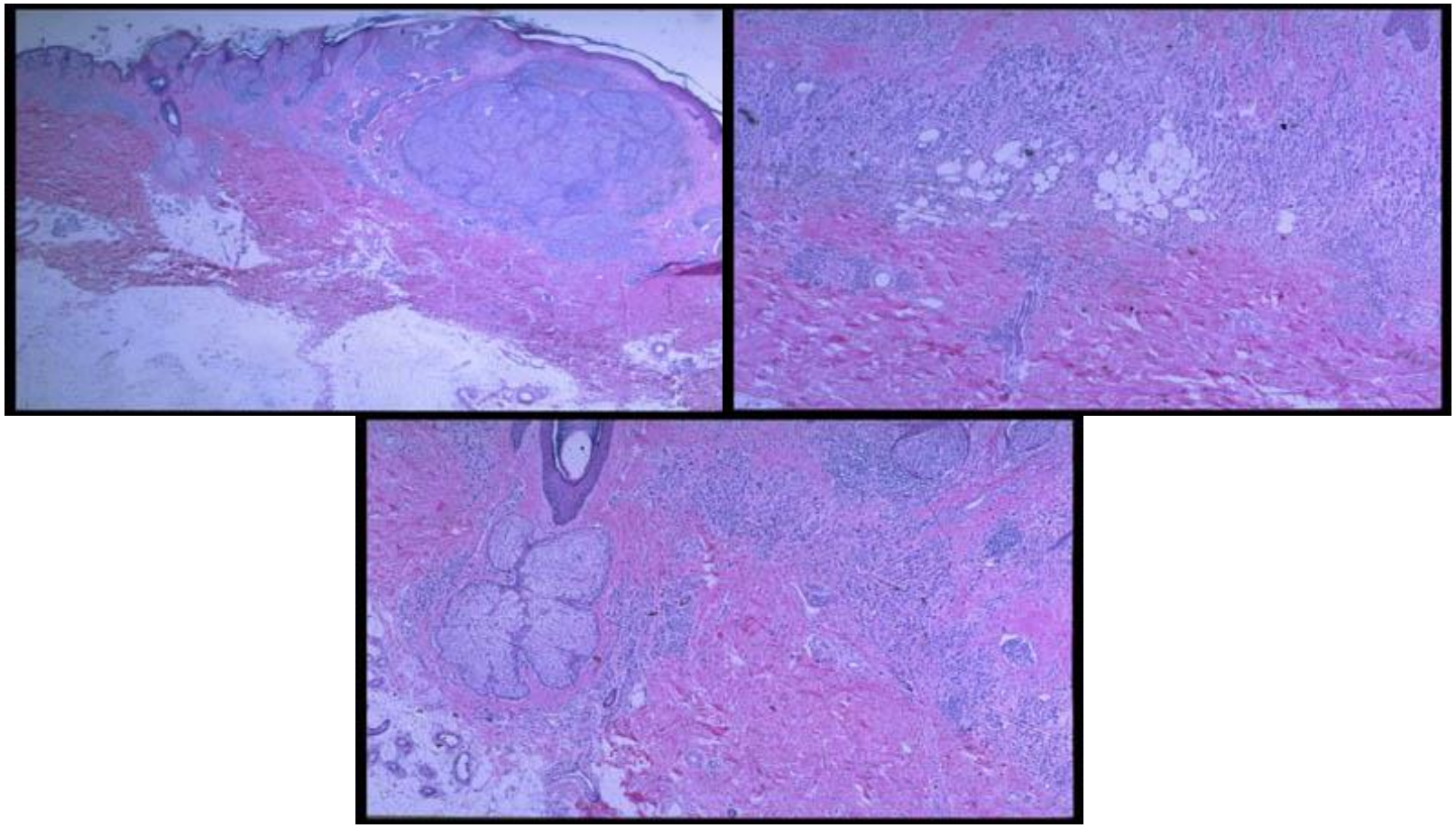
# Epithelioid Blue Nevus



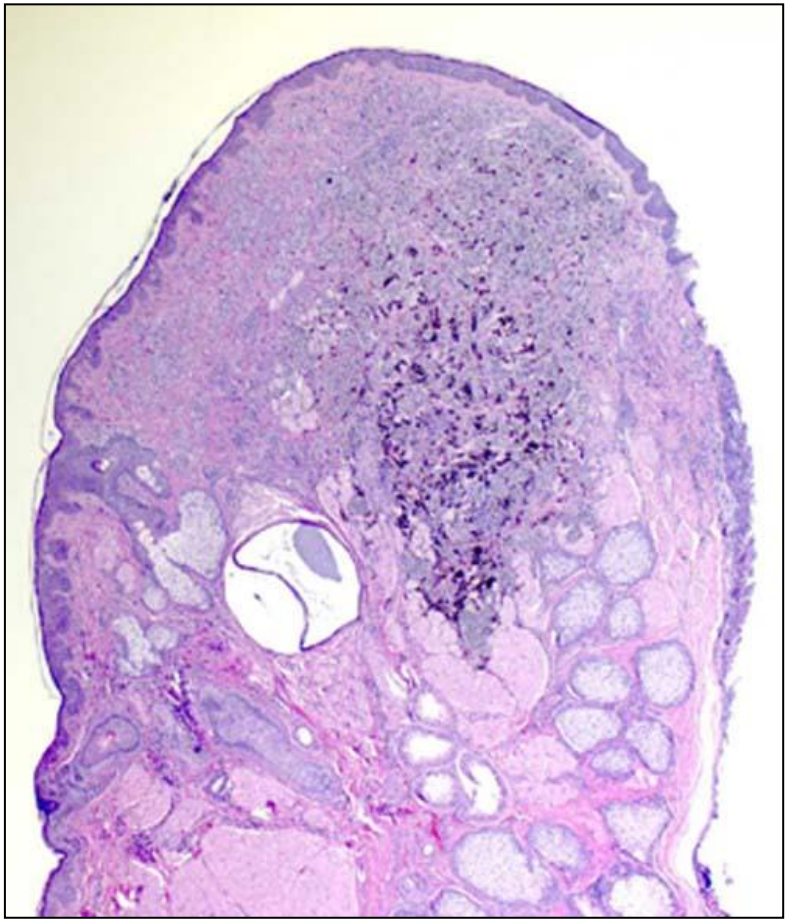
# Neurocrist Hamartoma

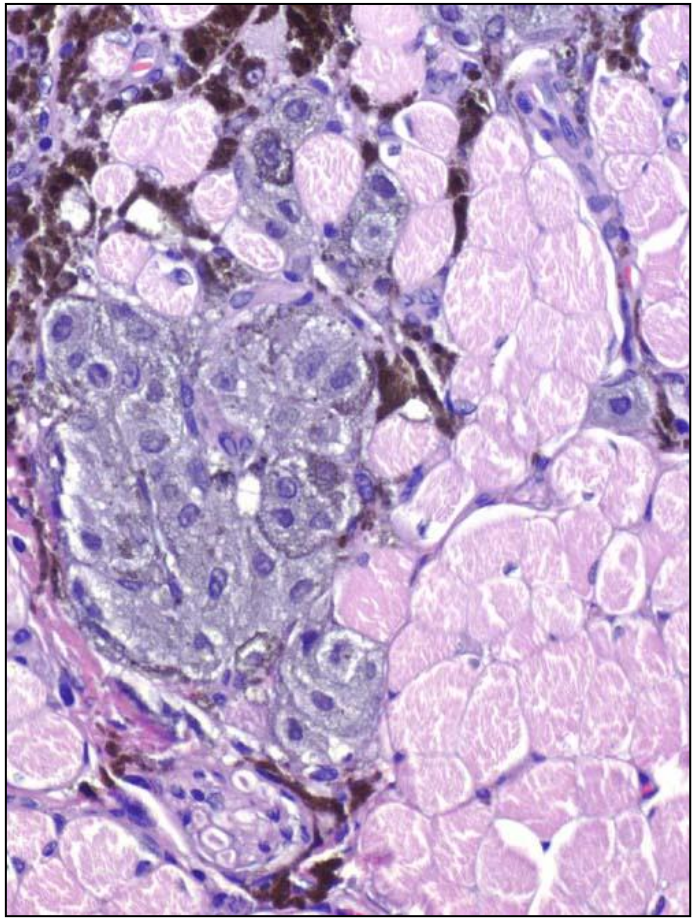


# Congenital Melanocytic Nevus



# Inverted Type