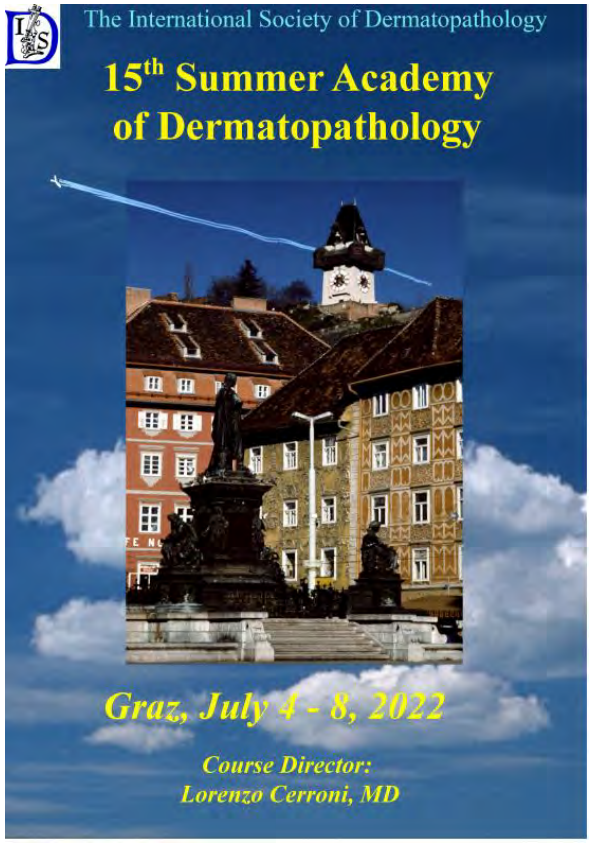


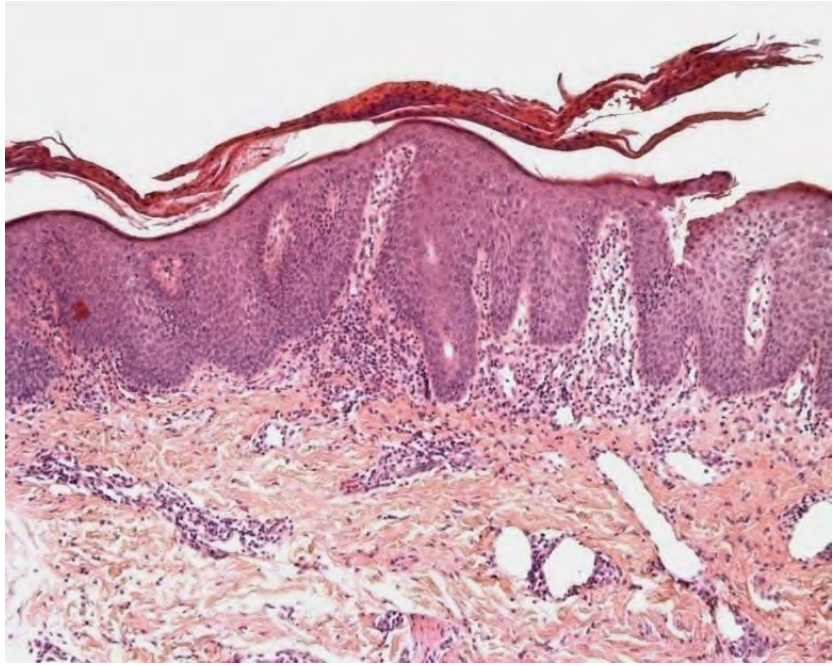
Selected issues in pediatric dermatopathology

S. Fraitag

Hôpital Necker-Enfants Malades, Paris

Lymphocytic infiltrates

Lymphocytic infiltrates

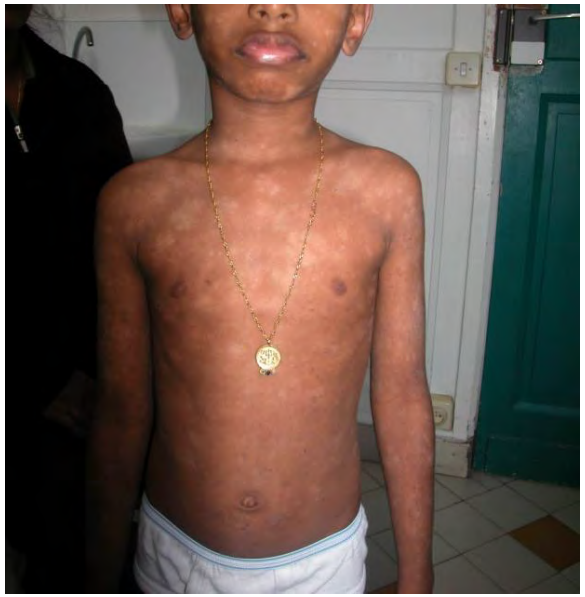


Superficial, horizontal dermal infiltrate

Inflammatory disorders

may be confused with mycosis fungoides!

- **The majority of pediatric MF** are of the hypopigmented variants (70 %)



Hypopigmented mycosis fungoides in childhood and adolescence: a long-term retrospective study

Patients with hypopigmented mycosis fungoides (HMF) present at a younger age than those with classic MF. Our goal was to describe the clinical presentation, histopathologic features and long-term outcome in patients who developed HMF before the age of 21. It was observed that among 69 pediatric patients diagnosed with MF between 1992 and 2010, 50 had HMF. Thirty-five patients had clinical follow-up. There were 37 males and 32 females with a mean age of 13.6 years. Most patients were African American or Hispanic and presented with multiple hypopigmented patches. All biopsies showed epidermotropism of T-lymphocytes, whereas fibroplasia and lichenoid infiltrate were variable. All specimens tested were CD8+. Treatment modalities included topical steroids, narrow band ultraviolet B and psoralen and ultraviolet A. HMF patients were followed for <1–12 years. Most children responded to treatment, but recurrence rates were high. One patient progressed to plaque/tumor stage. Others did not progress; however, many were lost to follow-up. We present a large cohort of children with HMF and report on the features of disease and progression. A major difference in histology of HMF was lack of fibroplasia and lichenoid infiltrate, probably because of presentation in the early patch stage. Most patients have a waxing-and-waning course and relapse after discontinuation of therapy, requiring repetitive treatment.

Keywords: mycosis fungoides, cutaneous T cell lymphoma, histopathology, T-cell receptor rearrangement, immunocytochemistry

Castano E, Glick S, Wolgast L, Naeem R, Sunkara J, Elston D, Jacobson M. Hypopigmented mycosis fungoides in childhood and adolescence: a long-term retrospective study. J Cutan Pathol 2013; 40: 924–934. © 2013 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Ekaterina Castano[1], Sharon Glick[2], Lucia Wolgast[1], Rizwan Naeem[1], Jaya Sunkara[1], Dirk Elston[3] and Mark Jacobson[1,4]

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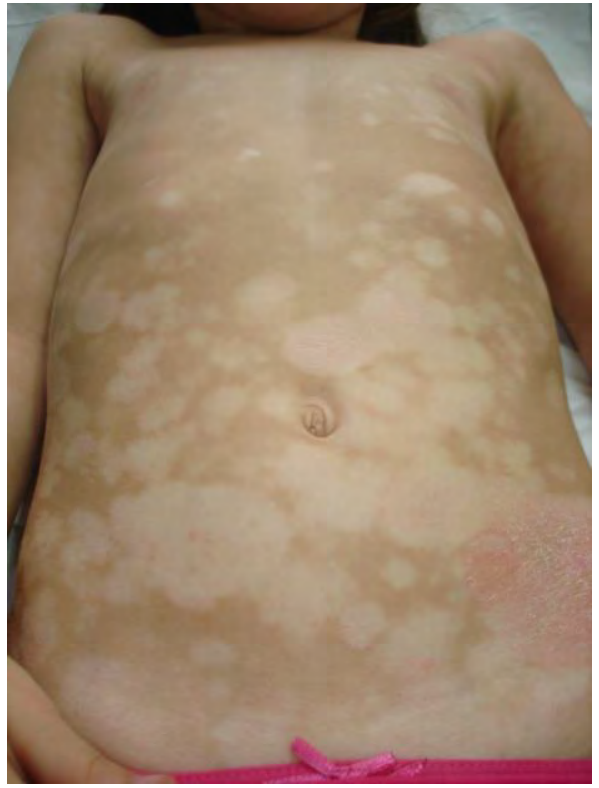
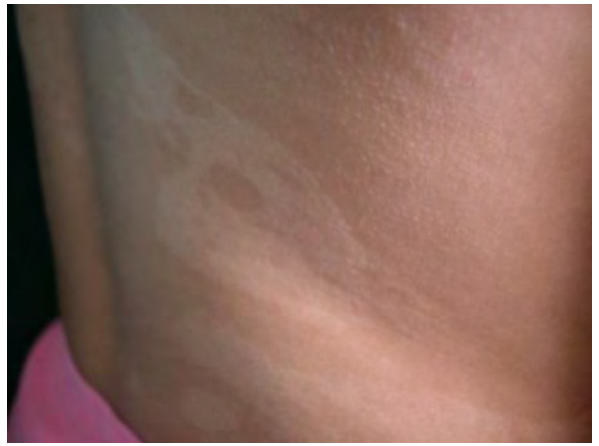
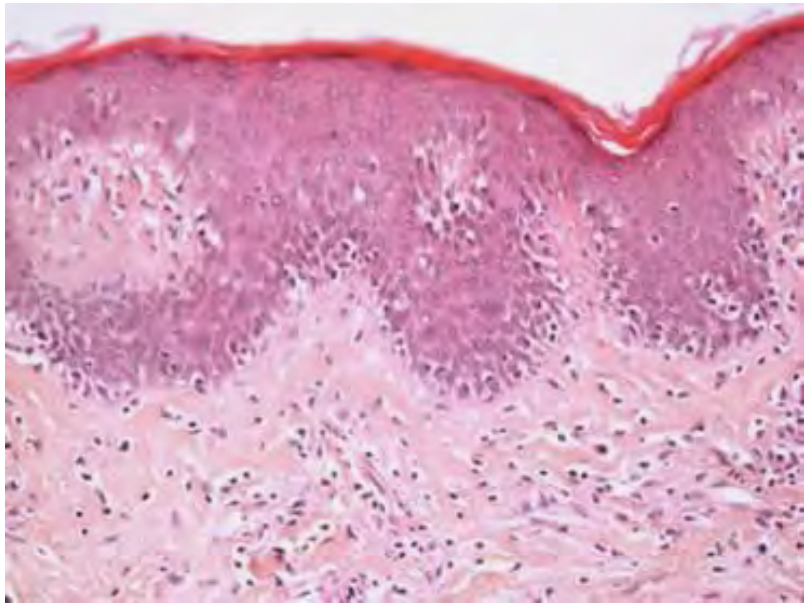
Accepted for publication August 11, 2013

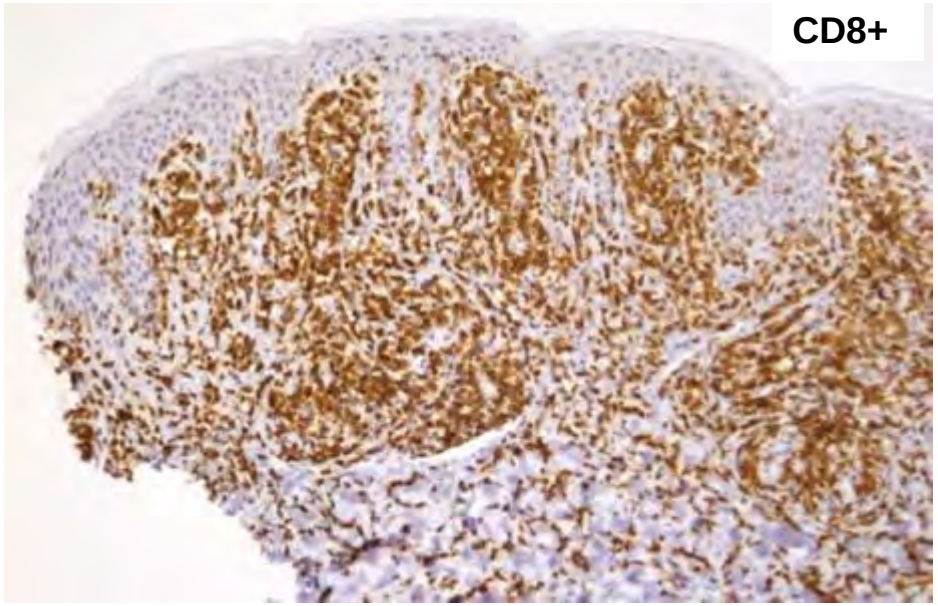


- **Clinical** differential diagnoses with other hypopigmented disorders may be **extremely tricky** :
  - tinea versicolor,
  - pityriasis alba,
  - post-inflammatory hypopigmentation,
  - *vitiligo*….



- Almost 100 % of the *hypopigmented MF cases* harbor **a cytotoxic CD8, Tia1 phenotype**
- So inflammatory conditions may be also extremely difficult to differentiate from **MF histologically**

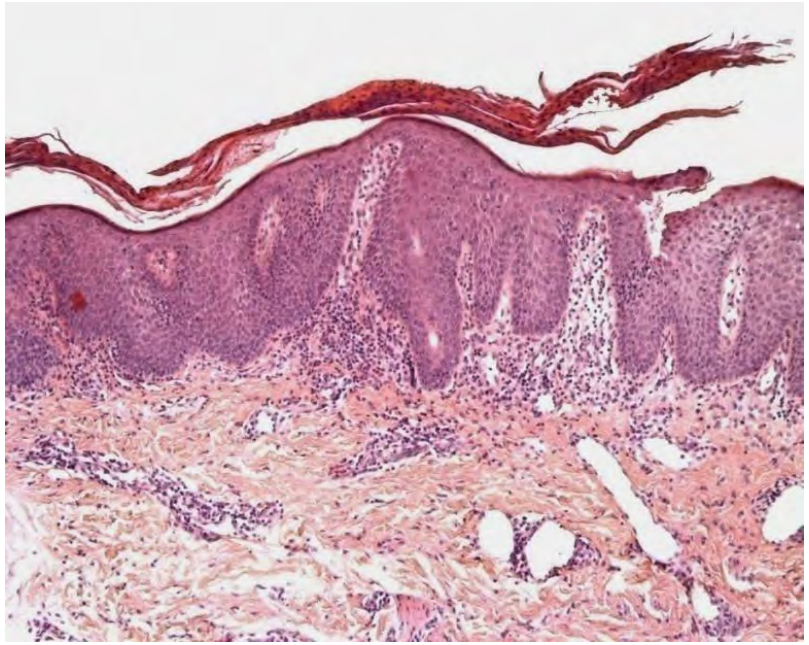


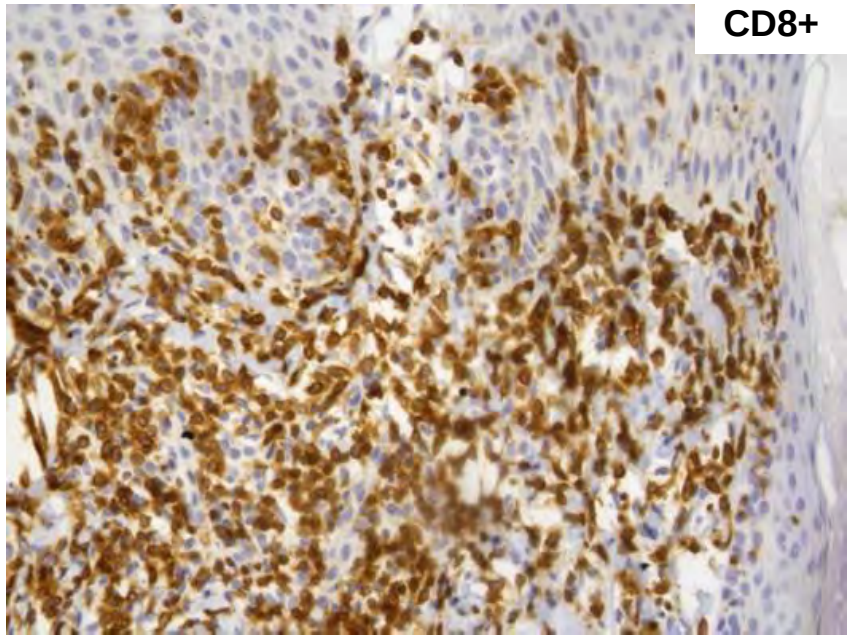


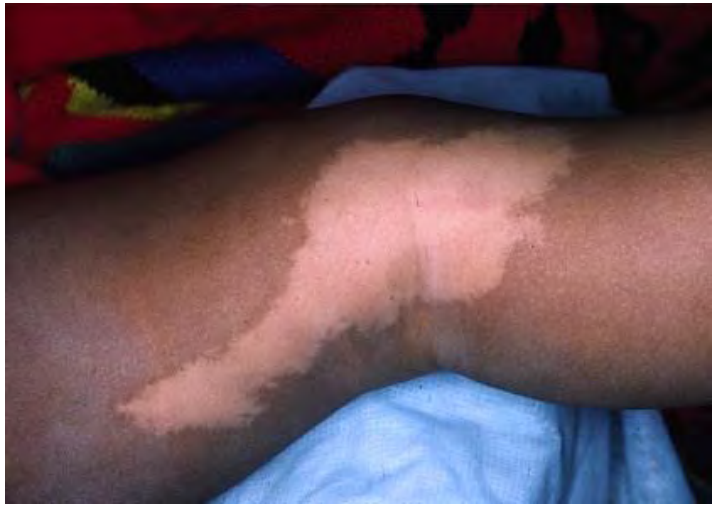
Mycosis fungoides

Werner B et al. Hypopigmented mycosis fungoides is not always mycosis fungoides!. Am J Dermatopathol. 2005; 27(1): 56-67

1. Inflammatory stages of vitiligo







- The number of melanocytes may be reduced in MF!

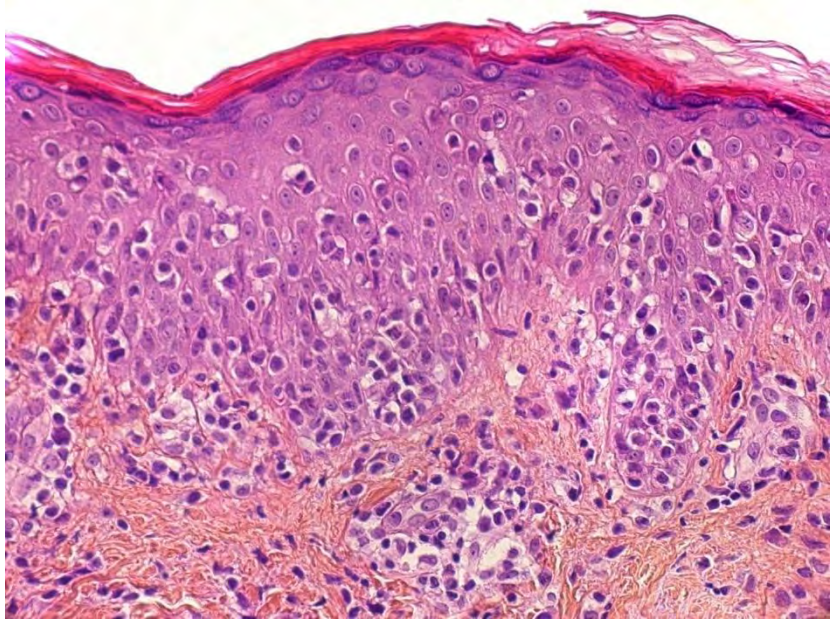
- **T-cell clone**
- **Follow-up**

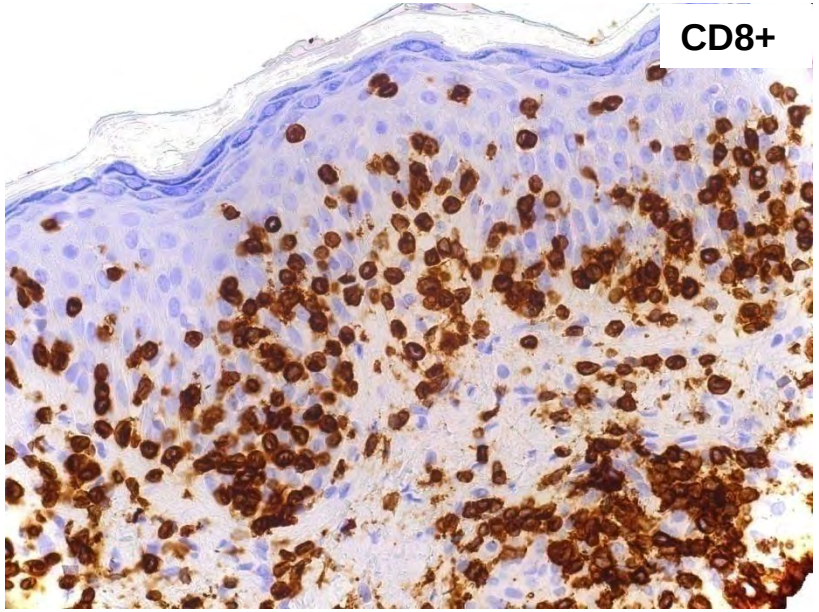
Ngo JT et al. 2009; 13(4): 230-3

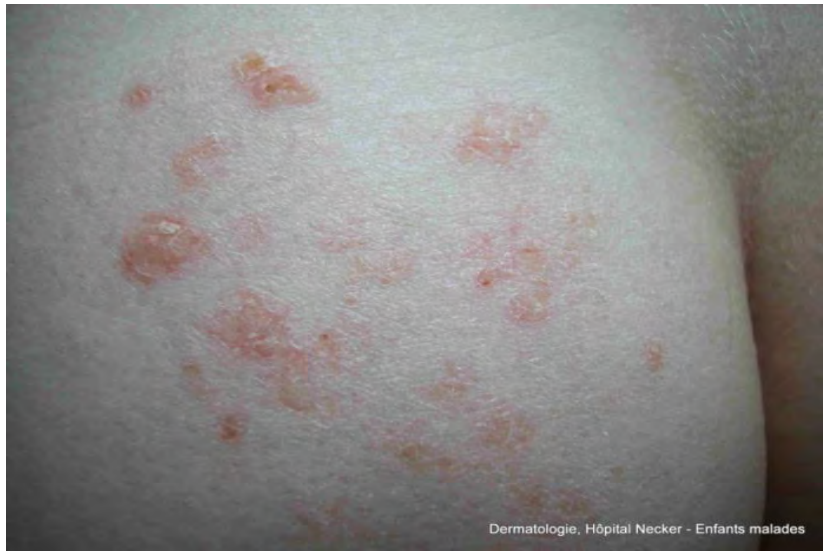
Hodak E et al. J Am Acad Dermatol 2014; 70: 993-1001

