Deep penetrating naevi

- Alan Evans

  Department of Pathology Ninewells Hospital Dundee

Deep penetrating naevus

- Deep penetrating naevus described by Seab et al.
- Am J Surg Path 1989 – series of 70 case
- Clinically and histologically simulates melanoma
- Commonly encountered in referral practice

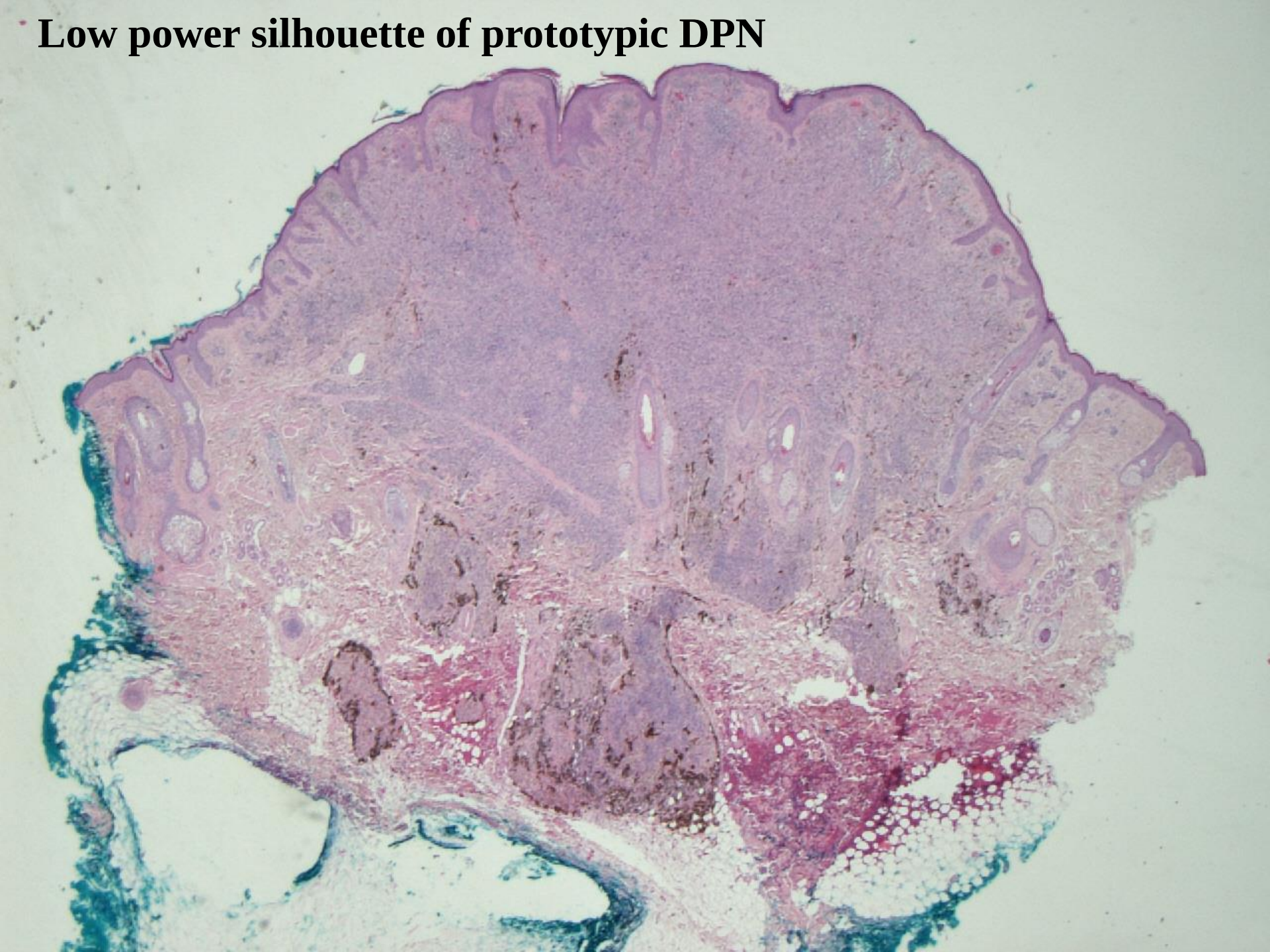
Deep penetrating naevus

- Occur over a wide age range
- Generally first three decades
- Commonest site is head and neck
- Followed by extremities and trunk
- Spare acral skin

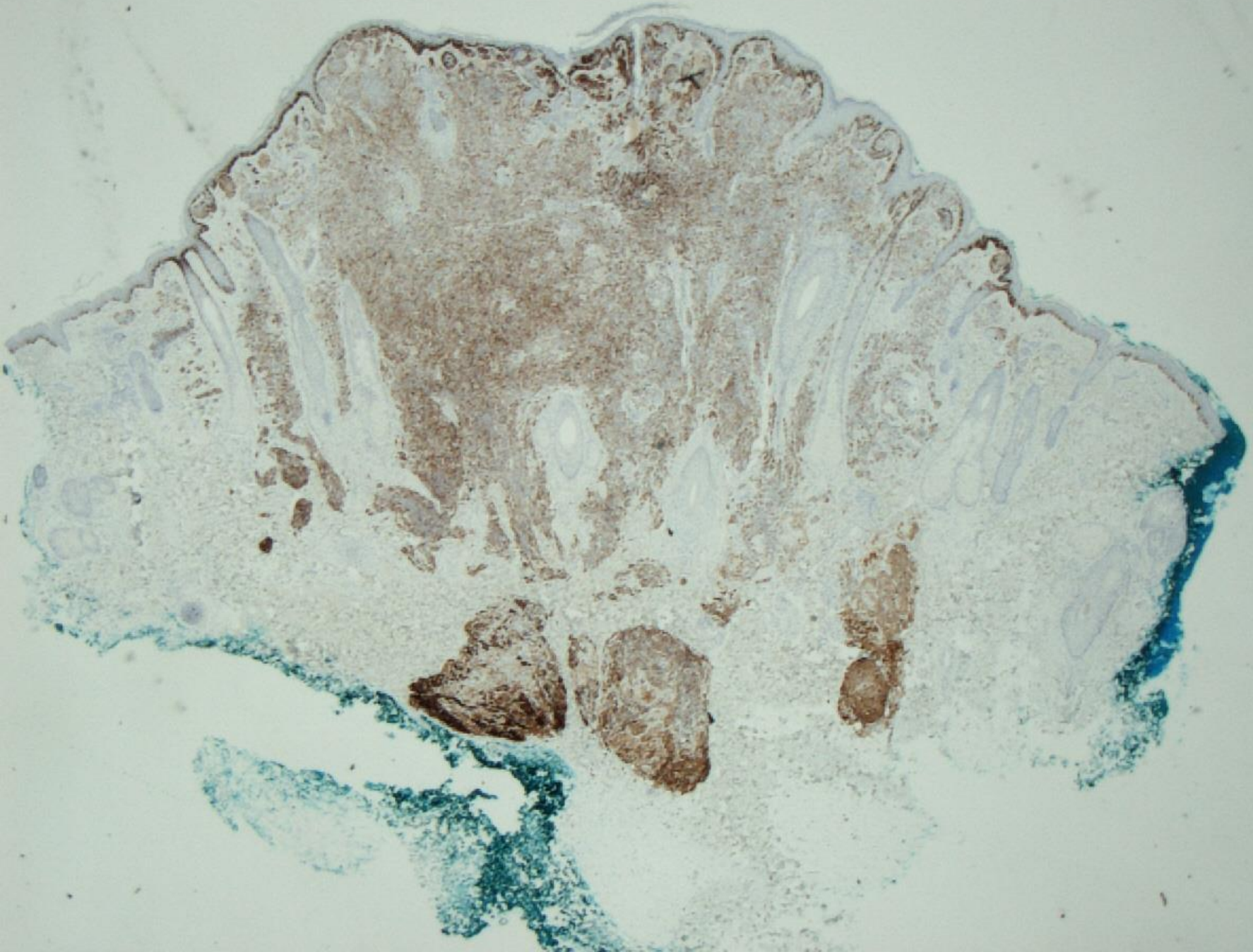
The classic deep penetrating naevus

- Generally <1cm and dome shaped
- Low power wedge shaped profile
- Extend into deep dermis or subcutis
- Black/blue/brown...or in combination

Low power silhouette of prototypic DPN



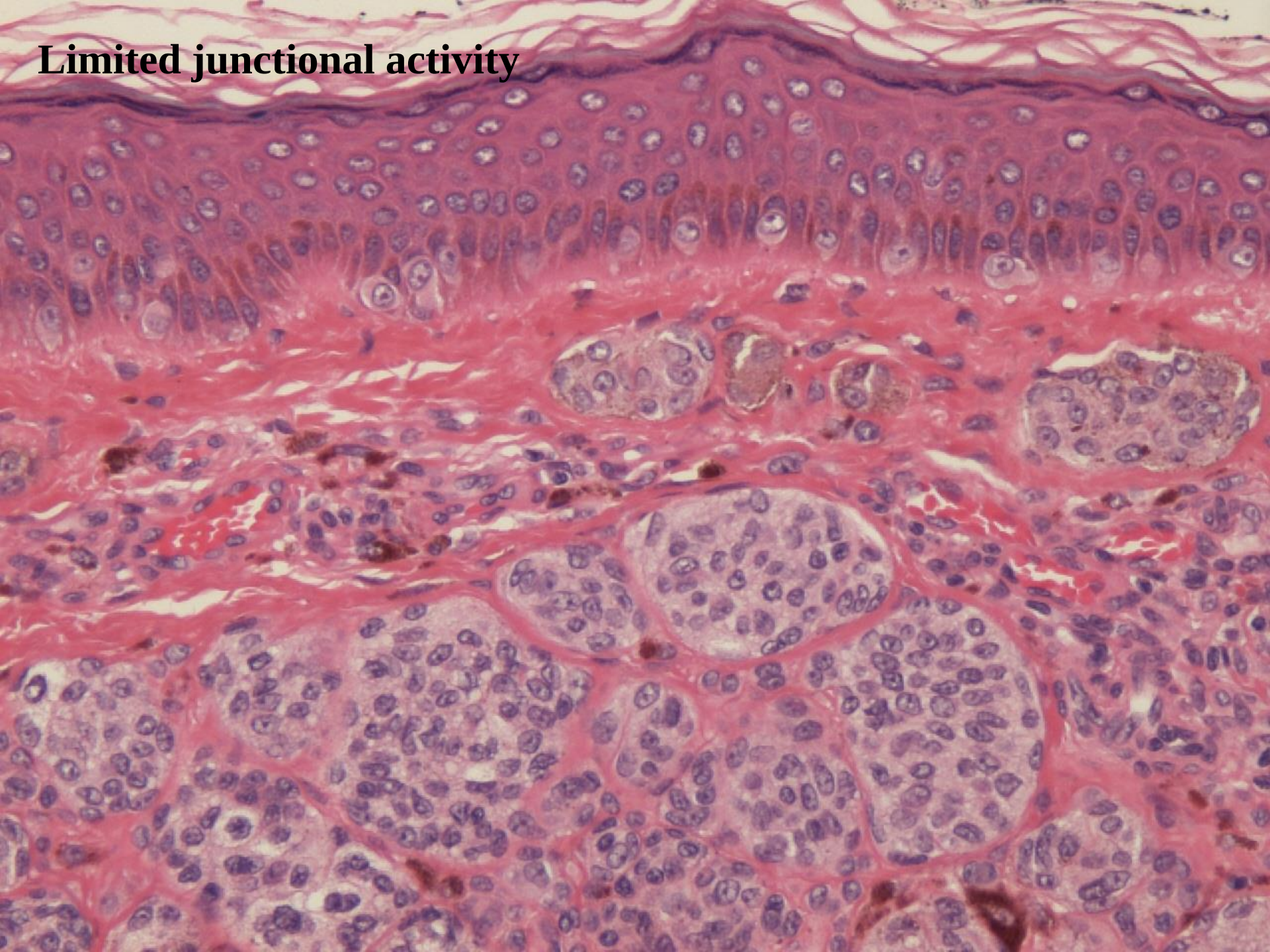
Low power silhouette – Melan-A.



The classic deep penetrating naevus

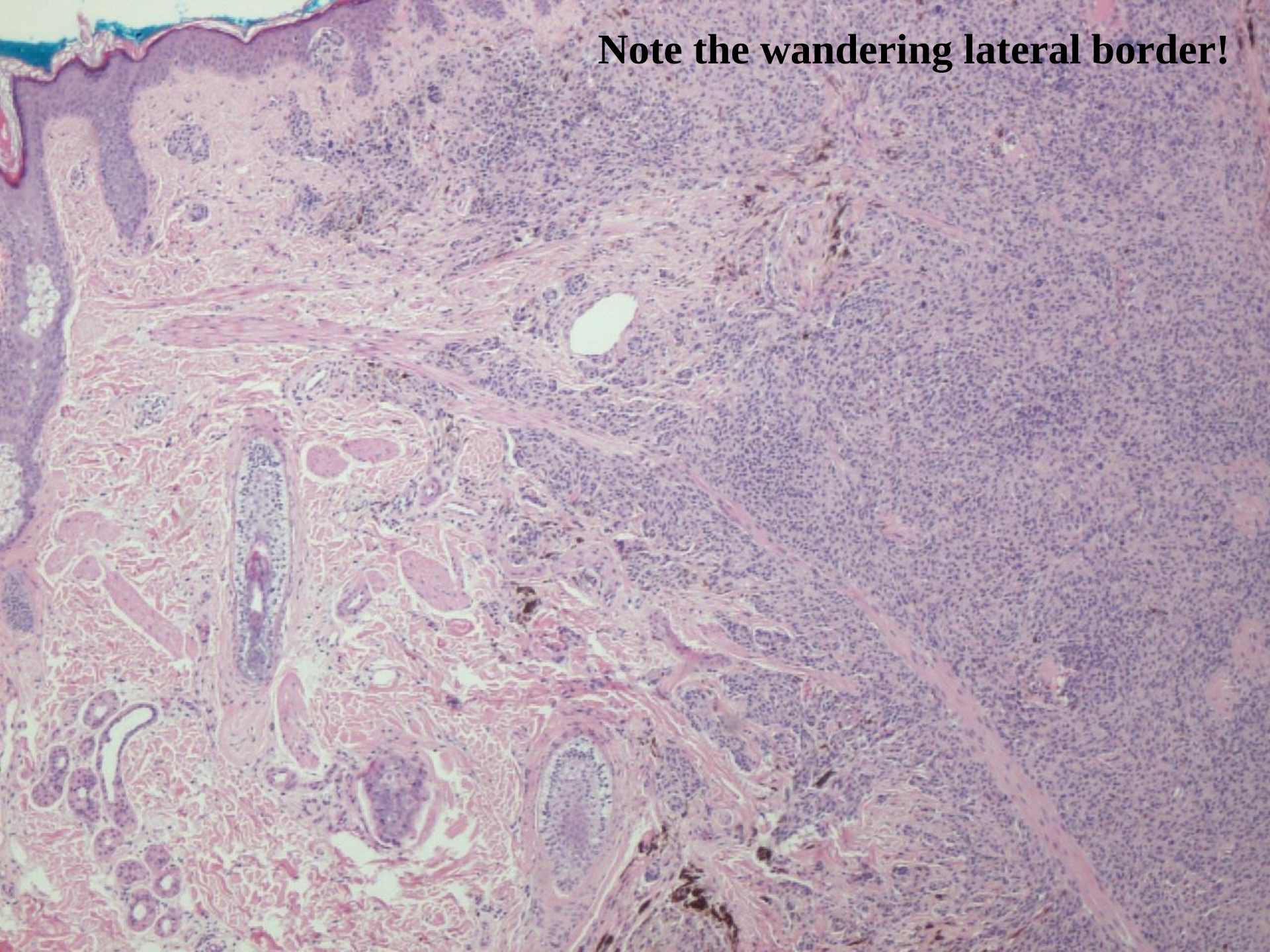
- Weak junctional proliferation
- At least 2/3 are combined lesions
- Most often combined with usual type naevus
- Pure DPN often lack junction and have Grenz zone
- Pagetoid ascent is very rare

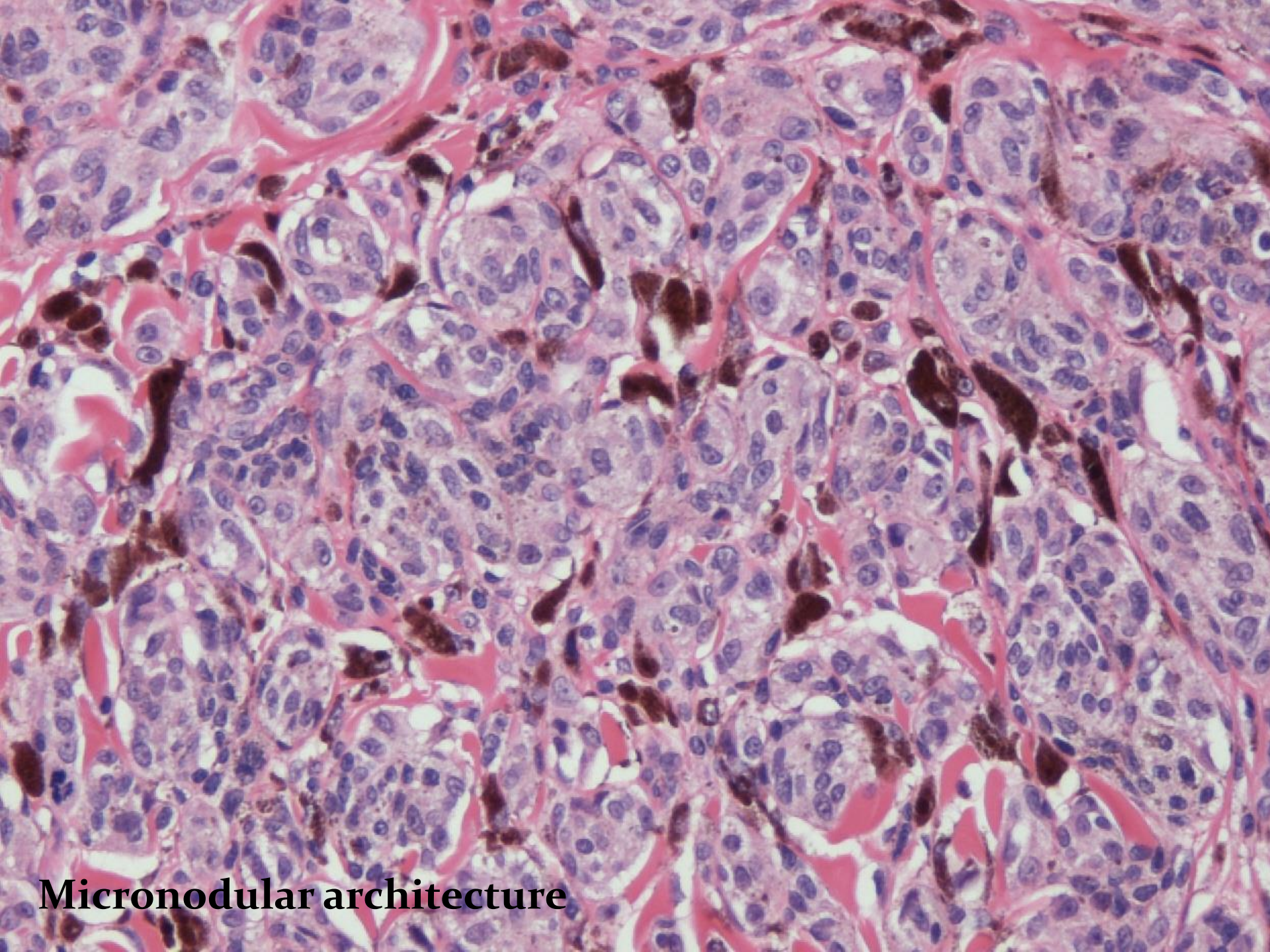
Limited junctional activity



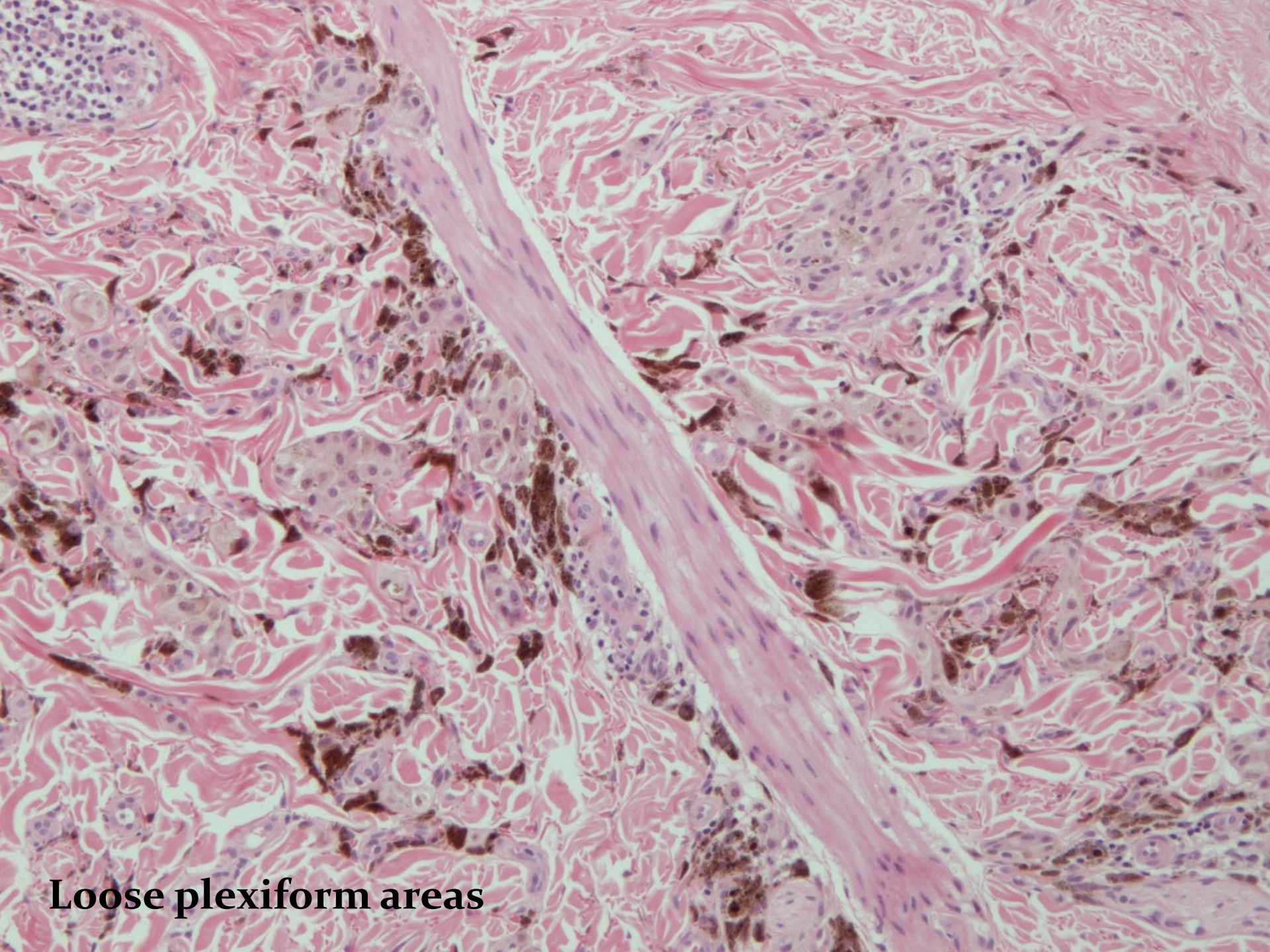
The classic deep penetrating naevus

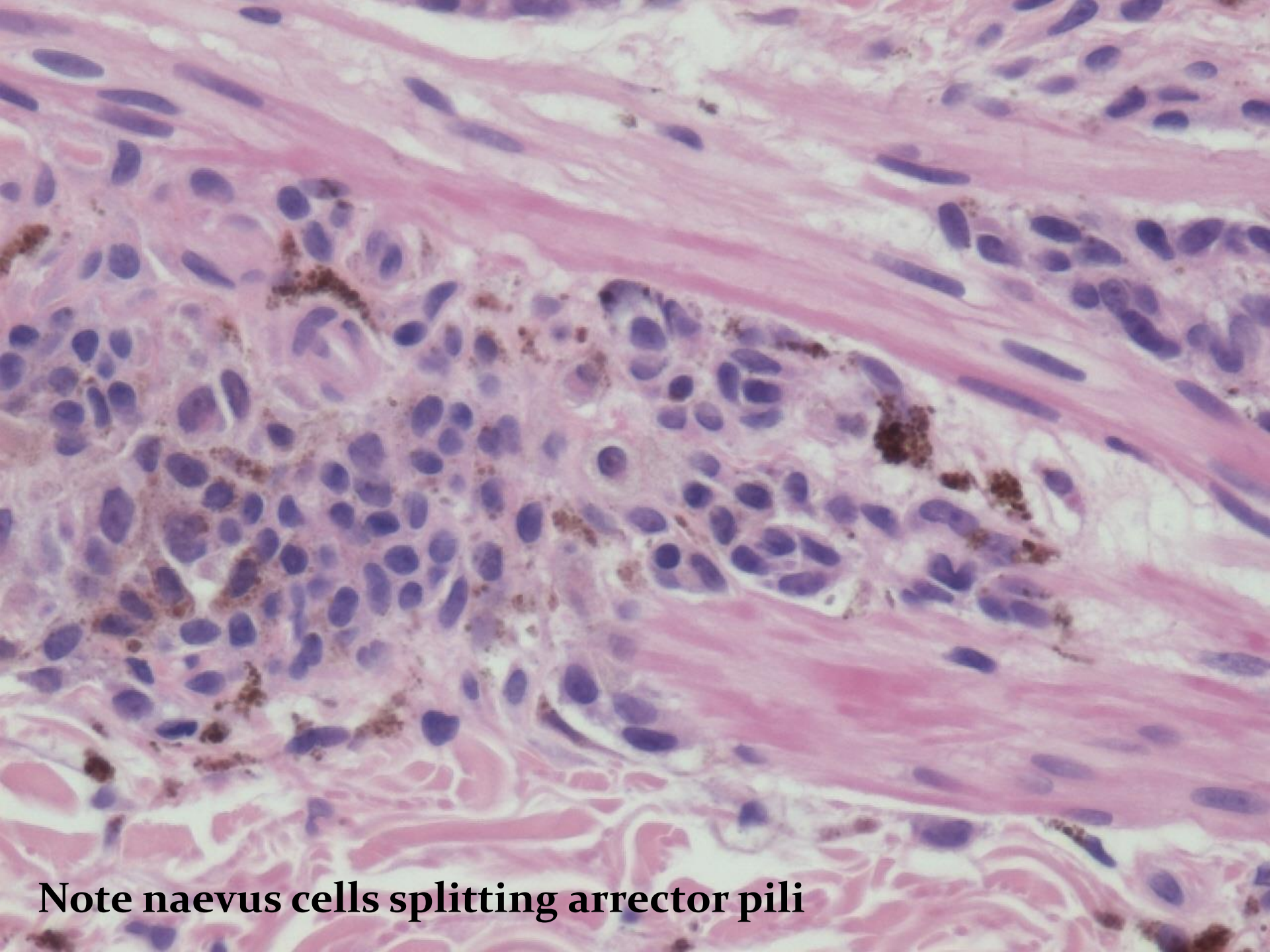
- Irregular lateral borders
- Track adnexal and neurovascular structures
- Epithelioid cells generally predominate
- Bulbous extension into deep dermis or subcutis
- Lack of basal maturation + deep melanin pigment


Note the wandering lateral border!