A Melanocytic Nevus





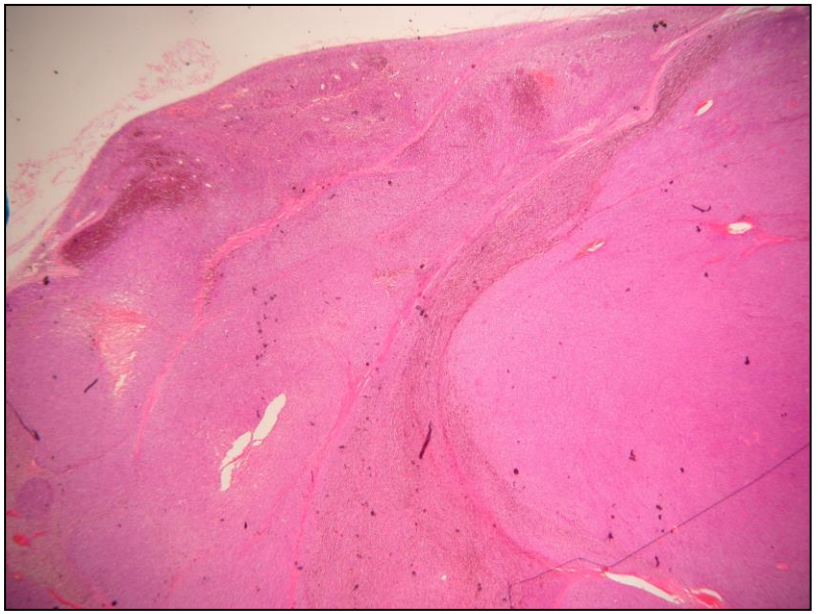
# Malignancy Criteria in Dermal Melanocytic Lesions

**Solid growth with tissue destruction**

**“Spontaneous” tumor cell necrosis**

**Cellular atypia**

**Mitotic