Furlan FC et al. J Cutan Pathol 2014; 41: 101-7

2. Pityriasis Lichenoides Chronica







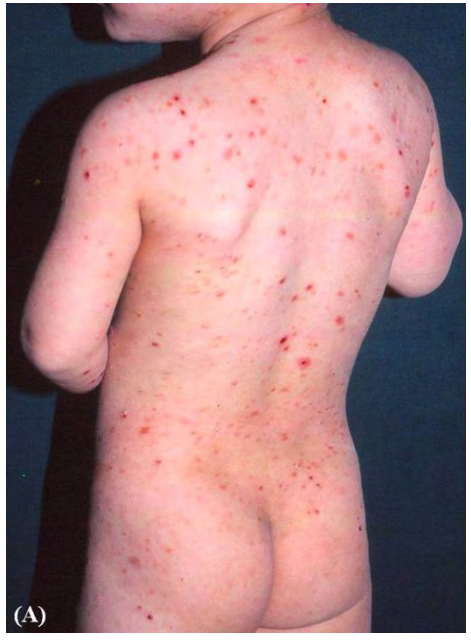
- **Epidermotropism** ++ (CD8 cells)
- Inconspicuous necrotic cells
- **T-cell clone in 50%**

- **PL-like MF** have been described in children
- **Pityriasis Lichenoides** …. *can be associated with MF*
  (8o % in our series) *(Boccara O et al. Pediatr Blood Cancer 2012; 58: 226-232)*

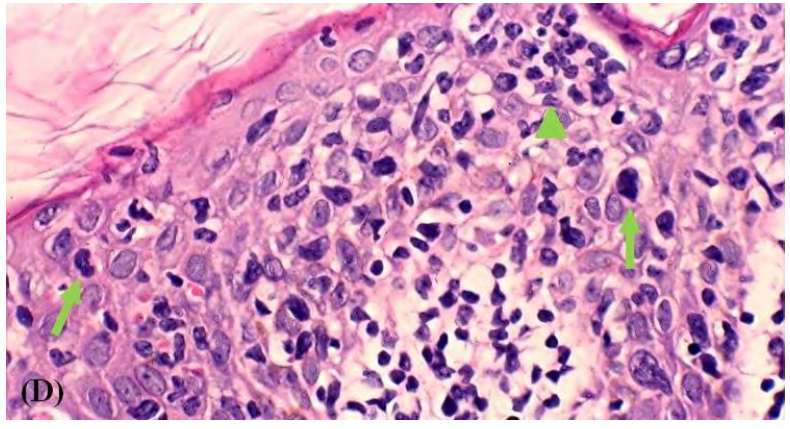
British Journal of Dermatology 2000; **142:** 347–352.

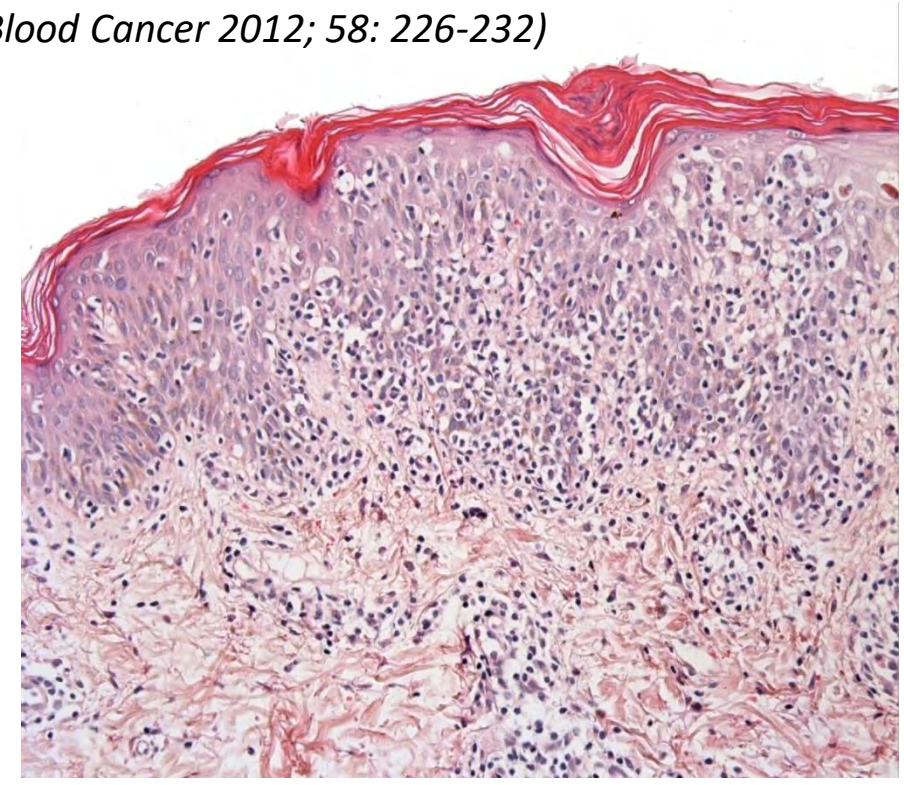
Pityriasis lichenoides-like mycosis fungoides in children

J-W.KO, J-Y.SEONG, K-S.SUH AND S-T.KIM
Department of Dermatology, Kosin Medical Center, 34 Amnam-Dong, Suh-ku, Pusan 602-702, South Korea
Accepted for publication 16 September 1999



MF



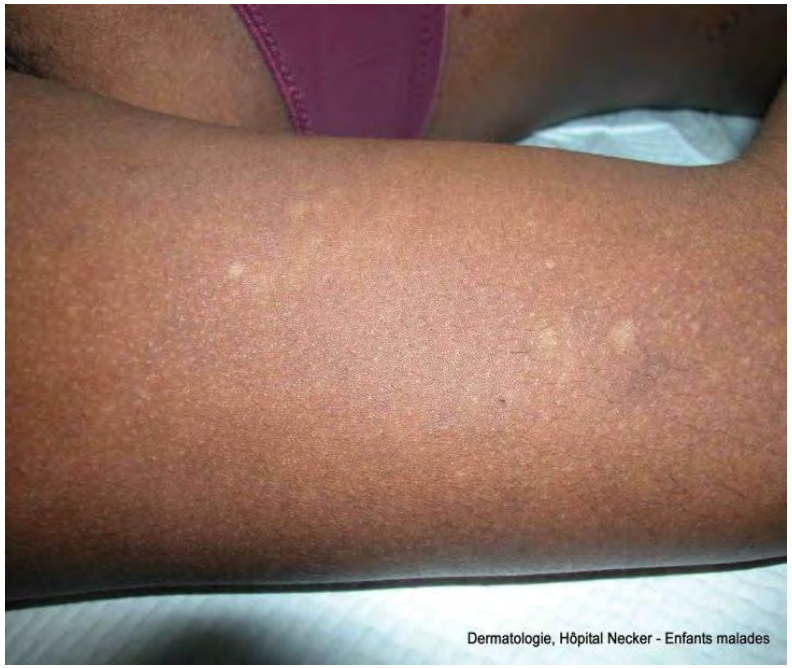


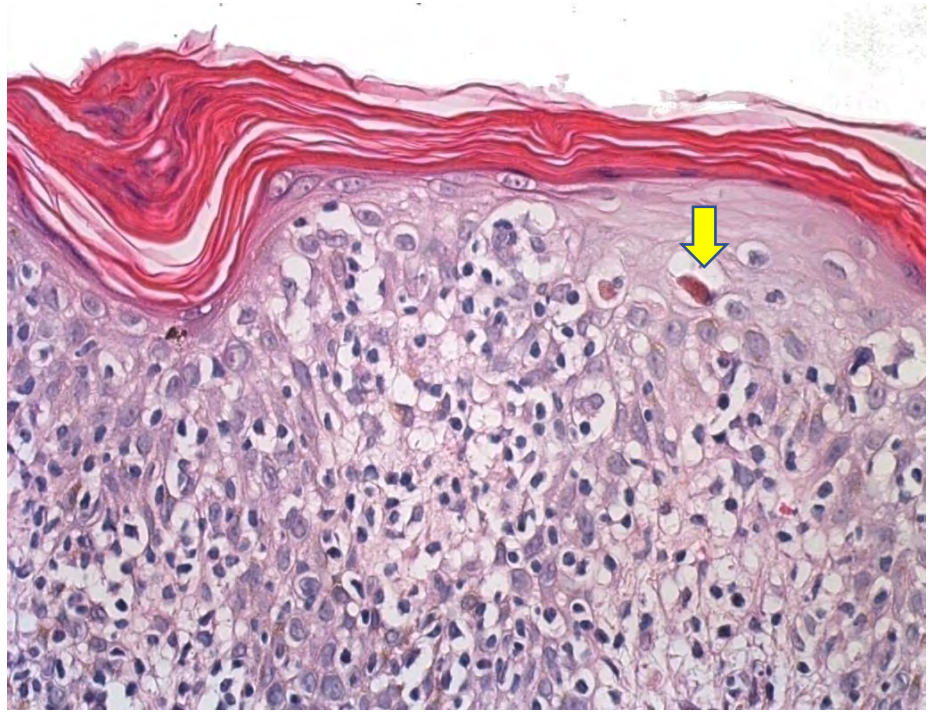
PLC

Pityriasis Lichenoides vs CD8 Mycosis Fungoides: challenging if no clinical correlations!

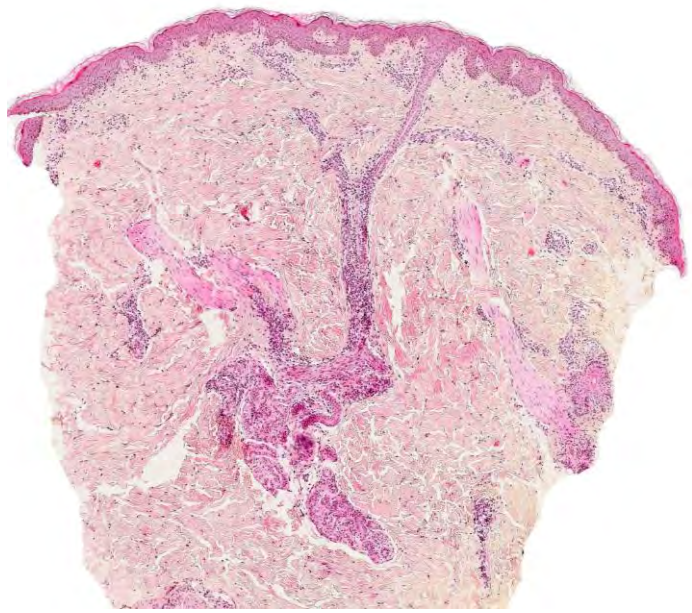
- epidermal hyperplasia,
- parakeratosis,
- **necrotic keratinocytes , RBC extravasation**
- « African tree » pattern, adnexotropism

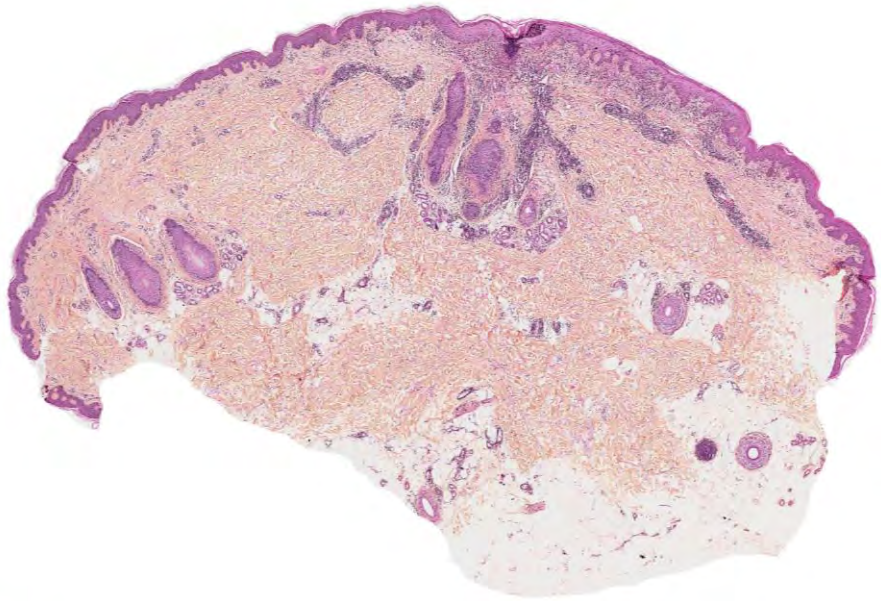
→ may favor PLC

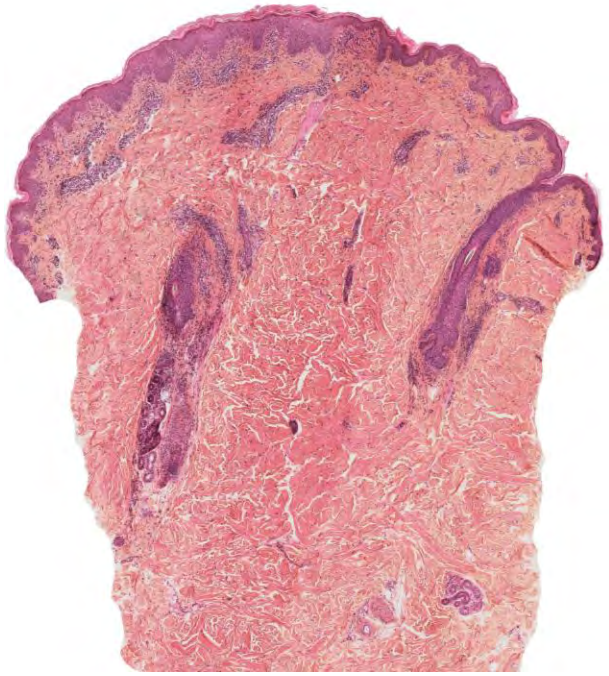


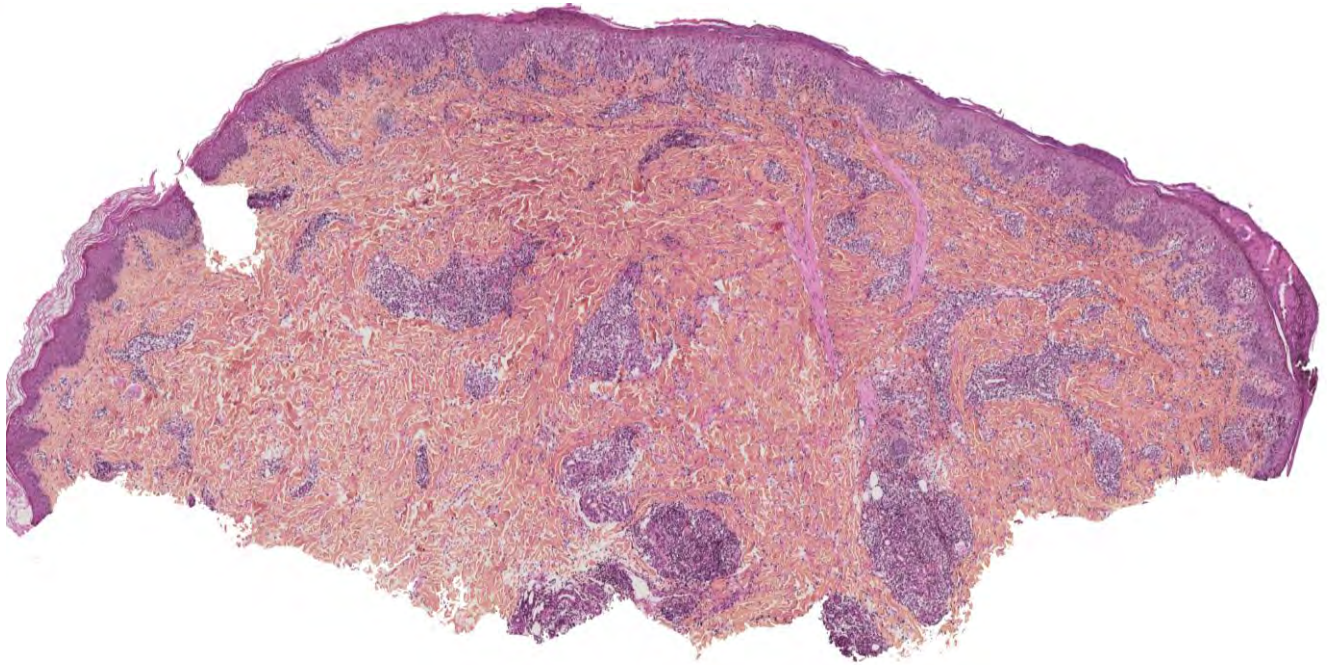


African tree !





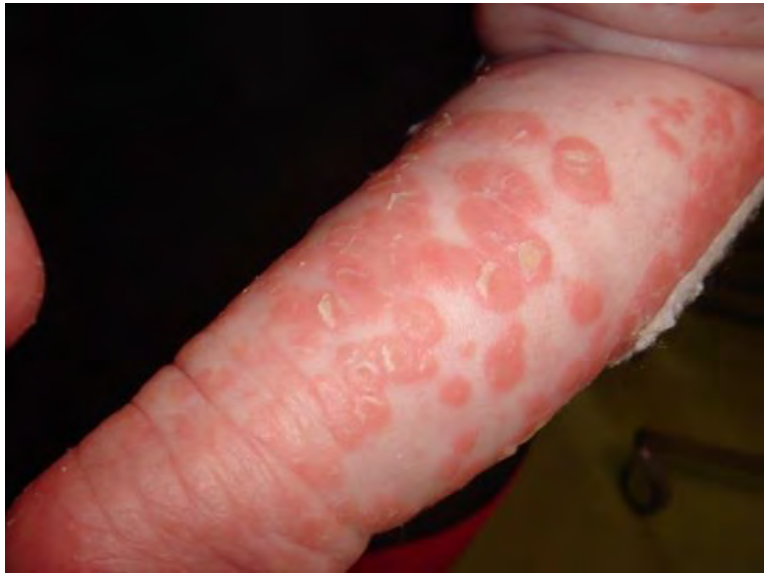


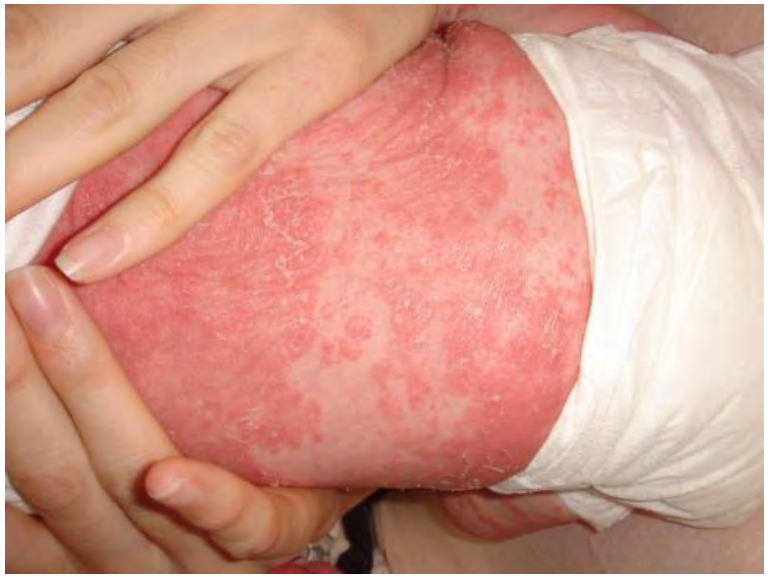


Menzinger, S.; Frassati-Biaggi, A.; Leclerc-Mercier, S.; Bodemer, C.; Molina, T.J.; Fraitag, S. Pityriasis Lichenoides: A Large Histopathological Case Series with a Focus on Adnexotropism. Am. J. Dermatopathol. 2020, 42, 1–10.