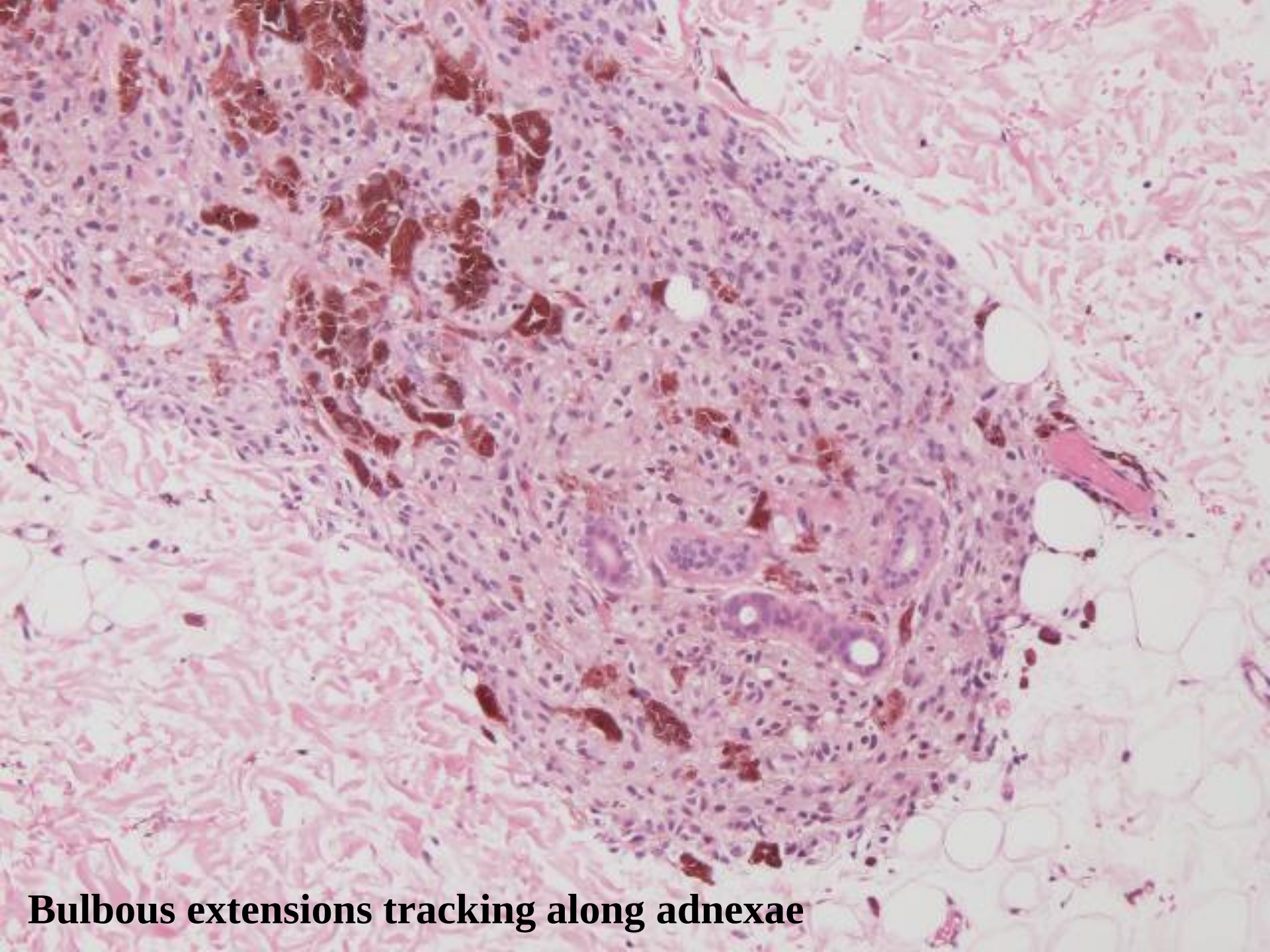


Micronodular architecture

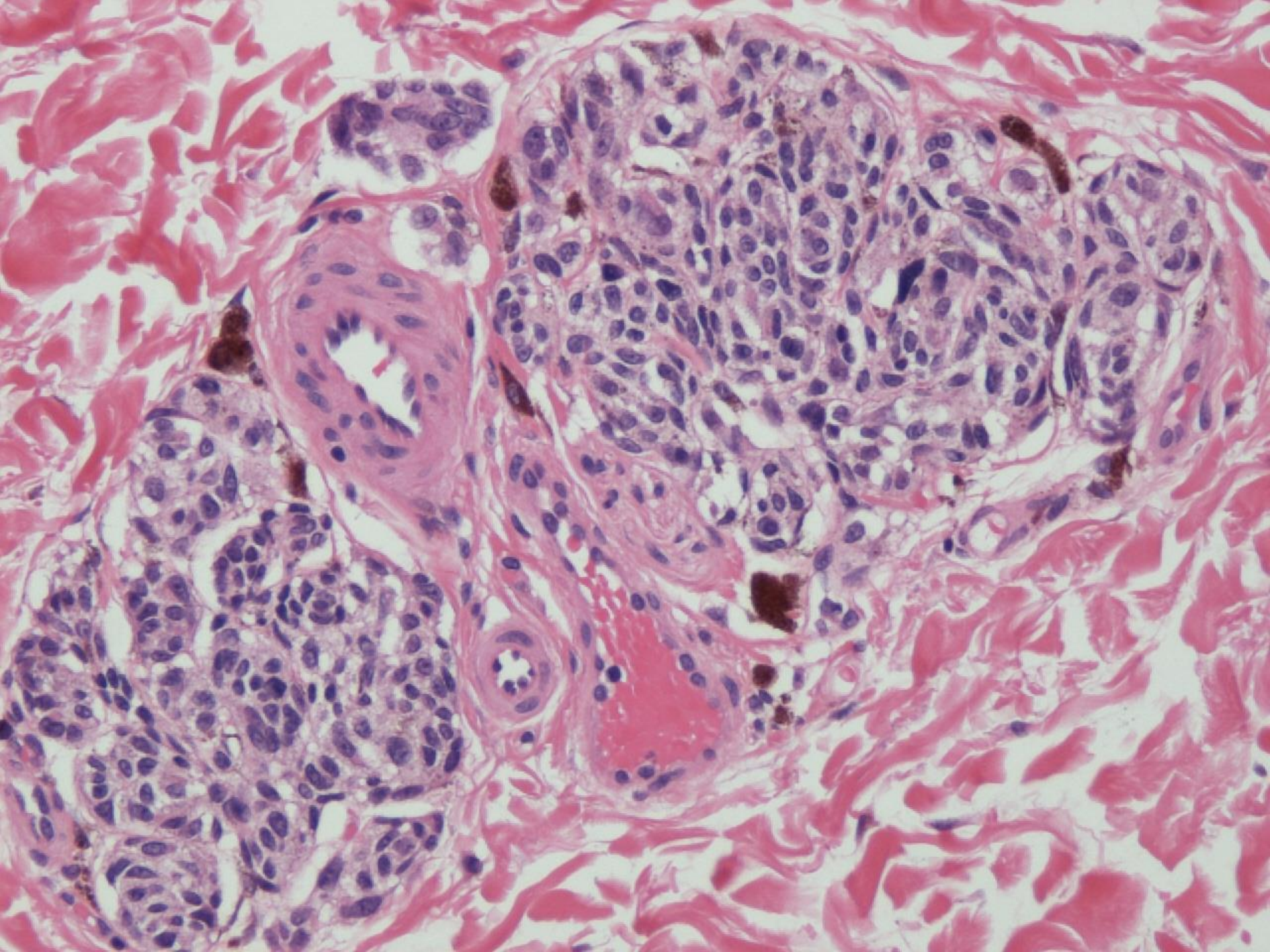

Loose plexiform areas

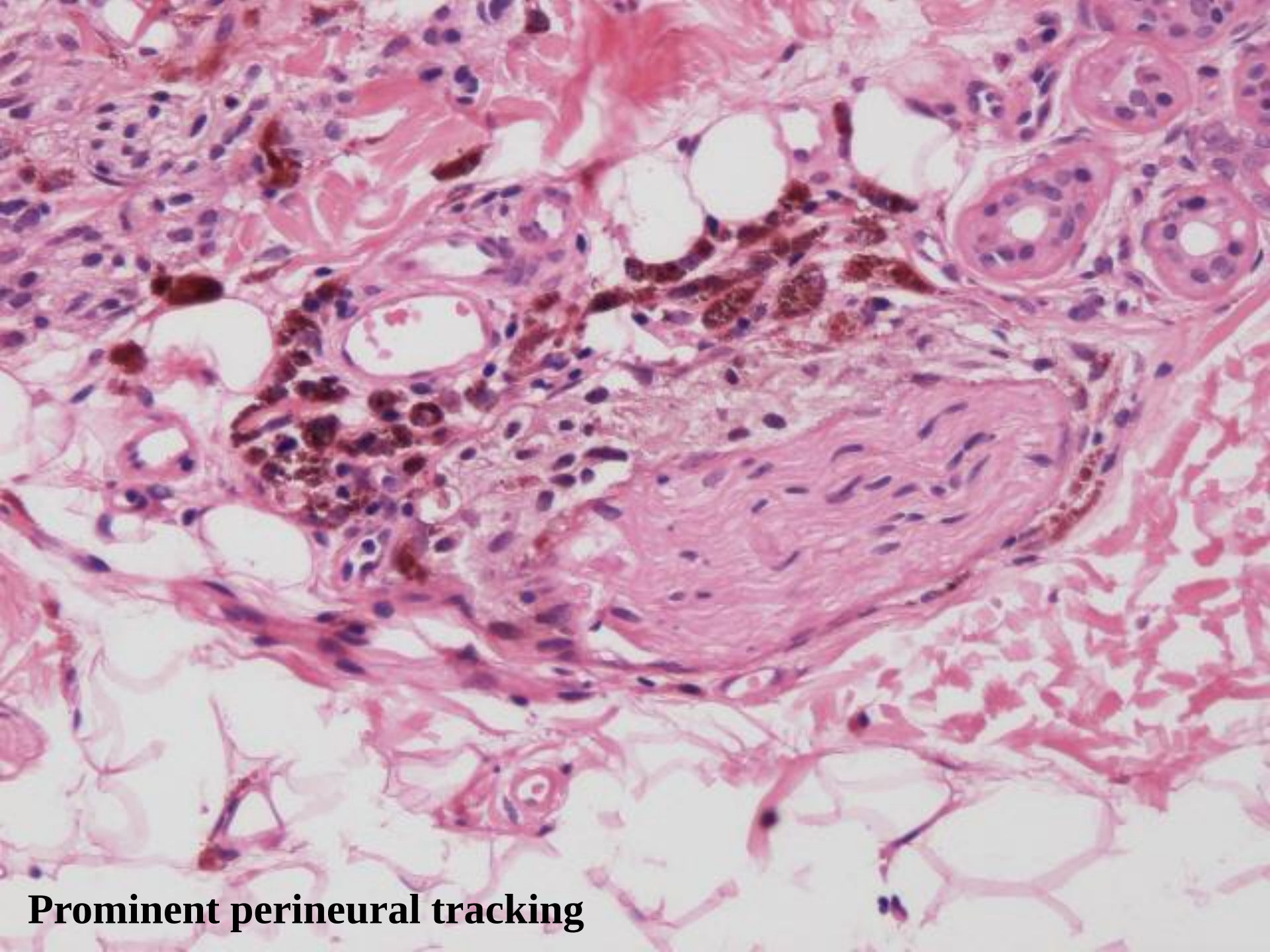


Note naevus cells splitting arrector pili

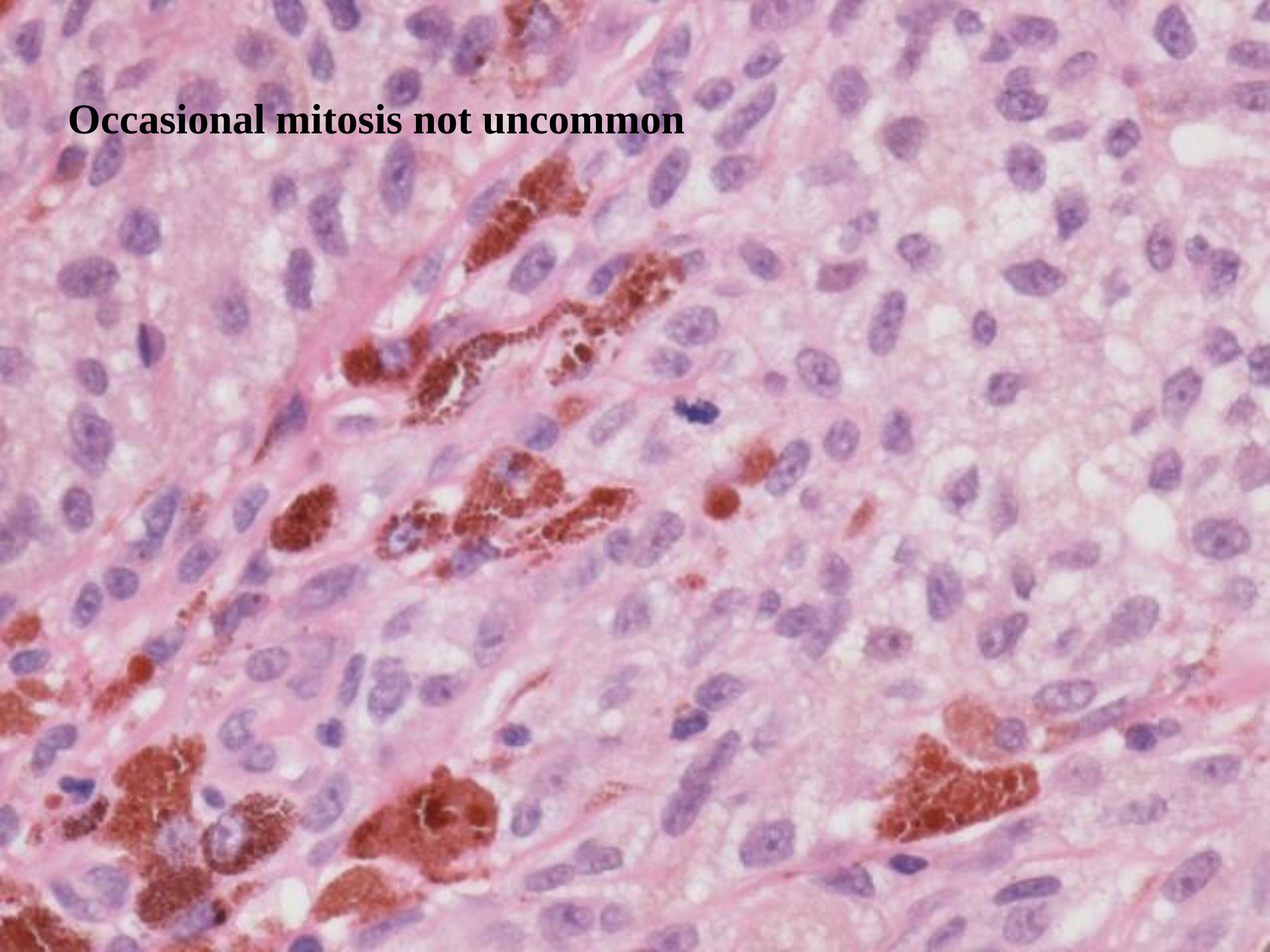


Bulbous extensions tracking along adnexae



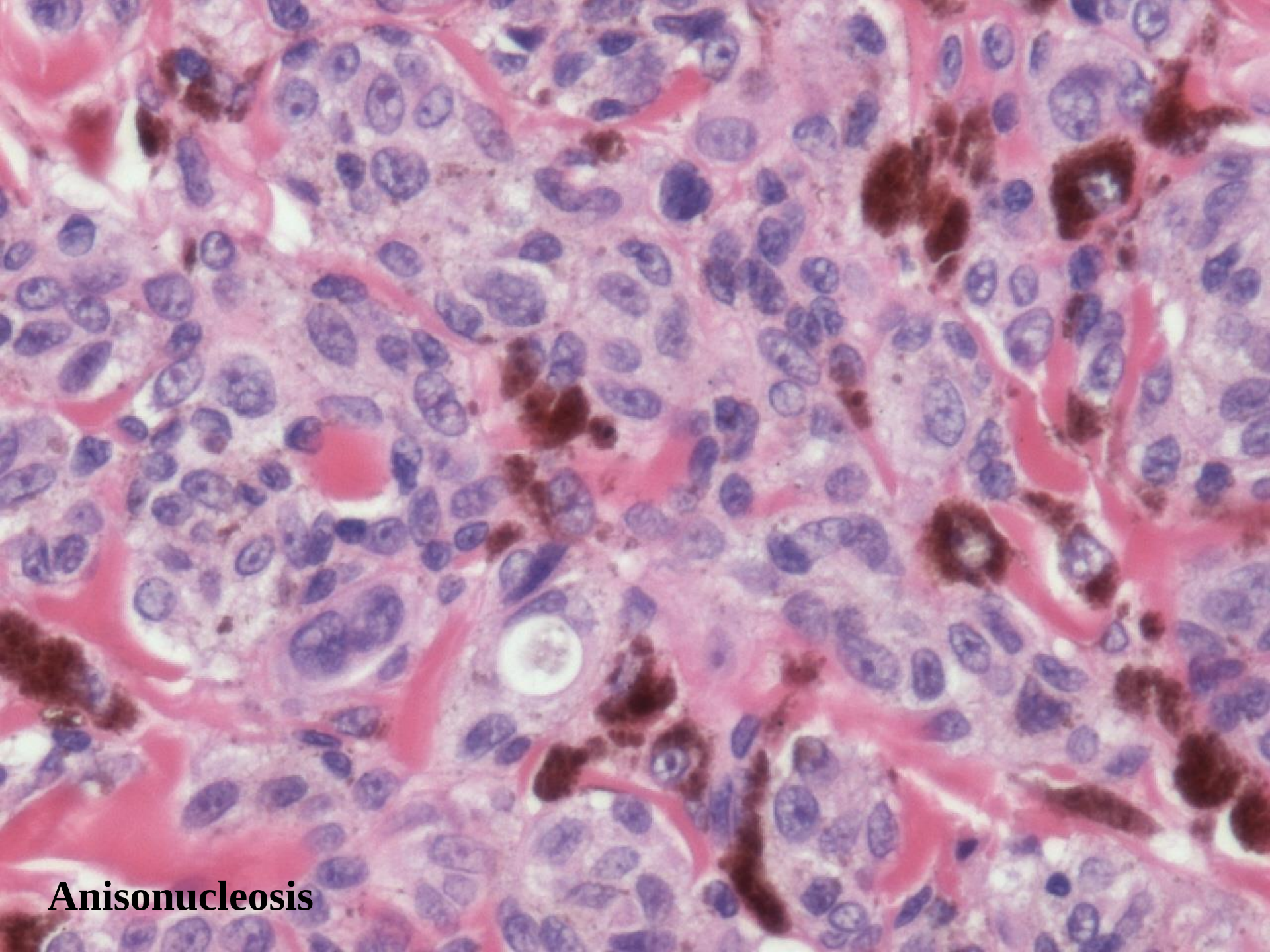


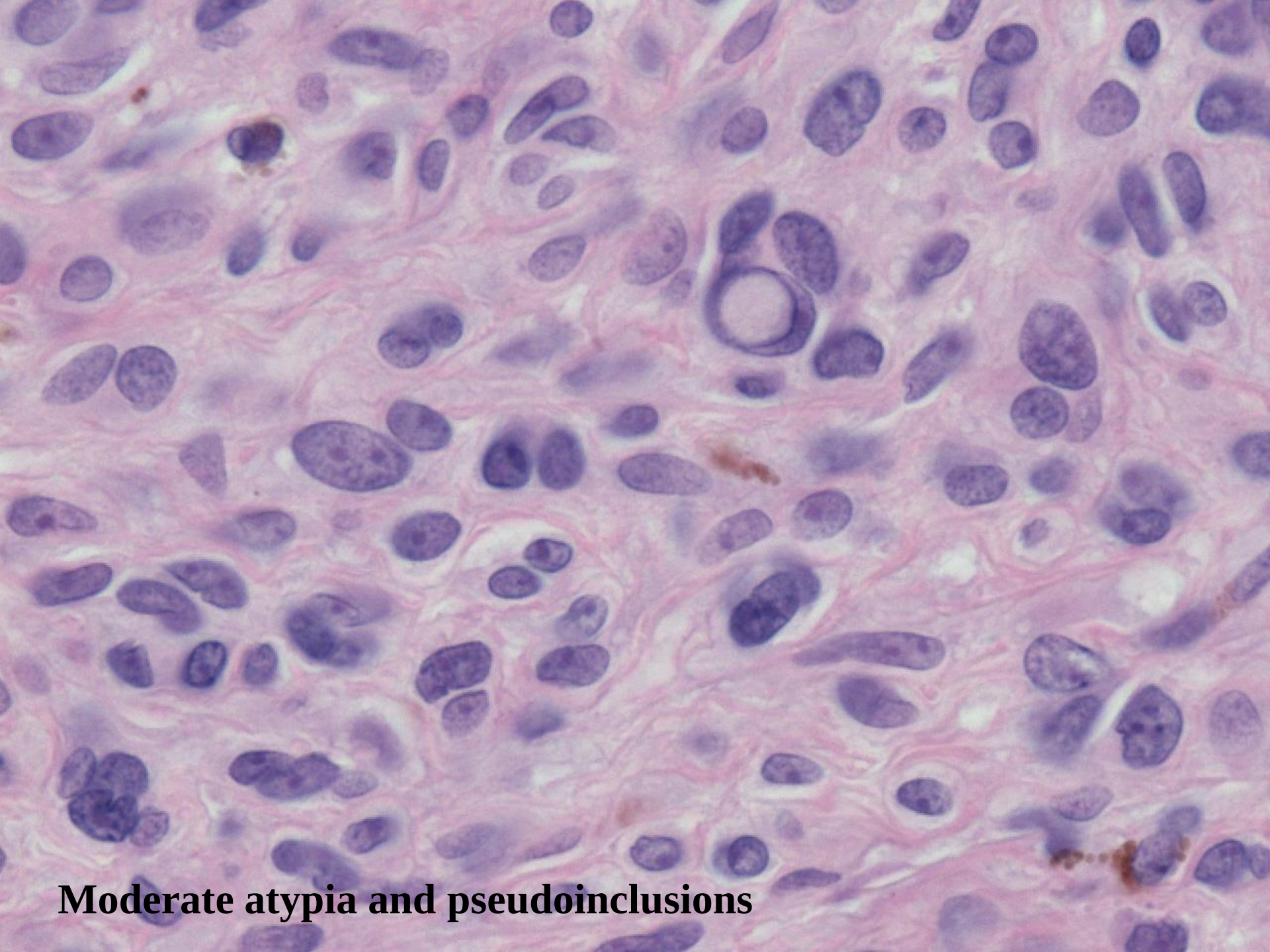
Prominent perineural tracking


Occasional mitosis not uncommon

The classic deep penetrating naevus

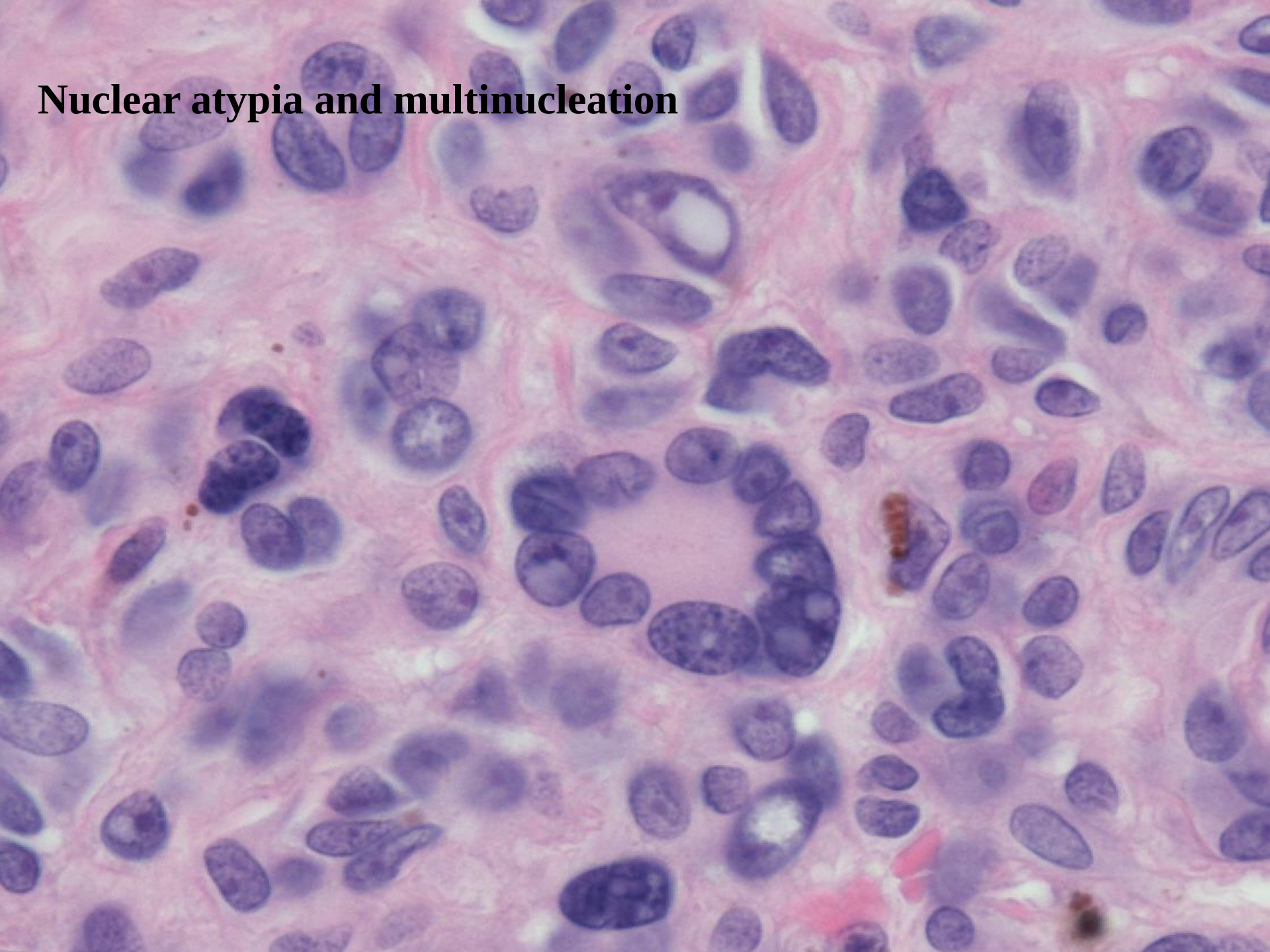
- Often show anisonucleosis
- Small to medium sized distinct nucleolus
- Random mild to moderate atypia
- Nuclear pseudoinclusions are not uncommon
- Generally < 1 mitosis per sq. mm