figures (±atypical mitosis)**



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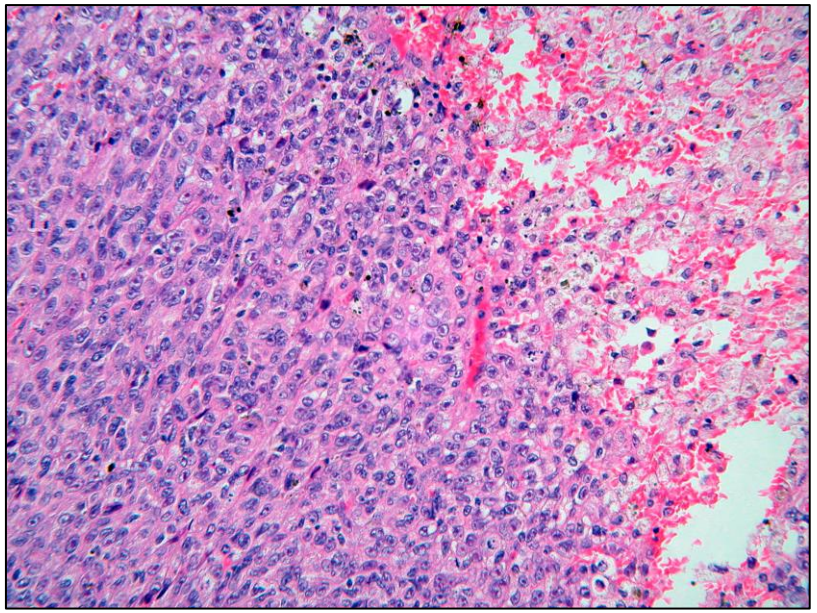

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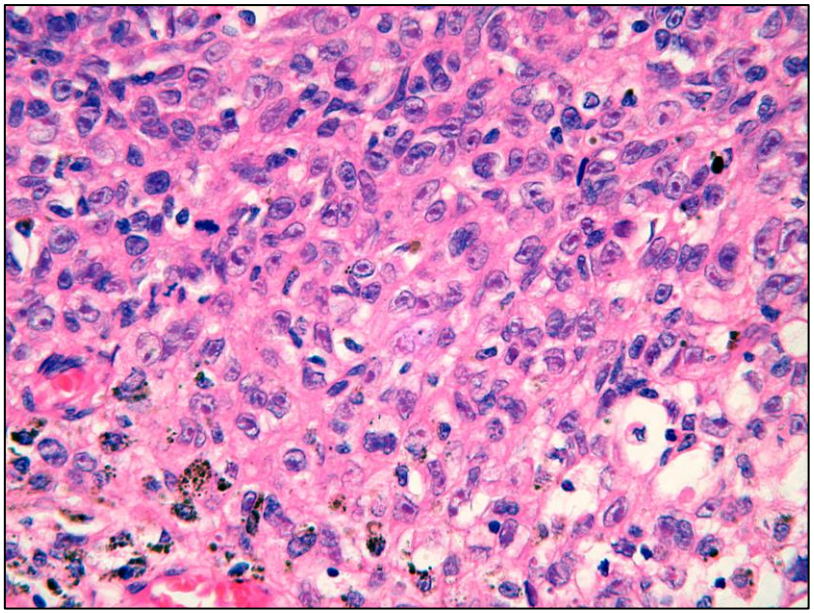