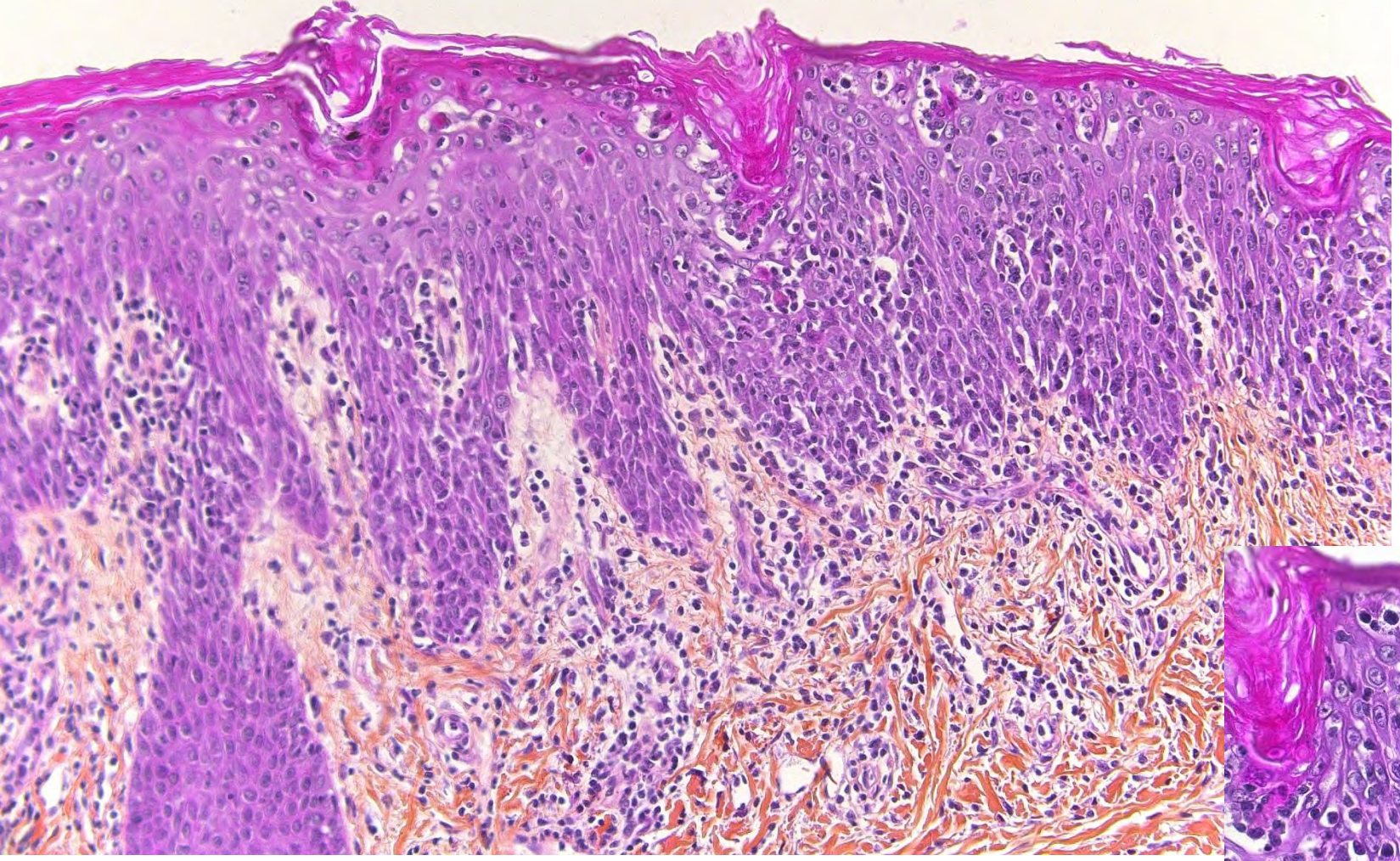
3. Quiz

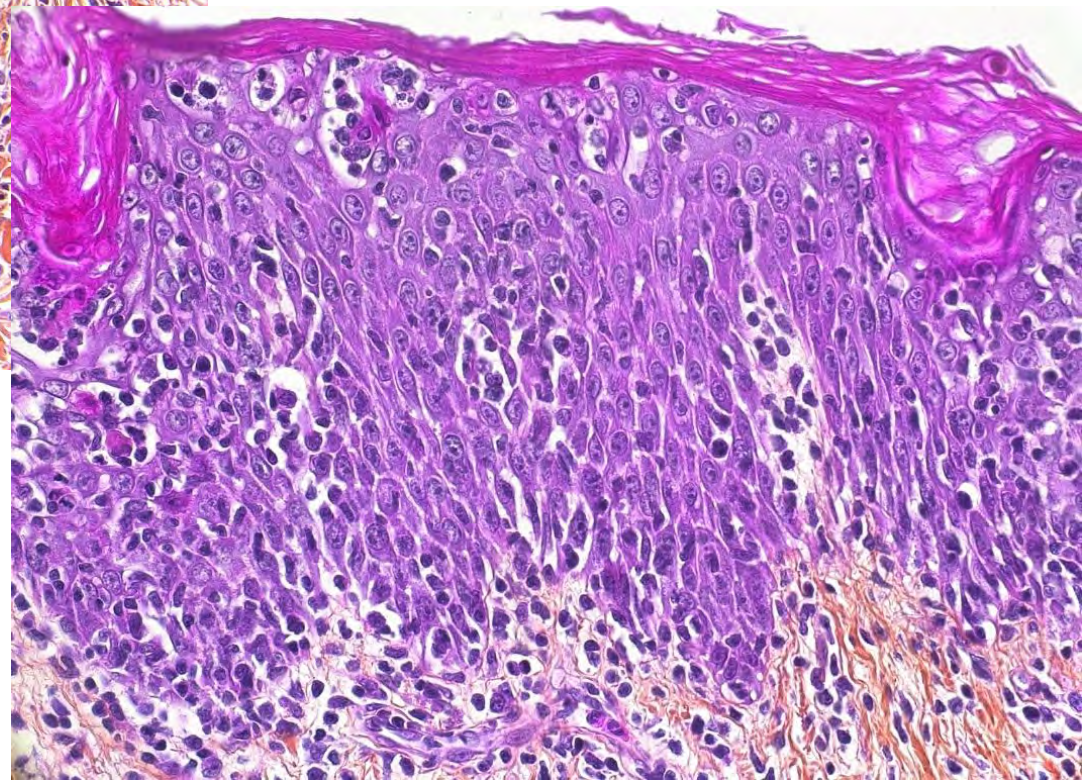
- 3-month-old boy.
- Full-term, non consanguineous parents
- Severe scaling neonatal itchy **erythroderma** + papular lichenoid lesions
- Failure to thrive, very bad condition
- Complicated by shock, cardiac arrest, diarrhea
- **ICU**



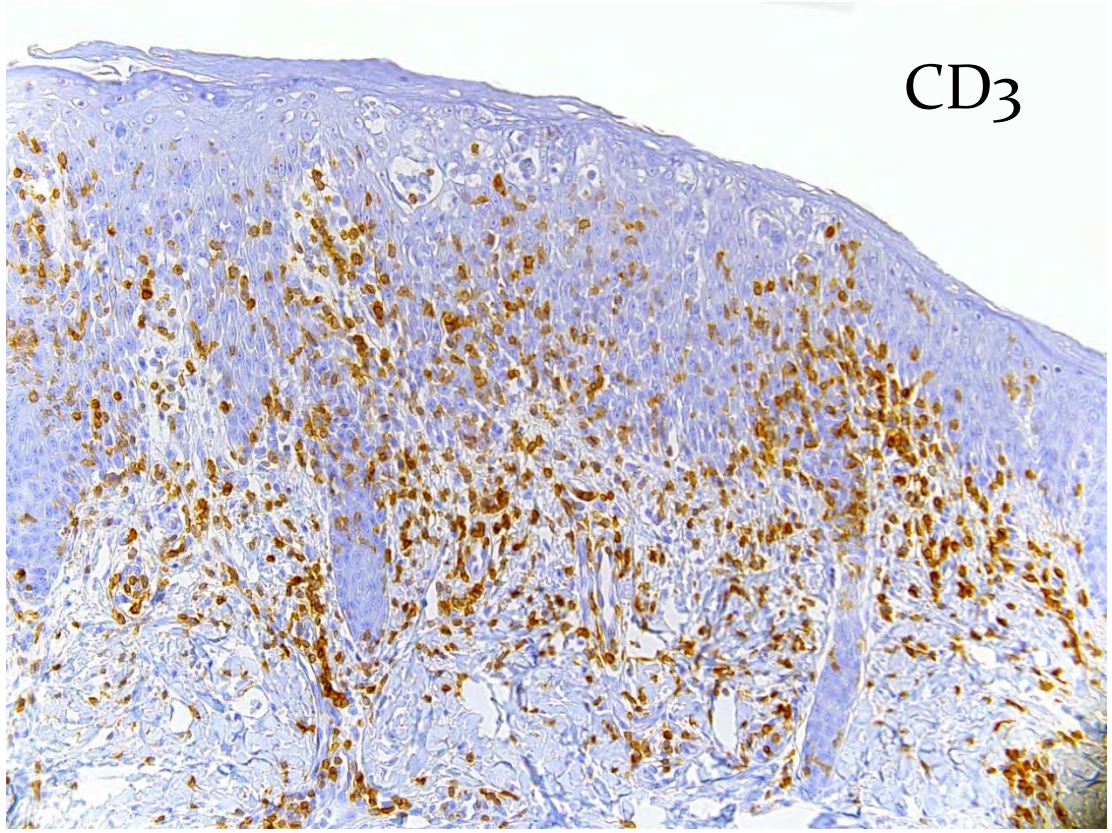


Pr Michel D'incan, Clermont-Ferrand

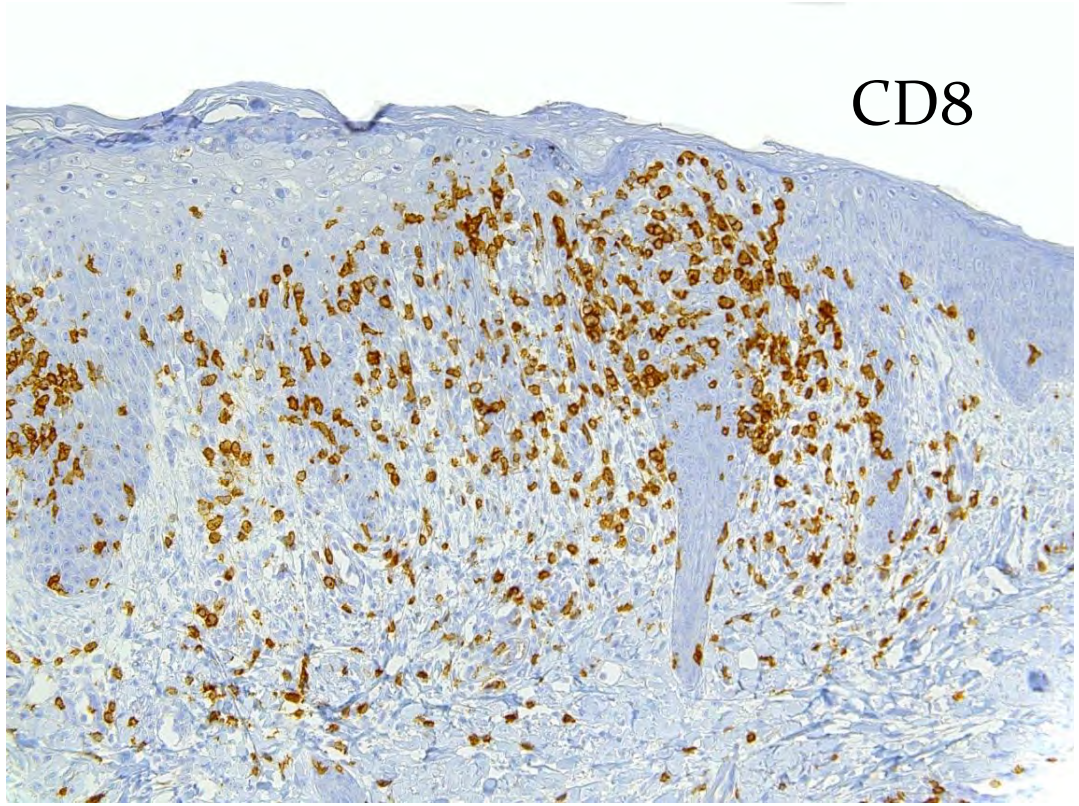




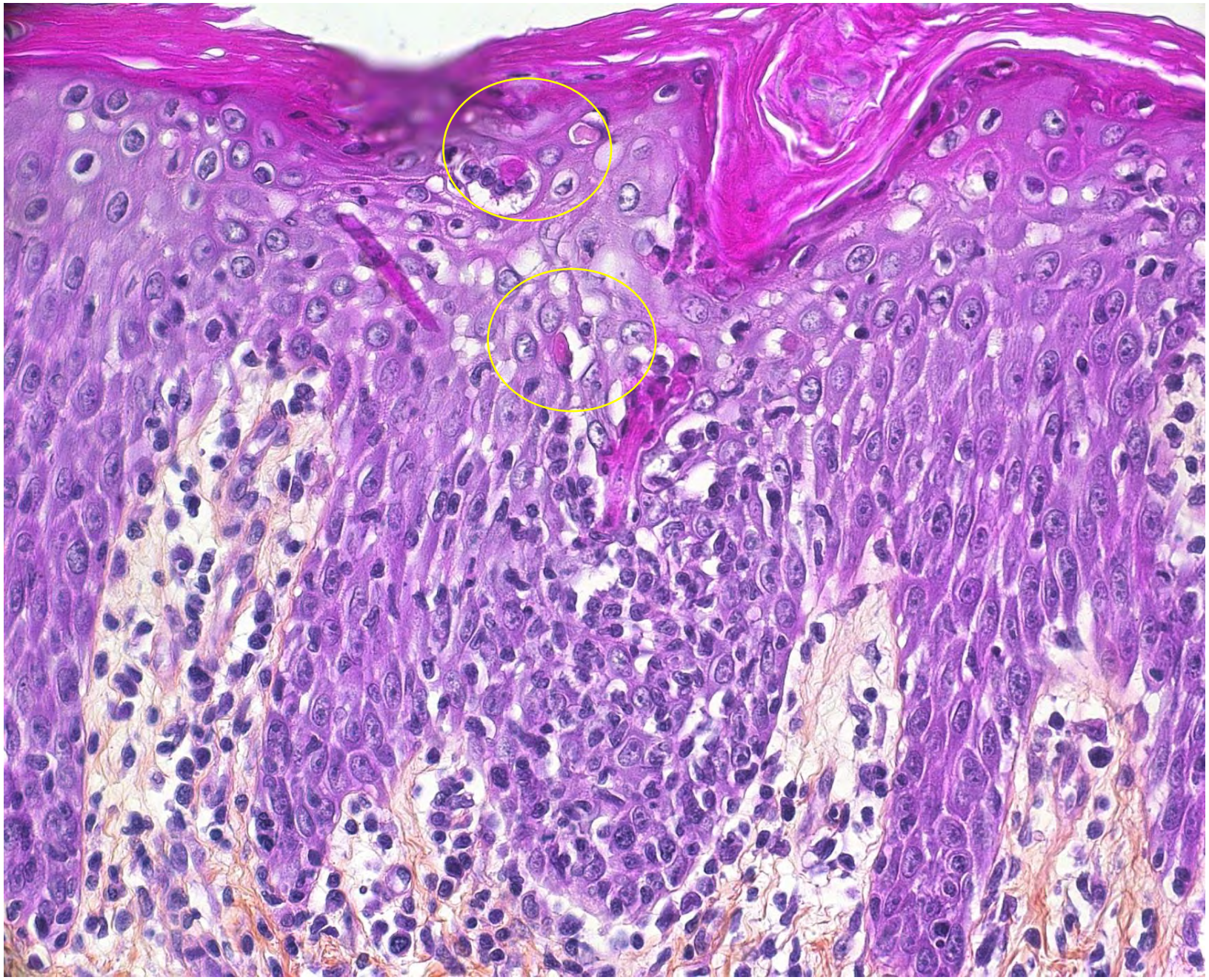
Lymphocytic exocytosis into the epidermis and **the adnexal structures**



Mycosis fungoides ???

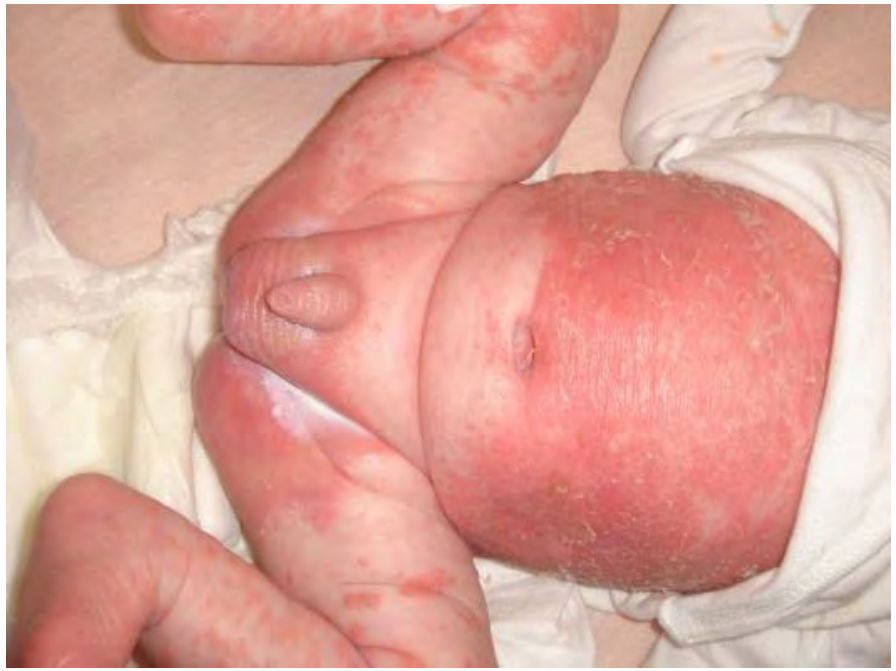


Clue!

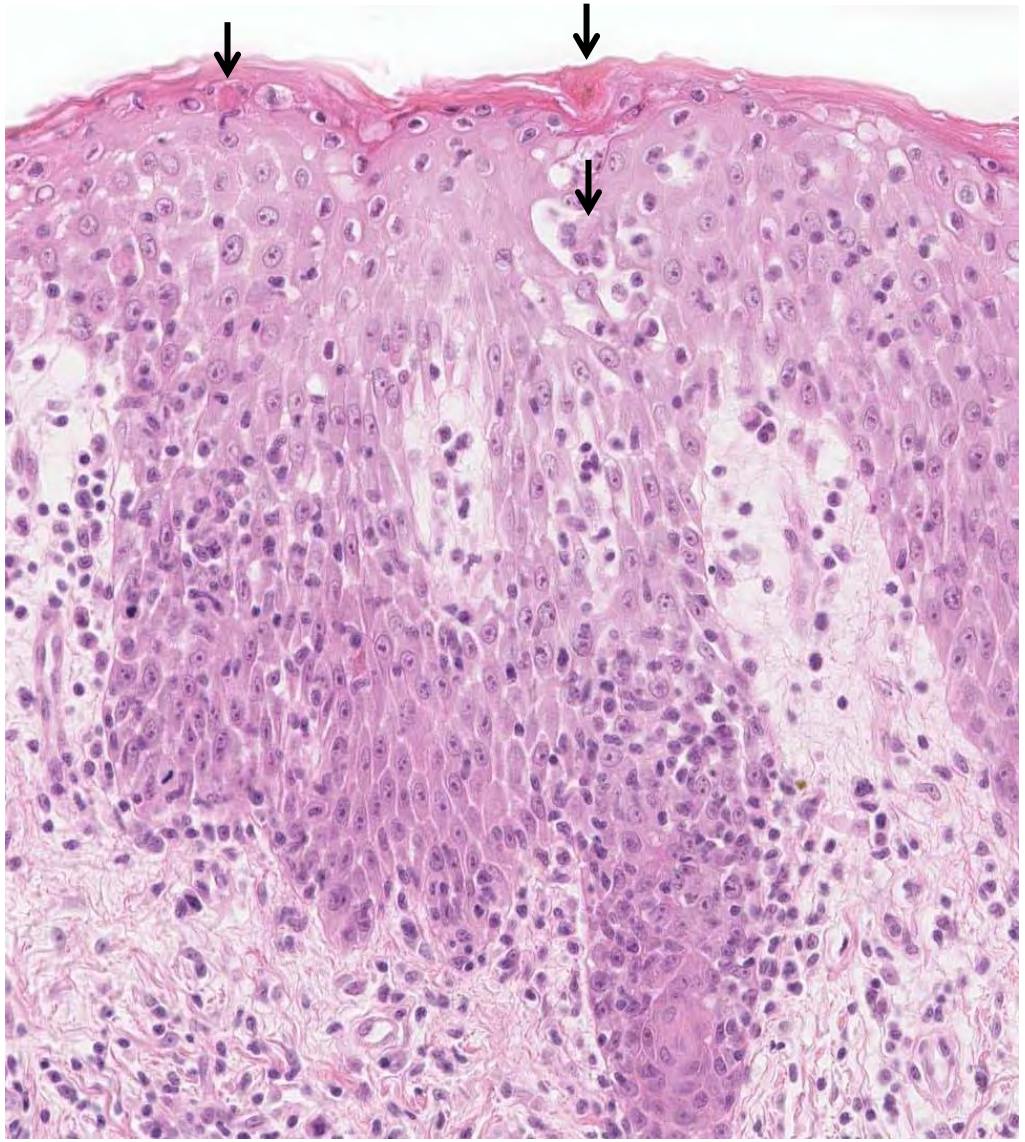


Congenital immunodeficiency

- Developed diabetes melitus
- Discovery of gene FOX P3 mutation
- **IPEX syndrome** (*Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked*)
- Blood marrow transplantation



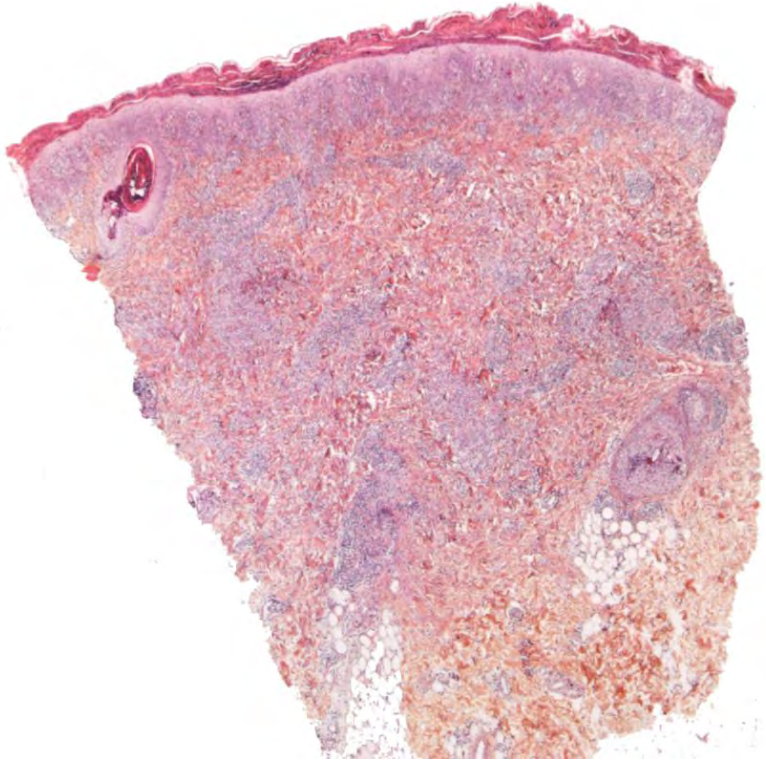
- **Lymphocytic exocytosis** into the epitheliae
- **Necrotic keratinocytes**



Think of immuno-deficiency!