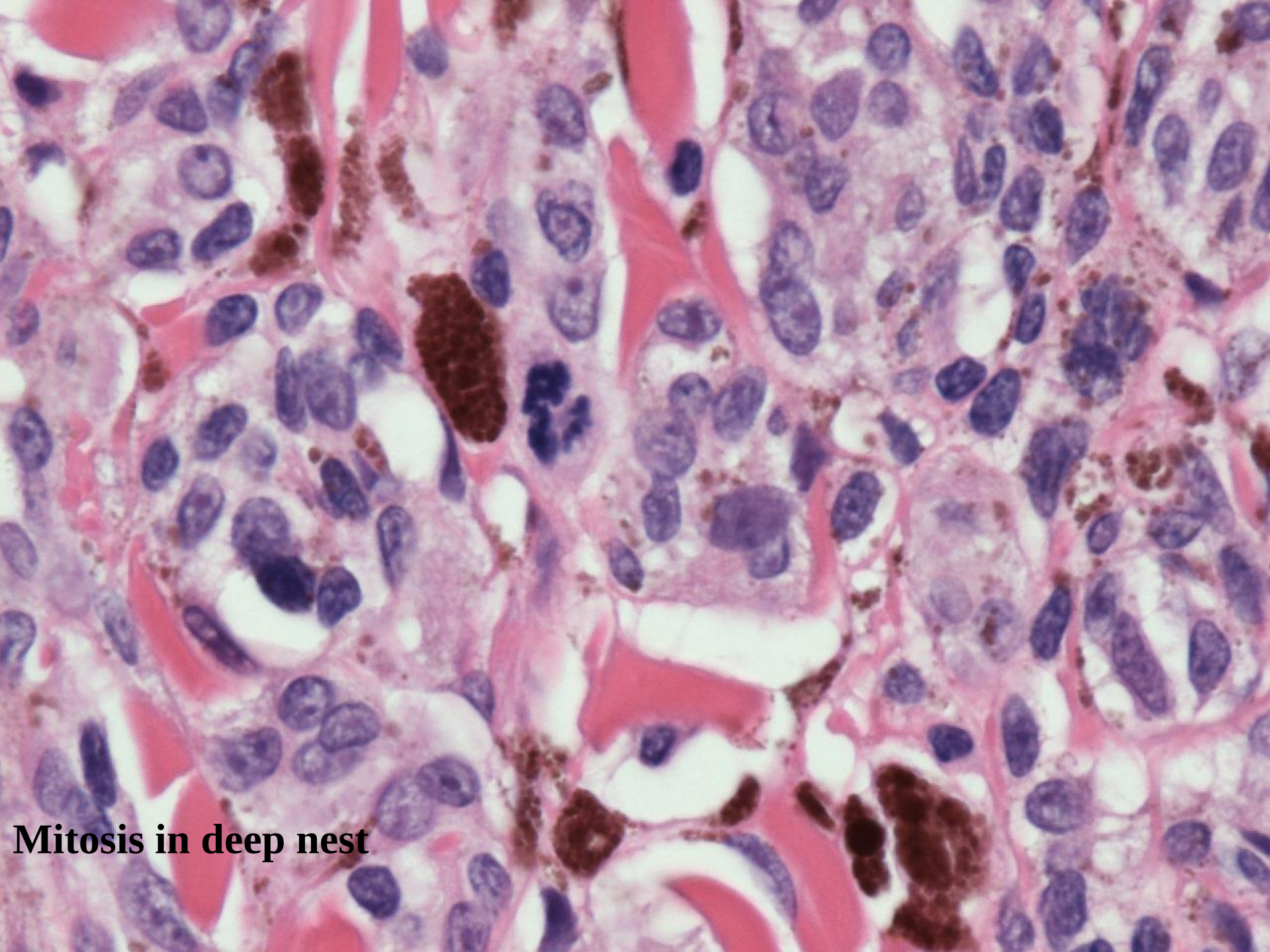

Anisonucleosis



Moderate atypia and pseudoinclusions

Nuclear atypia and multinucleation




Mitosis in deep nest


WIREWORKS
Diversion

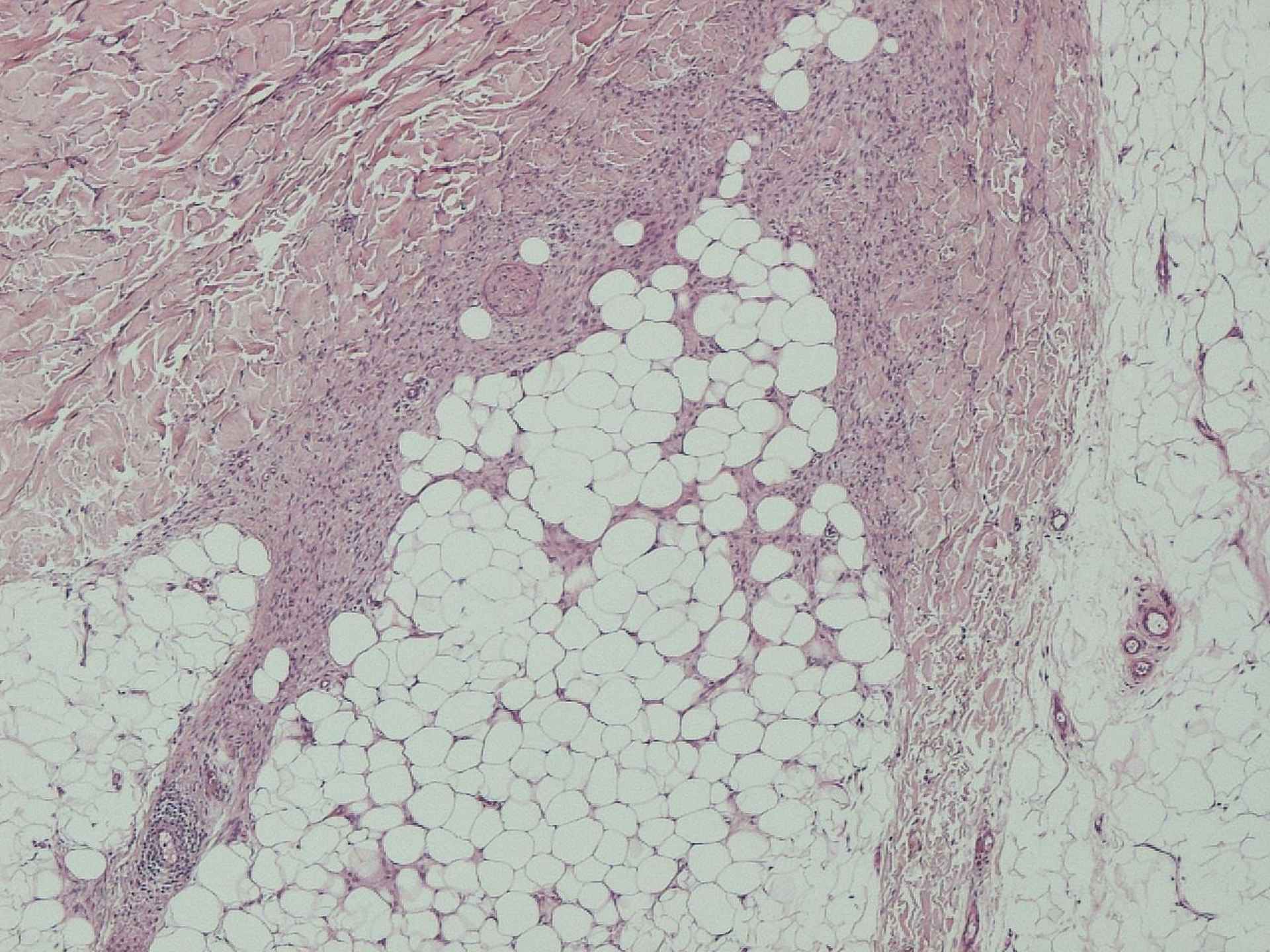
Plexiform spindle cell naevus

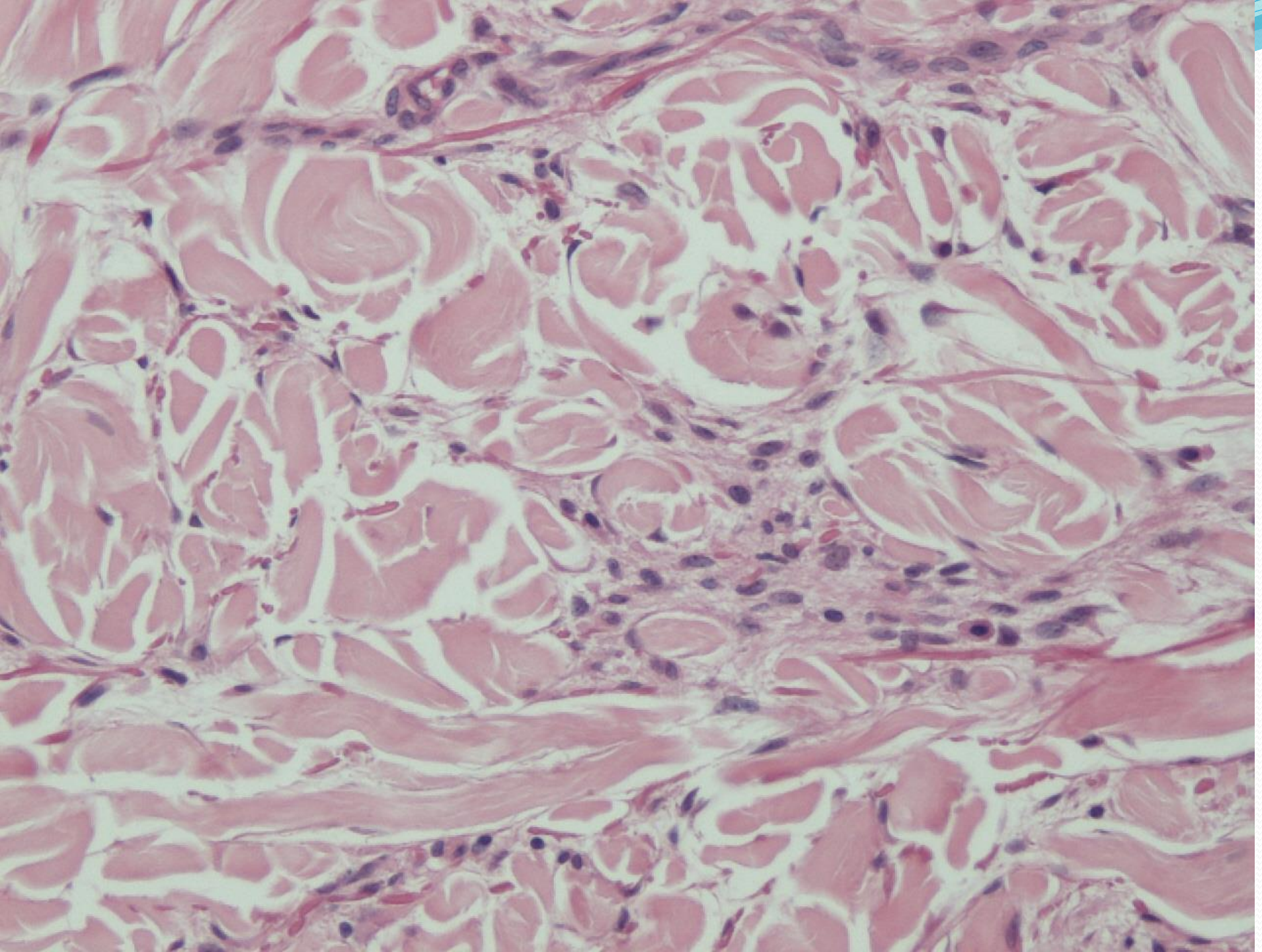
- Described soon after DPN in 1991 – Barnhill et al.
- Described a group of naevi occurring in young subjects
- Often trunk /shoulder region
- Fascicular/plexiform pattern track neurovascular bundles

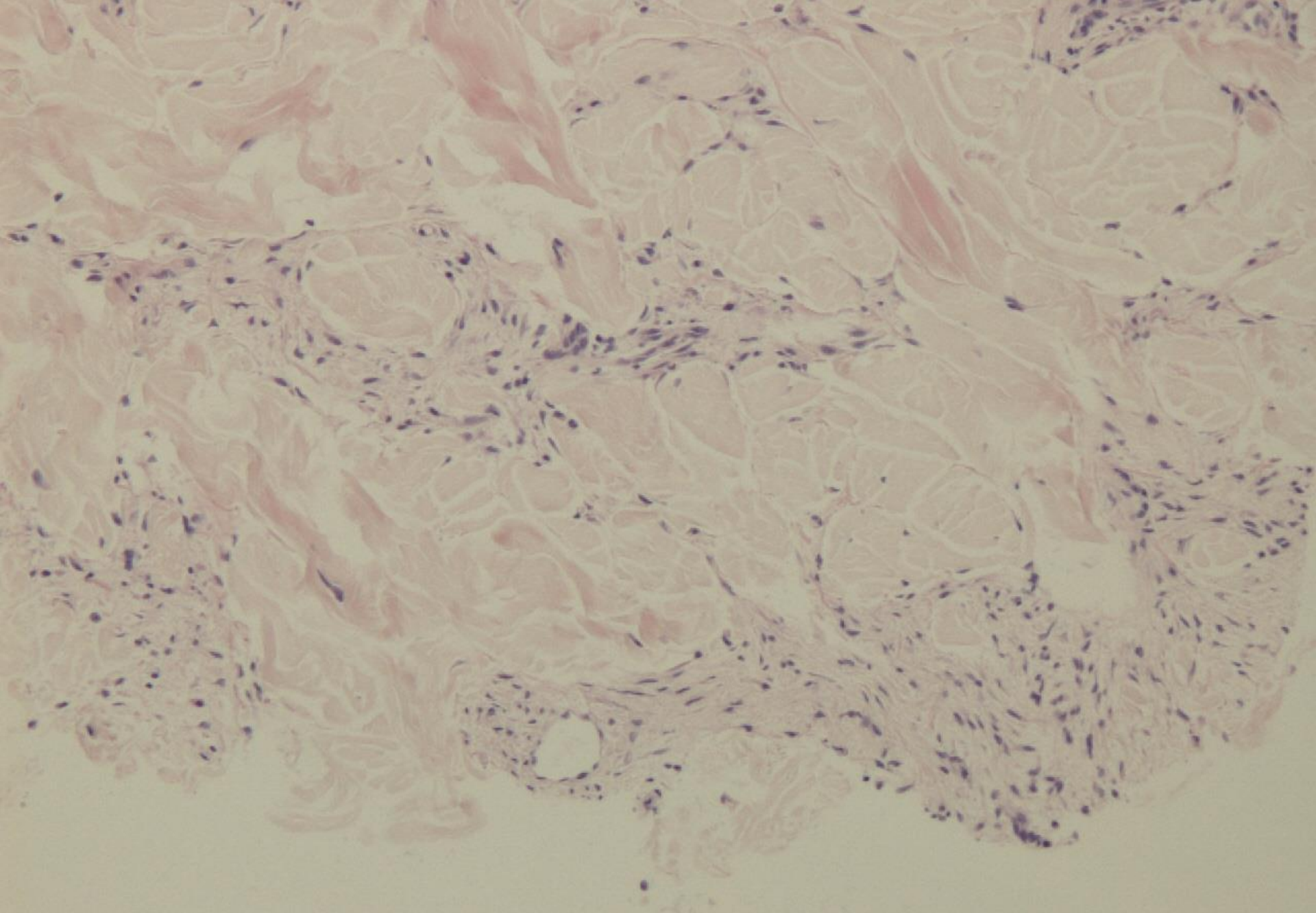
Plexiform spindle cell naevus

- **Some** features in common with DPN
- Wedge shaped - plexiform areas - low grade atypia
- Cooper 1992 ‘deep penetrating plexiform spindle cell naevus’
- Since them tended to be subsumed into DPN group

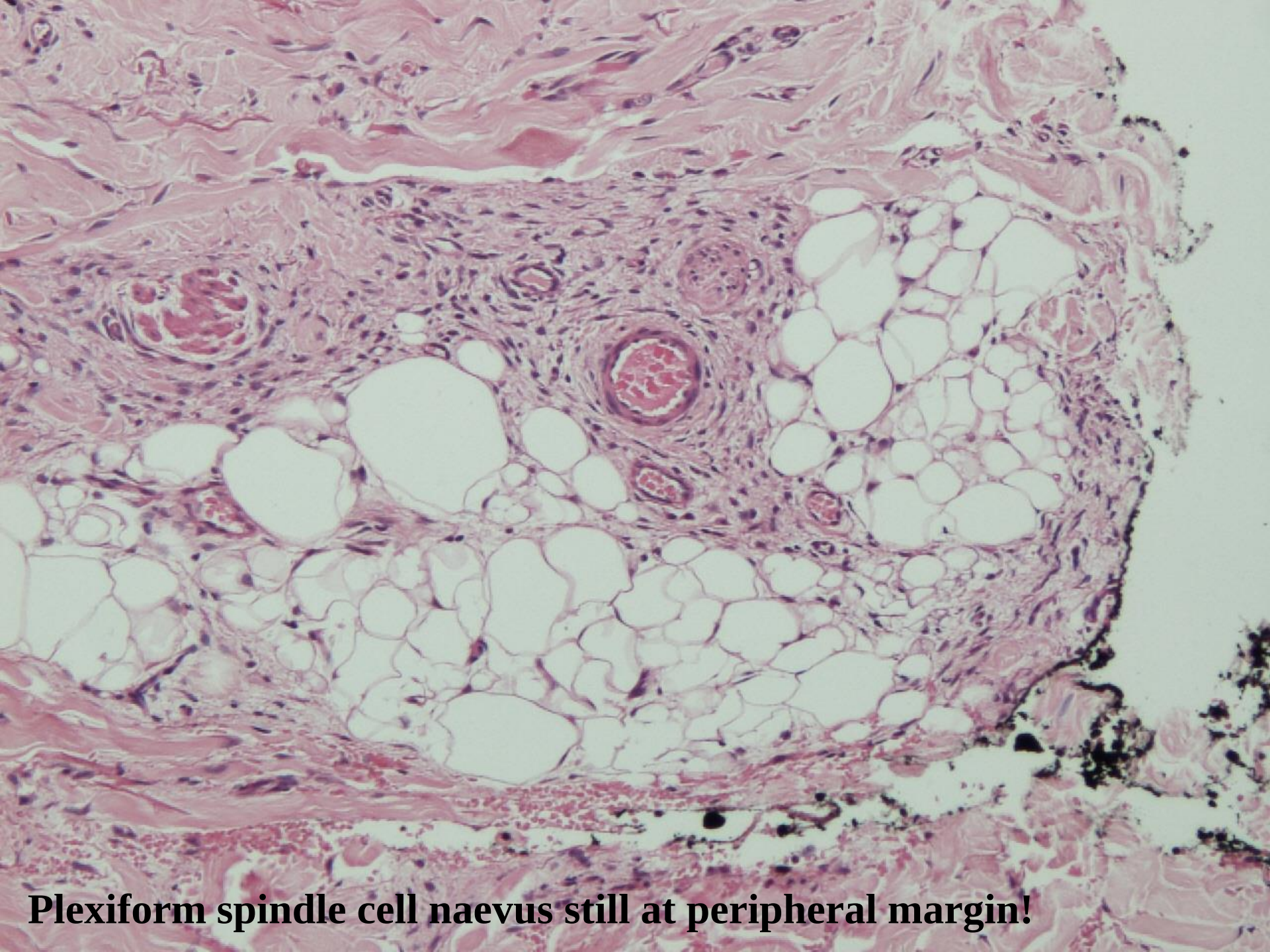
Plexiform spindle cell naevus-upper back/shoulder female aged 15



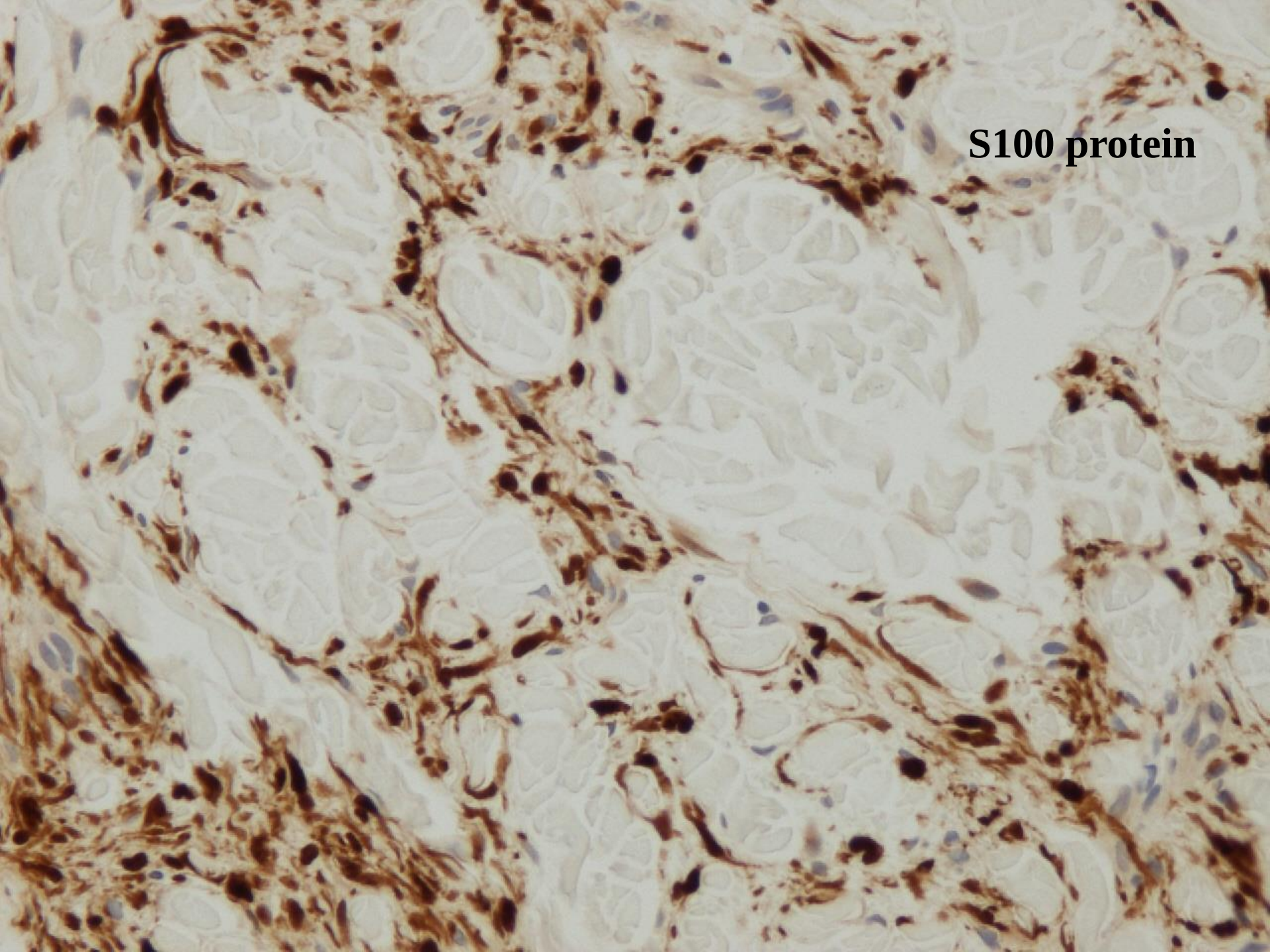


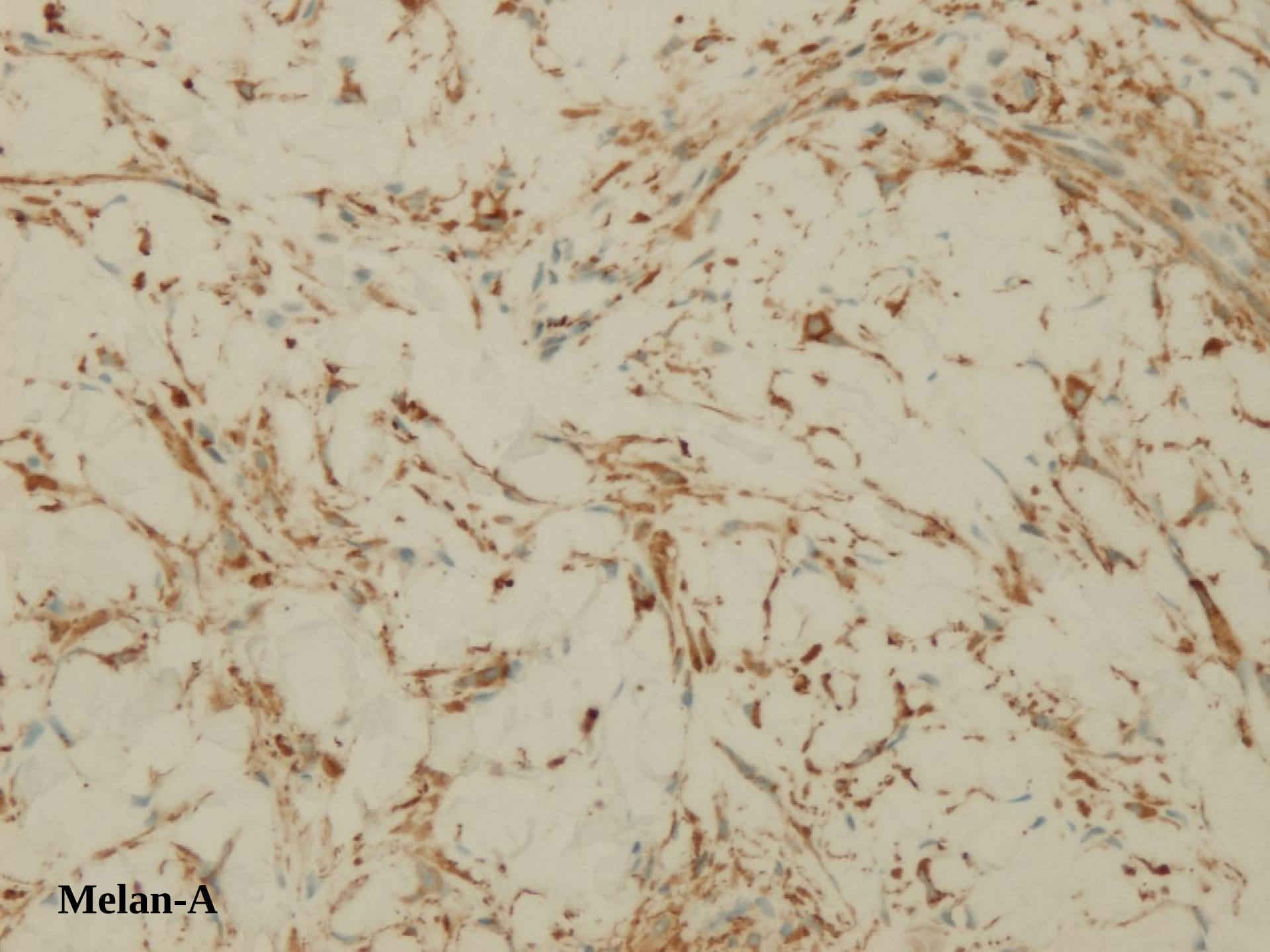


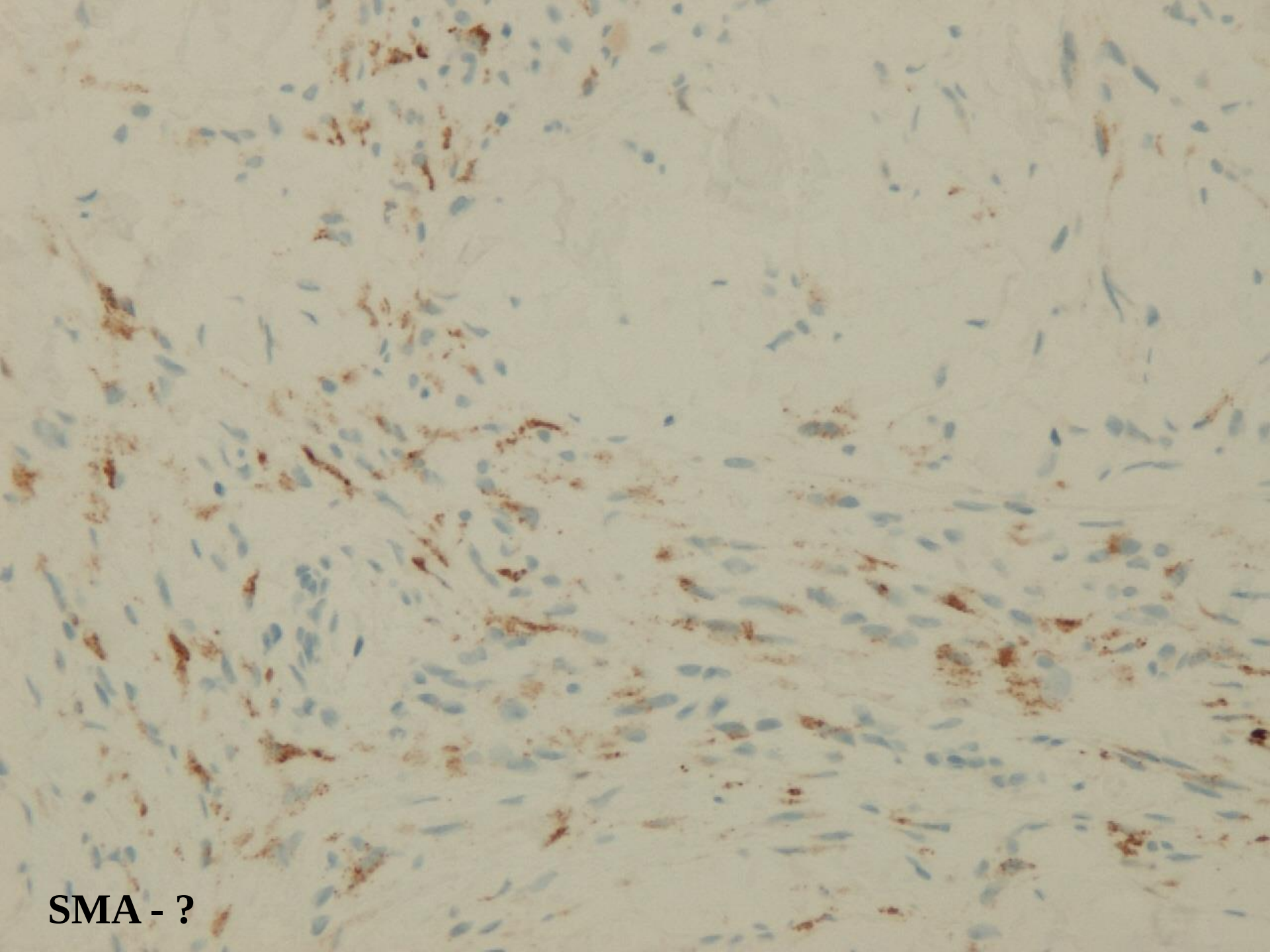
Lesion at deep resection margin



Plexiform spindle cell naevus still at peripheral margin!


S100 protein


Melan-A


SMA - ?