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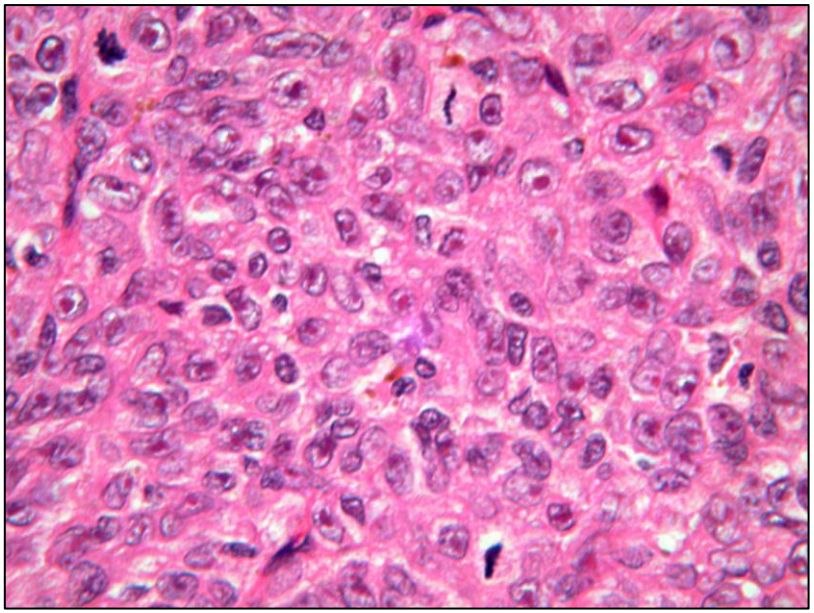


# MELANOCYTIC DYSPLASIA

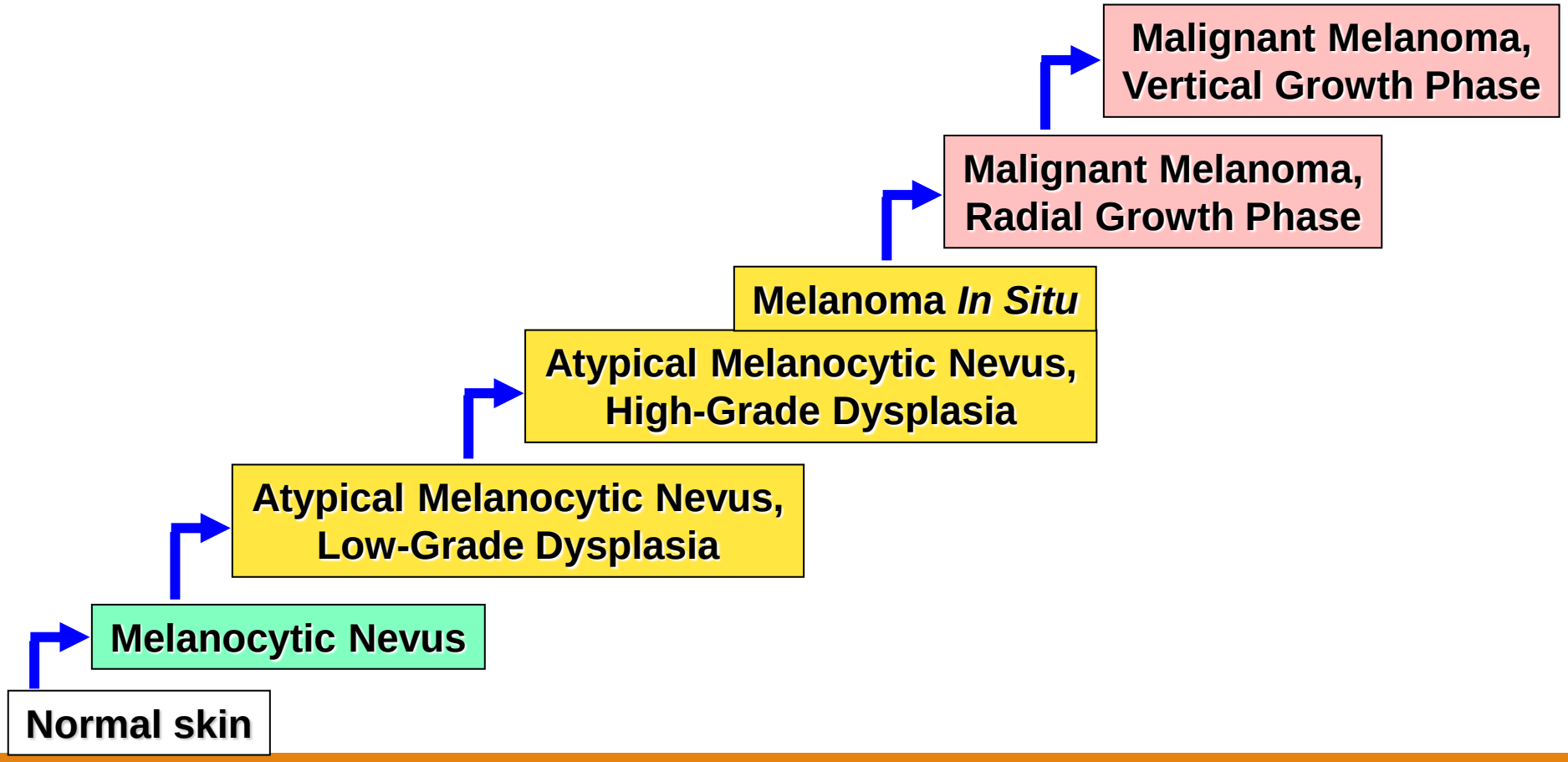
**Is melanocytic dysplasia a progressive lesion?**