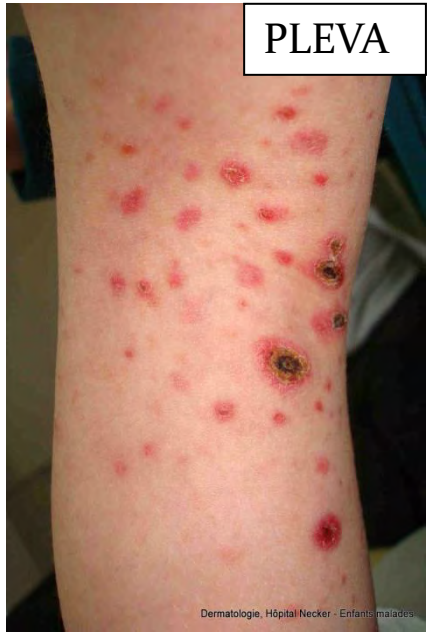
Leclerc-Mercier S, Bodemer C, Bourdon-Lanoy E, Larousserie F, Hovnanian A, Brousse N, Fraitag S.. J Cutan Pathol. 2010 Feb;37(2):249-55.

Lymphocytic infiltrates



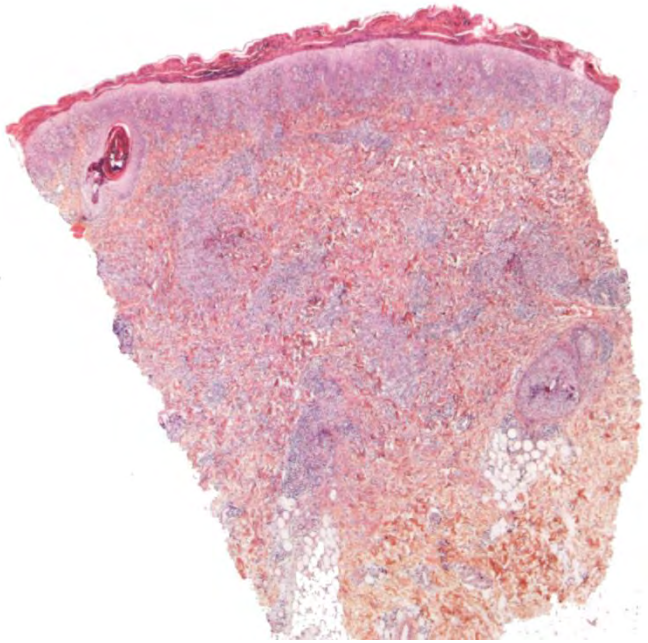
Deeper, vertical dermal lymphocytic infiltrate

May be confused with other primary cutaneous lymphomas!



1. Pityriasis Lichenoides Et Varioliformis Acuta

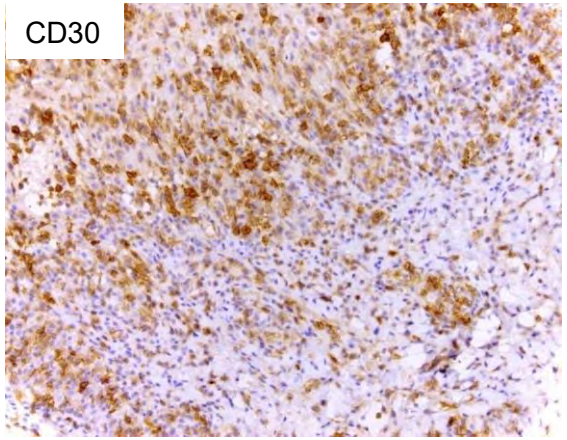
- May be clinically difficult to differentiate from *Lymphomatoid Papulosis*
- PLEVA may show **atypical** CD30+ cells, in the dermal and the epidermal component
- Can show **clonal T-cell rearrangement**

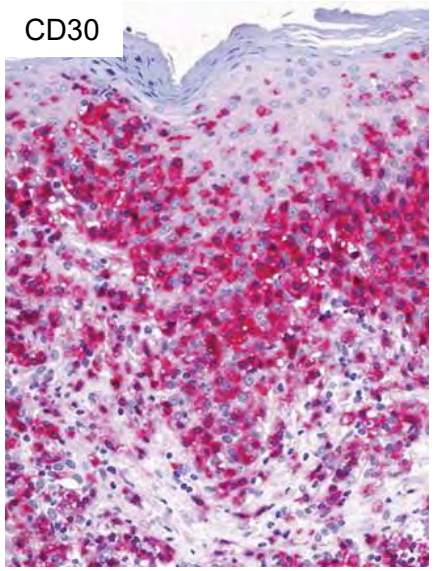


Pityriasis Lichenoides et Varioliformis Acuta With Numerous CD30⁺ Cells

A Variant Mimicking Lymphomatoid Papulosis and Other Cutaneous Lymphomas. A Clinicopathologic, Immunohistochemical, and Molecular Biological Study of 13 Cases

Werner Kempf, MD,† Dmitry V. Kazakov, MD, PhD,‡ Gabriele Palmedo, PhD,§ Sylvie Fraitag, MD,‖ Leo Schaerer, MD,§ and Heinz Kutzner, MD§¶*



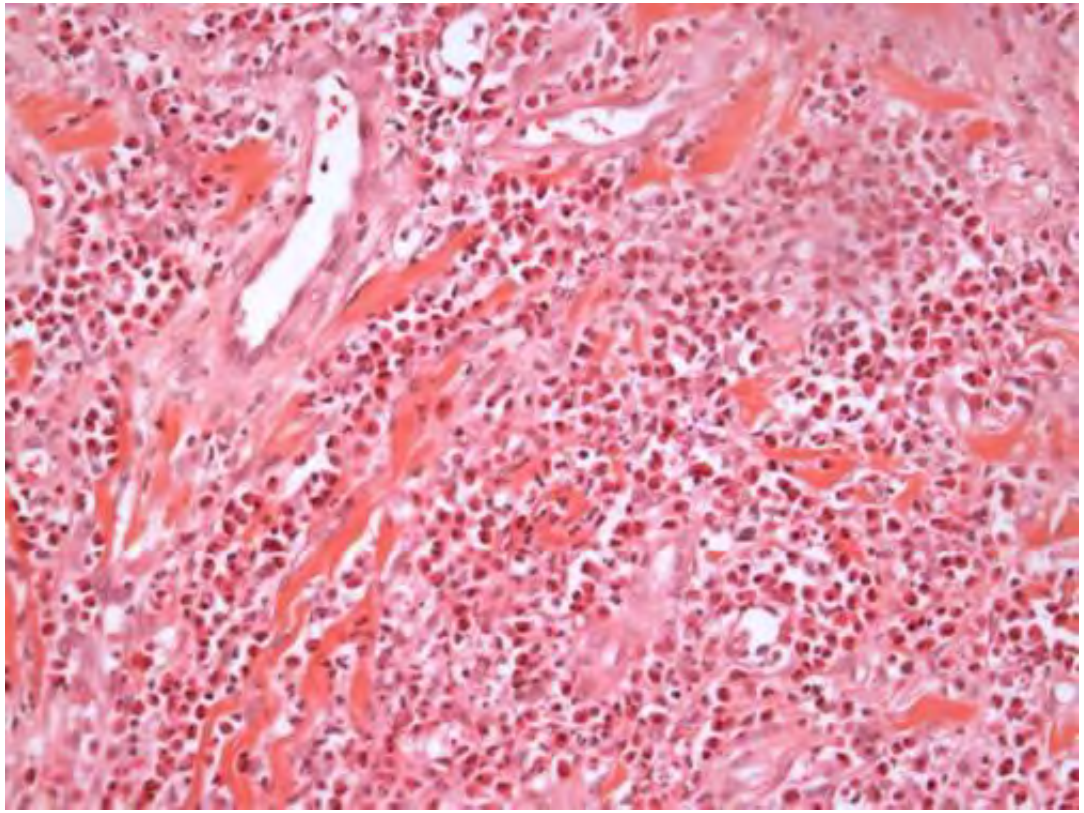


Lymphomatoid papulosis in children

Pityriasis lichenoides : **never eosinophils !**

Marked eosinophilic infiltrate is common

Miquel J, Fraitag S, Hamel-Teillac D, Molina T, Brousse N, de Prost Y, Bodemer C. Br J Dermatol. 2014 Nov;171(5):1138-46.



Clue!

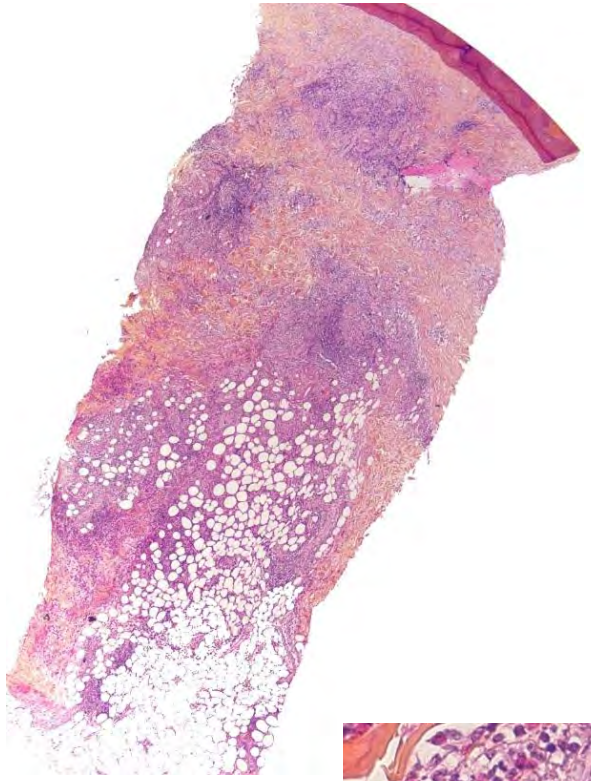
J Cutan Pathol 2012: 39: 413–418
doi: 10.1111/j.1600-0560.2012.01891.x
John Wiley & Sons. Printed in Singapore

Journal of Cutaneous Pathology

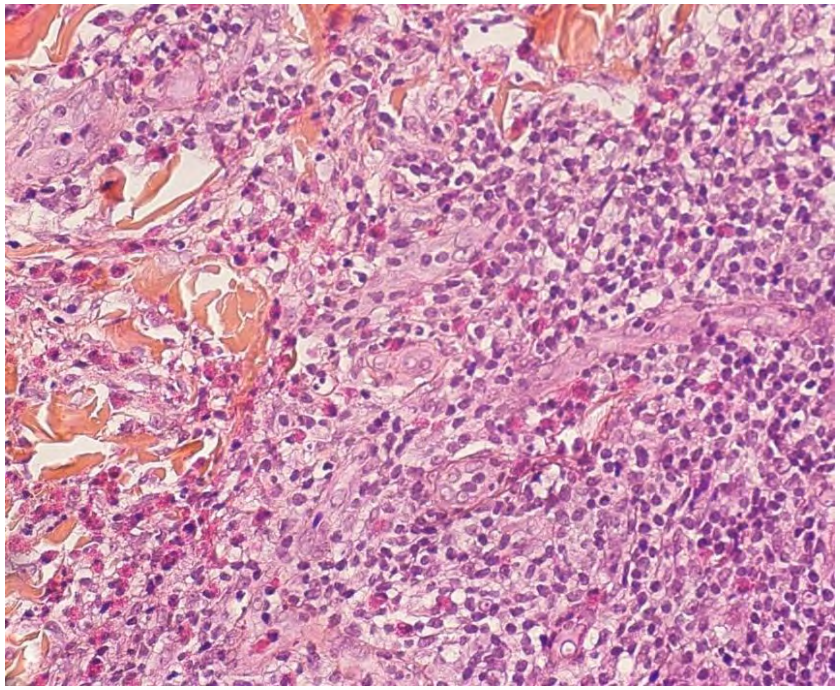
Assessment of the 'no eosinophils' rule: are eosinophils truly absent in pityriasis lichenoides, connective tissue disease, and graft-vs.-host disease?

- Clinical presentation
- **Follow-up**

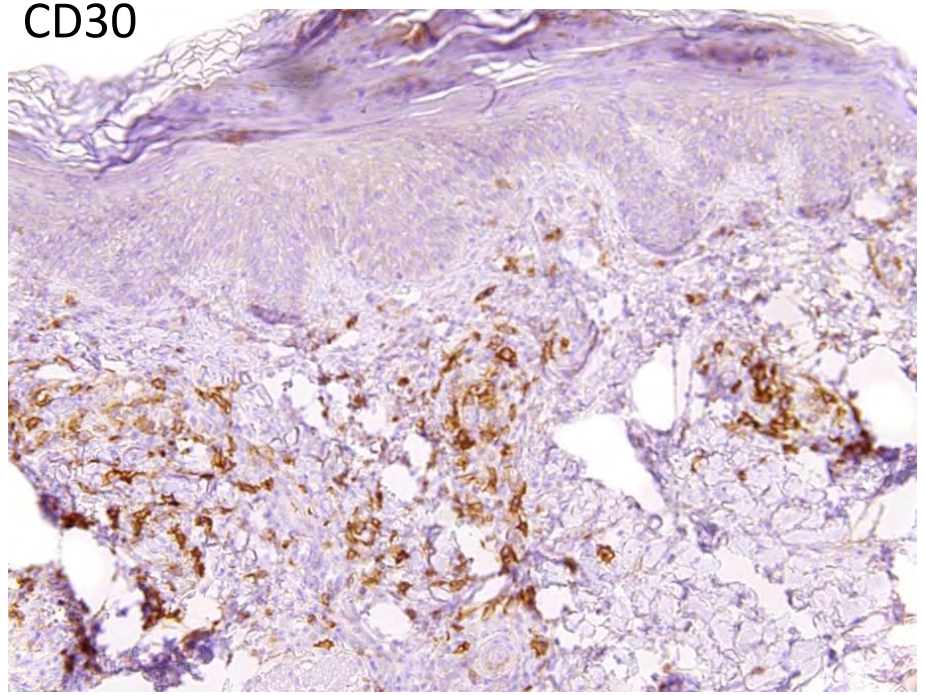
2.Insect bite reactions/ post-scabies nodules



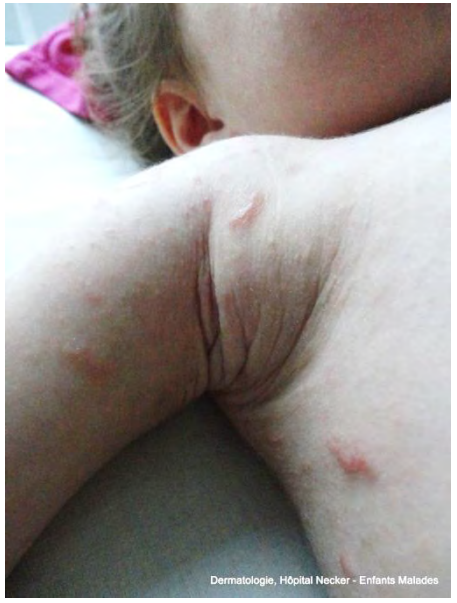
➢Insect bite reactions



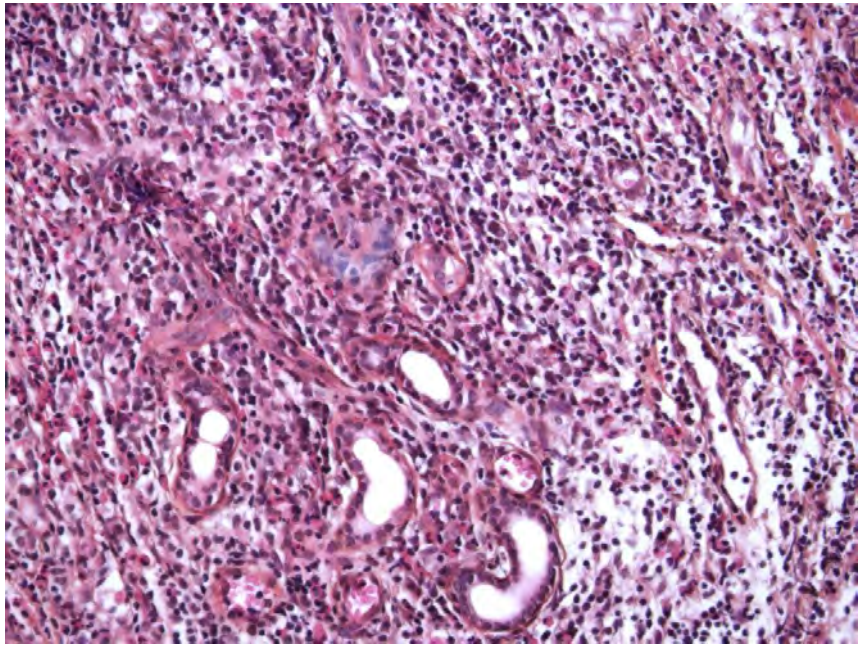
CD30

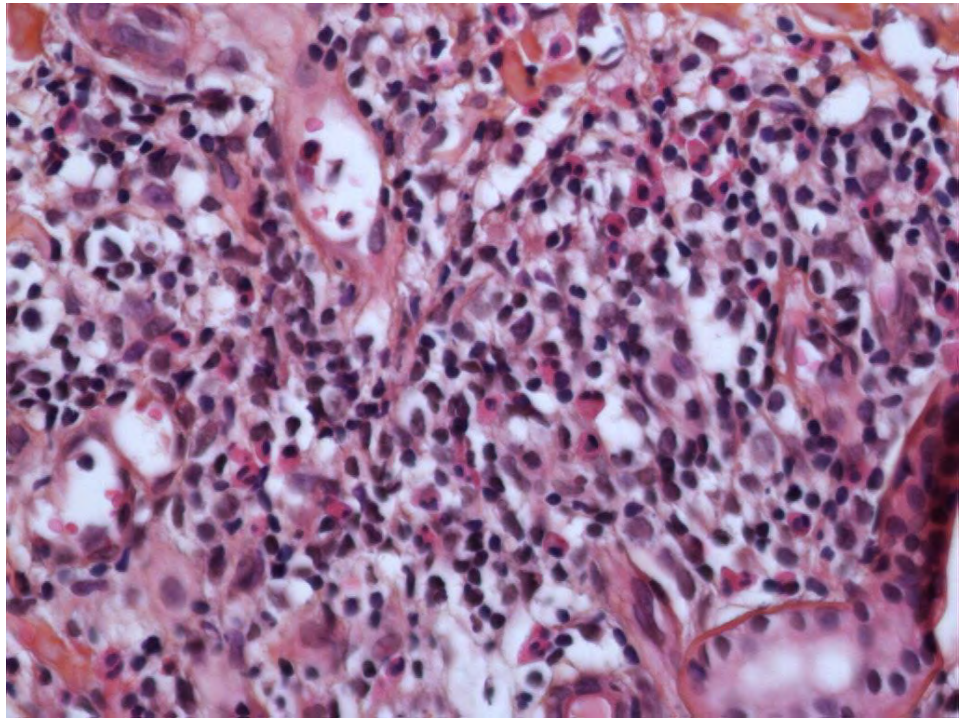


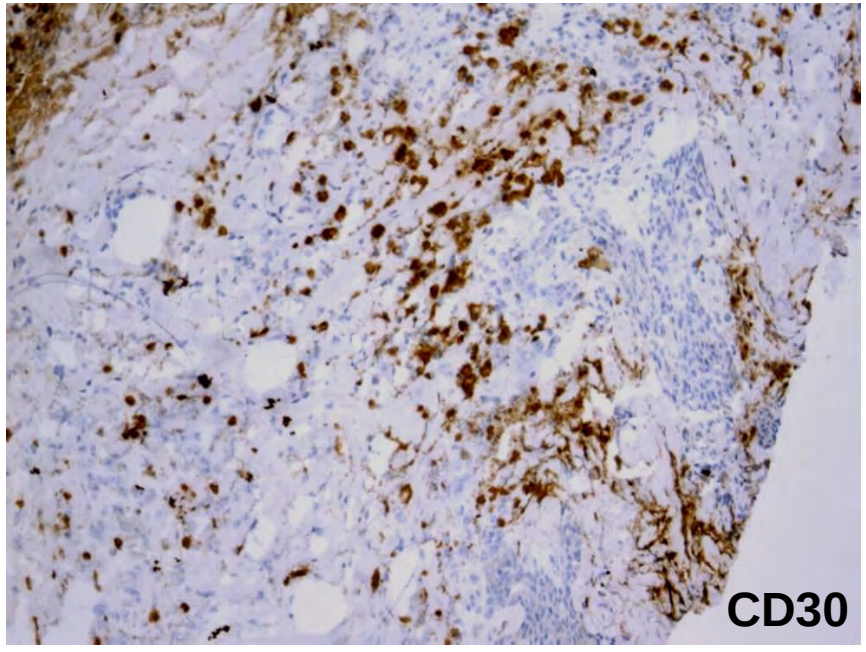
- **May be densily cellular**
- Slight cellular atypia
- **CD30+ cells**