Plexiform spindle cell naevus

- Hung et al. Human Pathol 2014: 45; 2369-2378
- ***The plexiform spindle cell nevus and atypical variants: report of 128 cases***
- Reclaimed the plexiform spindle cell naevus as entity

Plexiform spindle cell naevus

- Small lesions but not well delineated
- Fascicular and plexiform growth of mainly spindle cells
- Low grade atypia-sparse mitoses
- Always show angiotropism/neurotropism

Plexiform spindle cell naevus

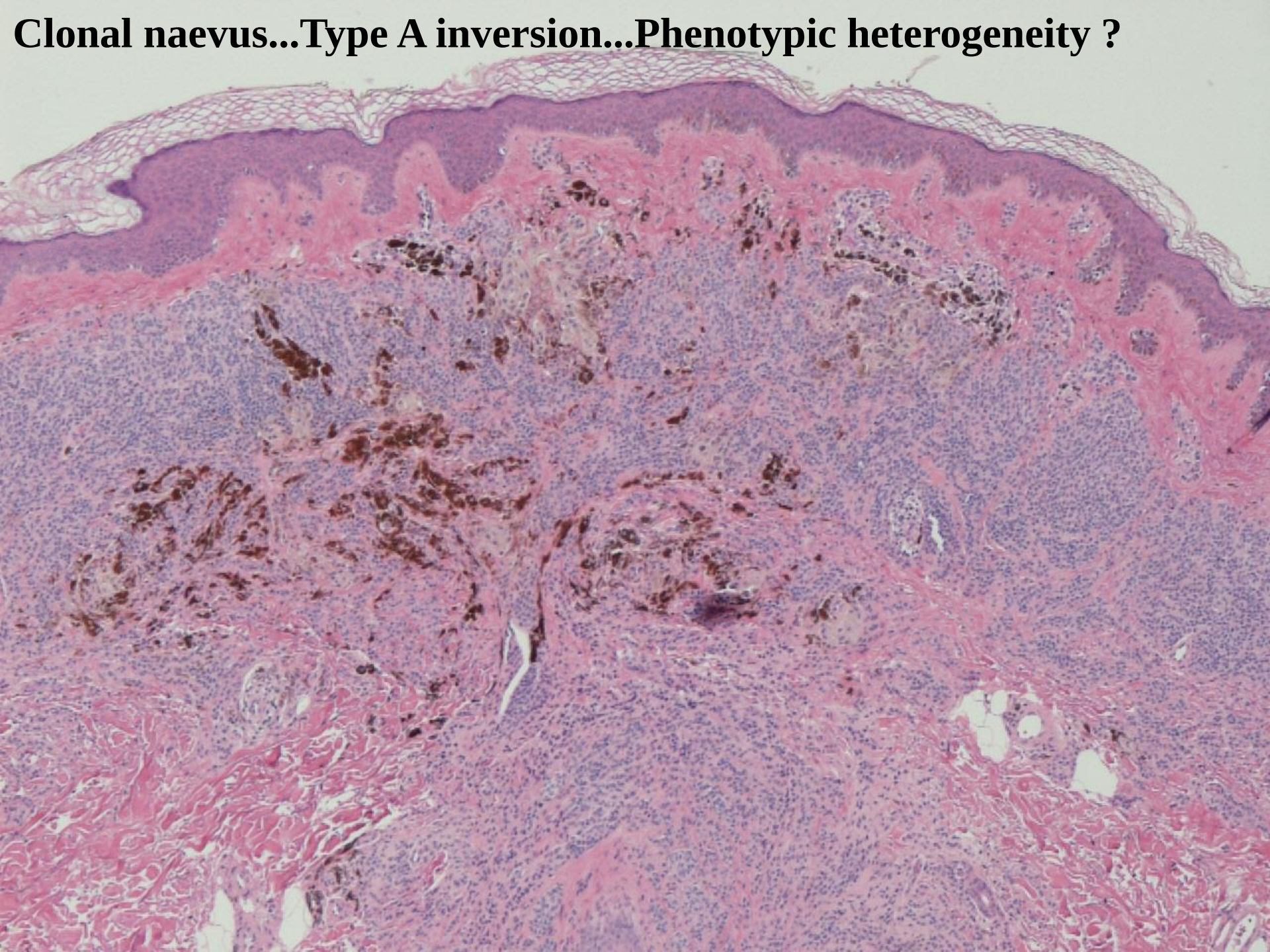
- Avoid a misdiagnosis of desmoplastic melanoma
- Clinical context is wrong for melanoma
- Small diameter – lacks severe atypia/frequent mitoses
- Lacks lymphoid aggregates and is Melan-A positive.

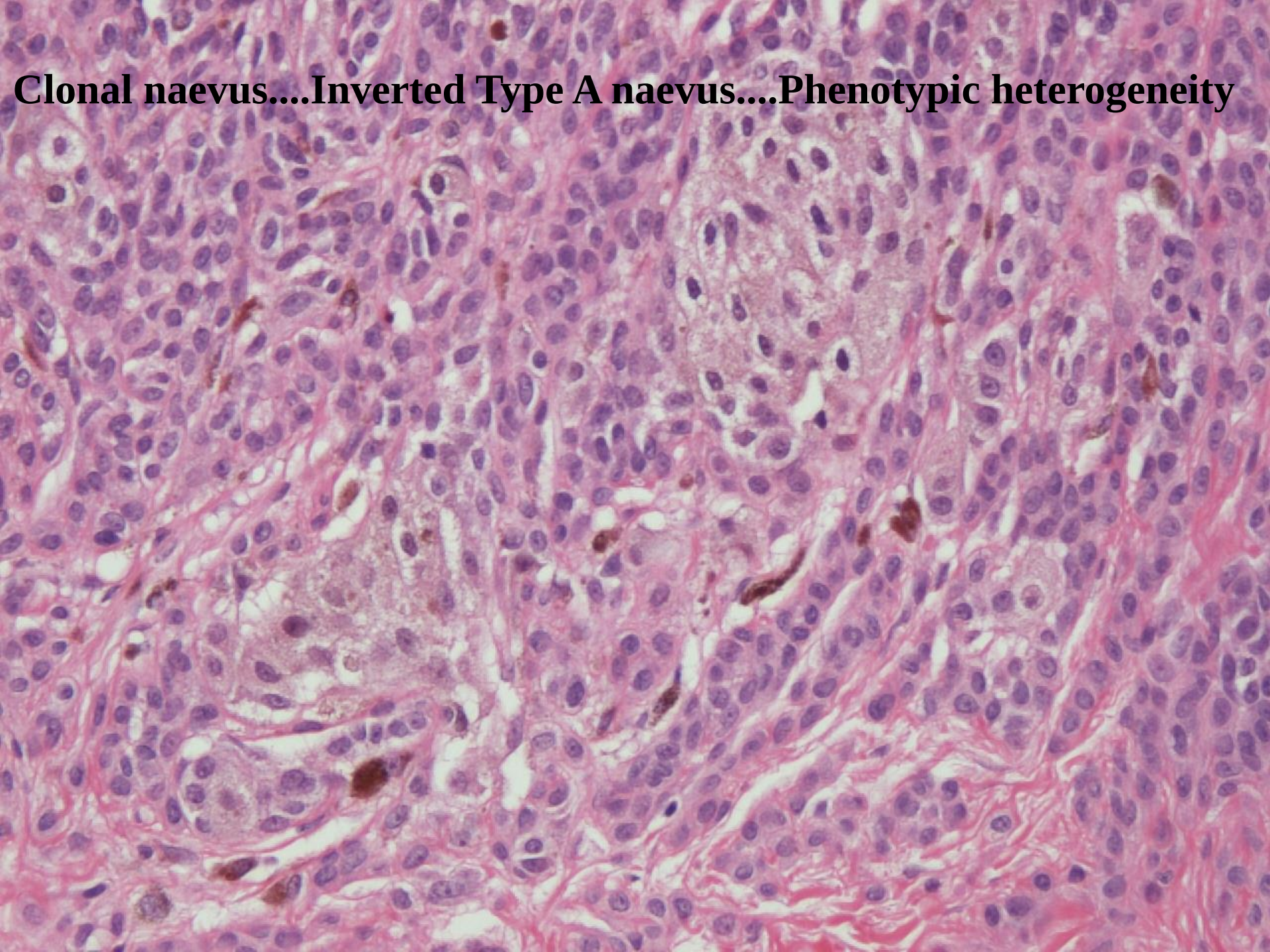

Back on Track

Back to DPN...is there a DPN family of lesions?

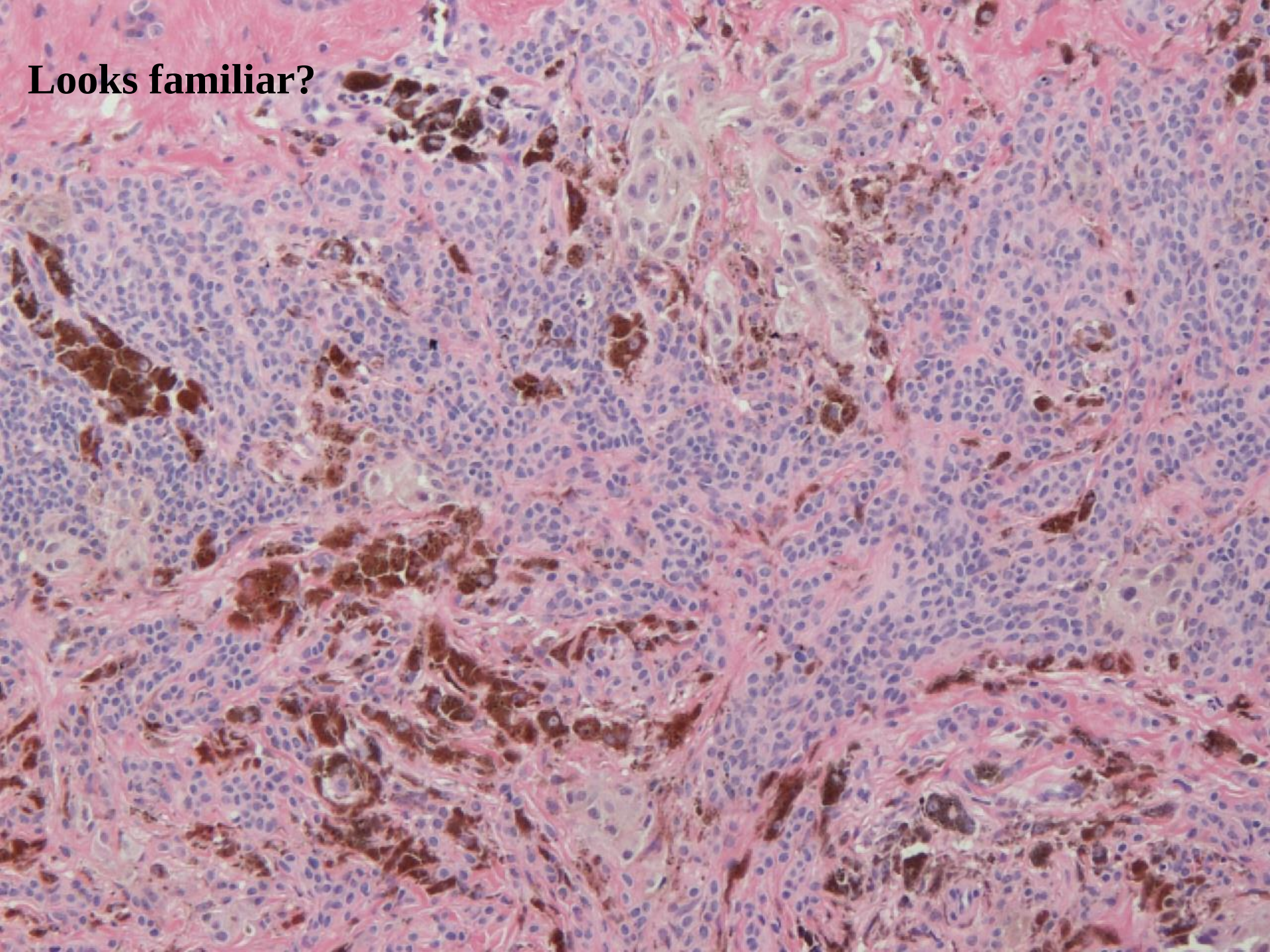
- DPN are unlikely to just appear de novo!
- The high incidence of combined lesions is relevant
- Can we discern early lesions?
- Do we see lesions at different stages of development?
- Are their borderline and malignant variants?

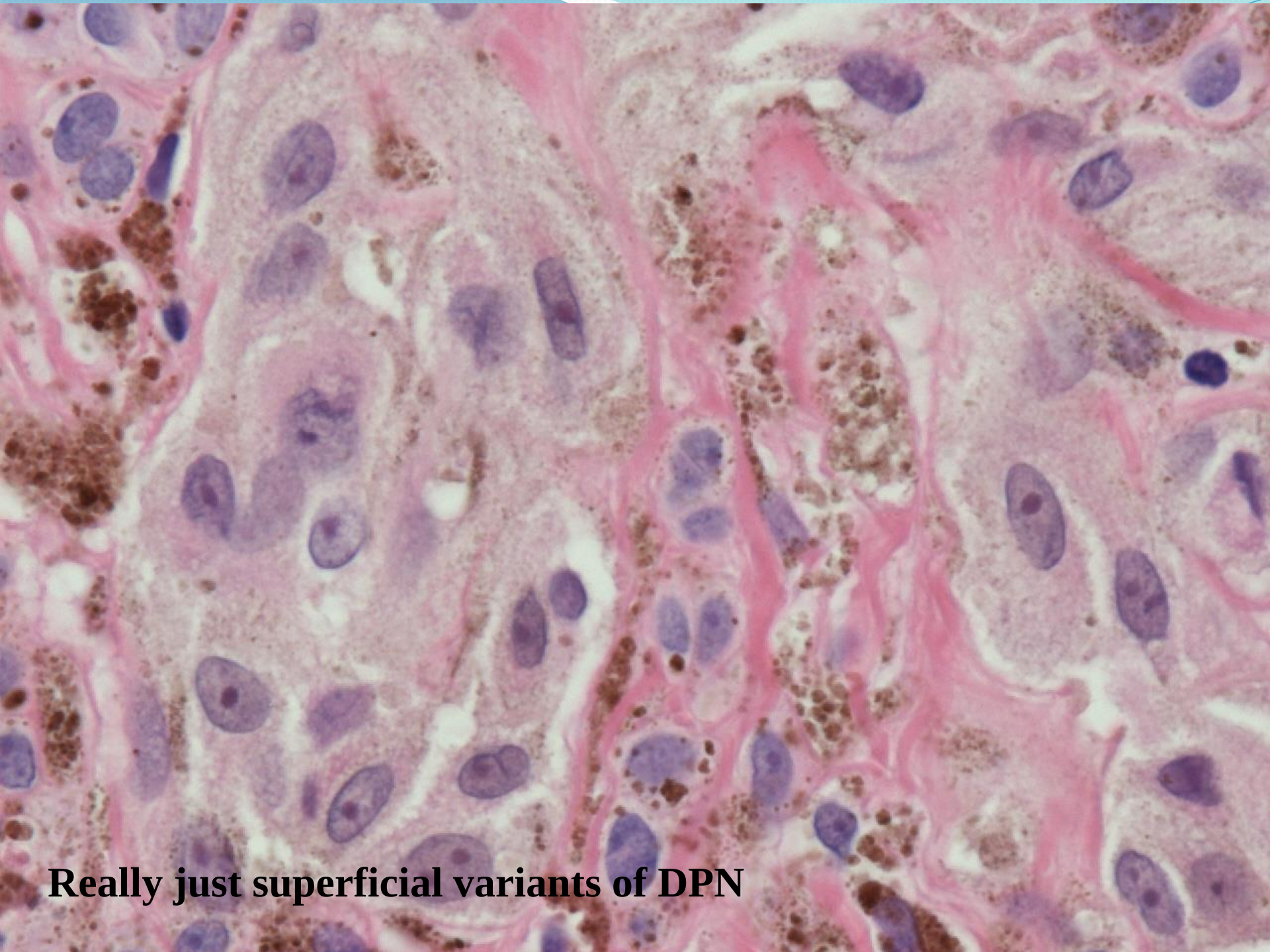
Clonal naevus...Type A inversion...Phenotypic heterogeneity ?




Clonal naevus....Inverted Type A naevus....Phenotypic heterogeneity

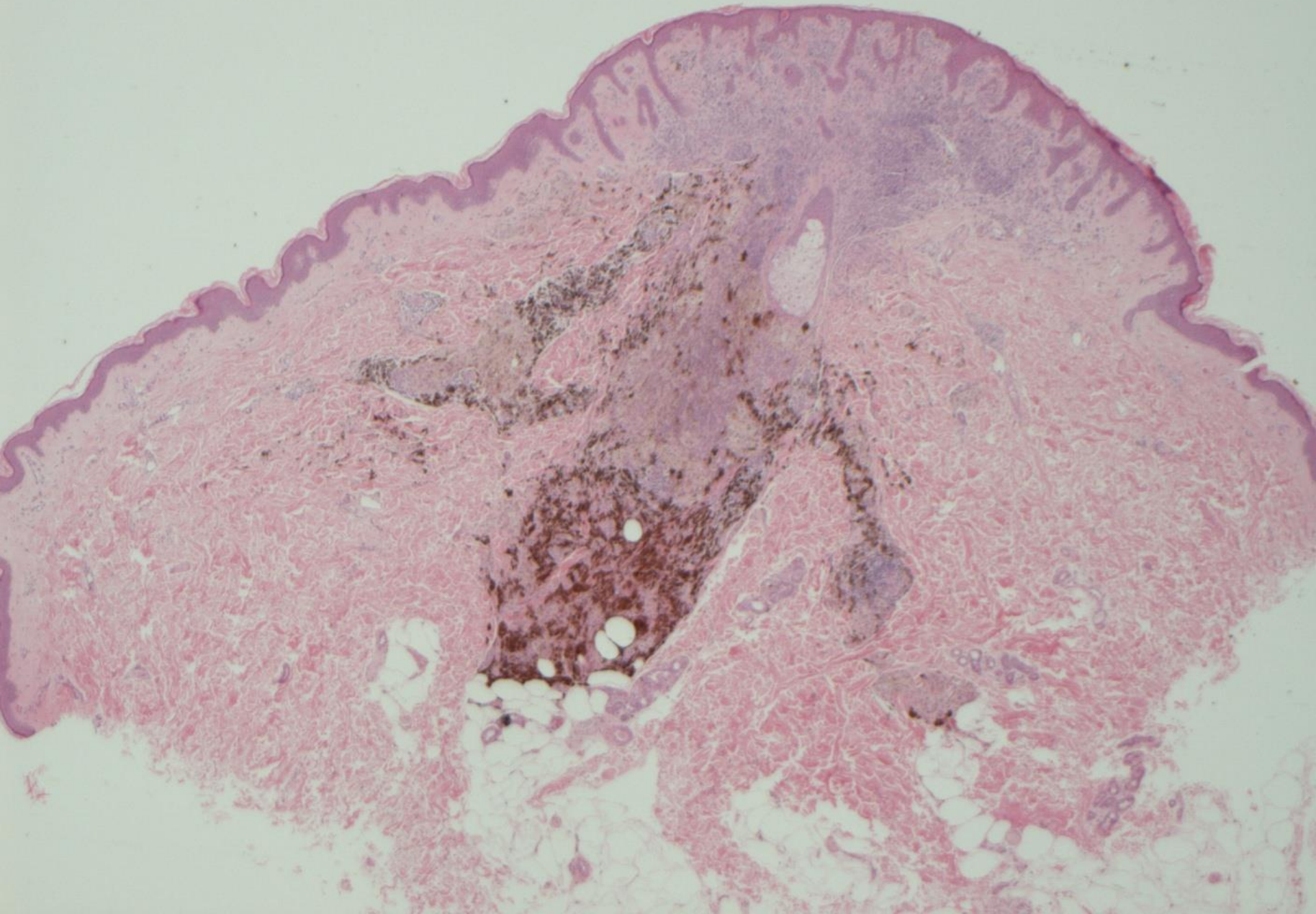
Looks familiar?



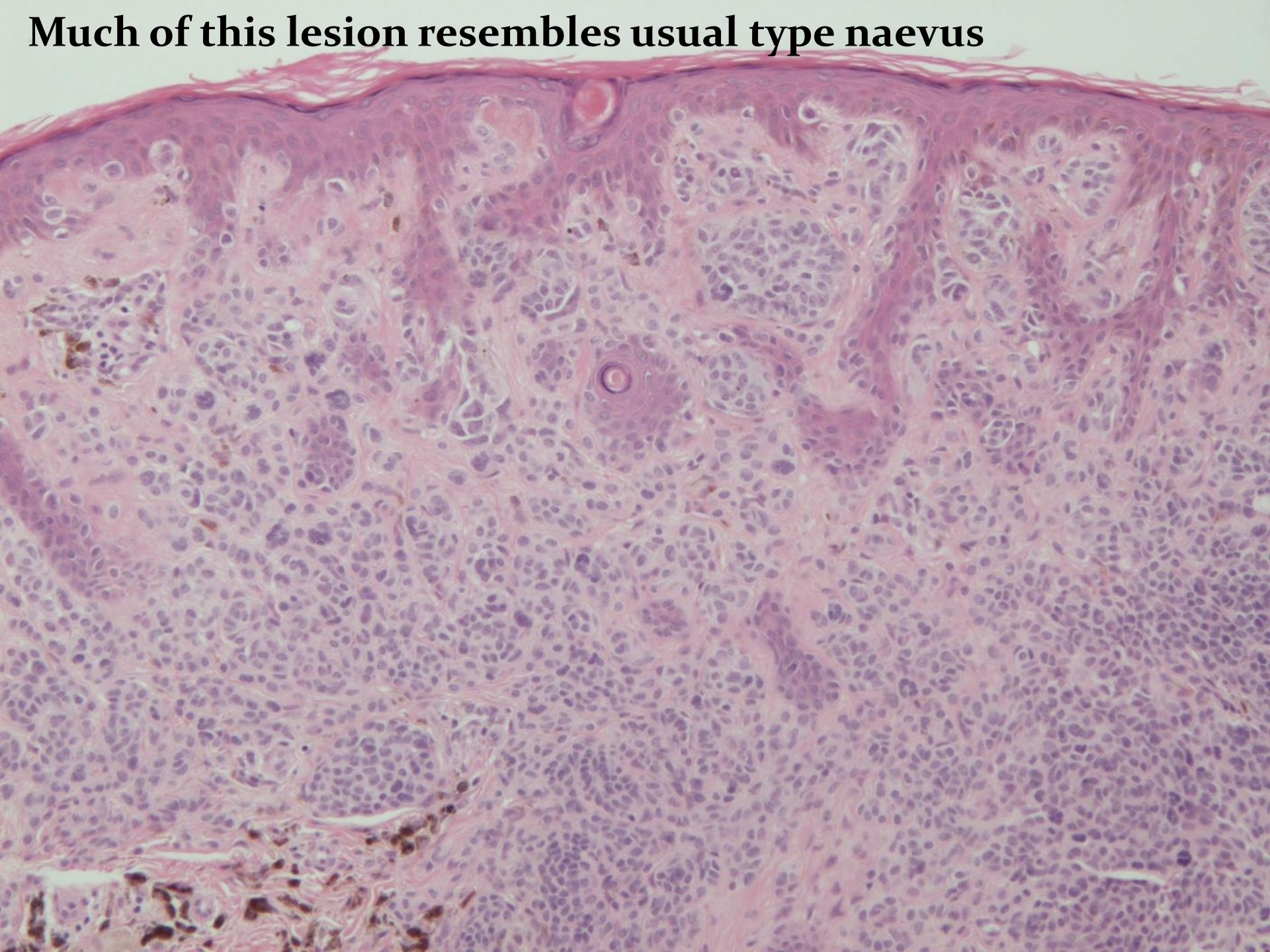

Really just superficial variants of DPN

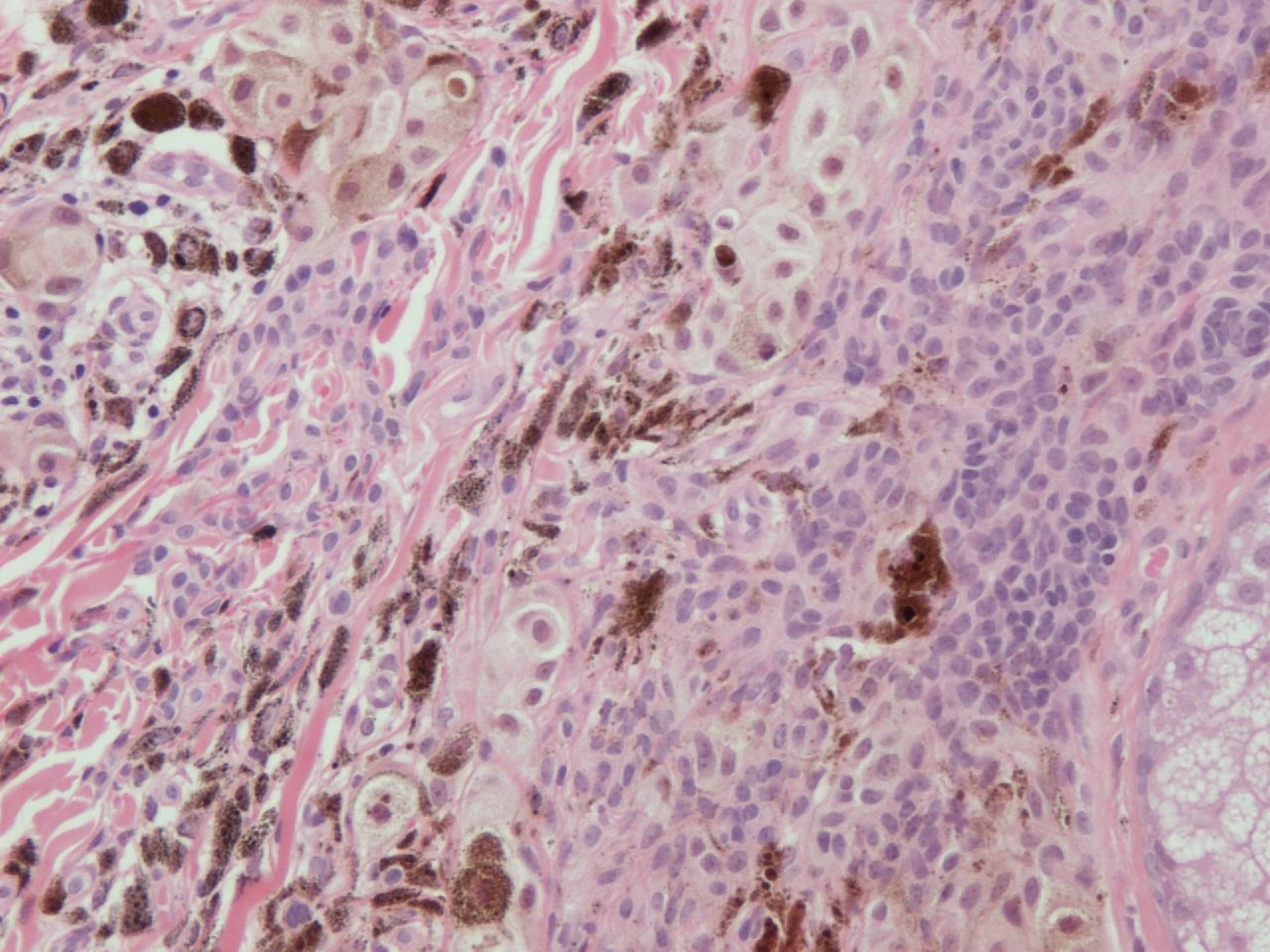
Is there a DPN family of lesions?

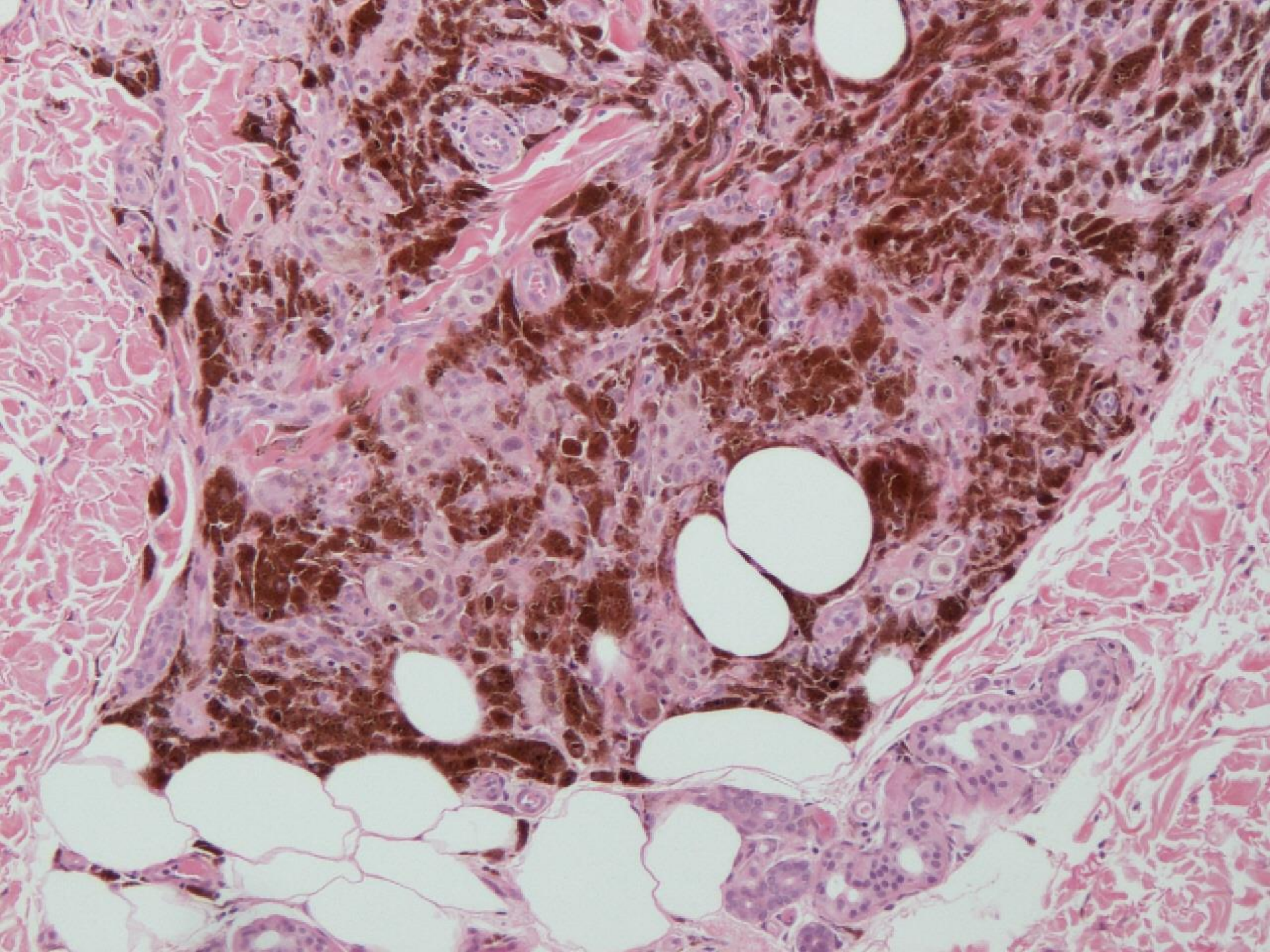
- Some lesions are better developed!