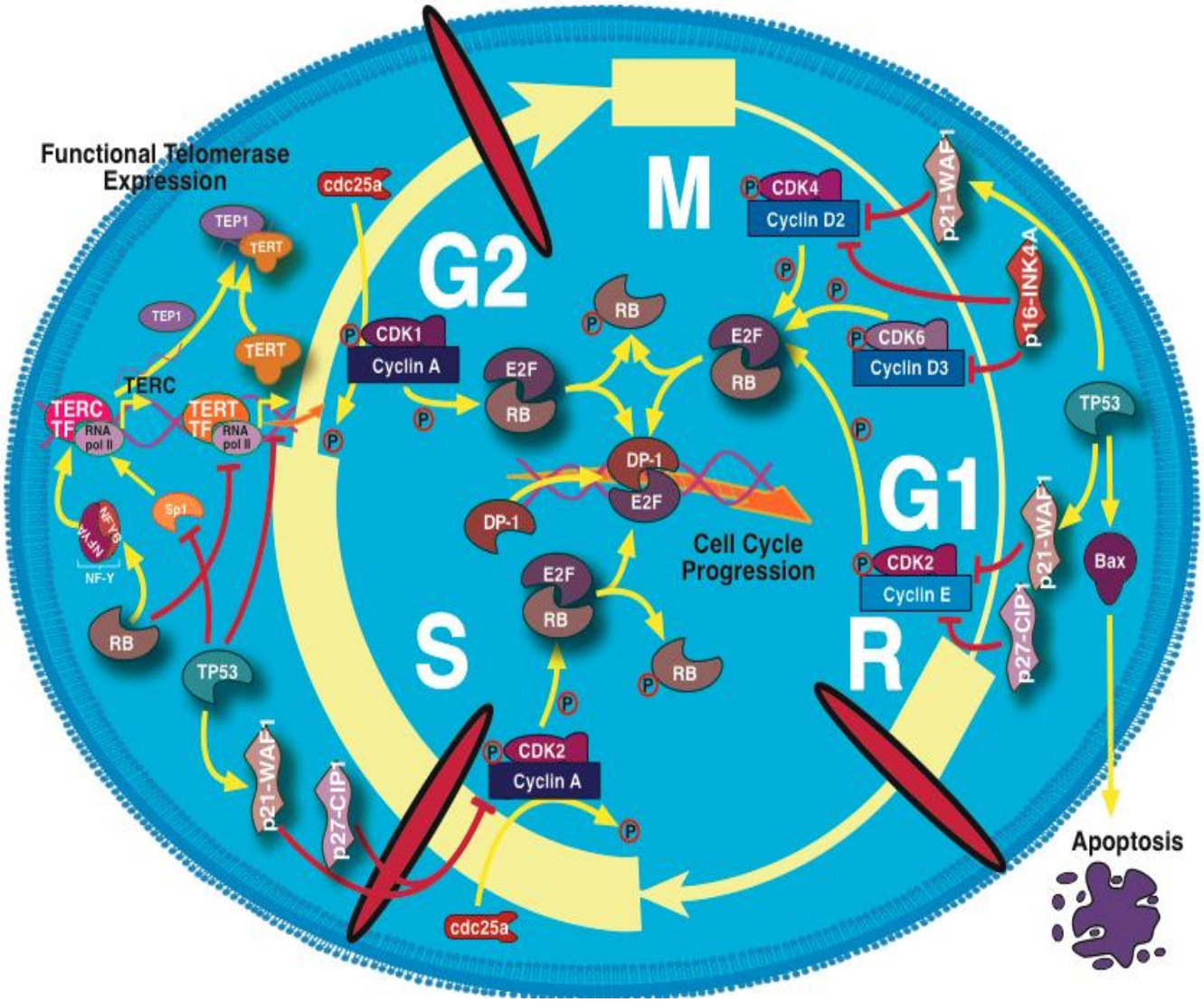
# Progression

## Dual concept

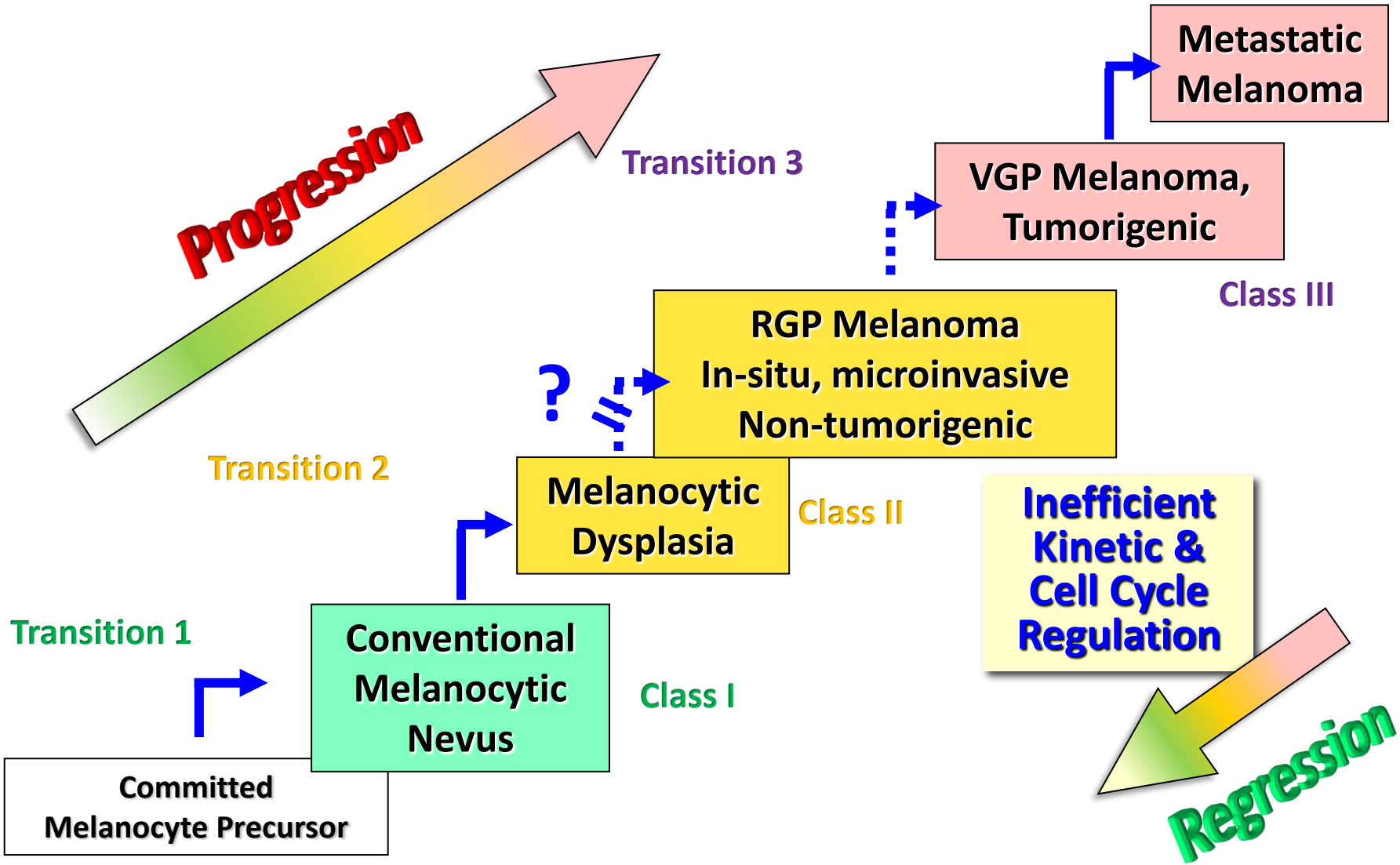
- **Intraepithelial lesions**: Acquisition of invasive potential by tumor cells
- **Invasive lesions**: Additional genetic alterations providing metastatizing capabilities to a tumor cell subpopulation