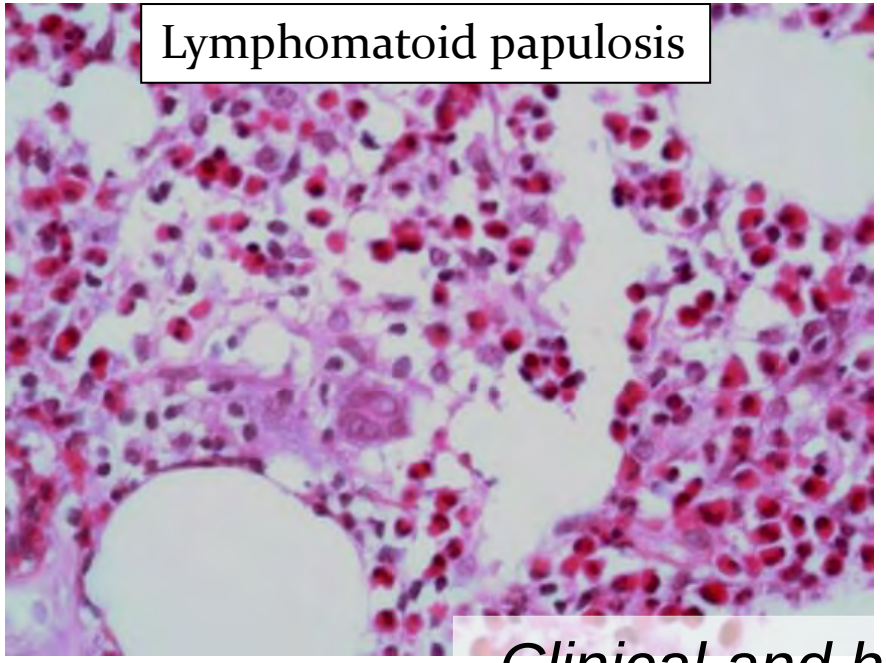
➢Post-scabies nodules

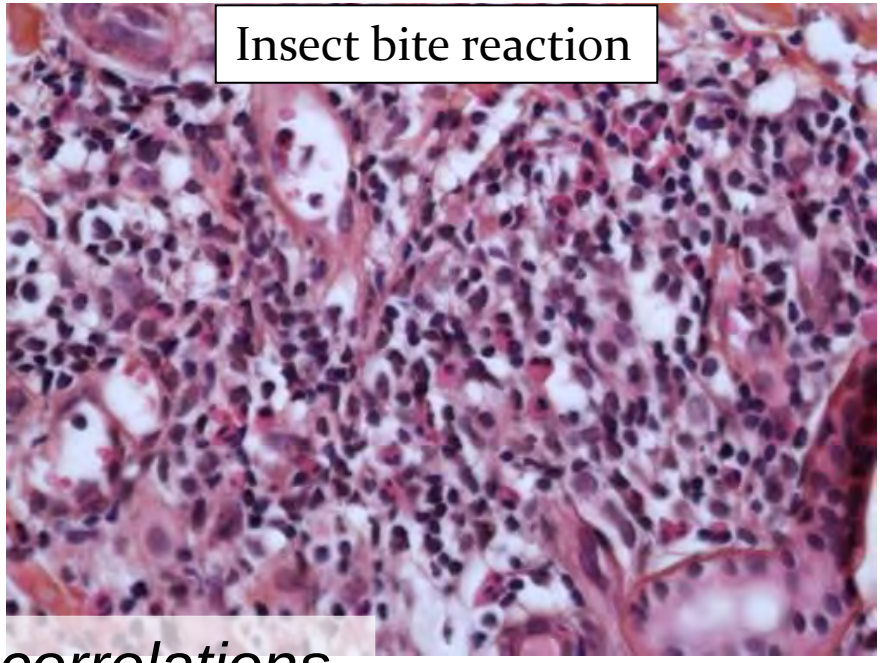




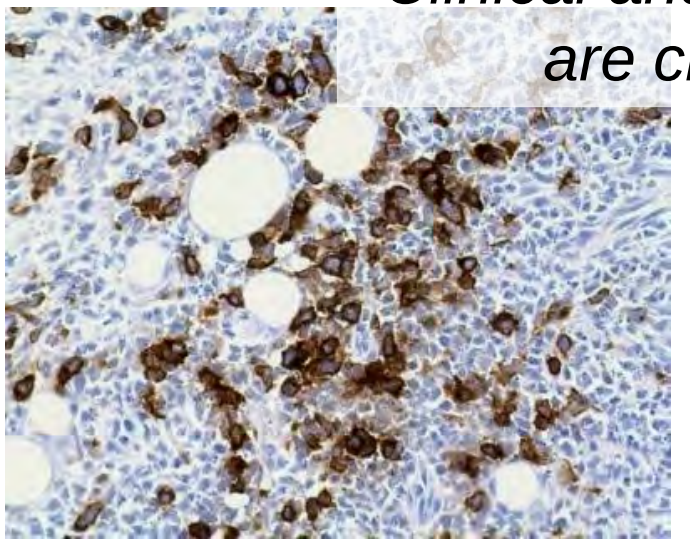


In both there can be a marked eosinophilic infiltrate

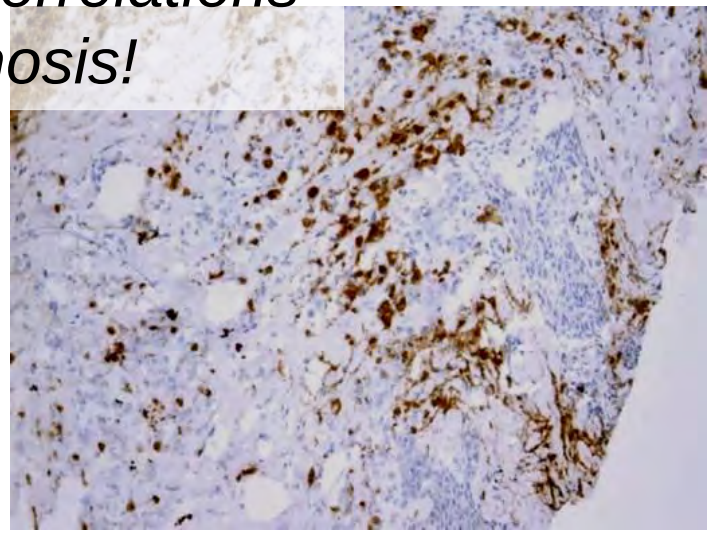




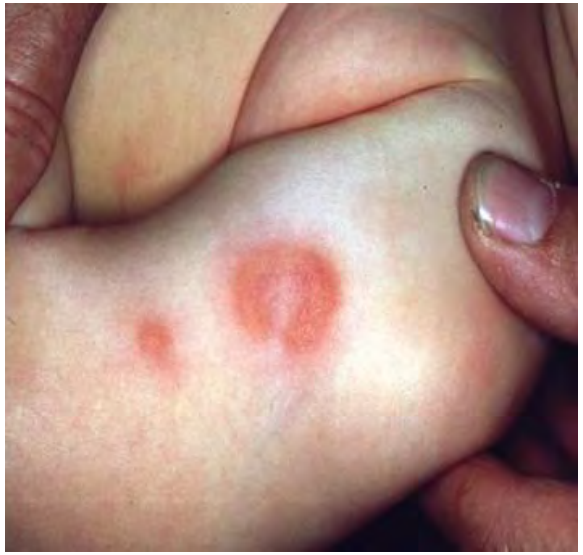
Clinical and histological correlations are crucial for diagnosis!

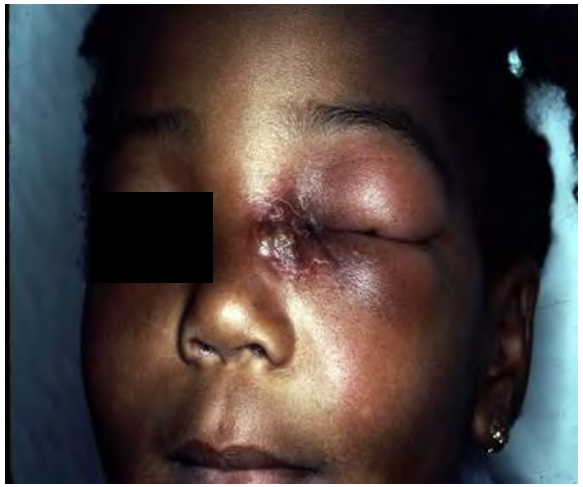


CD30



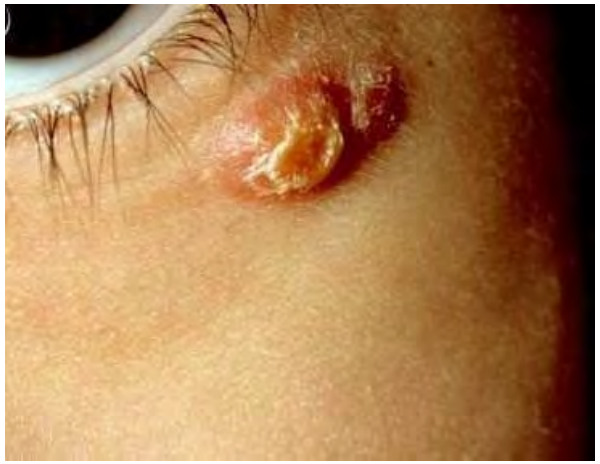
Insect bites

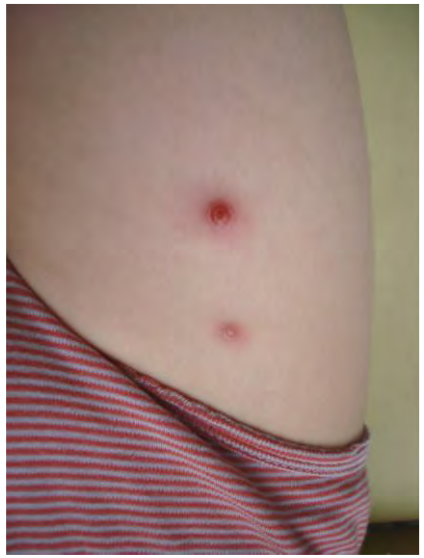




Follow-up!

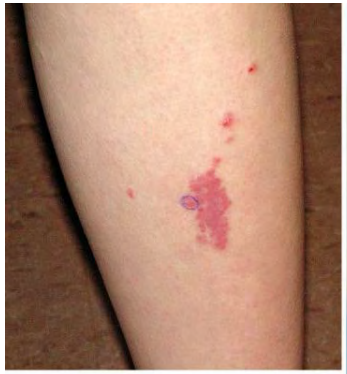
Lymphomatoid papulosis

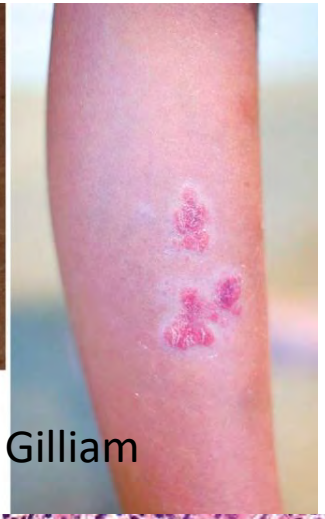




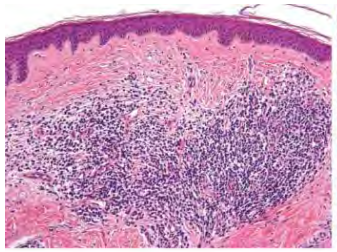
3.Lymphoplasmacytic plaque

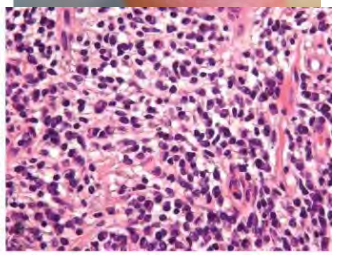
Recently recognized clinicopathologic entity

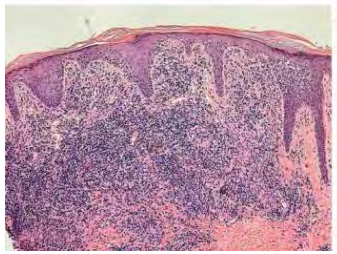


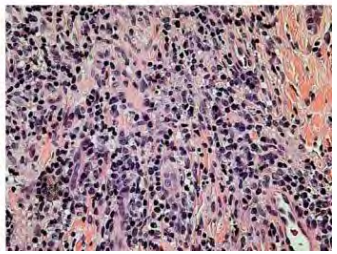


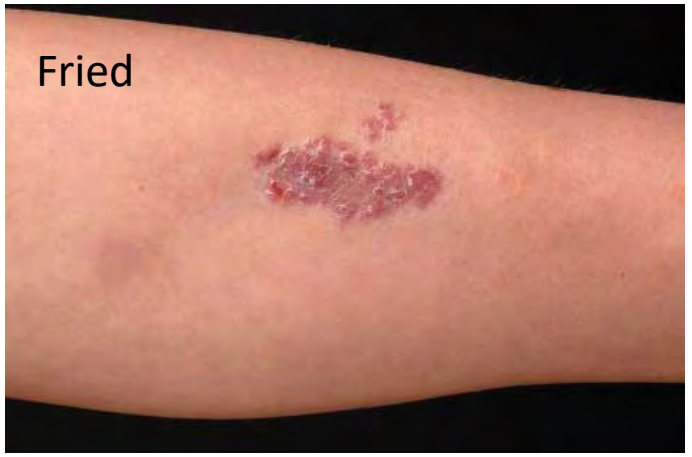
Gilliam



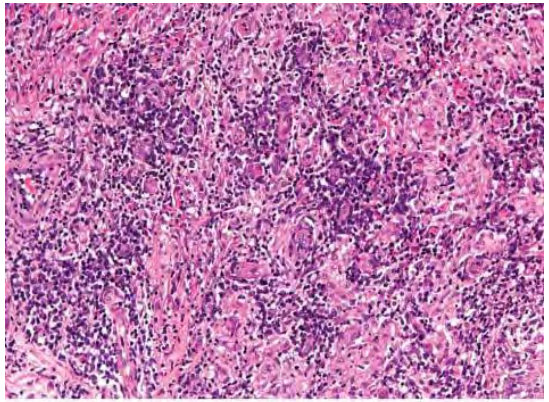


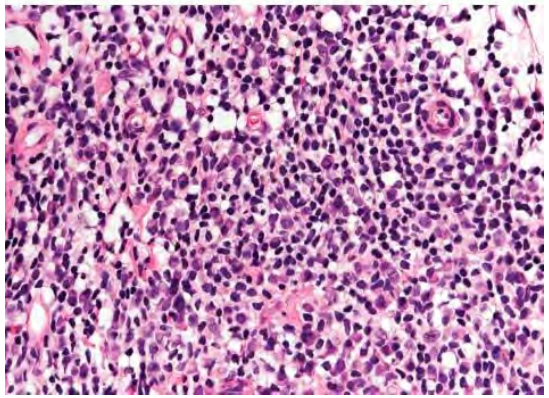


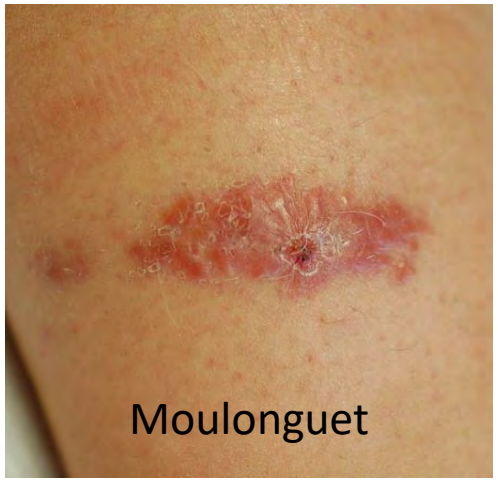




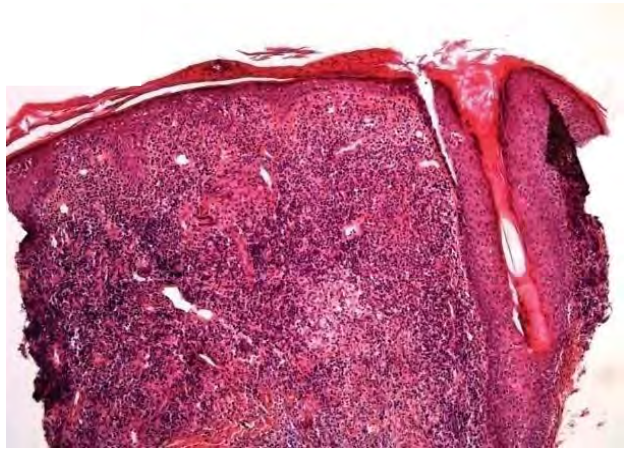
Fried







Moulonguet



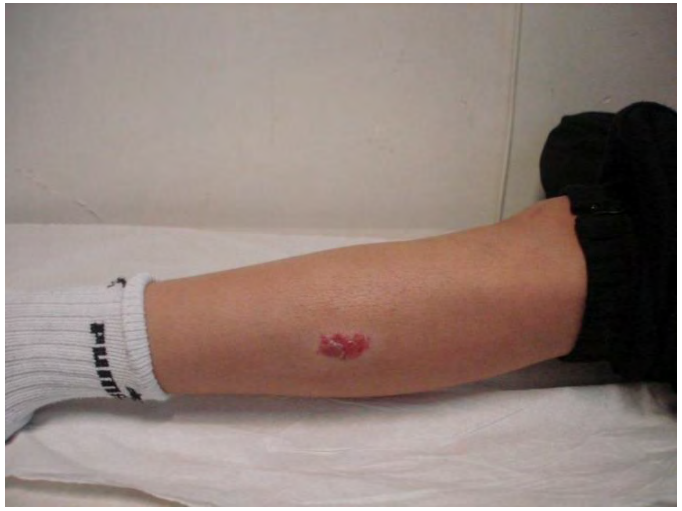
Gilliam AC et al. Arch Dermatol 2009; 145(3): 299-302

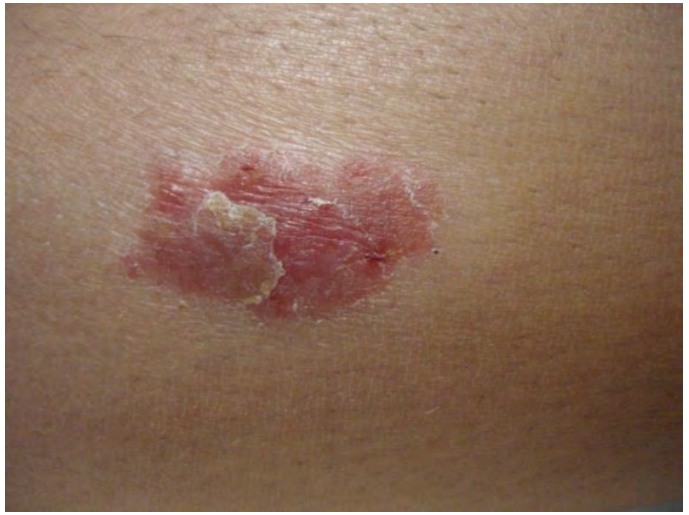
Fried I et al. Arch Dermatol 2010; 146(1): 95-6

I Moulonguet et al. Am J Dermatopathol, 2012, 34 (1), 113-116

All cases are clinically stereotyped!

- Around 20 published cases
- Affects mainly **children** and adolescents
- Clear female predominance
- They all have in common:
  - asymptomatic or slightly pruritic, reddish-brown, violaceous plaque (3 to 5 cm),
  - preferred localization: **leg**, especially the tibial region,
  - **without any recognized cause** yet,
  - **desperately chronic** (from 10 months to 11 years),
  - **no effective treatment** (Imiquimod ?)