Much of this lesion resembles usual type naevus

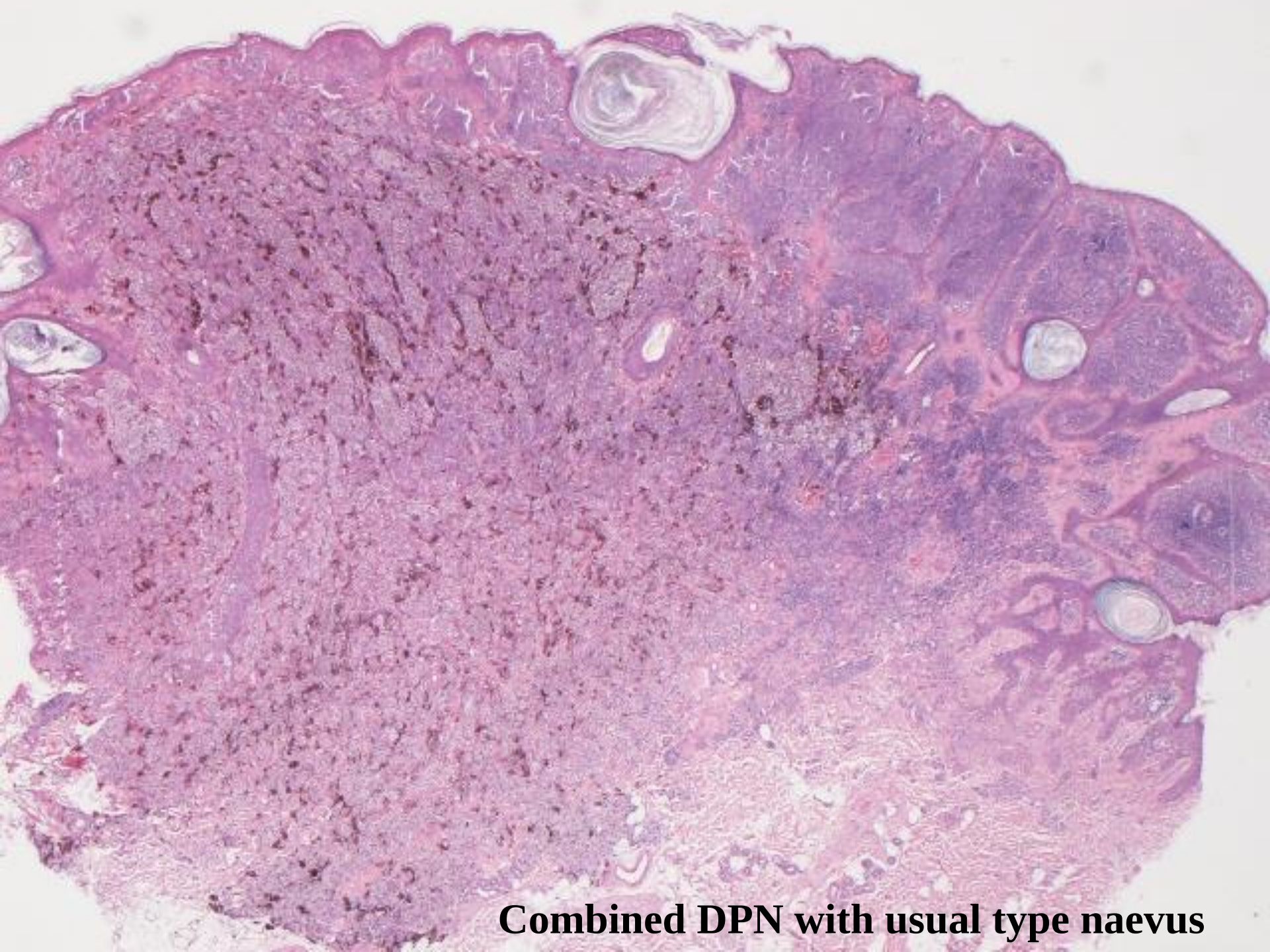






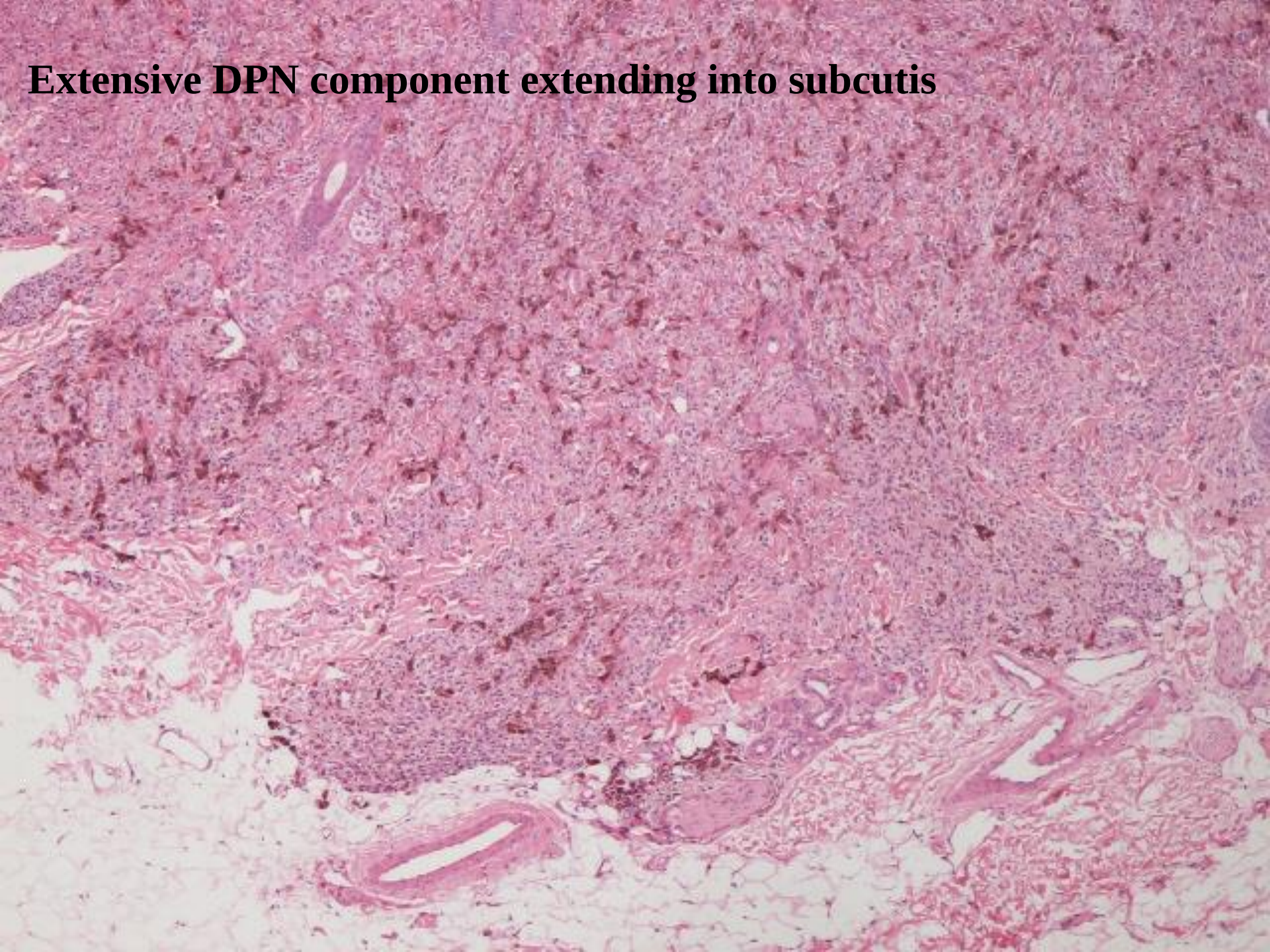
Is there a DPN family of lesions?

- Eventually some become dominated by DPN component



Combined DPN with usual type naevus

Extensive DPN component extending into subcutis



Is there a DPN family of lesions?

- Pretty good evidence of different stages of development

- **Early -** lesions with cytological features of DPN
- **Intermediate -** combined lesions with co-existing UTN
- **Late -** fully evolved lesions where DPN dominates

Is there a DPN family of lesions?

- Recent molecular evidence to support the DPN concept

- Yeh et al. Nature Communications published on-line Sept

Combined activation of MAP kinase pathway and B-catenin signaling cause deep penetrating naevi.

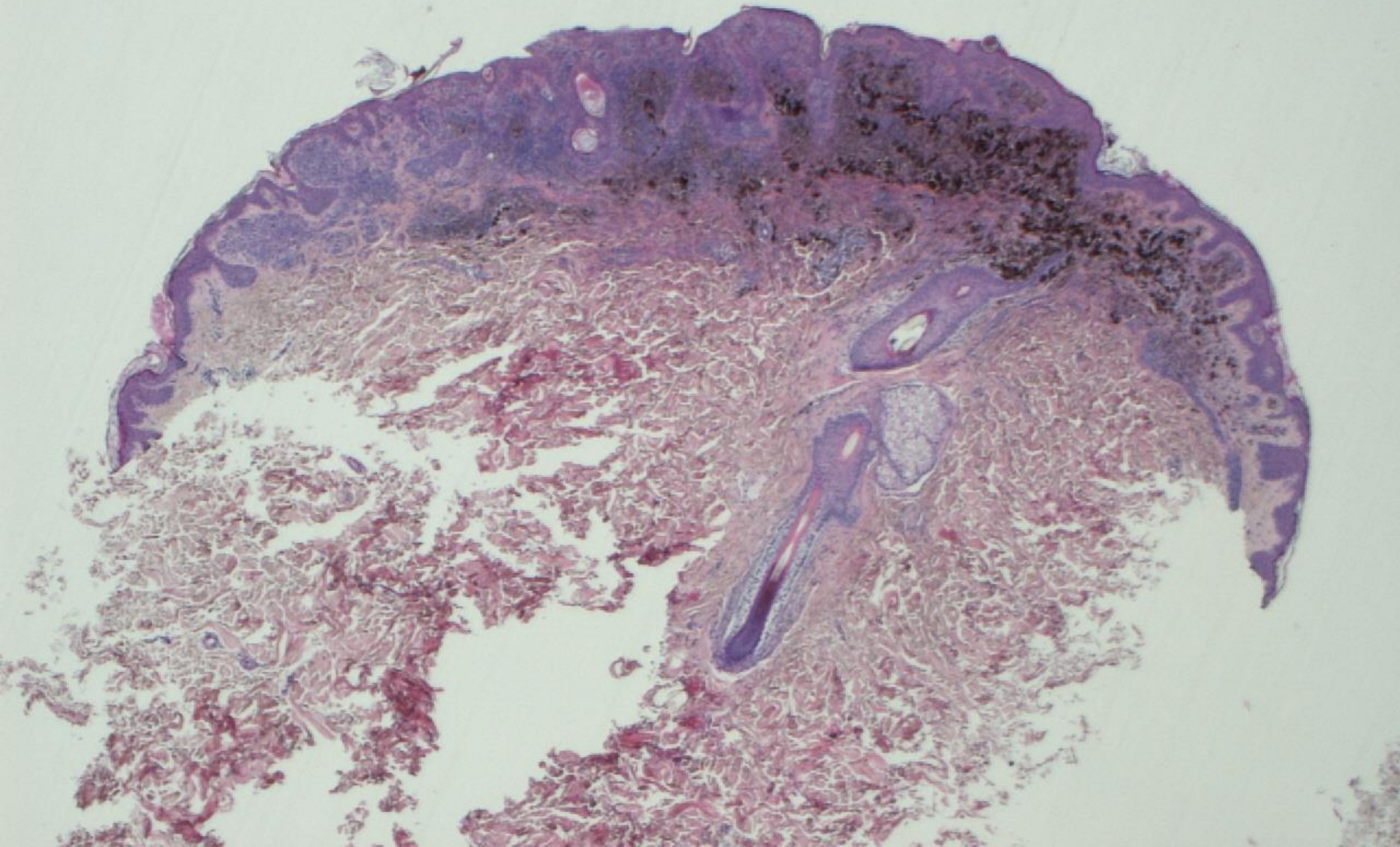
Is there a DPN family of lesions?

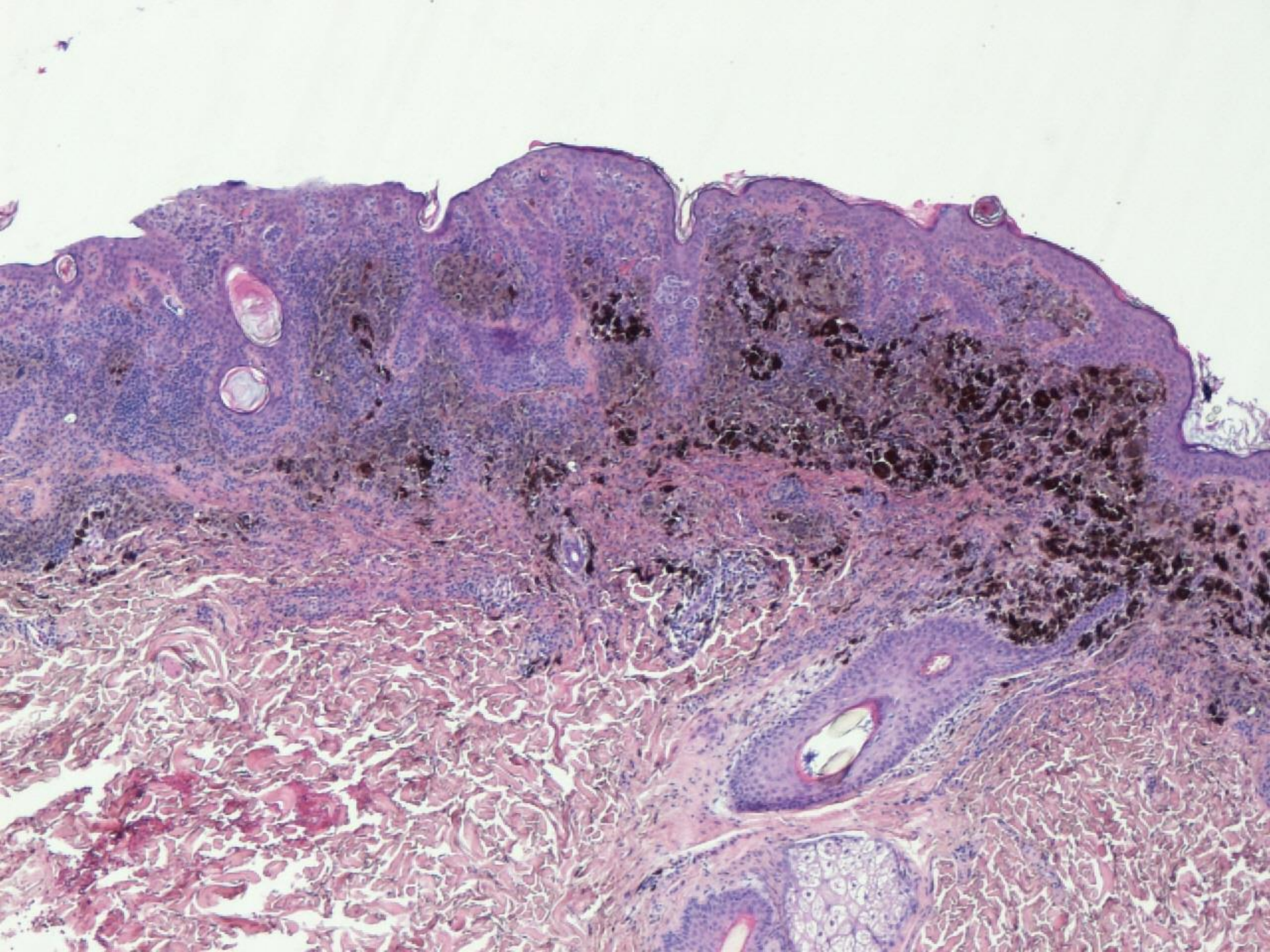
- Majority of common naevi are clonal proliferations of melanocytes harbouring BRAF V600 E mutation
- Hitherto the genetic drivers in DPN not known
- Lack the GNAQ and GNA11 mutations of blue naevi
- Lack HRAS mutations often found in Spitz naevi

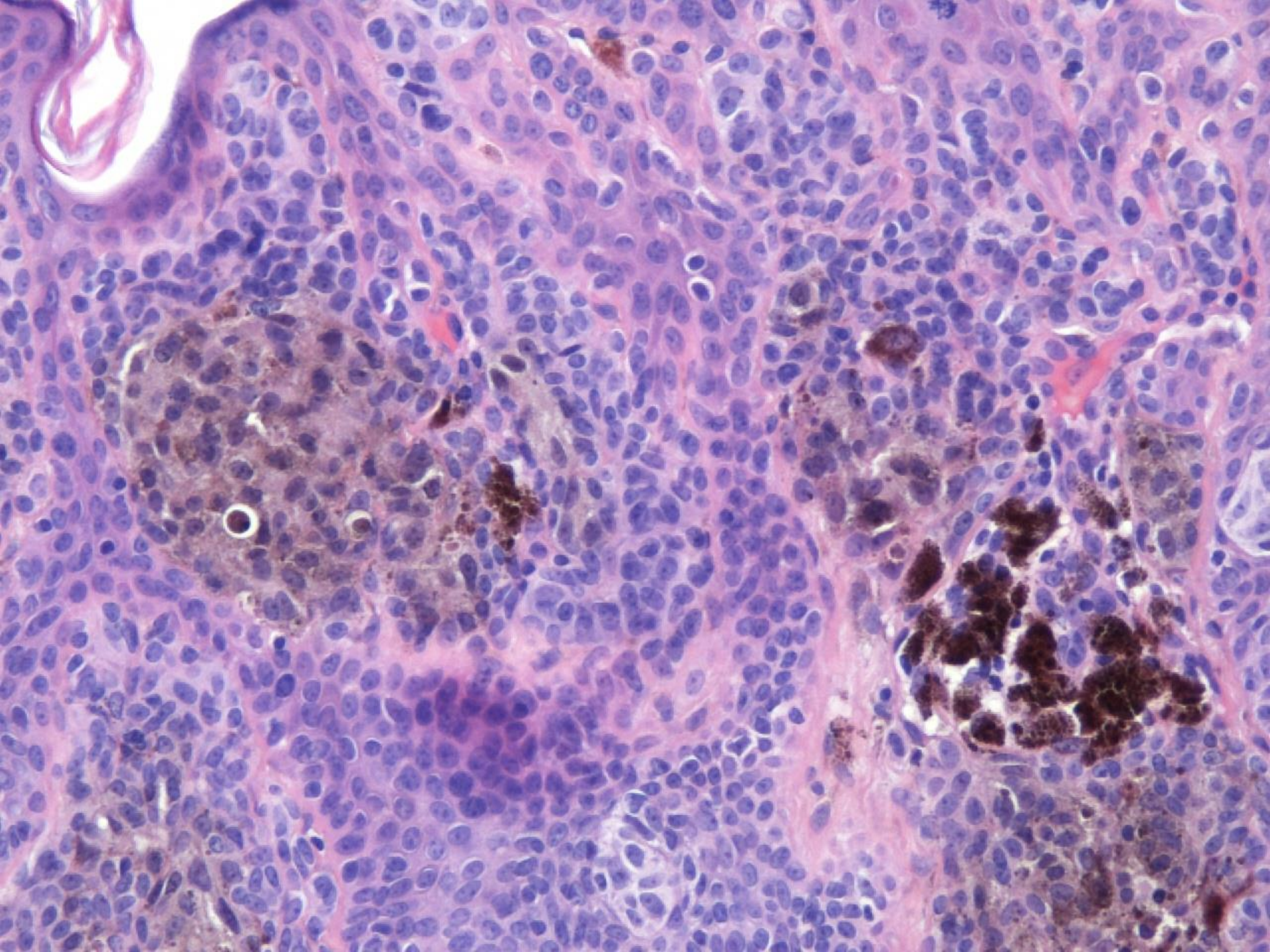
Is there a DPN family of lesions?

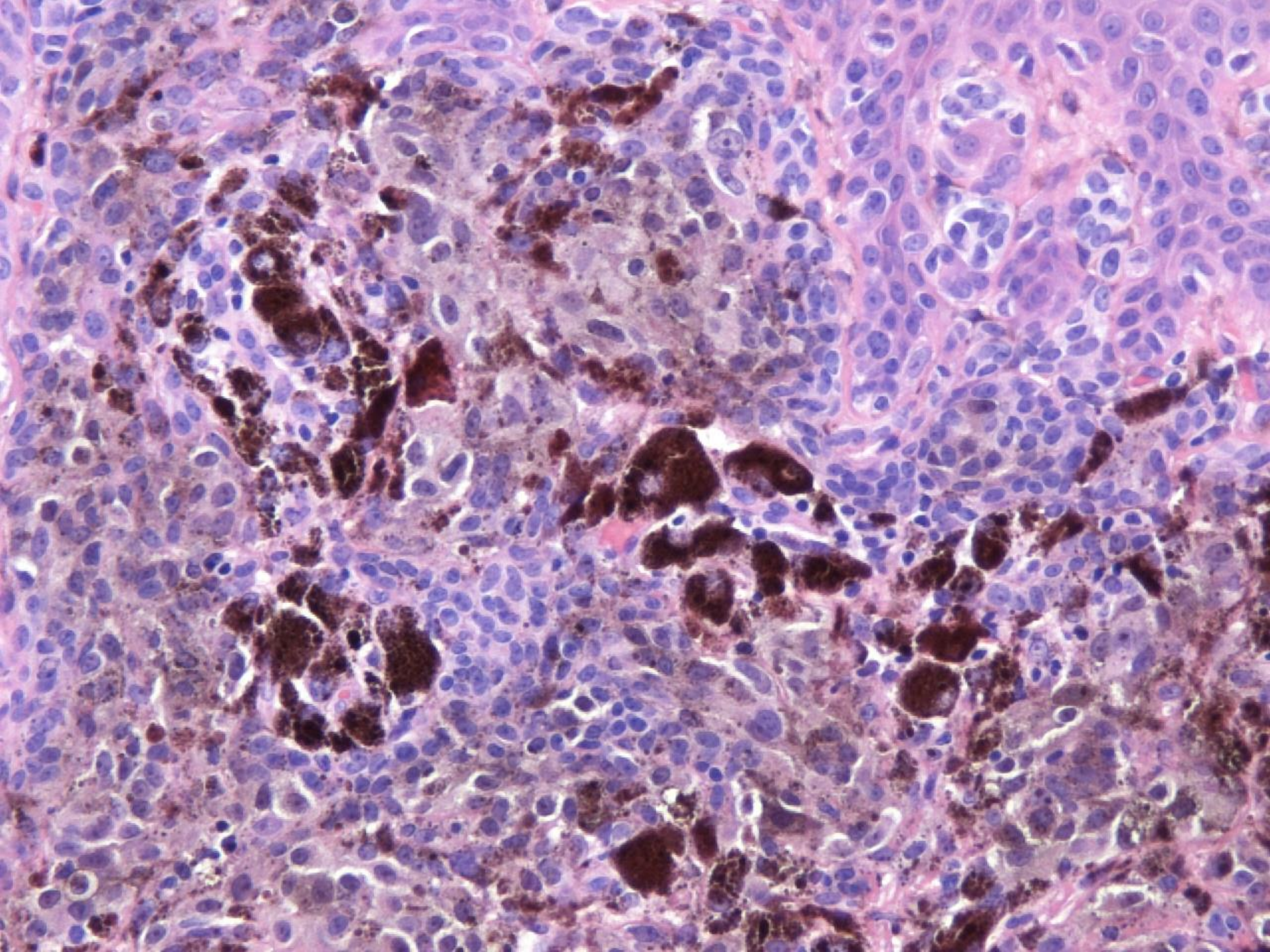
- Yeh et al. Found 17/18 DPN had activating mutations in CTNNB1 the gene encoding beta catenin
- 16/18 also had mutations in the MAP kinase pathway
- Cyclin-D1 direct transcriptional target of beta catenin
- DPN show strong and uniform expression of Cyclin D1
- Acquisition of these mutations determines cell size and pigmentation

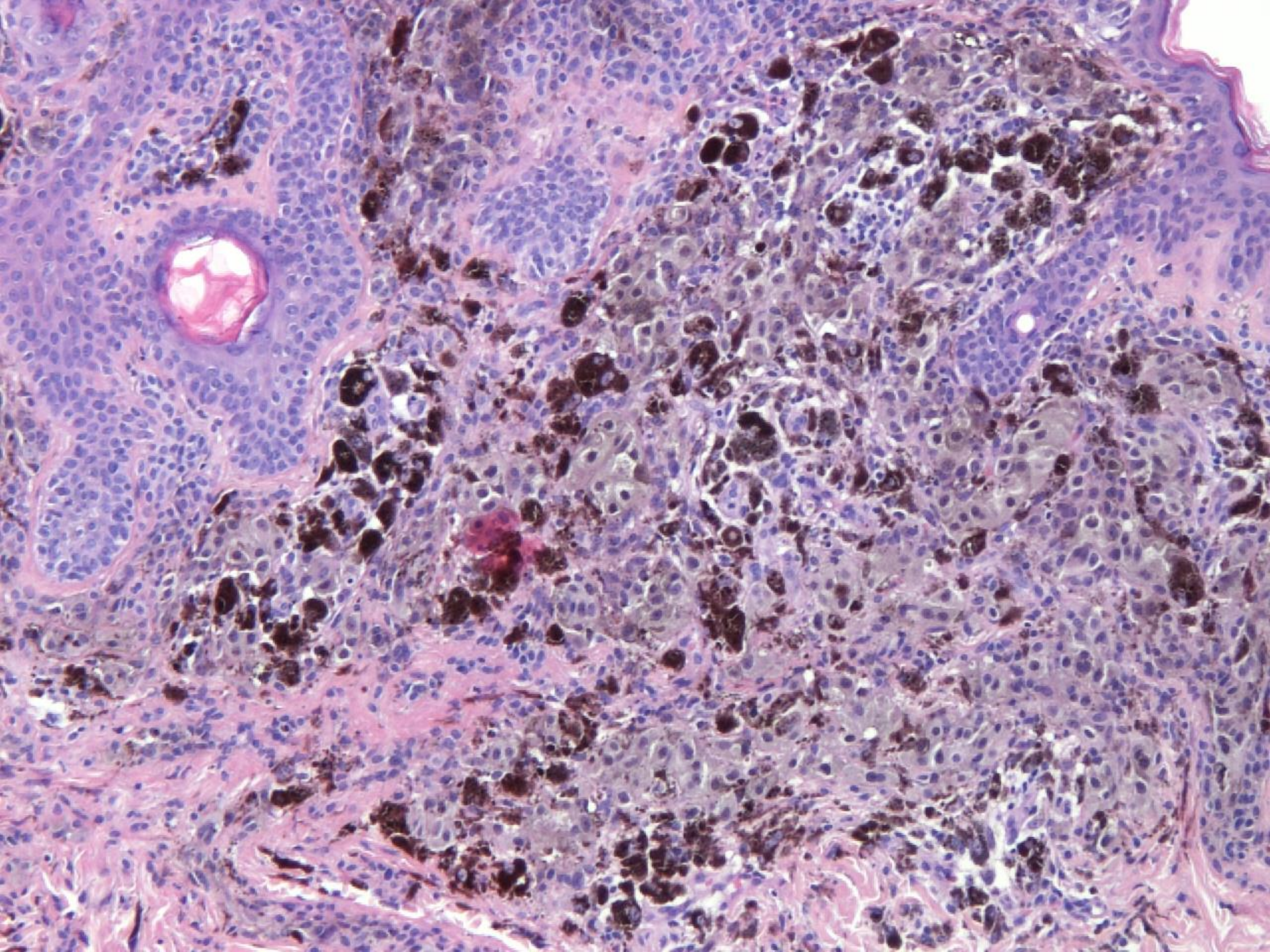
Challenging lesion from breast of F. aged 24