# Linear Progression in Melanocytic Lesions

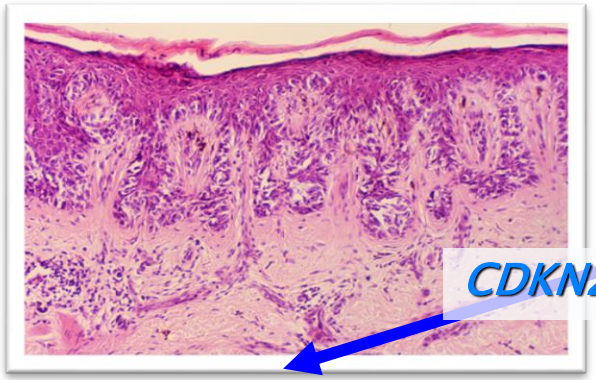



Functional Telomerase Expression
TEP1
TERT
TEP1
TERT
TERC
TERC TF
RNA pol II
TERT TF
RNA pol II
Sp1
NF-Y
RB
TP53
p21-WAF1
p27-CIP1
cdc25a
G2
CDK1
Cyclin A
E2F
RB
P
RB
E2F
RB
M
CDK4
Cyclin D2
p21-WAF1
p16-INK4A
CDK6
Cyclin D3
TP53
DP-1
E2F
DP-1
Cell Cycle Progression
G1
CDK2
Cyclin E
p21-WAF1
Bax
p27-CIP1
E2F
RB
S
RB
R
CDK2
Cyclin A
cdc25a
Apoptosis