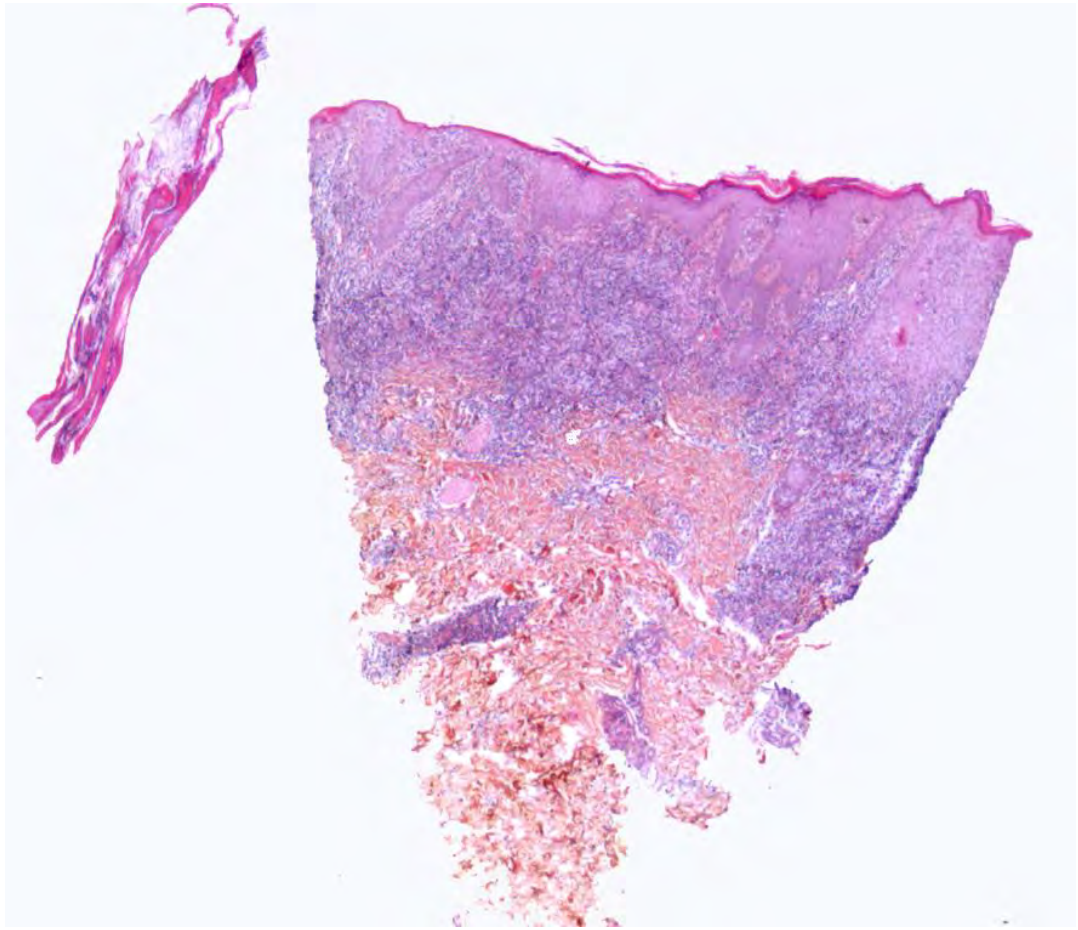


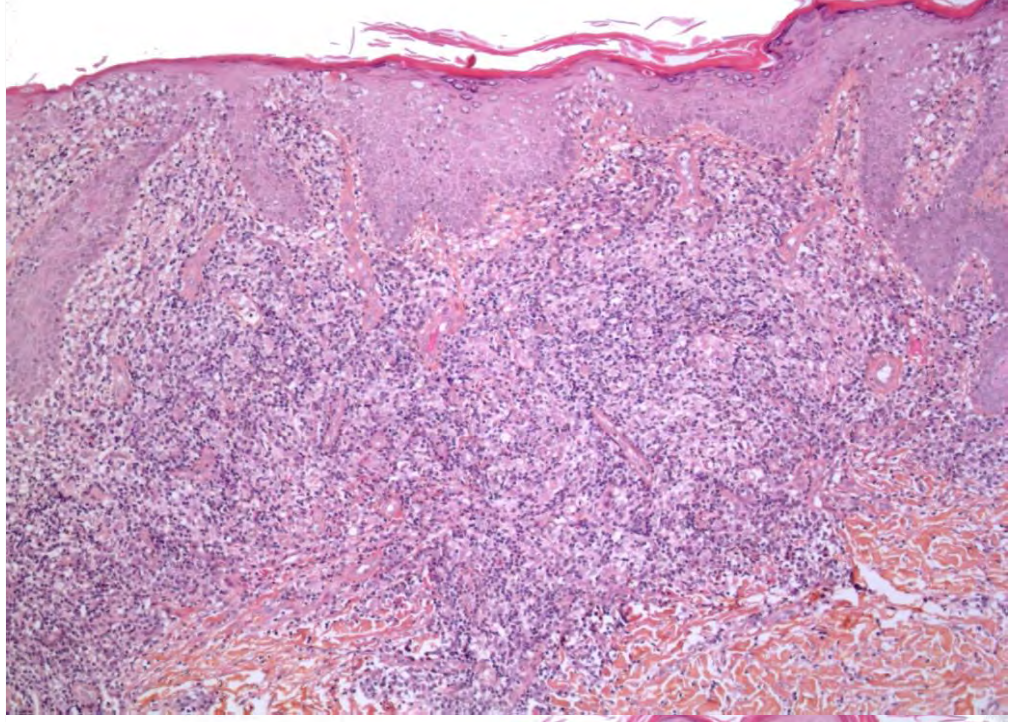


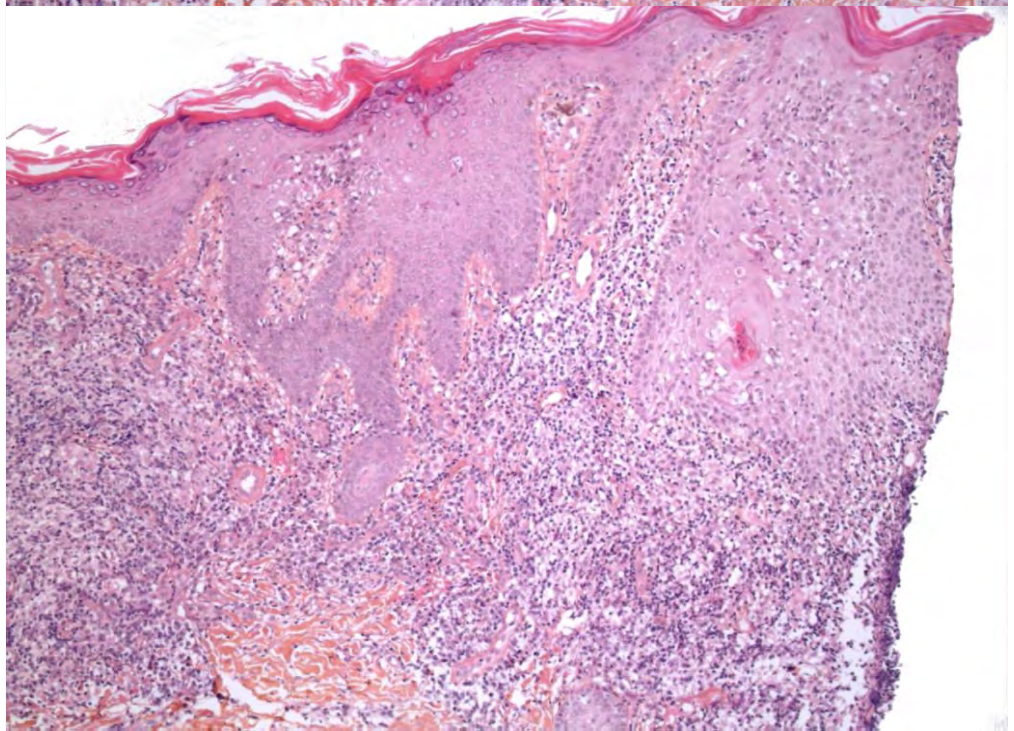
Mitteldorf C, Palmedo G, Kutzner H, Kauer F, Prestin M, Schuster C, Hübscher E, Kirsch A, Tronnier M, Kempf W. Diagnostic approach in lymphoplasmacytic plaque. J Eur Acad Dermatol Venereol. 2015 Nov;29(11):2206-15

Harkemanne E, Dargent J-L, Roquet-Gravy P-P, Bulinckx A. Lymphoplasmacytic plaque in children: Case report and literature review. Pediatr Dermatol. 2019;36:365–367

Maurelli M, Colato C, Giannetti L, Girolomoni G. Lymphoplasmacytic plaque effectively treated with imiquimod. Ital J Dermatol Venerol. 2021 Dec;156(Suppl. 1 to No. 6):17-18.



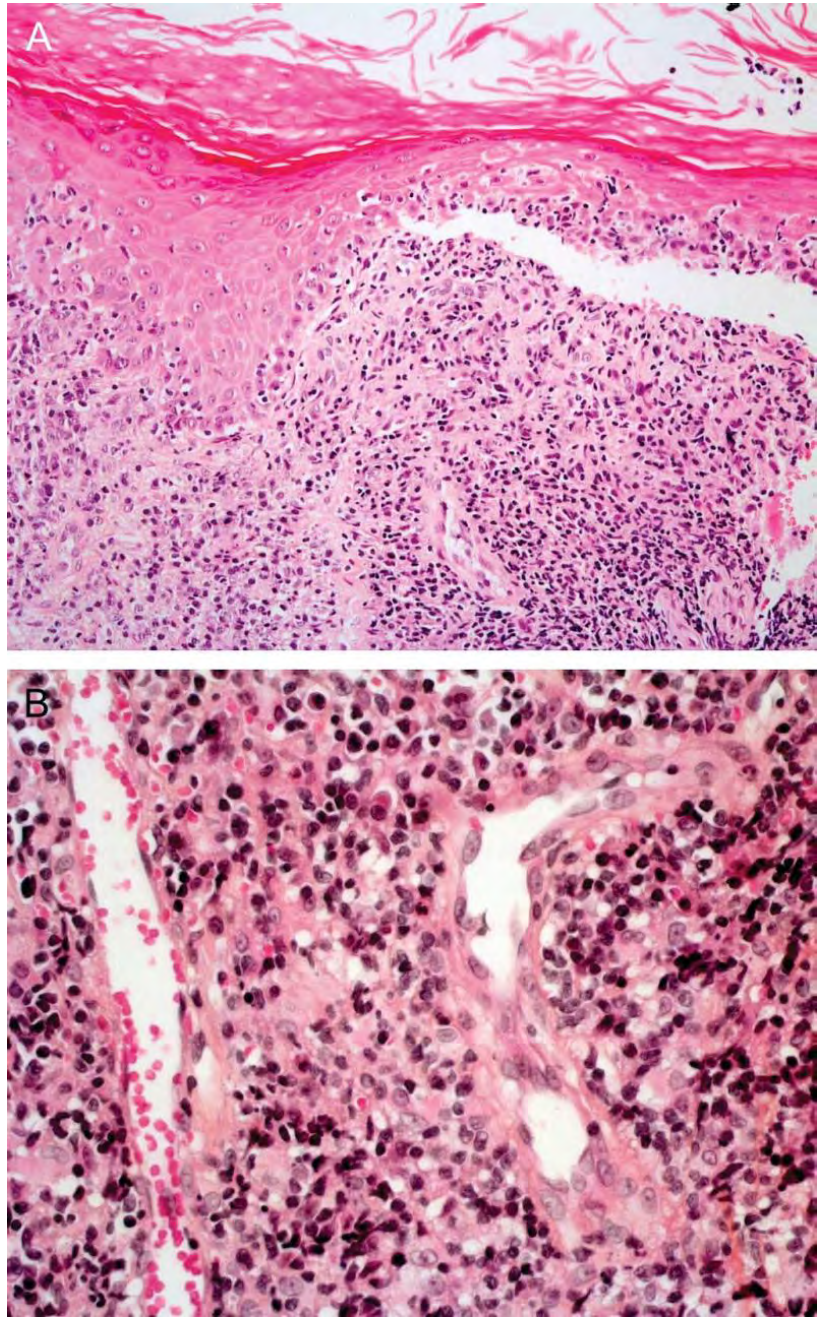




- Marked superficial and deep infiltrate
- Eczematiform changes of the epidermis

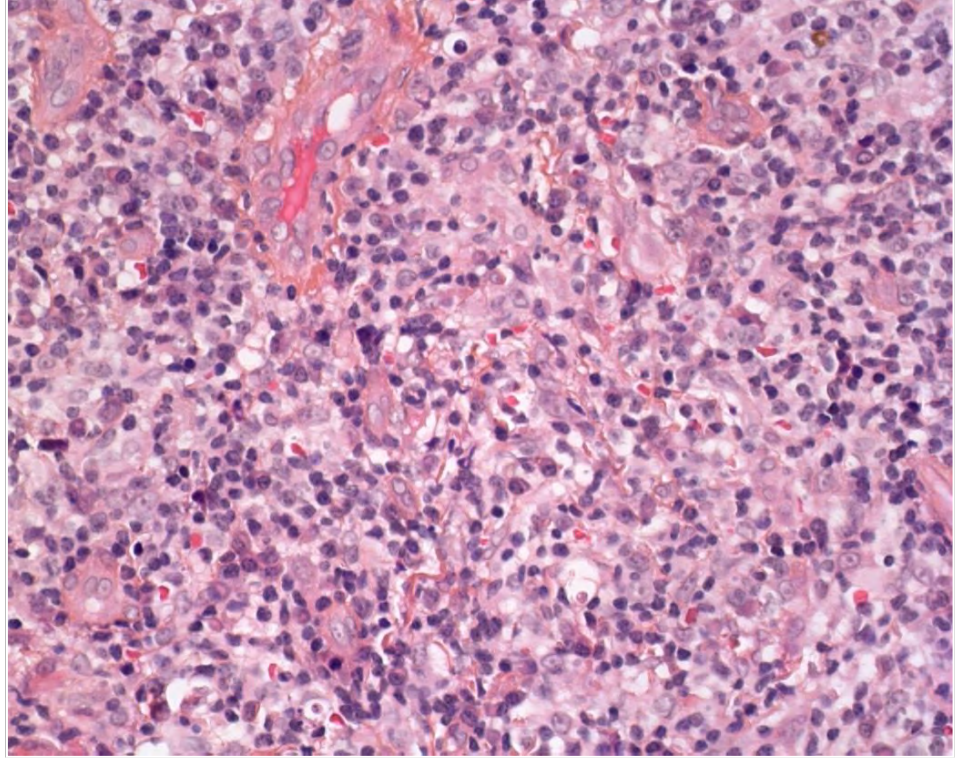
In some cases:

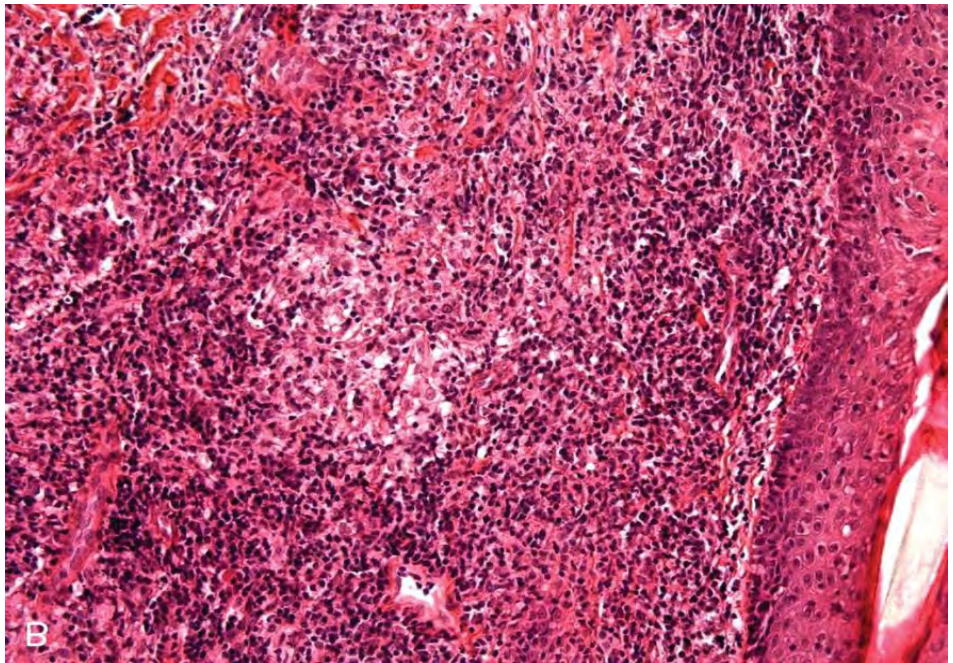
- **lichenoid** tissue reaction
- vertically-arranged, **thick walled vessels** lined with plump endothelial cells



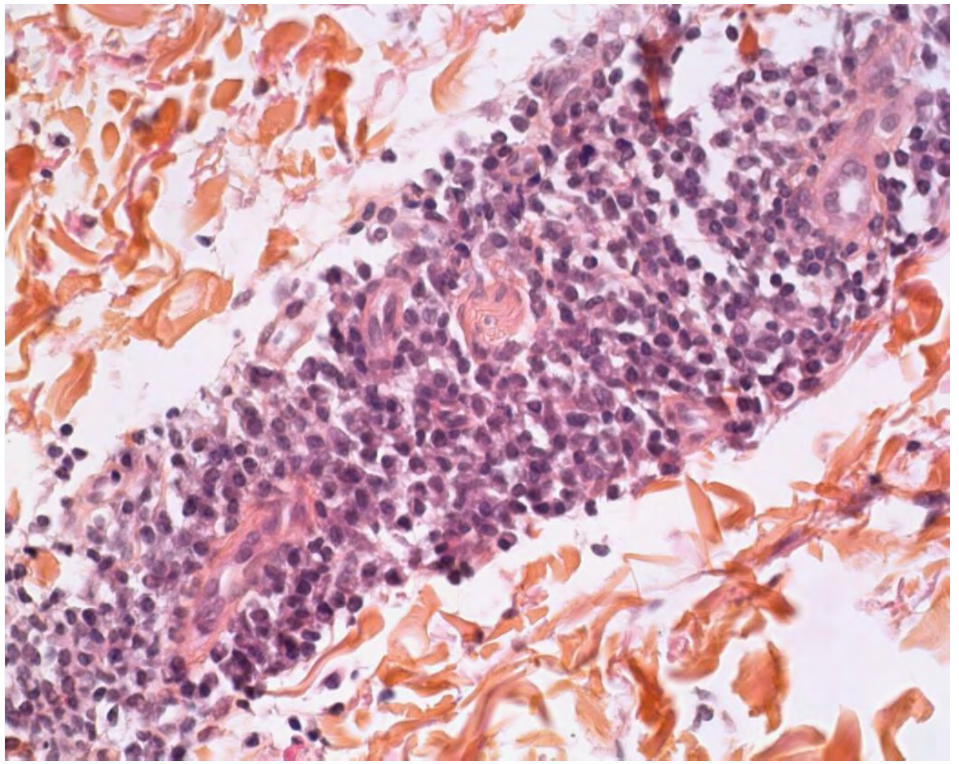
I Moulonguet

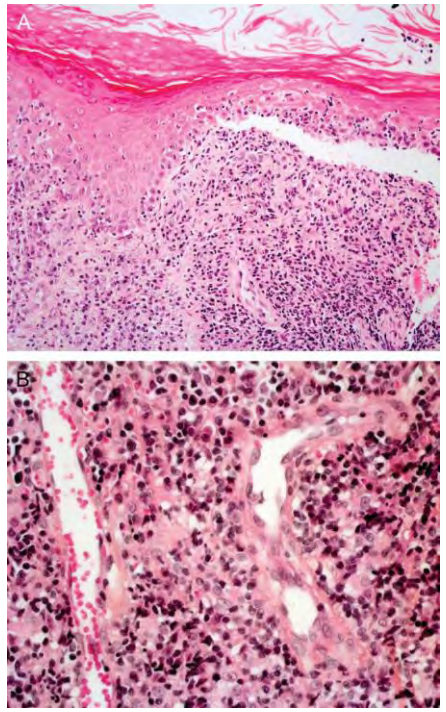
I Moulonguet et al. Am J Dermatopathol, 2012, 34 (1), 113-116





- T and B cell non atypical lymphocytes
- + plasma cells
- Small granulomas
- Polyclonal; occasionally B-cell clone
- Special stains for infectious germs all negative
- Serological tests or fresh tissue cultures, PCR: negative