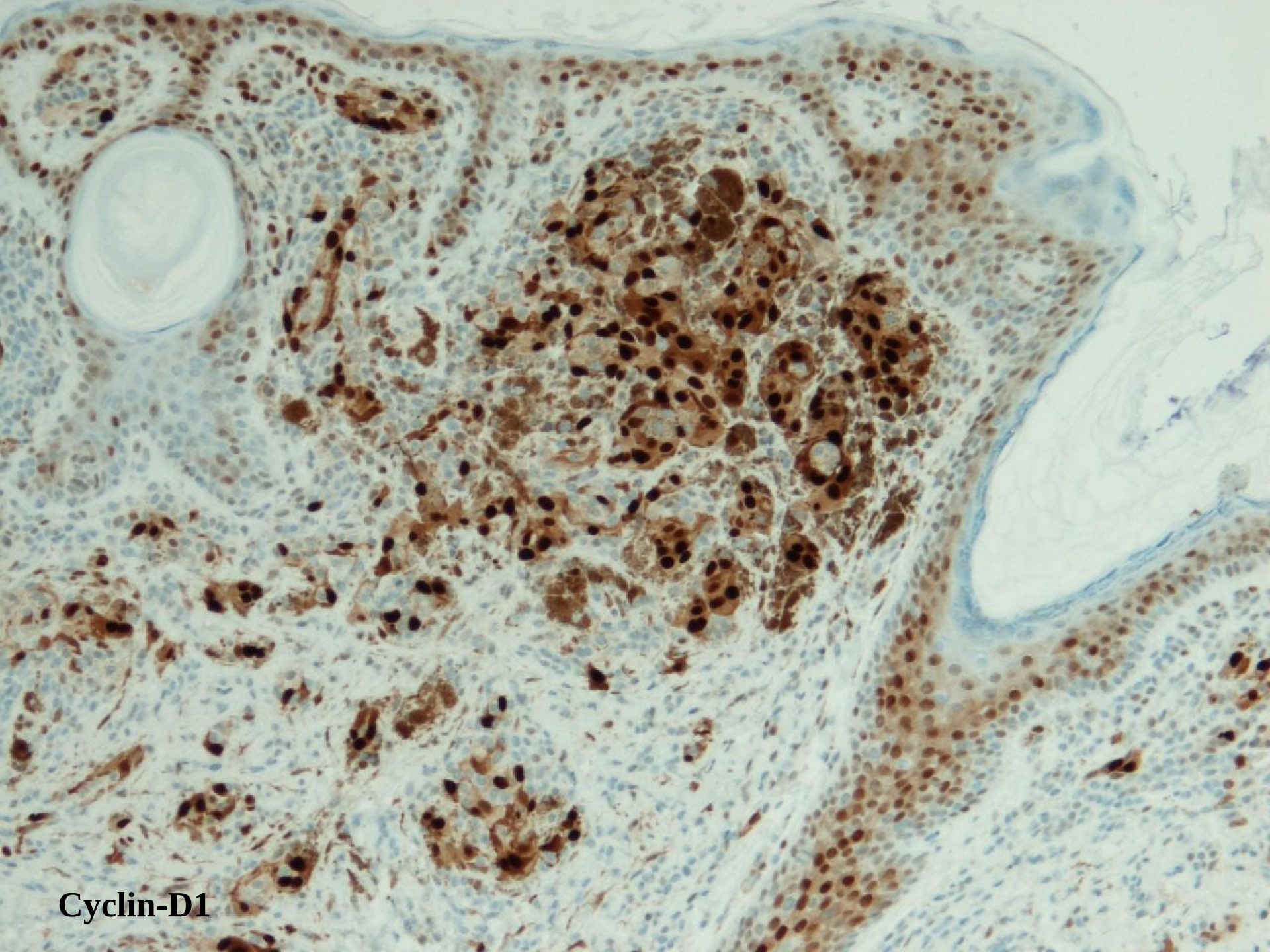


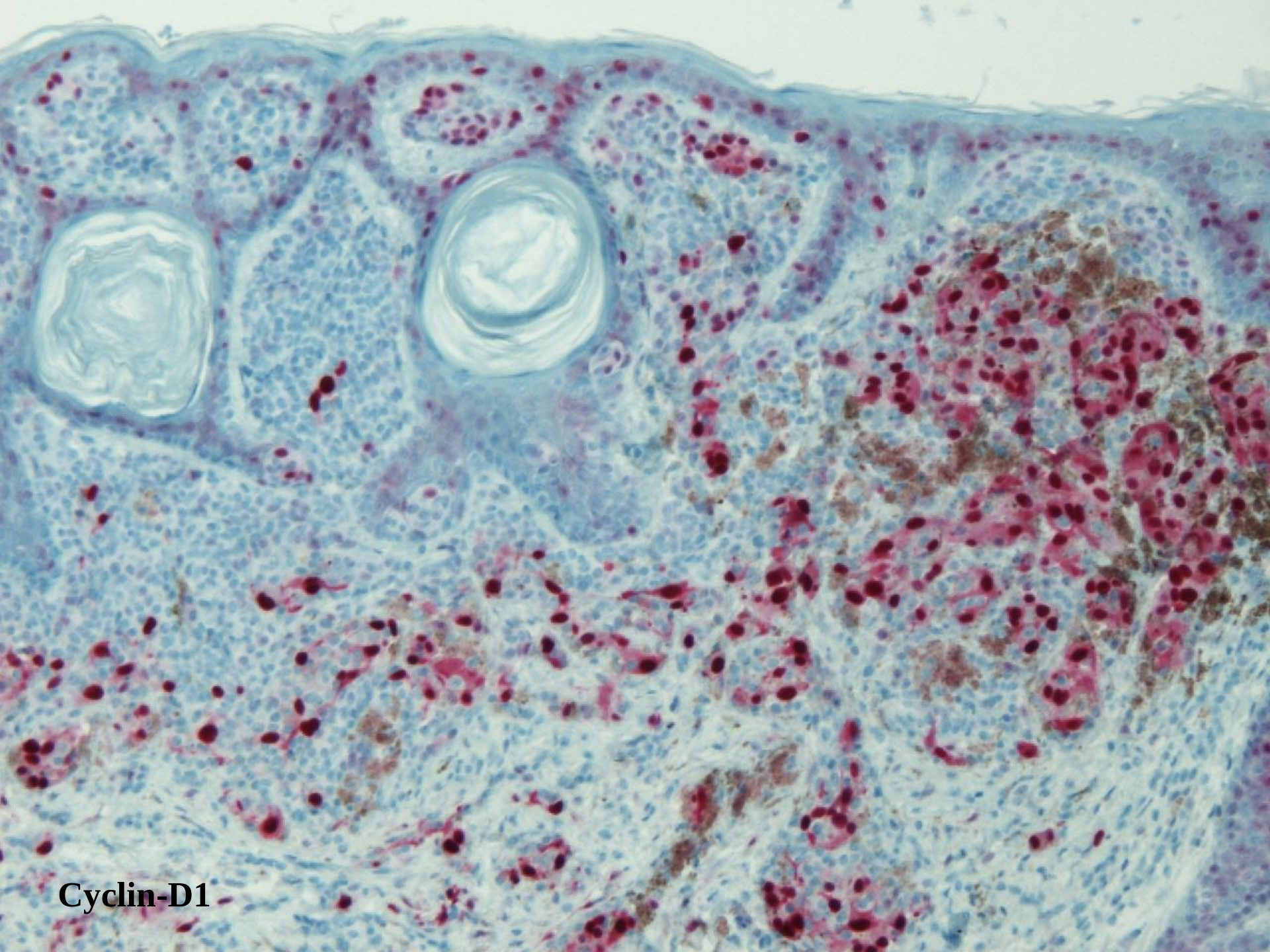


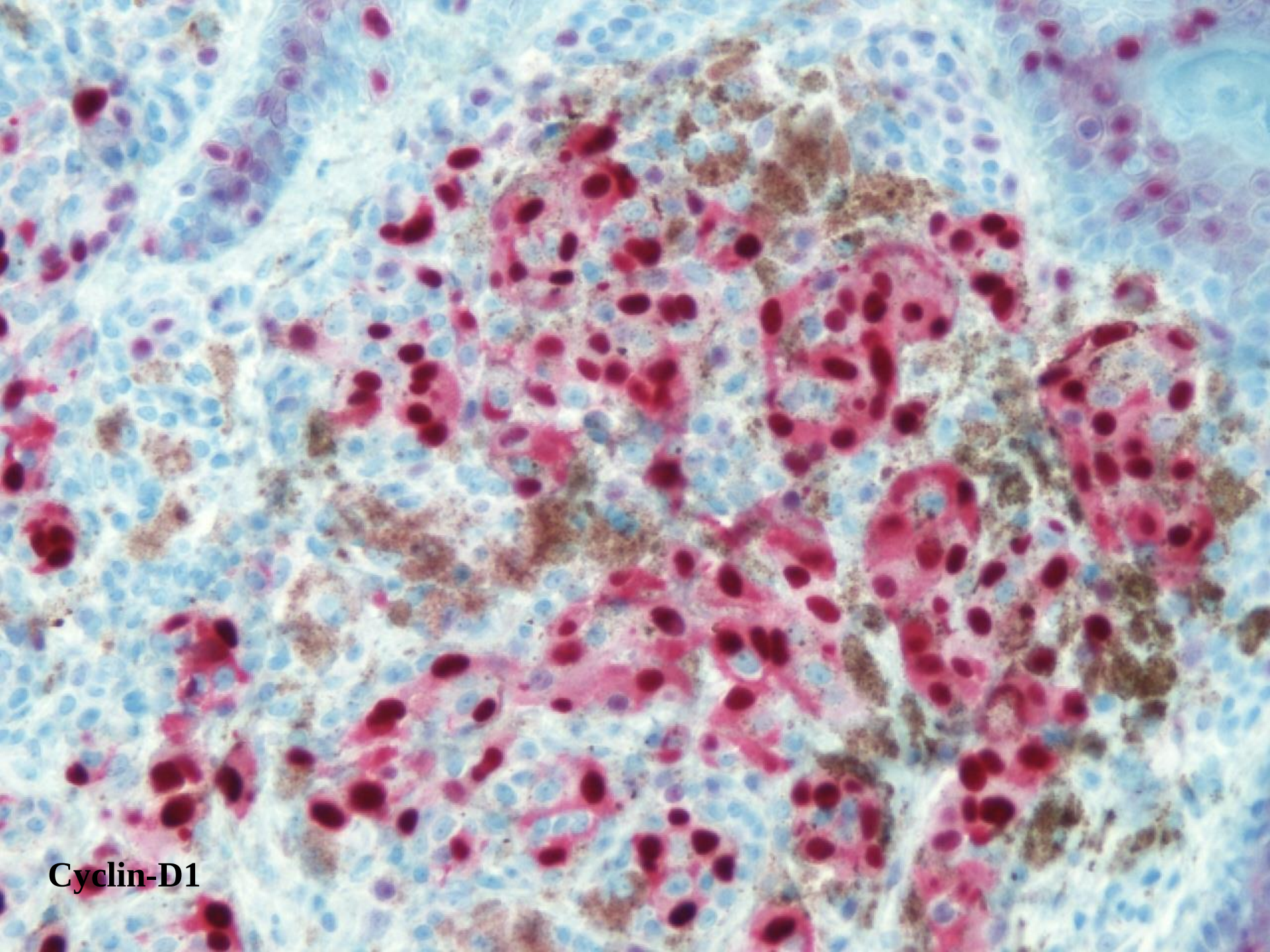


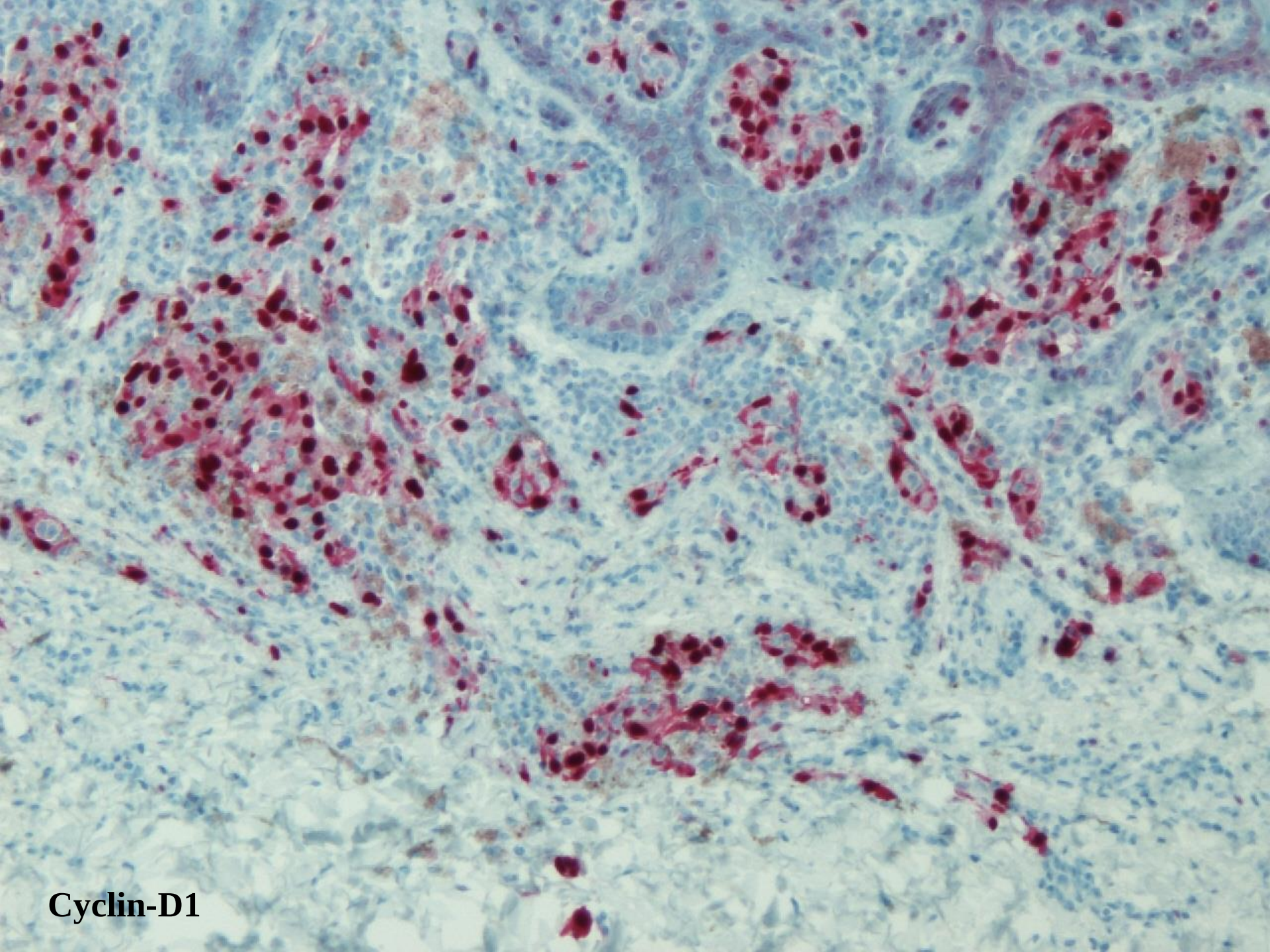


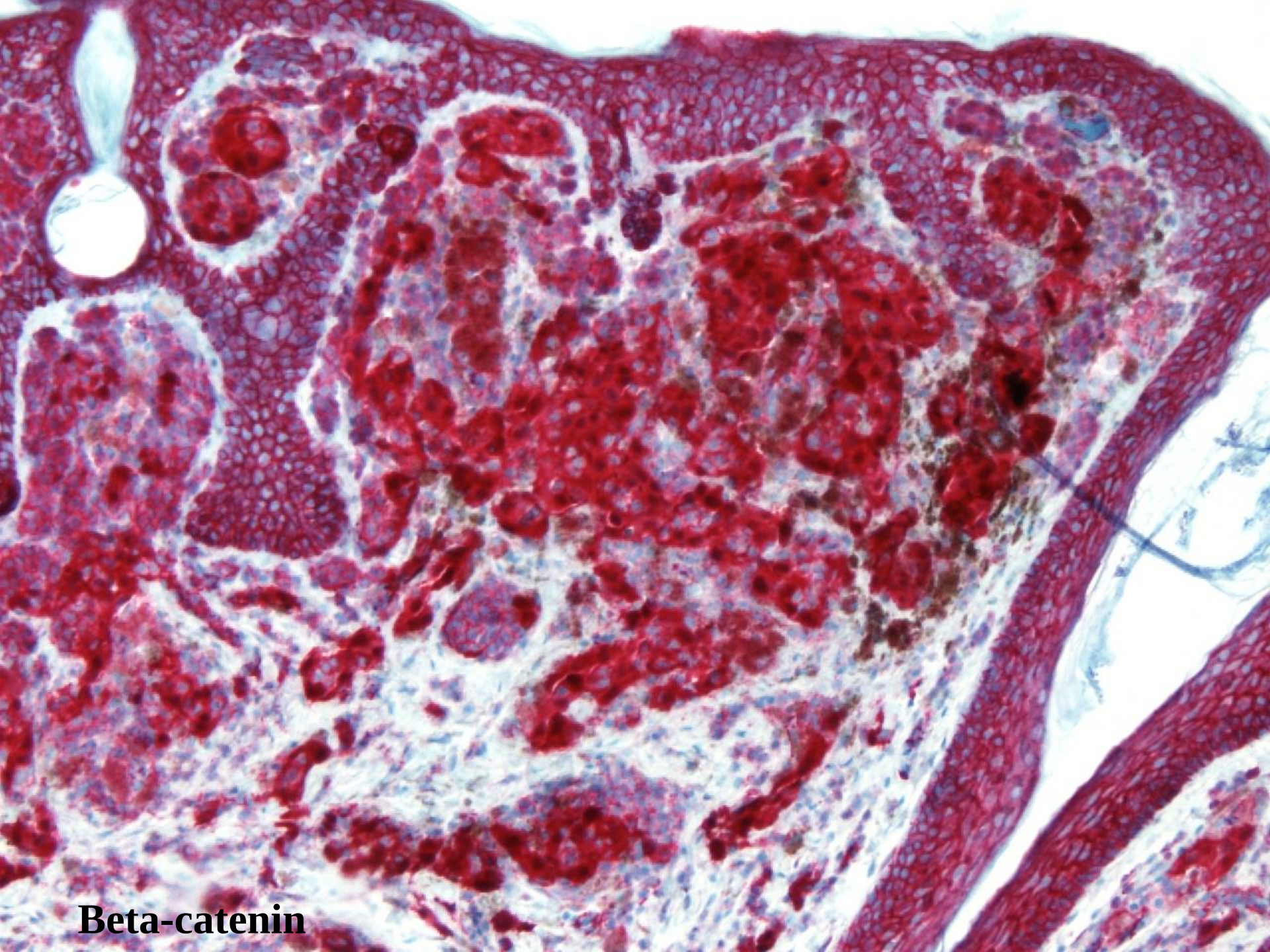



Cyclin-D1


Cyclin-D1


Cyclin-D1


Cyclin-D1


Beta-catenin

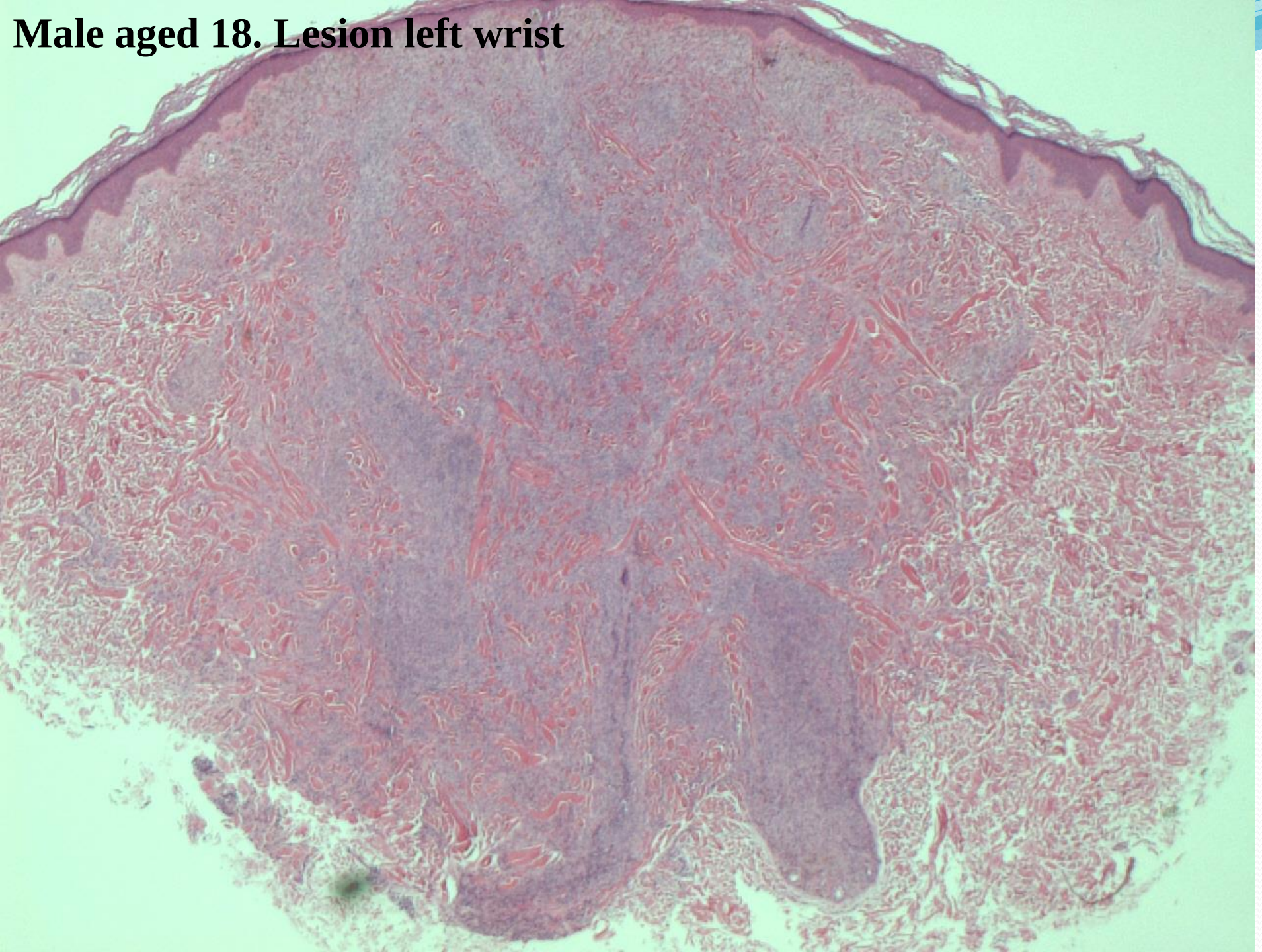
Is there a DPN family of lesions?

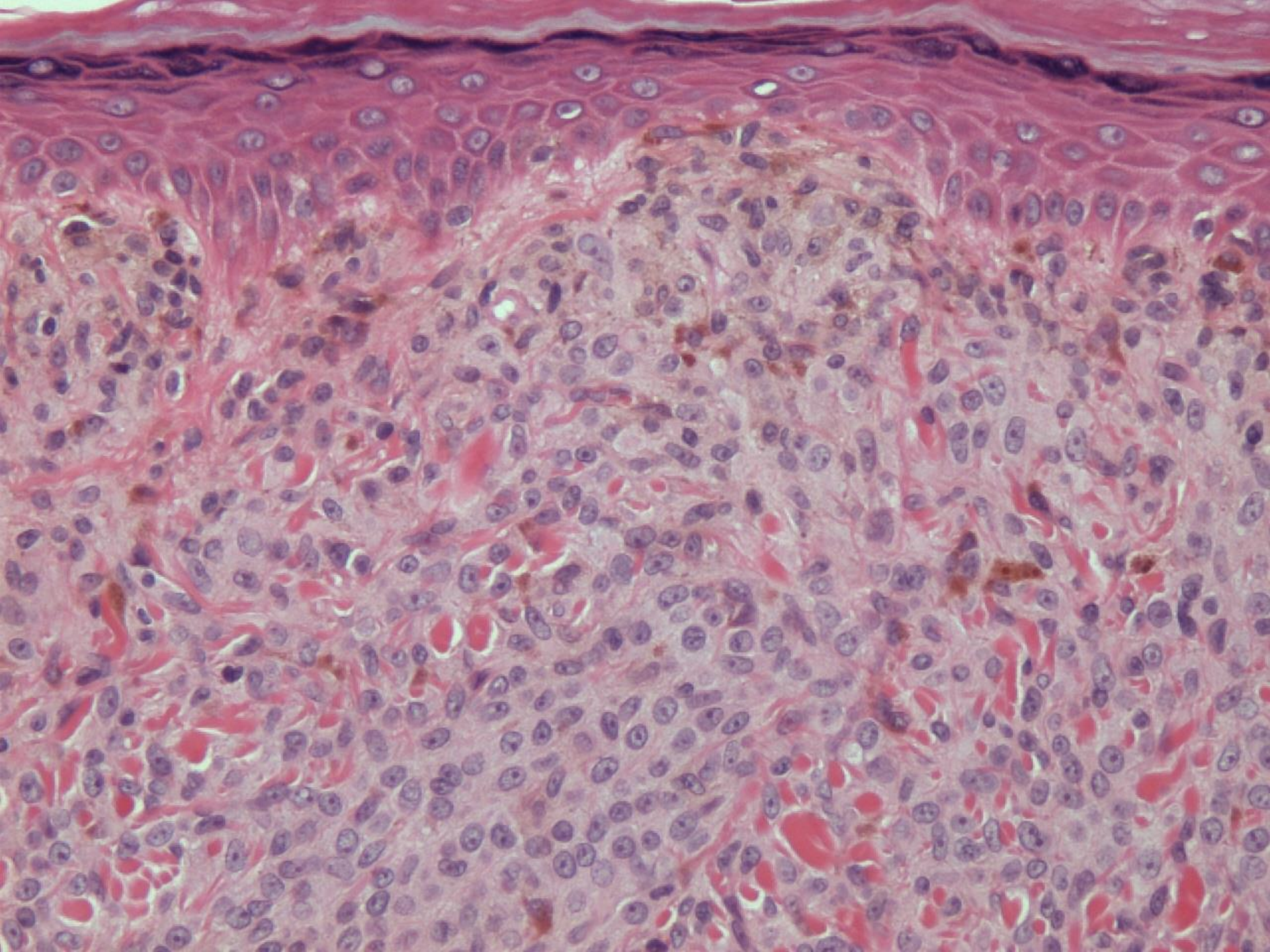
- **Do DPN-like lesions with atypia or malignancy exist?**

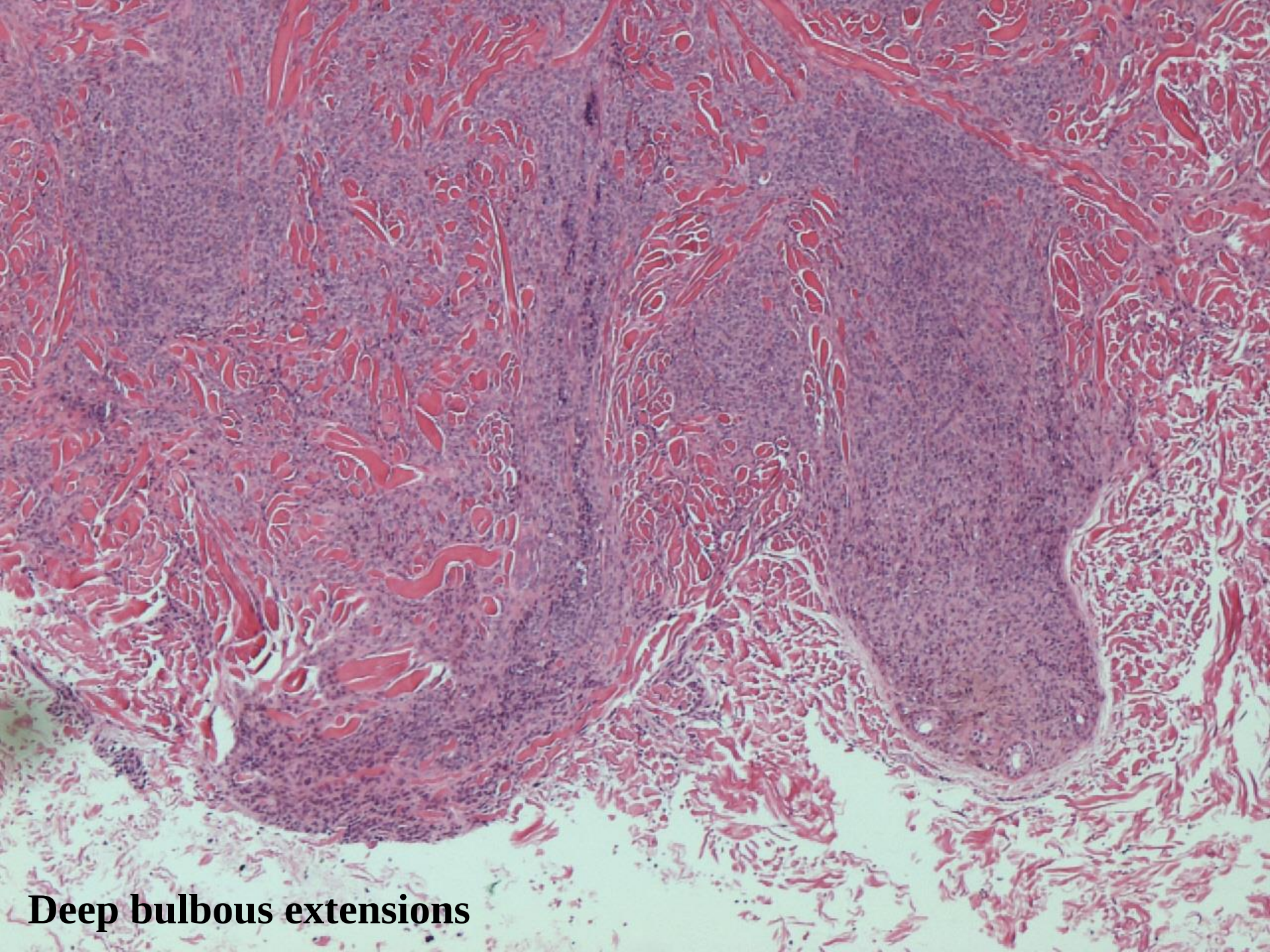
- Magro et al. Eur J Dermatol 2014: 24 (5) :594-602