# Challenging the Linear Model

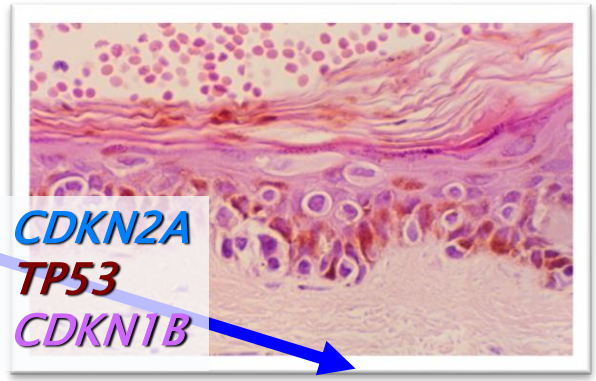


# Progression Model in AMN



*CDKN2A*

Normal skin



*CDKN2A*
*TP53*
*CDKN1B*

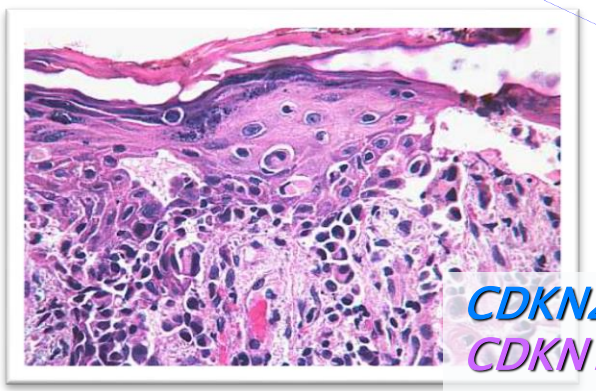
Melanocytic Nevus

Atypical Melanocytic Nevus, Low-Grade Dysplasia

Melanocytic Dysplasia – High Grade
Melanoma *In-Situ*

Microinvasive RGP Melanoma

Class I

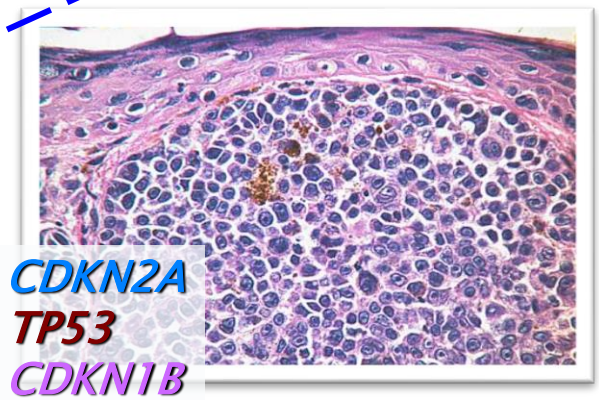


*CDKN2A*
*CDKN1B*

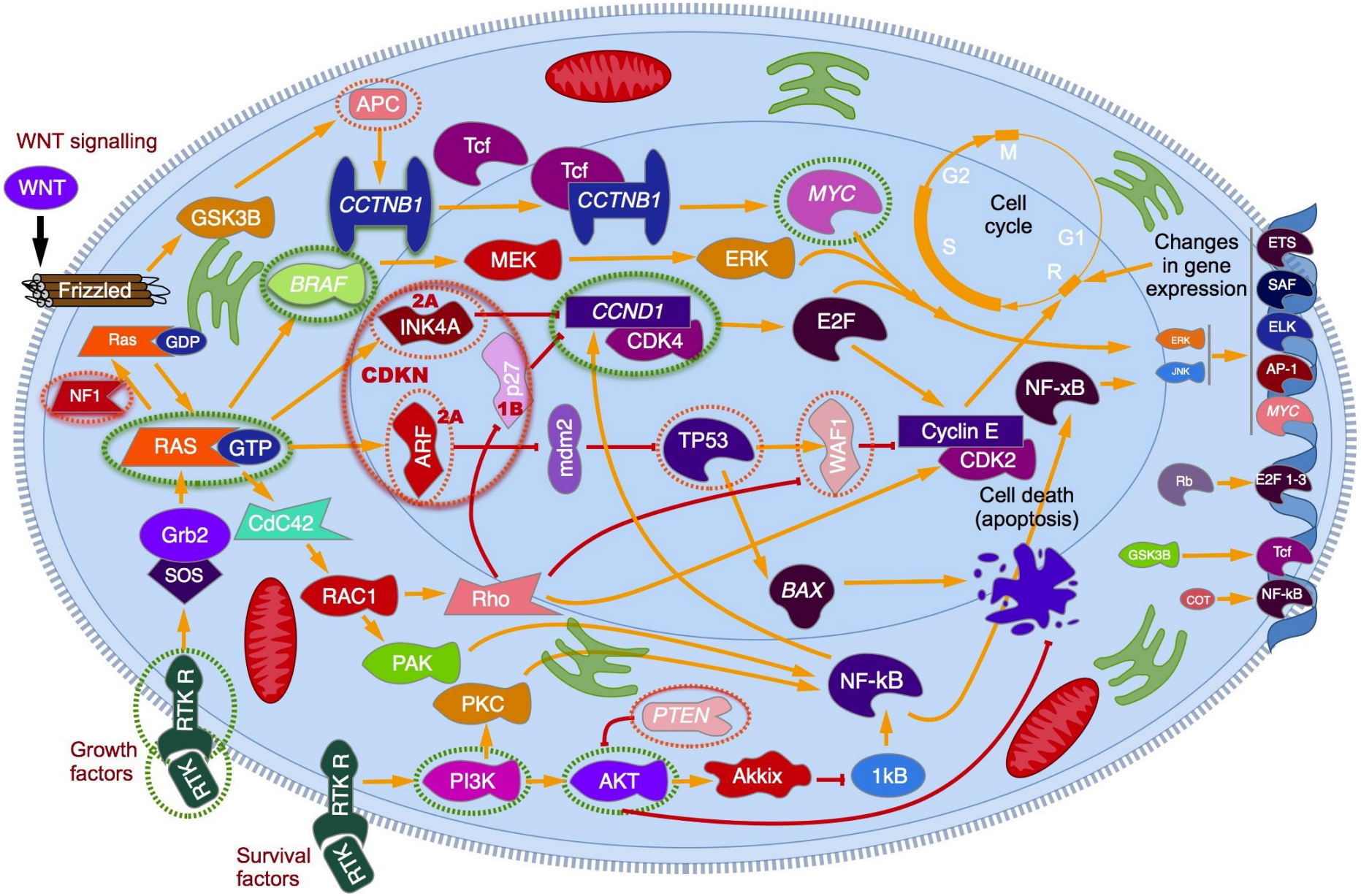
Malignant Melanoma, VGP & Metastatic

Class III

Class II



*CDKN2A*
*TP53*
*CDKN1B*


WNT signalling
WNT
Frizzled
GSK3B
APC
CCTNB1
Tcf
Tcf
CCTNB1
MYC
M
G2
Cell
cycle
G1
S
R
Changes
in gene
expression
ETS
SAF
ELK
AP-1
MYC
BRAF
MEK
ERK
2A
INK4A
CCND1
CDK4
E2F
Ras
GDP
NF1
CDKN
p27
1B
ARF
2A
RAS
GTP
mdm2
TP53
WAF1
Cyclin E
CDK2
NF-xB
ERK
JNK
Rb
E2F 1-3
Cell death
(apoptosis)
Grb2
SOS
CdC42
RAC1
Rho
BAX
GSK3B
Tcf
COT
NF-kB
PAK
PKC
NF-kB
PTEN
RTK R
RTK
Growth
factors
PI3K
AKT
Akkix
1kB
RTK R
RTK
Survival
factors

# Melanocytic Dysplasia

- Concept and criteria. Grading
- Pathologic conditions
- Differential diagnosis
  - Atypia and regenerative changes
  - Inflammation and regression
- Is melanocytic dysplasia a progressive lesion?