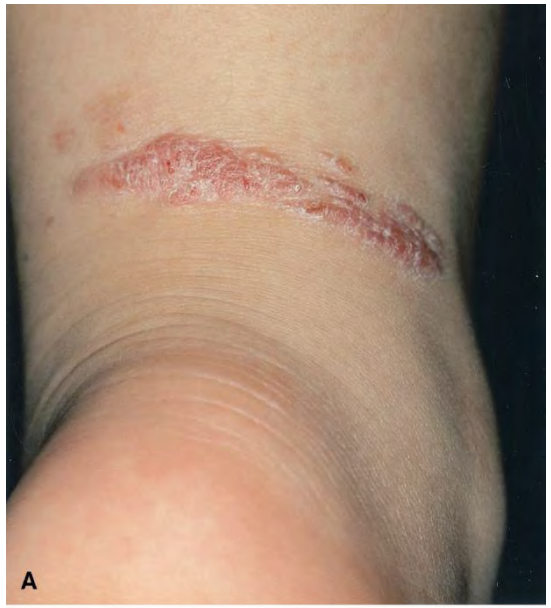


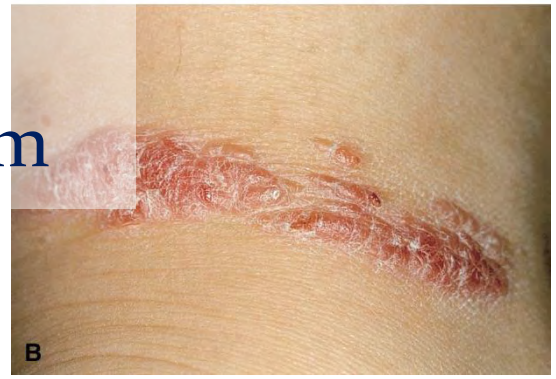


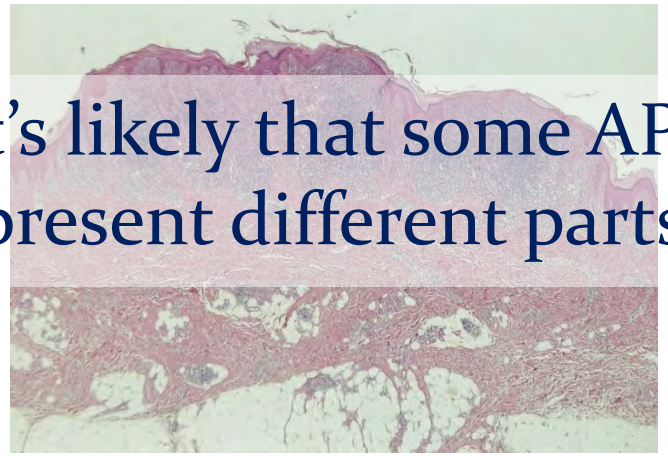
I Moulonguet

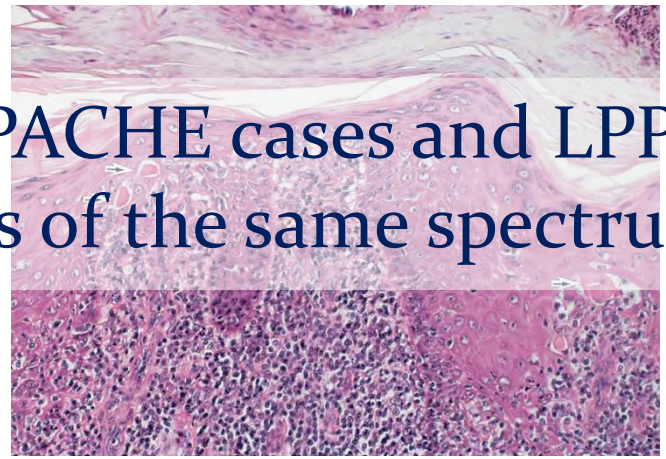
- **Acral pseudo-lymphomatous angiokeratoma of children** (APACHE)

Kiyohara









It's likely that some APACHE cases and LPP represent different parts of the same spectrum

Linear acral pseudolymphomatous angiokeratoma of children (APACHE): Further evidence that APACHE is a cutaneous pseudolymphoma
T Kiyohara et al. J Am Acad Dermatol 2003;48:S15-7

- Cutaneous plasmacytosis
- Infectious lesion
- **Marginal Zone Lymphoma**

Asymptomatic Red Plaque on the Leg of a 7-Year-Old Girl

Heather A. Brandling-Bennett, MD; Sameera Husain, MD; Michael A. Weiner, MD; Kimberly D. Morel, MD; Columbia University, New York, New York

REPORT OF A CASE

A 7-year-old girl presented with a 2½-year history of an asymptomatic lesion on her lower left leg. There had been no recent change in size or color. The lesion had been treated with flurandrenolide tape in the past and got slightly smaller but then returned to its original size. It had never bled or ulcerated. The patient's medical history and a review of systems were unremarkable. She had no significant family history. Her parents were from India, but she had never traveled there; she had been to Guyana but only after the lesion had appeared. Physical examination revealed a 3.6 × 1.3-cm, erythematous, firm plaque with an adjacent 0.6 × 0.4-cm, erythematous, firm papule on the anterior aspect of the lower part of her left leg (**Figure 1**). She had no lymphadenopathy or other notable cutaneous lesions. The skin biopsy findings are shown in **Figure 2** and **Figure 3**.

What is your diagnosis?

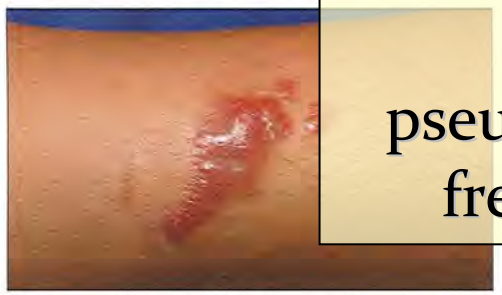


Figure 1.

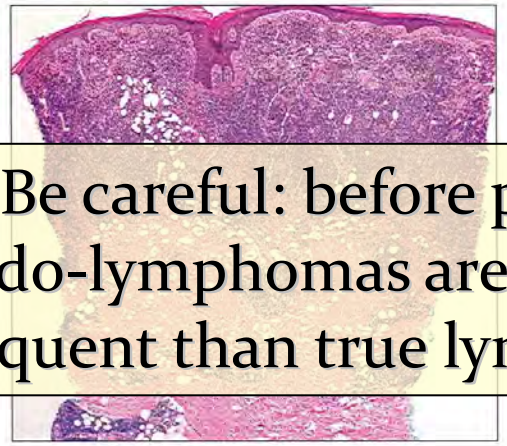


Figure 2.

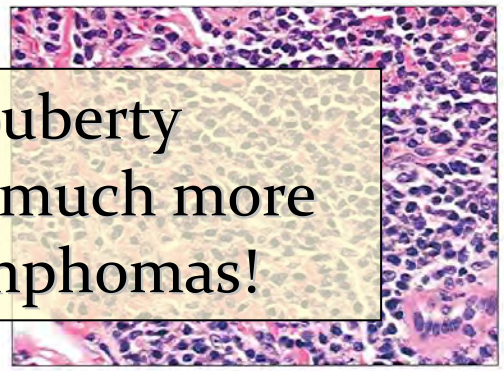


Figure 3.

Be careful: before puberty pseudo-lymphomas are much more frequent than true lymphomas!

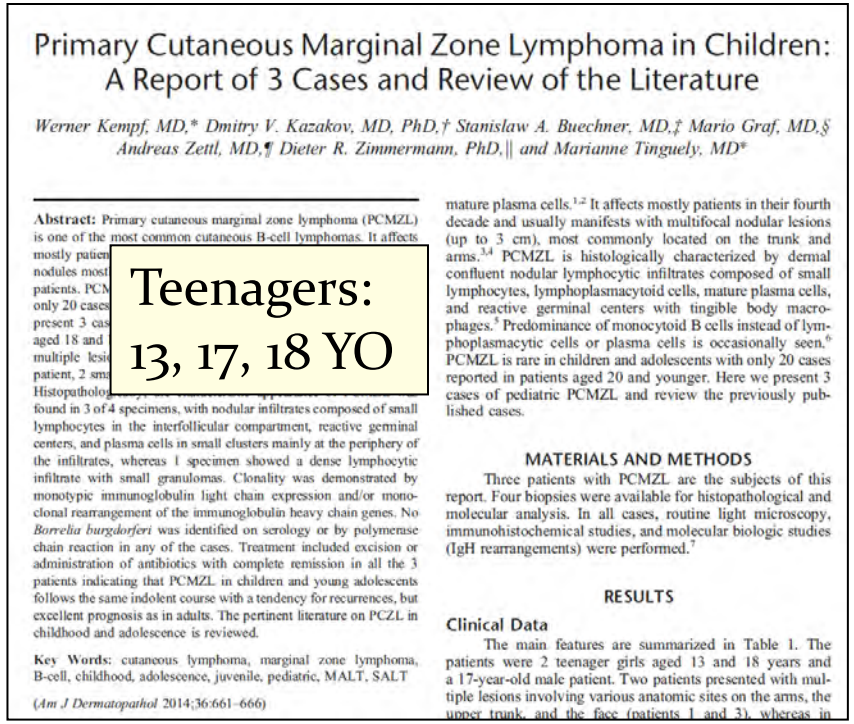
Primitive cutaneous lymphomas in childhood

- The « most frequent »:
  - **mycosis fungoides**
  - **primary cutaneous CD30+ lymphoproliferative disorders**
- Then:
  - primitive lymphoblastic lymphomas
  - subcutaneous panniculitis-like T-cell lymphomas
  - EBV-associated lymphoproliferative disorders

Before 13 years

- the most common are **T-cell** lymphomas
- almost **no** mature B-cell lymphomas

Rare!!



Primary Cutaneous Marginal Zone Lymphoma in Children: A Report of 3 Cases and Review of the Literature

Werner Kempf, MD, Dmitry V. Kazakov, MD, PhD,† Stanislaw A. Buechner, MD,‡ Mario Graf, MD,§ Andreas Zettl, MD,¶ Dieter R. Zimmermann, PhD,‖ and Marianne Tinguely, MD**

Abstract: Primary cutaneous marginal zone lymphoma (PCMZL) is one of the most common cutaneous B-cell lymphomas. It affects mostly patien… nodules most… patients. PCM… only 20 cases… present 3 cas… aged 18 and… multiple lesi… patient, 2 sm… Histopatholo… found in 3 of 4 specimens, with nodular infiltrates composed of small lymphocytes in the interfollicular compartment, reactive germinal centers, and plasma cells in small clusters mainly at the periphery of the infiltrates, whereas 1 specimen showed a dense lymphocytic infiltrate with small granulomas. Clonality was demonstrated by monotypic immunoglobulin light chain expression and/or monoclonal rearrangement of the immunoglobulin heavy chain genes. No *Borrelia burgdorferi* was identified on serology or by polymerase chain reaction in any of the cases. Treatment included excision or administration of antibiotics with complete remission in all the 3 patients indicating that PCMZL in children and young adolescents follows the same indolent course with a tendency for recurrences, but excellent prognosis as in adults. The pertinent literature on PCZL in childhood and adolescence is reviewed.

Key Words: cutaneous lymphoma, marginal zone lymphoma, B-cell, childhood, adolescence, juvenile, pediatric, MALT, SALT

(*Am J Dermatopathol* 2014;36:661–666)

Teenagers:
13, 17, 18 YO

mature plasma cells.[1,2] It affects mostly patients in their fourth decade and usually manifests with multifocal nodular lesions (up to 3 cm), most commonly located on the trunk and arms.[3,4] PCMZL is histologically characterized by dermal confluent nodular lymphocytic infiltrates composed of small lymphocytes, lymphoplasmacytoid cells, mature plasma cells, and reactive germinal centers with tingible body macrophages.[5] Predominance of monocytoid B cells instead of lymphoplasmacytic cells or plasma cells is occasionally seen.[6] PCMZL is rare in children and adolescents with only 20 cases reported in patients aged 20 and younger. Here we present 3 cases of pediatric PCMZL and review the previously published cases.

MATERIALS AND METHODS

Three patients with PCMZL are the subjects of this report. Four biopsies were available for histopathological and molecular analysis. In all cases, routine light microscopy, immunohistochemical studies, and molecular biologic studies (IgH rearrangements) were performed.[7]

RESULTS

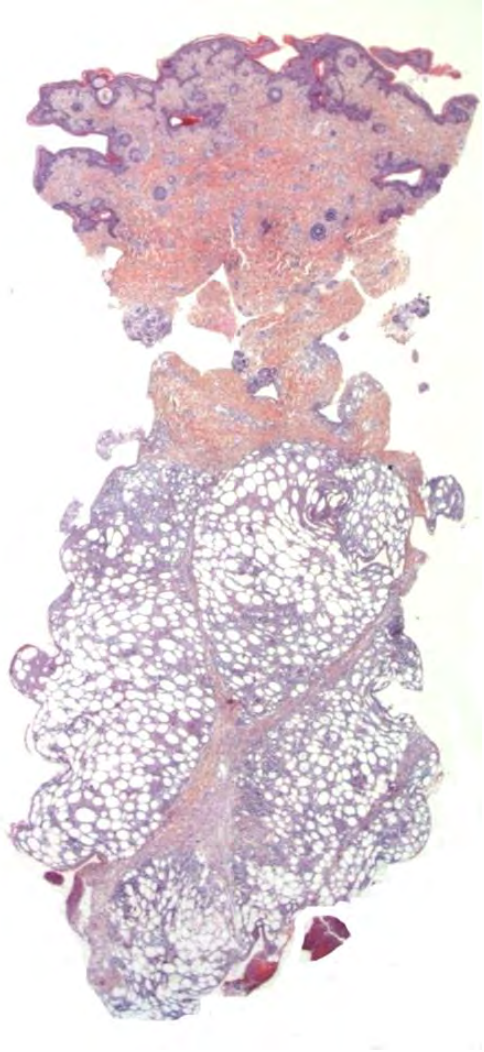
Clinical Data

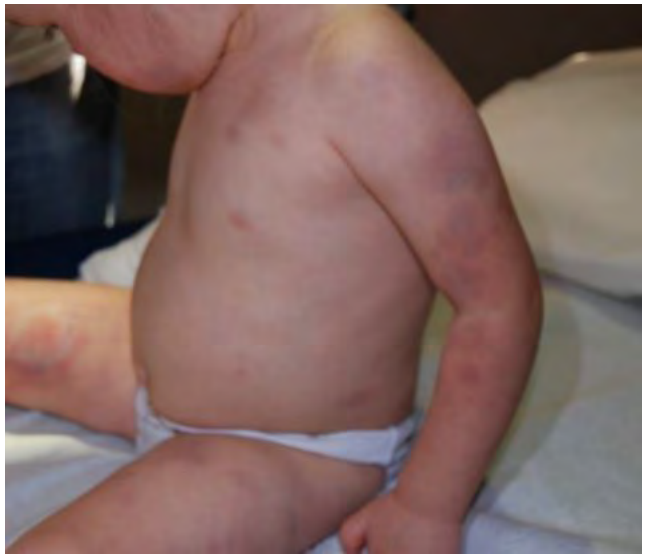
The main features are summarized in Table 1. The patients were 2 teenager girls aged 13 and 18 years and a 17-year-old male patient. Two patients presented with multiple lesions involving various anatomic sites on the arms, the upper trunk, and the face (patients 1 and 3), whereas in

Fink-Puches R et al. Ped Dermatol. 2004; 21: 525-533
Boccara O et al. Pediatr Blood Cancer. 2012; 58: 226-232
Torre-Castro J et al. Pediatr Dermatol. 2021 Nov;38(6):1506-1509

4 **Subcutaneous panniculitis-like T-cell lymphoma**

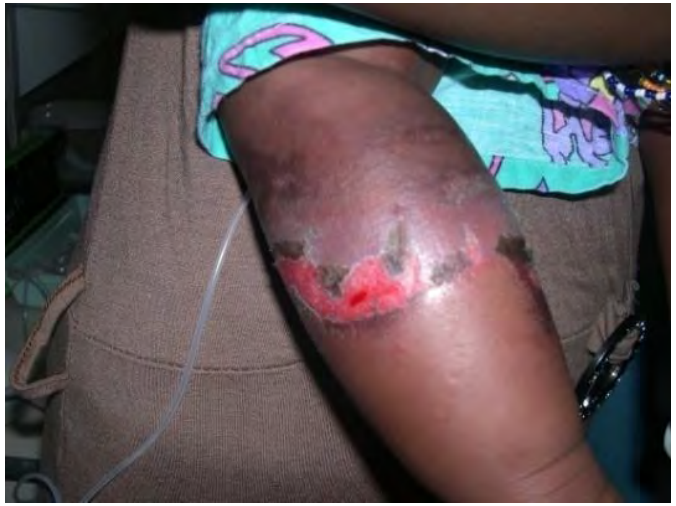
Very rare in children, previously called
« clonal cytophagic histiocytic panniculitis »

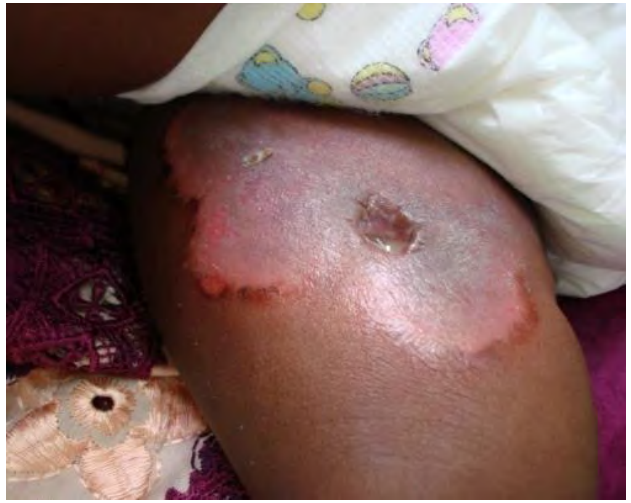


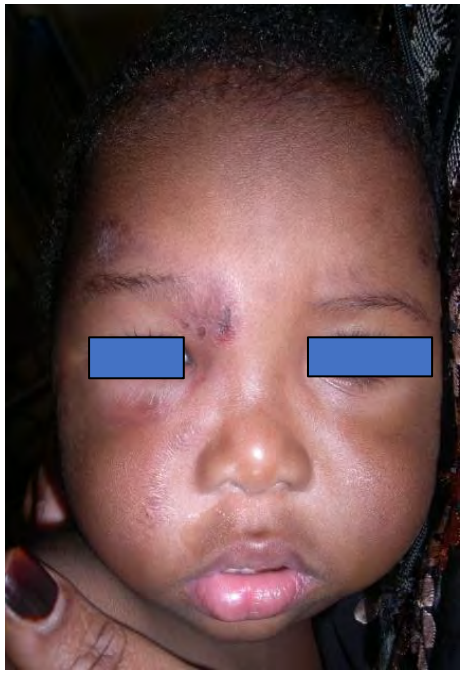


Subcutaneous nodules/plaques often associated with
systemic symptoms and **hemophagocytic syndrome**