Deep penetrating nevus-like borderline tumors: a unique subset of ambiguous melanocytic tumours with malignant potential and normal cytogenetics

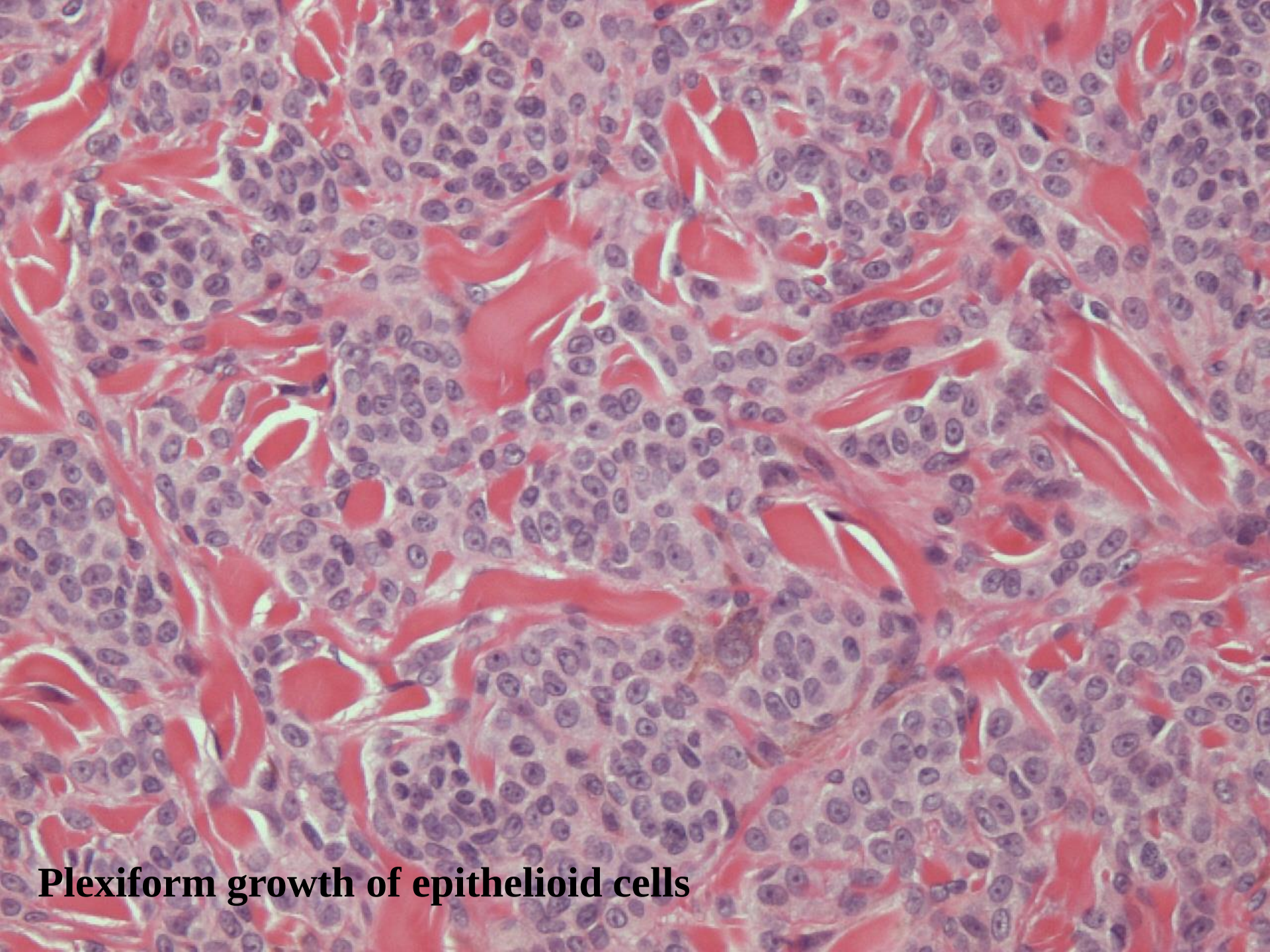
Male aged 18. Lesion left wrist



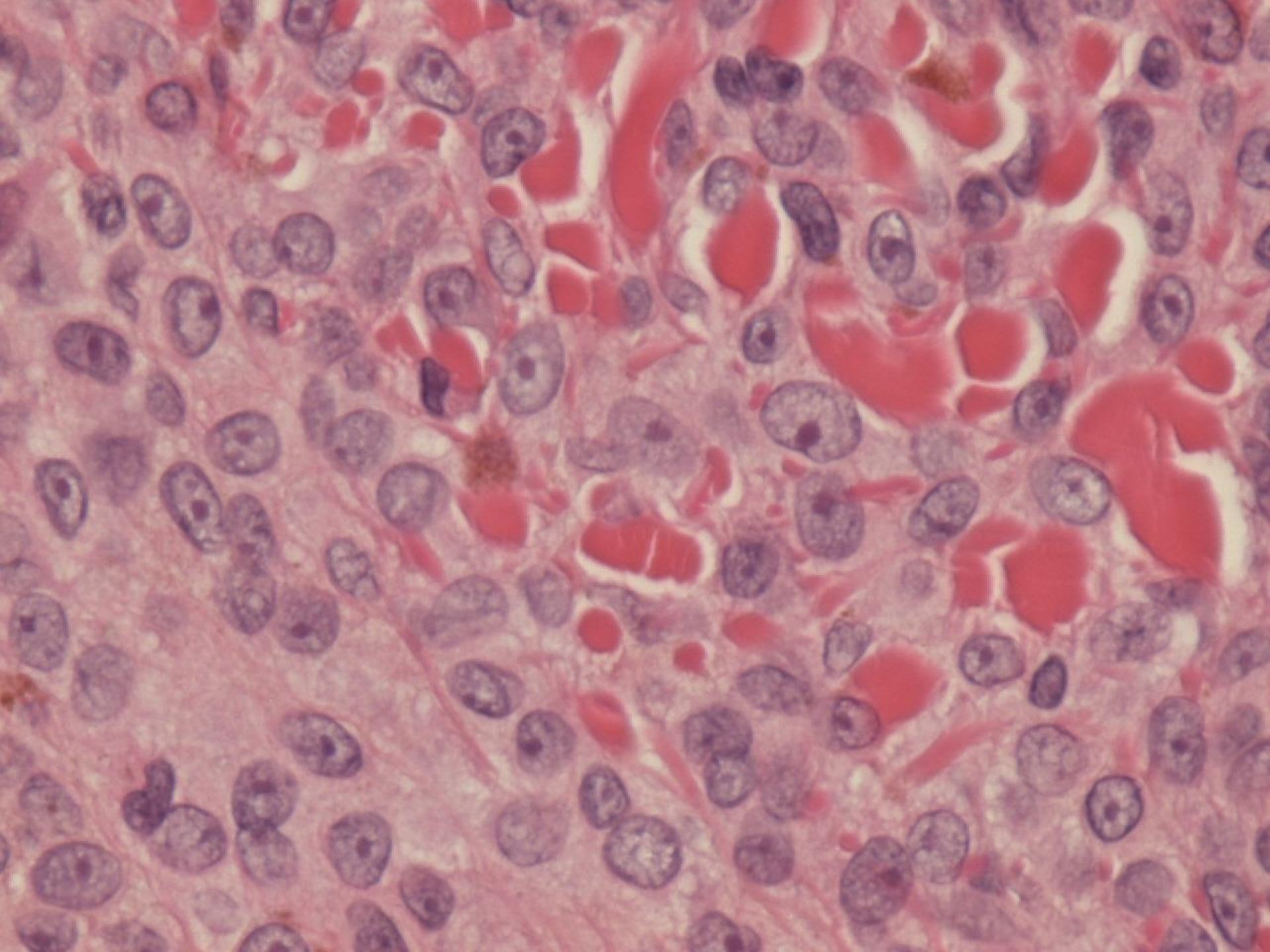


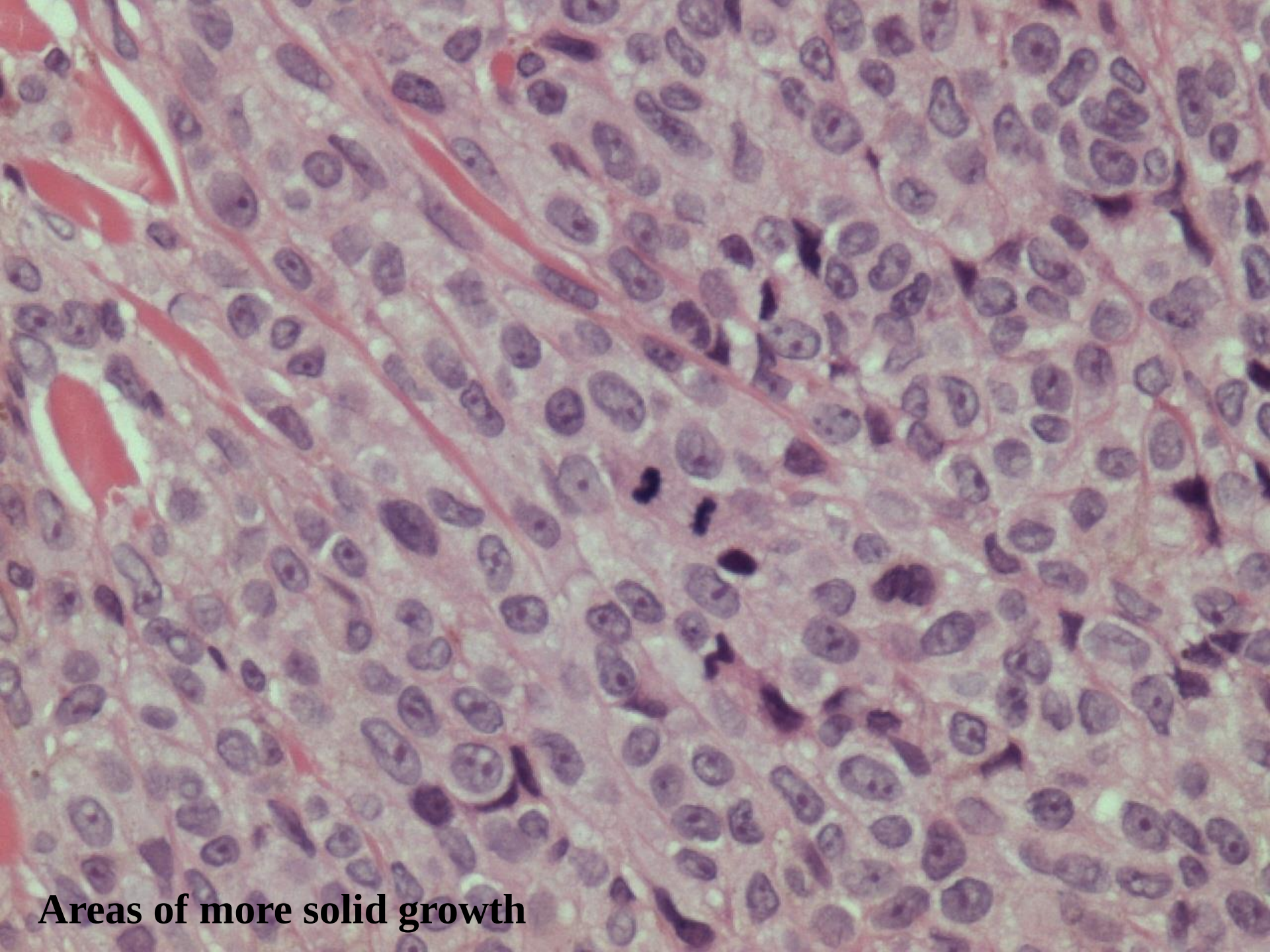


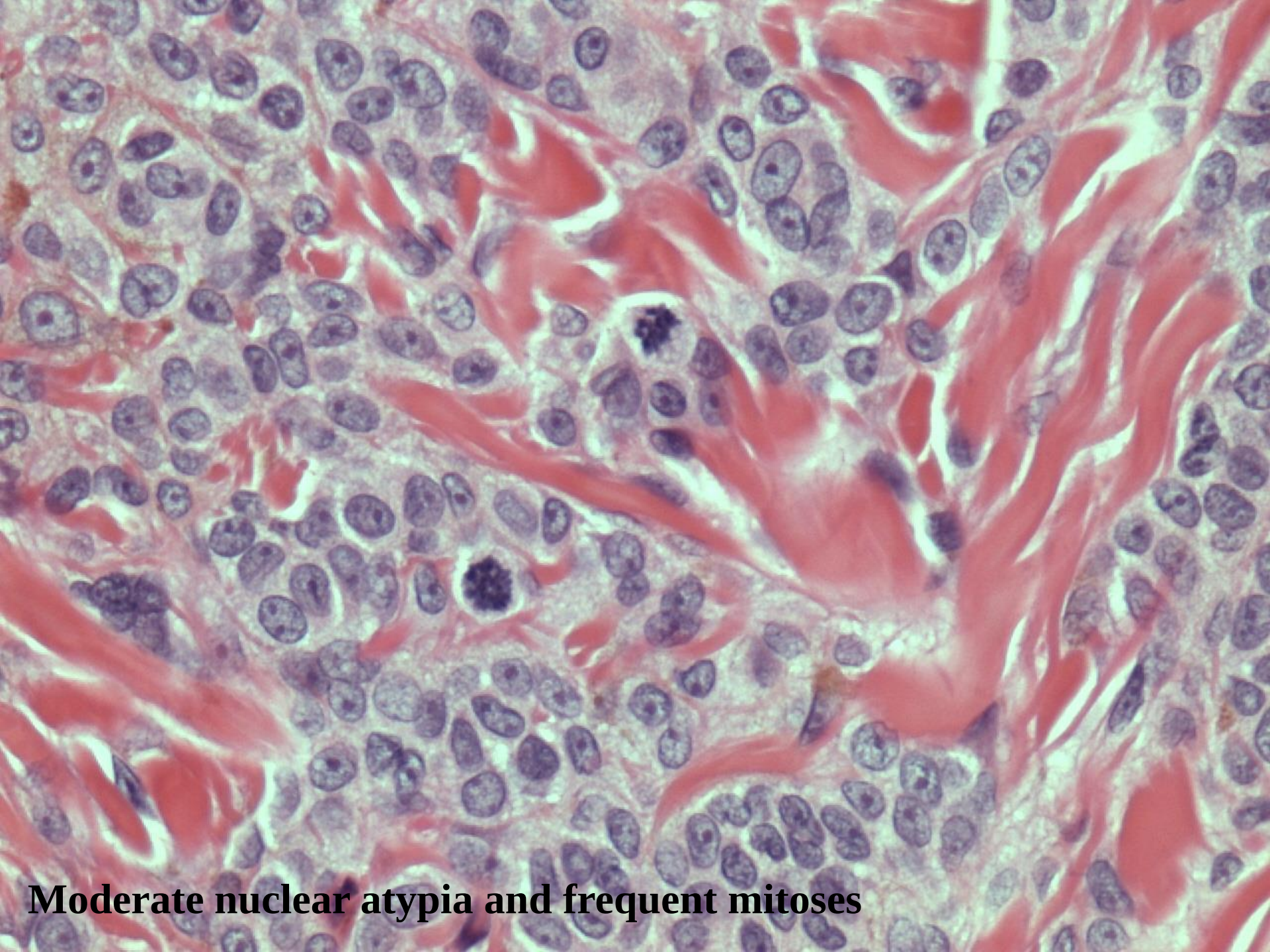
Deep bulbous extensions



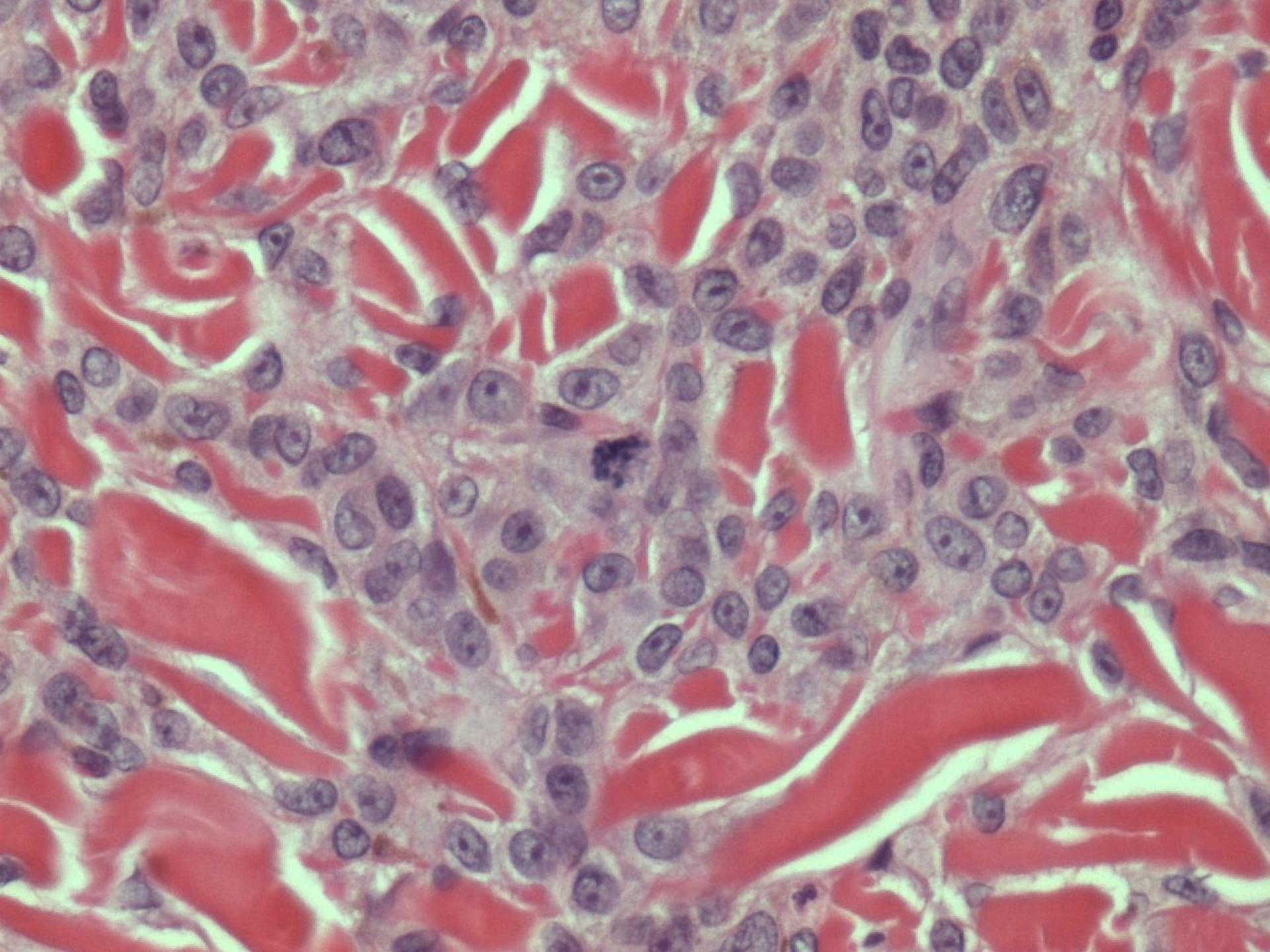
Plexiform growth of epithelioid cells

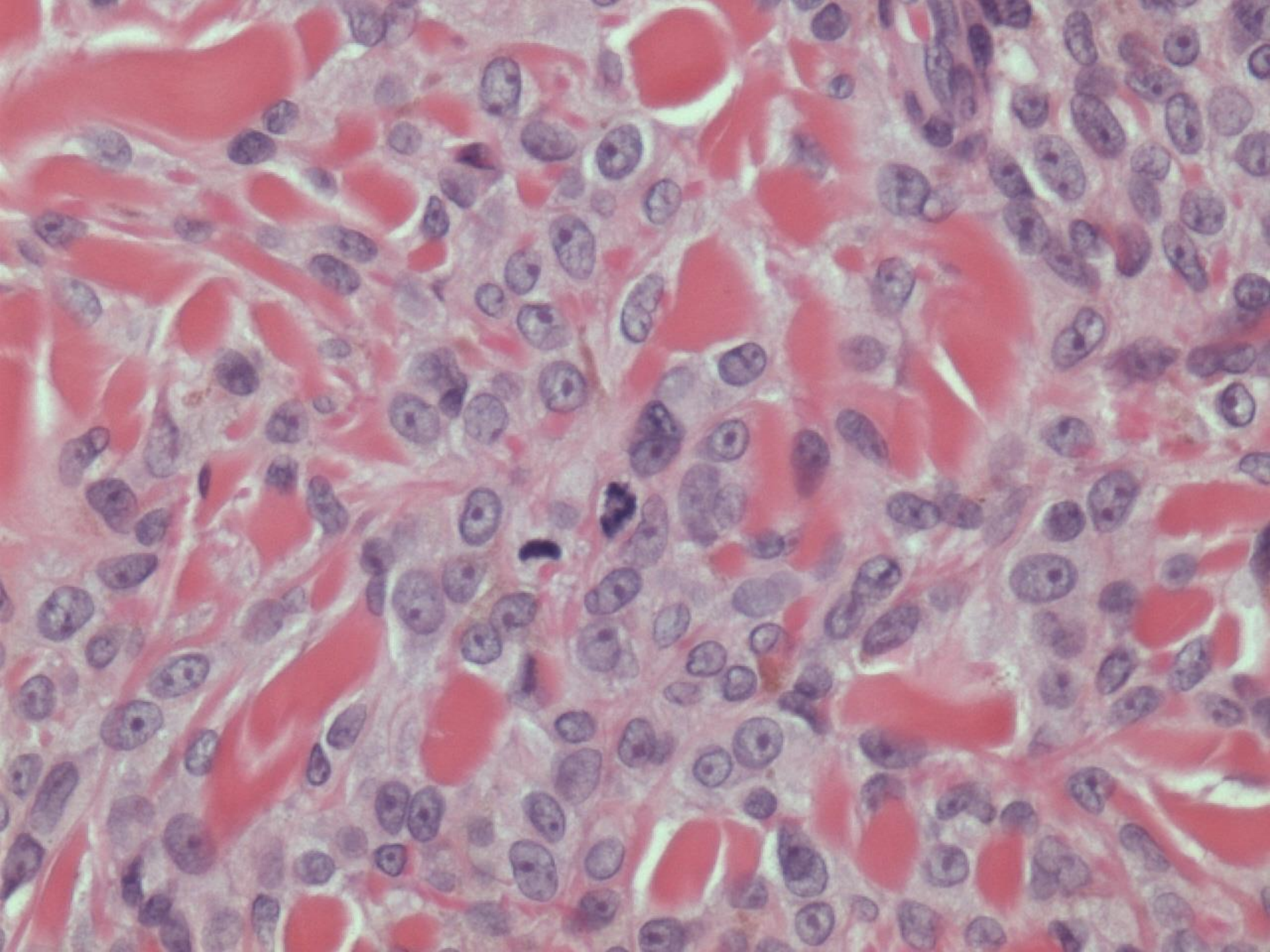


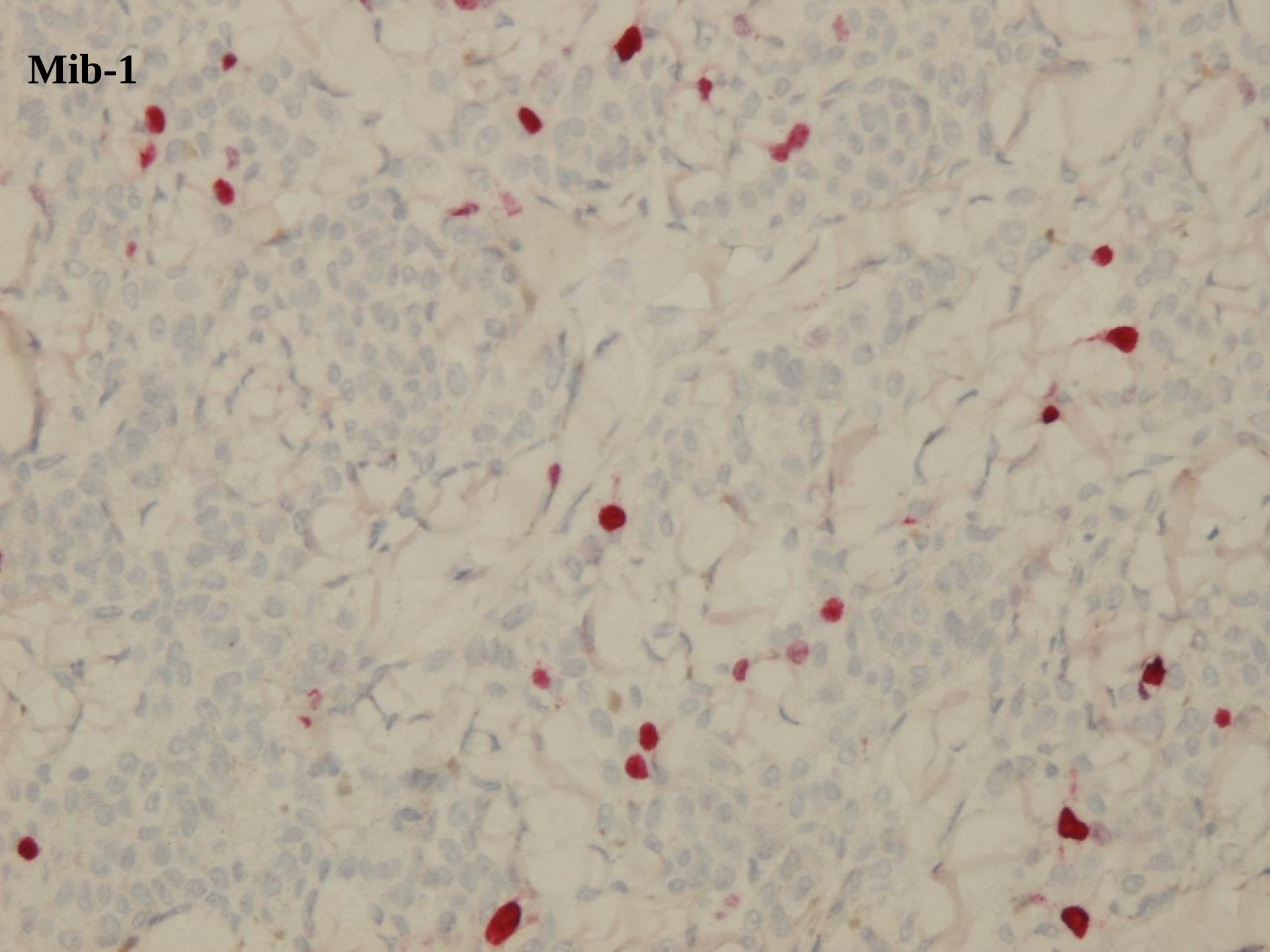

Areas of more solid growth

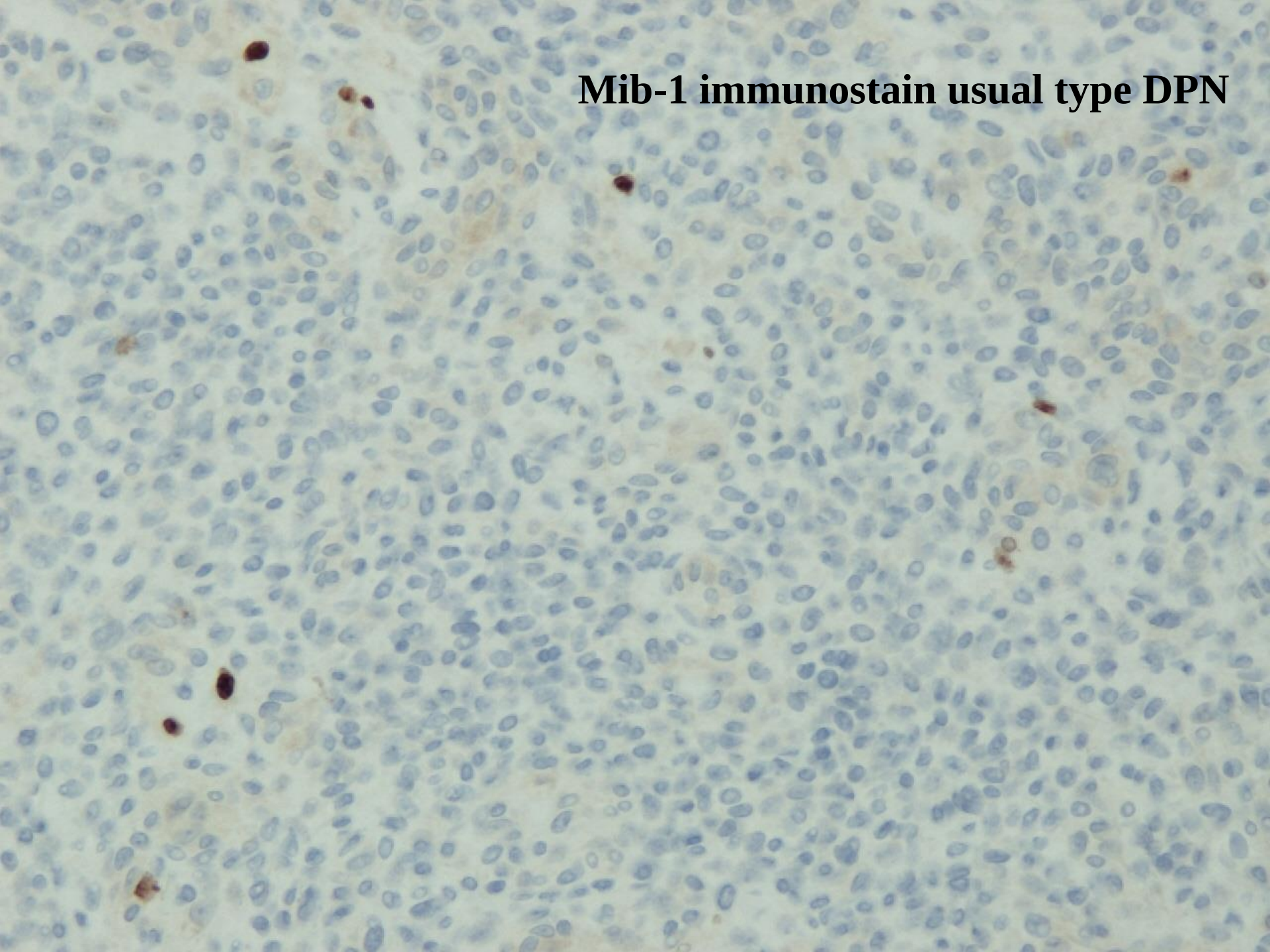


Moderate nuclear atypia and frequent mitoses






Mib-1


Mib-1 immunostain usual type DPN

Concepts of atypia and malignancy in DPN

- Magro's paper - 40 cases of DPN-like borderline tumours
- 24 F: 16M
- Commonest on face, mid-back and forearm
- Some described longstanding lesion which enlarged

Concepts of atypia and malignancy in DPN

- Described nodules and fascicles of melanocytes
- DPN-like tracking around nerves, vessels and adnexae
- Areas of increased cellularity and expansile solid growth
- More atypia than in conventional DPN-moderate/severe

Concepts of atypia and malignancy in DPN

- Some displayed an atypical junction with pagetoid ascent
- Mitoses generally 1 to 3 per sq. Mm
- Most lacked cytogenetic abnormalities of melanoma
- 19 cases had SNB...and 7 showed tumour

Concepts of atypia and malignancy in DPN

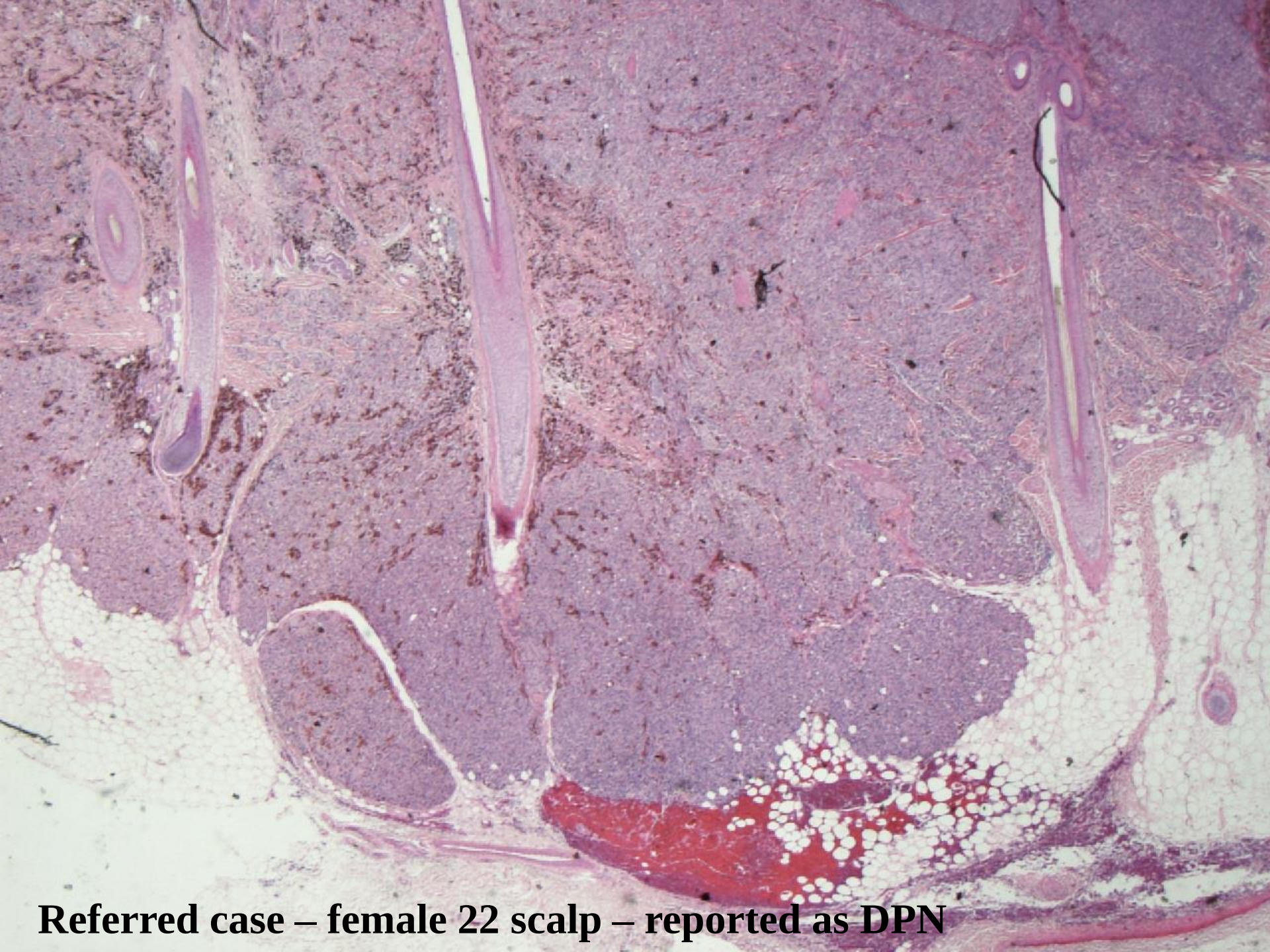
- None of the patients had further nodes on node dissection
- After limited follow-up no patient has yet died

Concepts of atypia and malignancy in DPN

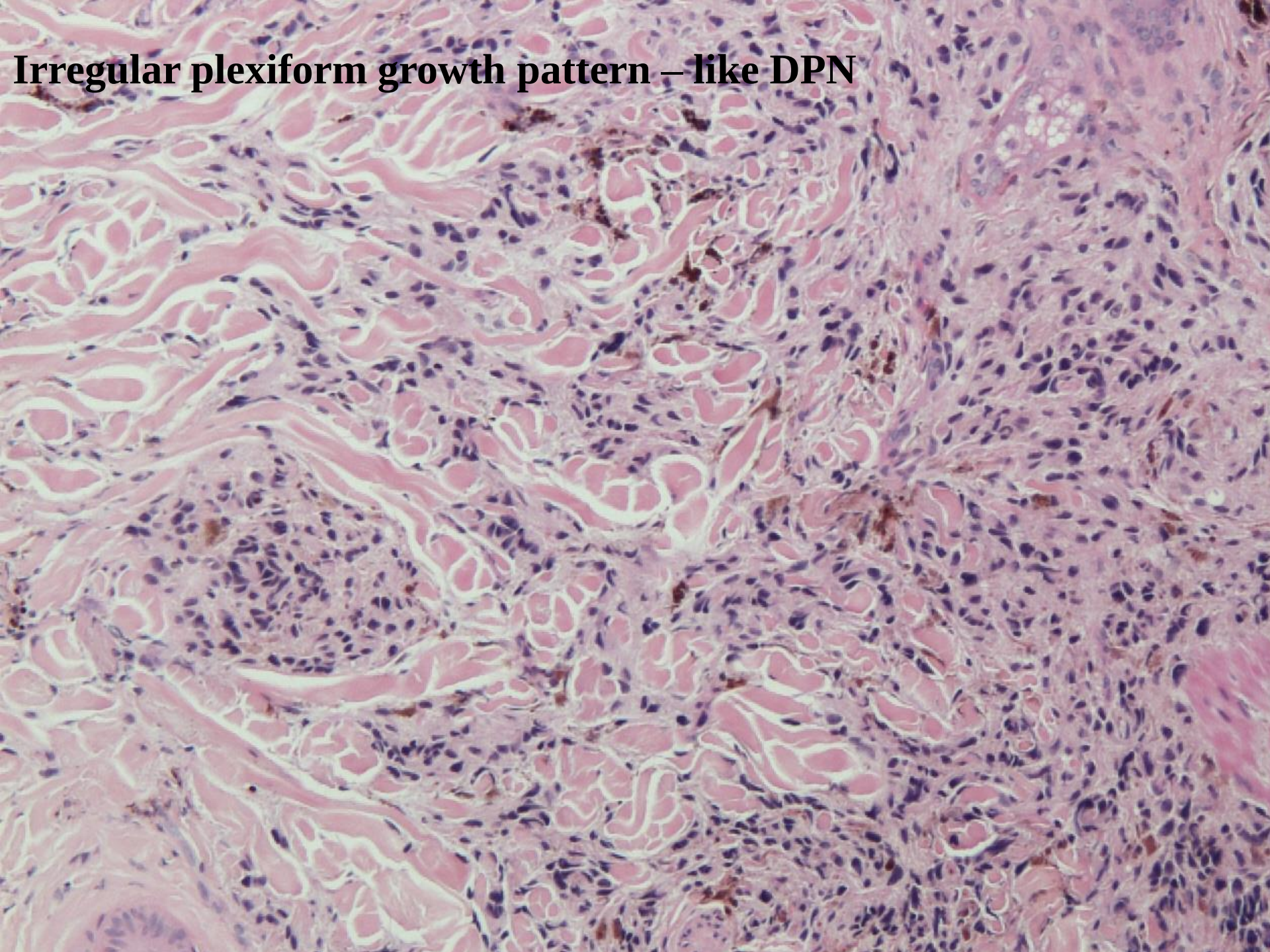
- A minority of patients showed overt melanoma
- Background of DPN-like borderline tumour
- Overt melanoma generally showed a *'plexiform'* pattern
- Four out of six patients died of widespread metastases

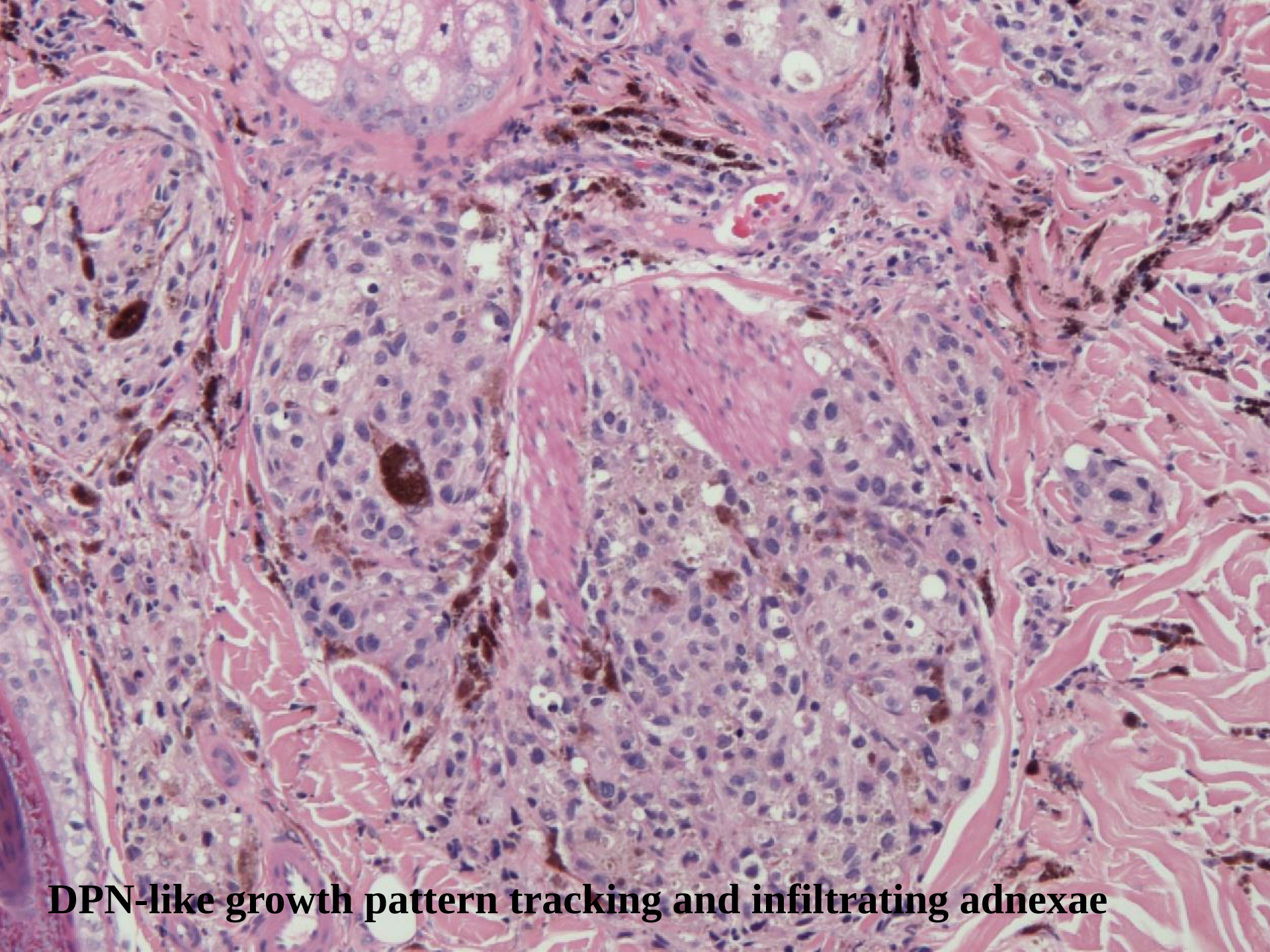
Concepts of atypia and malignancy in DPN

- Yeh et al. assessed two lesions diagnosed as DPN that metastasised
- Both harboured characteristic MAPK and CTNNB1 Mutations of DPN
- Both showed multiple DNA copy number alterations - a genetic feature common in melanomas
- One had an additional TERT promoter mutation and one a TP53 mutation



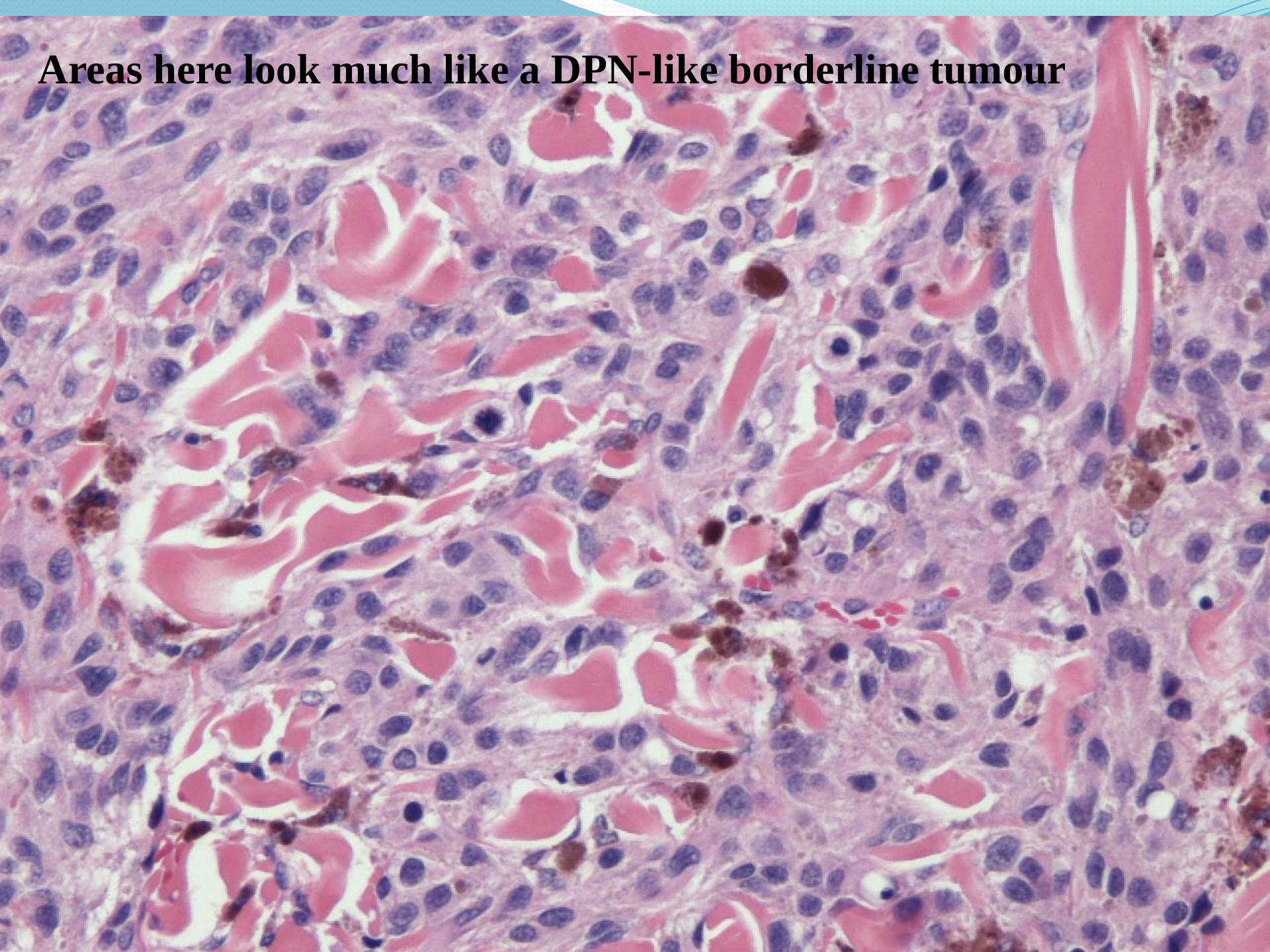
Referred case – female 22 scalp – reported as DPN

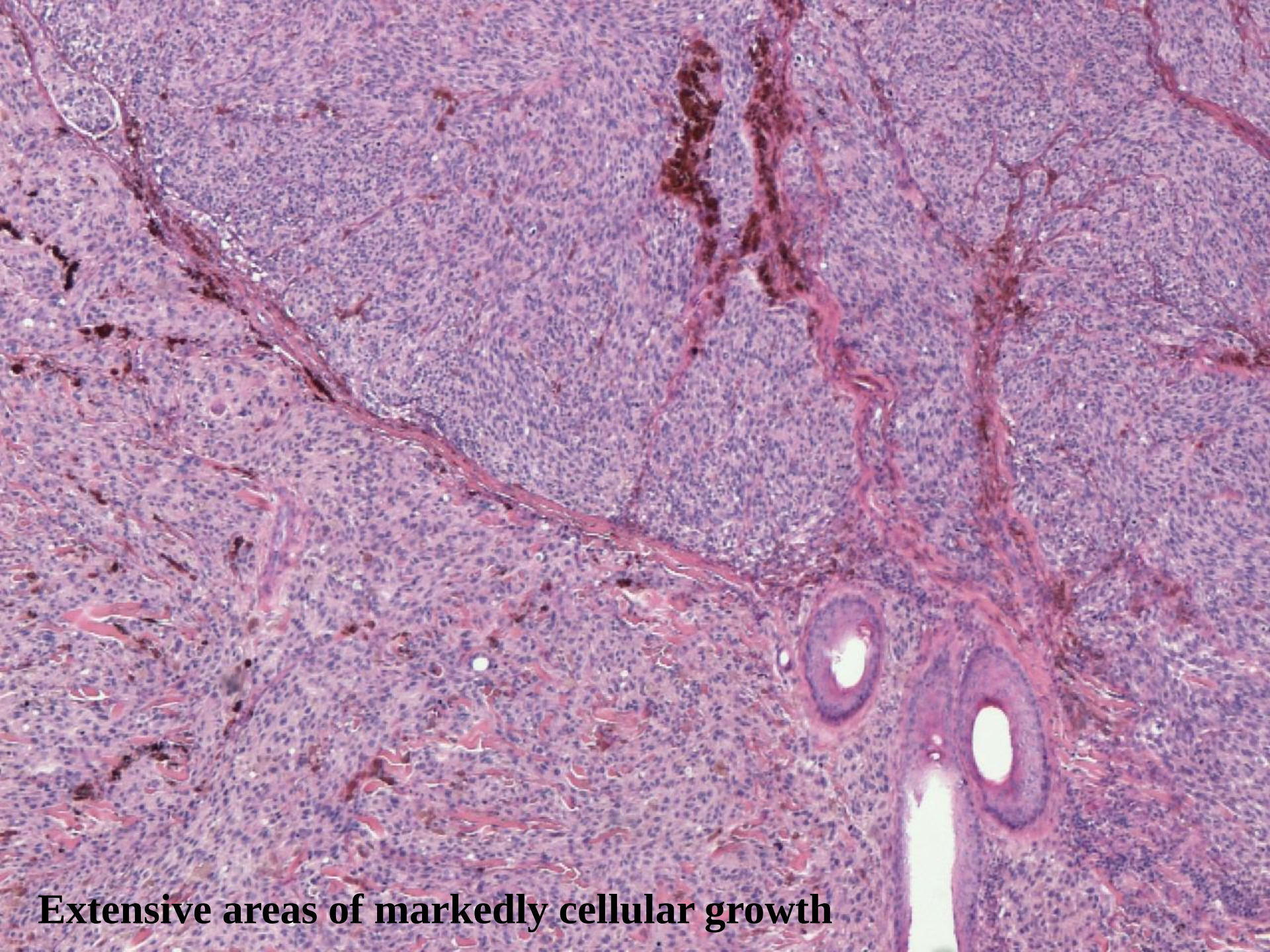

Irregular plexiform growth pattern – like DPN



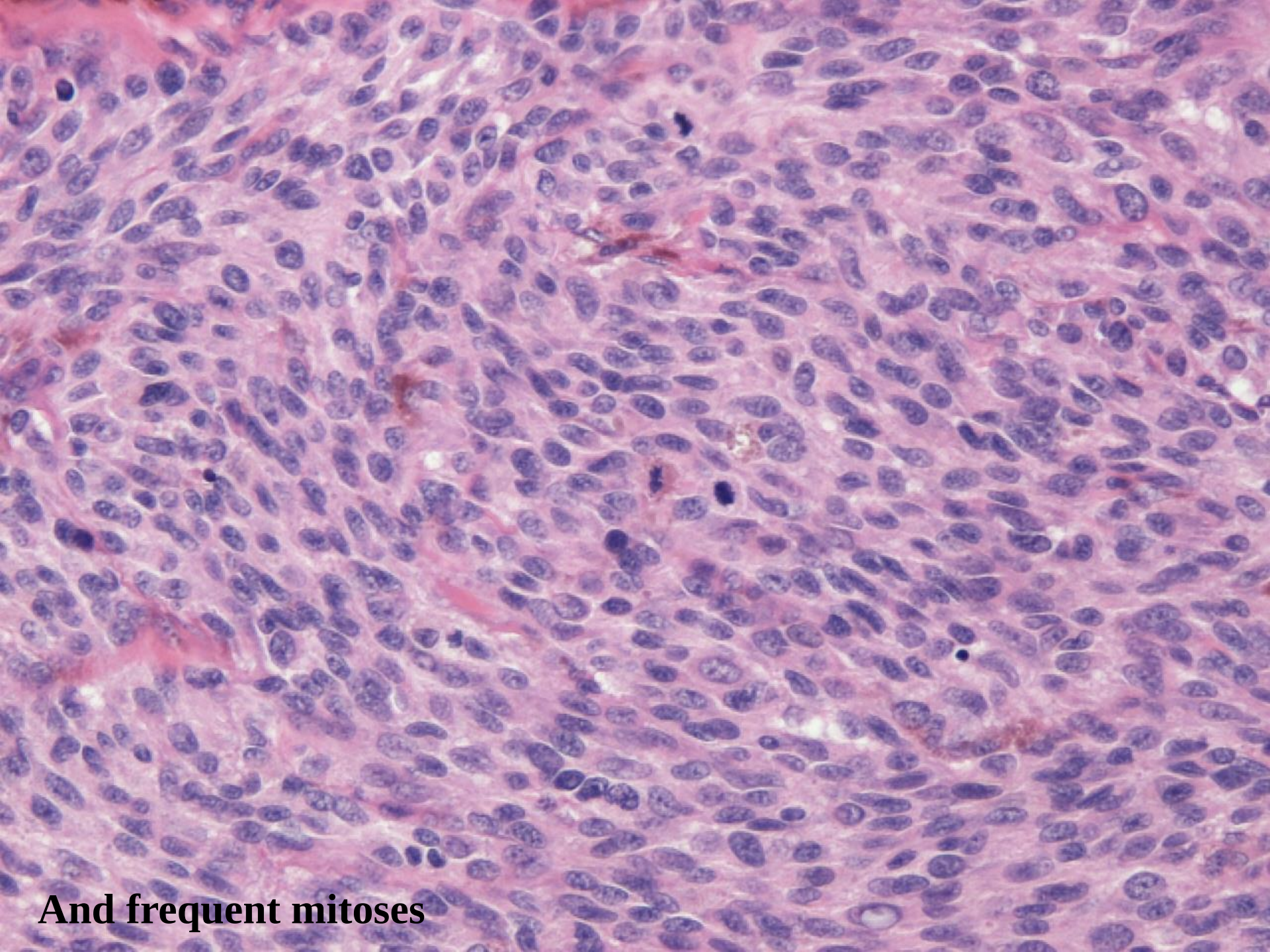
DPN-like growth pattern tracking and infiltrating adnexae

Areas here look much like a DPN-like borderline tumour





Extensive areas of markedly cellular growth


And frequent mitoses

Conclusions - DPN family is evolving

- DPN-at different stages of evolution can be determined
- DPN-like borderline tumour-good Px even if +ve SNB
- Overt melanoma arising in a DPN-like BT. Poor Px.
- Analogous to spectrum of lesions in the Spitz family

Conclusions - DPN family is evolving

- Molecular genetic advances are key to our understanding
- DPN defined by specific mutations in MAPK and CTNNB1
- DPN distinct from common naevi - morphology and genetics
- Form an intermediate stage in stepwise tumour progression
- Analogous to spectrum of lesions in the Spitz family

Conclusions - DPN family is evolving

- Envisage a stepwise model of progression
- BRAF mutation in melanocyte triggers development of naevus
- Acquisition of CTNNB1 mutation - development of DPN
- Additional mutations (e.g. CDKN2A, TERT, TET2) or increased DNA copy numbers result in borderline and malignant DPN


Dundee V. & A. Opening in 2018