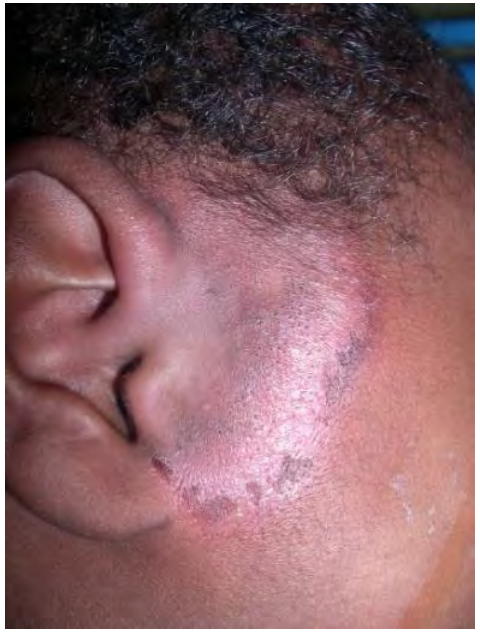
Quiz

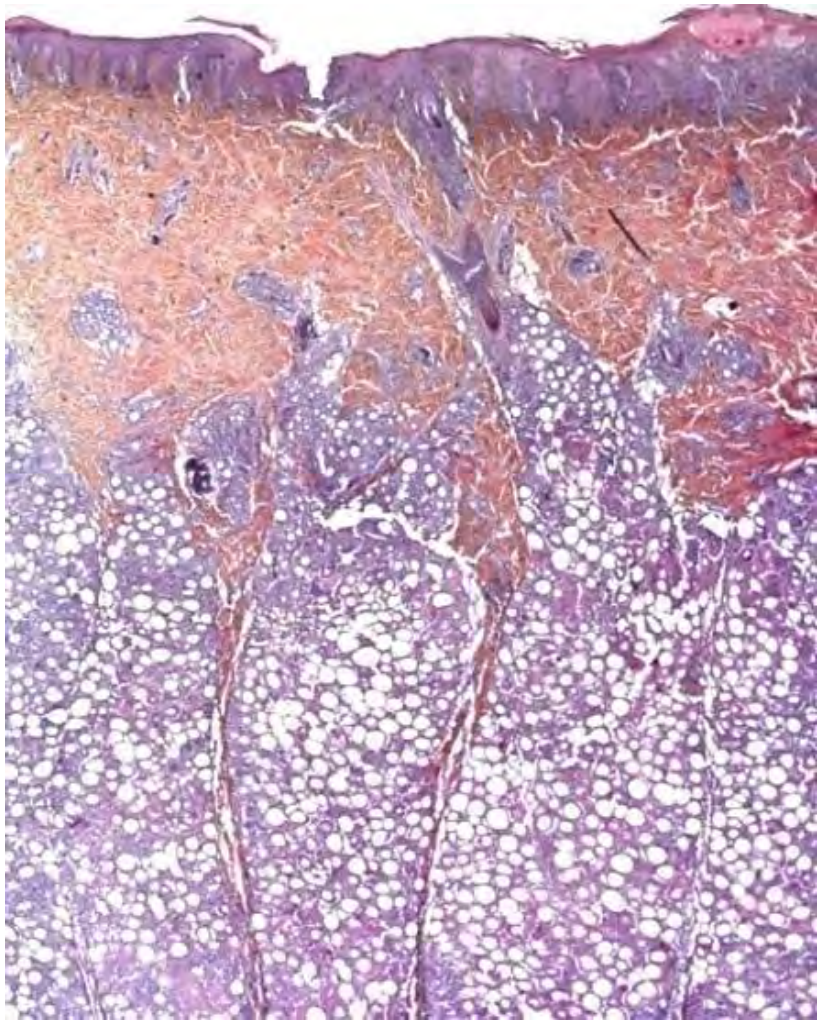




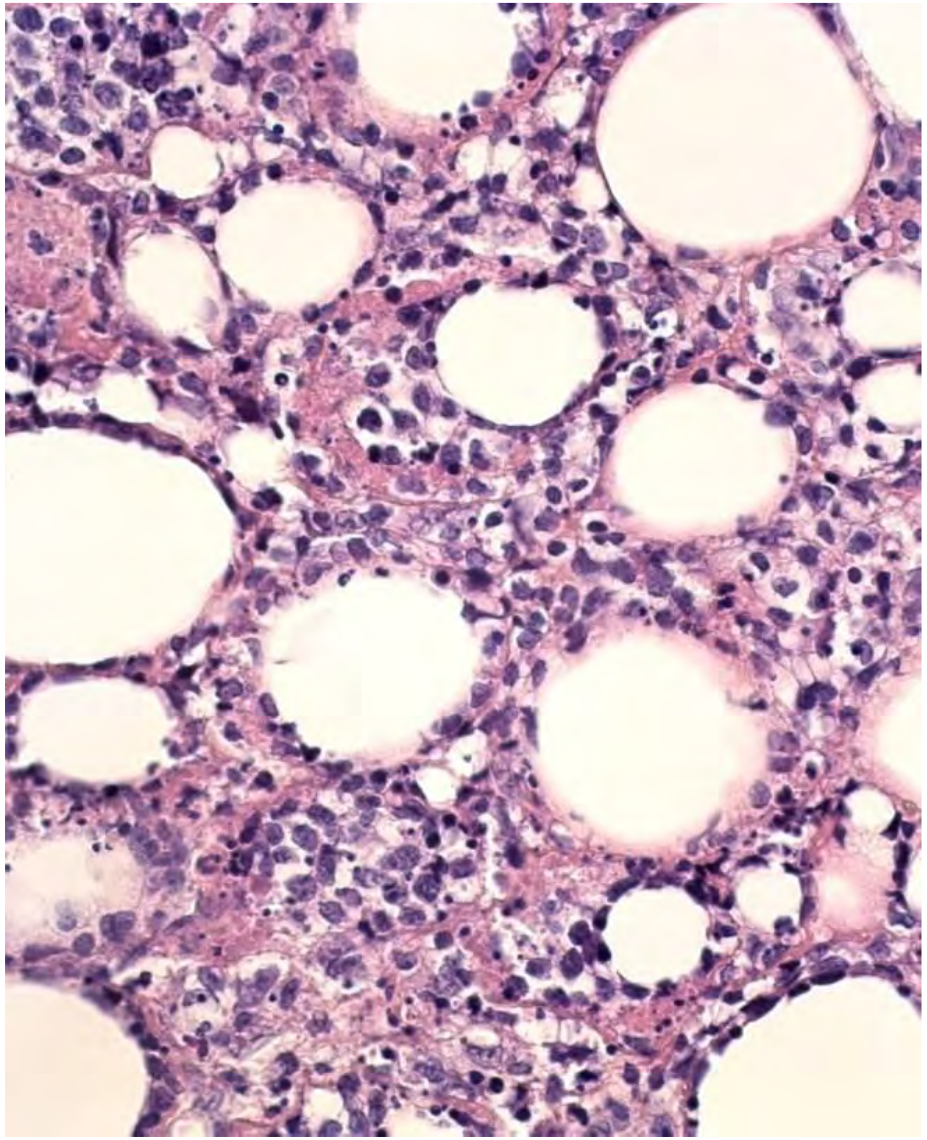


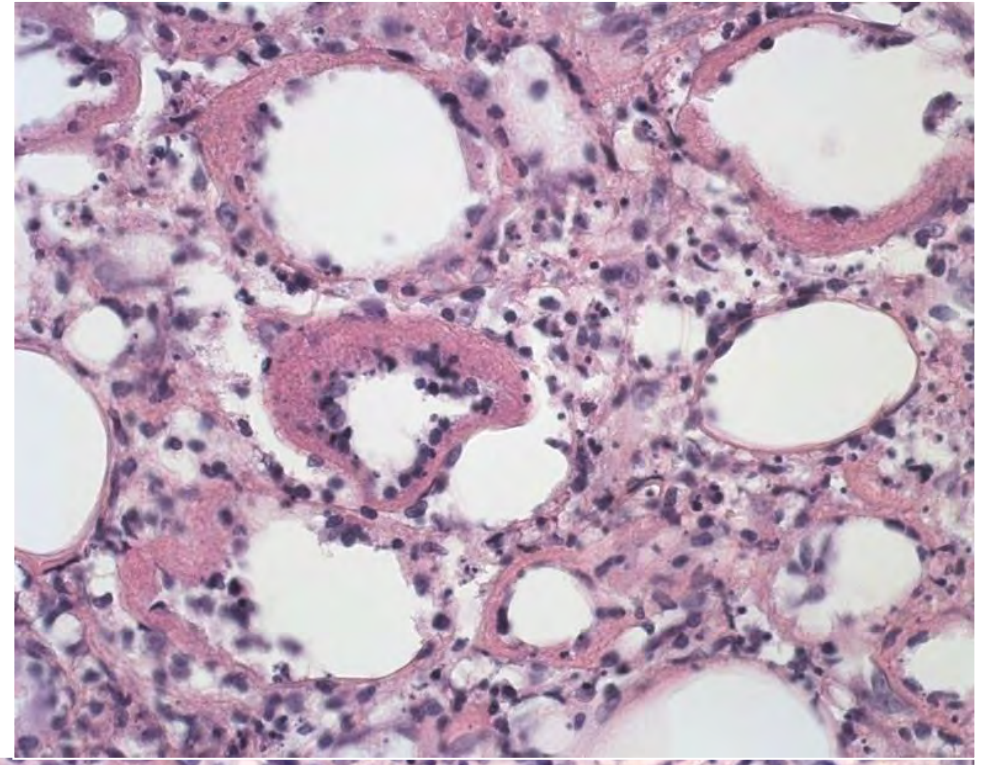
- **6-month-old boy** with a history of chicken pox
- High fever and deteriorating general condition
- Multiple infiltrated and ulcerated plaques

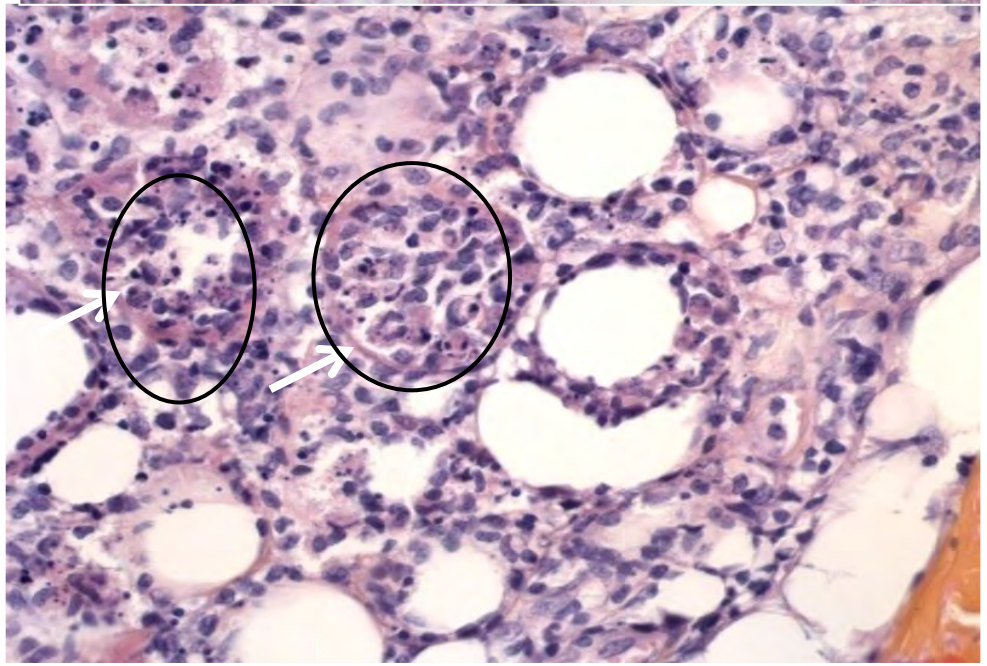




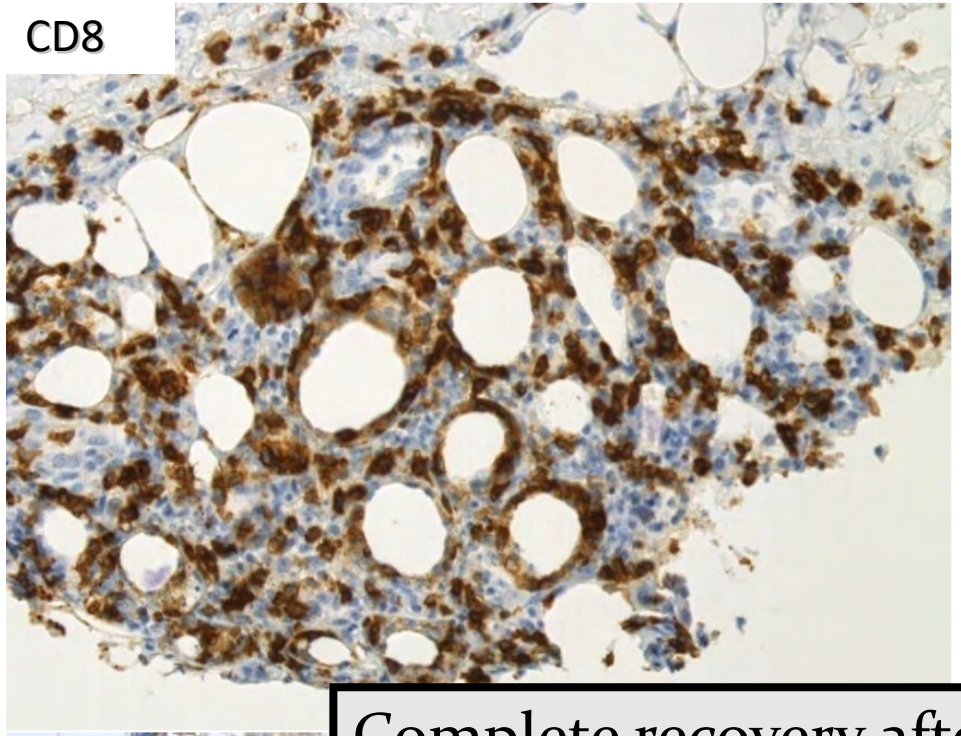
- Superficial and deep infiltrate with lymphocytic exocytosis
- Lobular panniculitis pattern

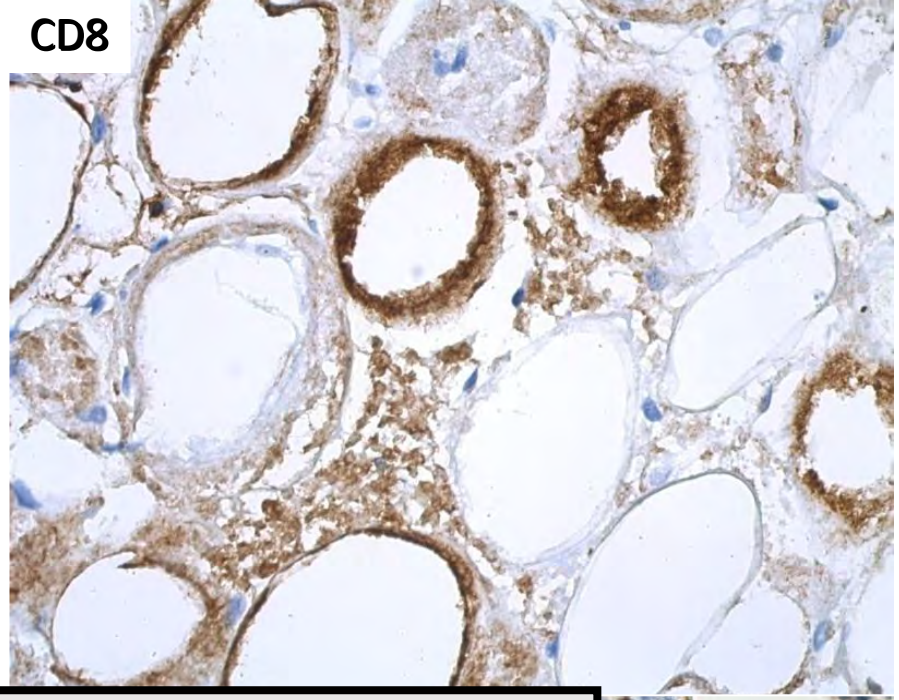




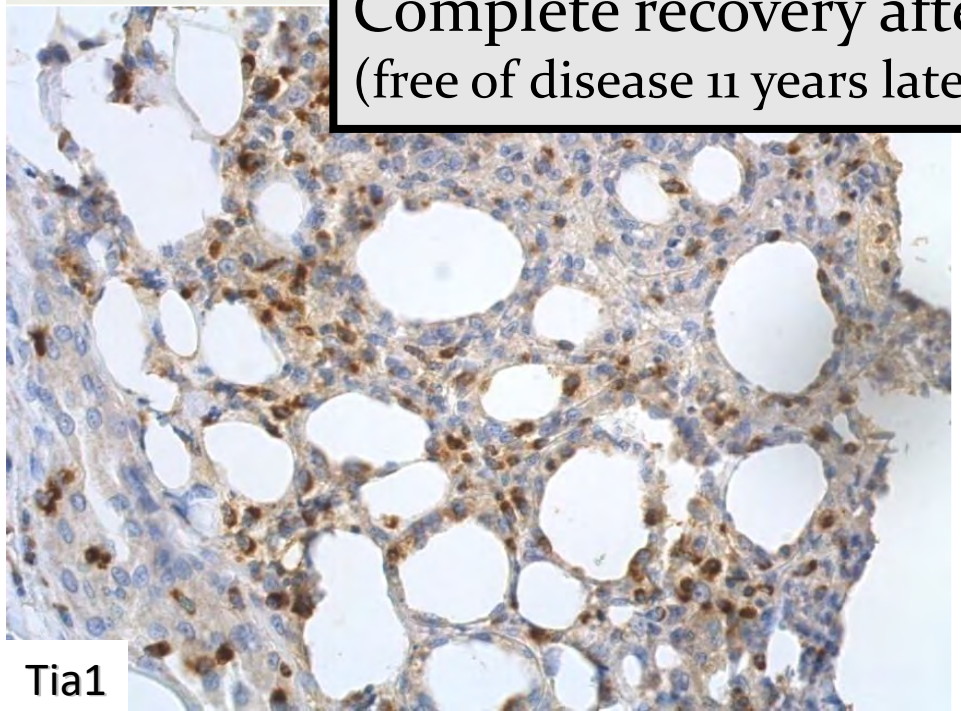


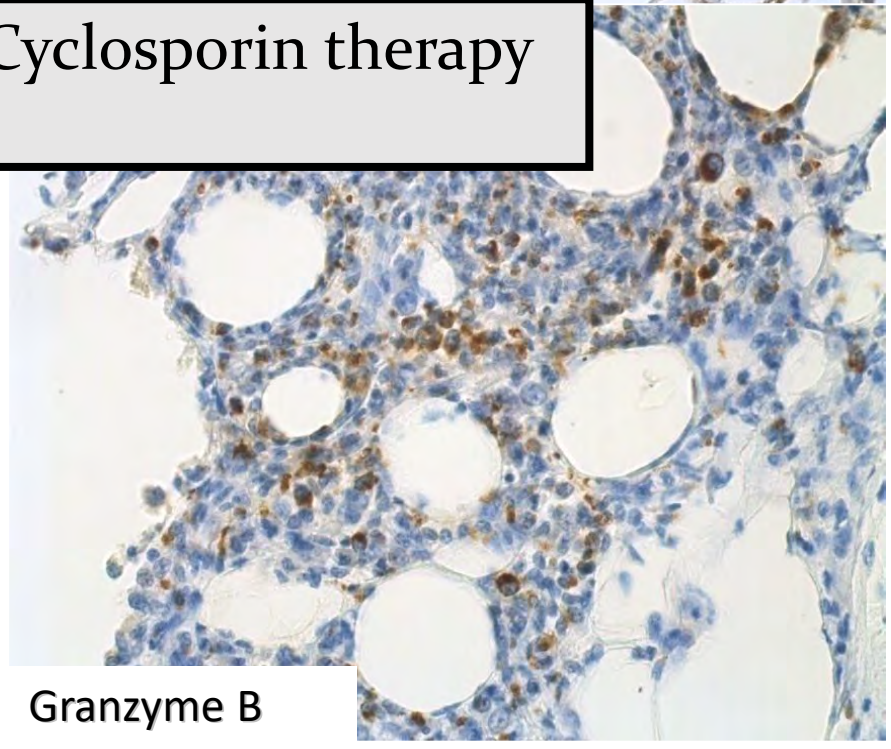
- Small to medium-sized lymphocytes with irregular nuclei
- Adipocytic « rimming », hyaline necrosis
- Nuclear debris, haemophagocytosis





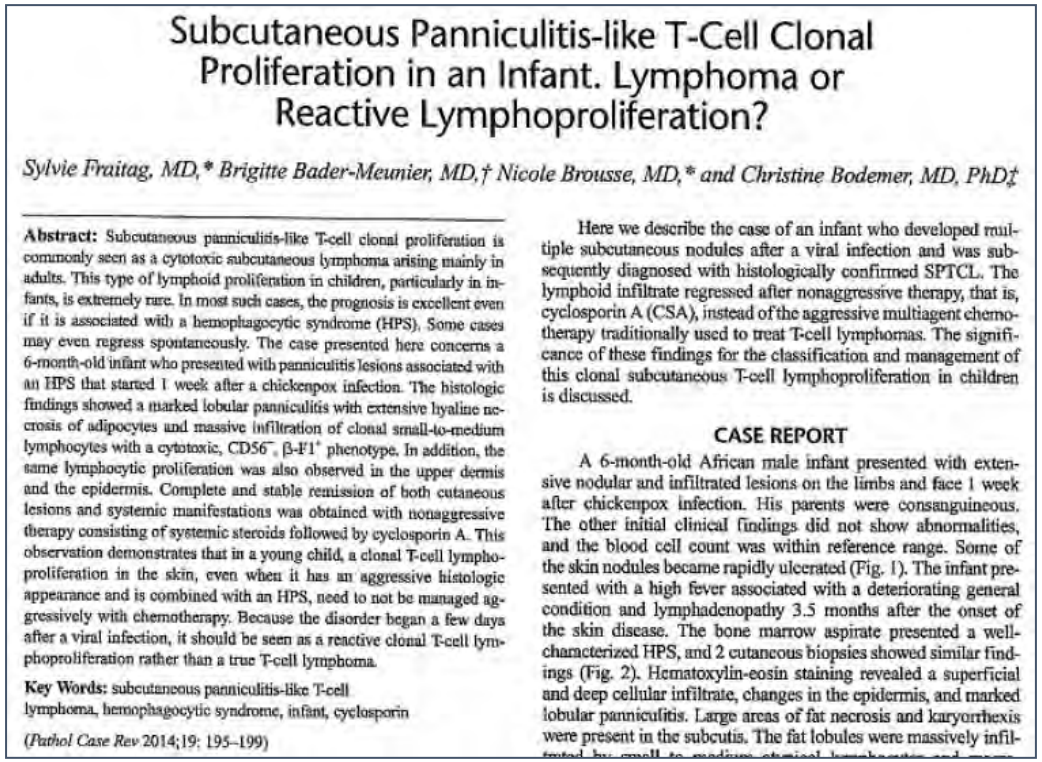
Complete recovery after Cyclosporin therapy
(free of disease 11 years later)





What is the meaning of this T-cell clonal cytotoxic proliferation?

- **Reactive clonal proliferation > true lymphoma**
  - often preceded by an infection (chicken-pox, other virus)
  - spontaneous regressions



Subcutaneous Panniculitis-like T-Cell Clonal Proliferation in an Infant. Lymphoma or Reactive Lymphoproliferation?

Sylvie Fraitag, MD, Brigitte Bader-Meunier, MD,† Nicole Brousse, MD,* and Christine Bodemer, MD, PhD‡*

Abstract: Subcutaneous panniculitis-like T-cell clonal proliferation is commonly seen as a cytotoxic subcutaneous lymphoma arising mainly in adults. This type of lymphoid proliferation in children, particularly in infants, is extremely rare. In most such cases, the prognosis is excellent even if it is associated with a hemophagocytic syndrome (HPS). Some cases may even regress spontaneously. The case presented here concerns a 6-month-old infant who presented with panniculitis lesions associated with an HPS that started 1 week after a chickenpox infection. The histologic findings showed a marked lobular panniculitis with extensive hyaline necrosis of adipocytes and massive infiltration of clonal small-to-medium lymphocytes with a cytotoxic, $CD56^-$, $\beta\text{-}F1^+$ phenotype. In addition, the same lymphocytic proliferation was also observed in the upper dermis and the epidermis. Complete and stable remission of both cutaneous lesions and systemic manifestations was obtained with nonaggressive therapy consisting of systemic steroids followed by cyclosporin A. This observation demonstrates that in a young child, a clonal T-cell lymphoproliferation in the skin, even when it has an aggressive histologic appearance and is combined with an HPS, need to not be managed aggressively with chemotherapy. Because the disorder began a few days after a viral infection, it should be seen as a reactive clonal T-cell lymphoproliferation rather than a true T-cell lymphoma.

Key Words: subcutaneous panniculitis-like T-cell lymphoma, hemophagocytic syndrome, infant, cyclosporin

(*Pathol Case Rev* 2014;19: 195–199)

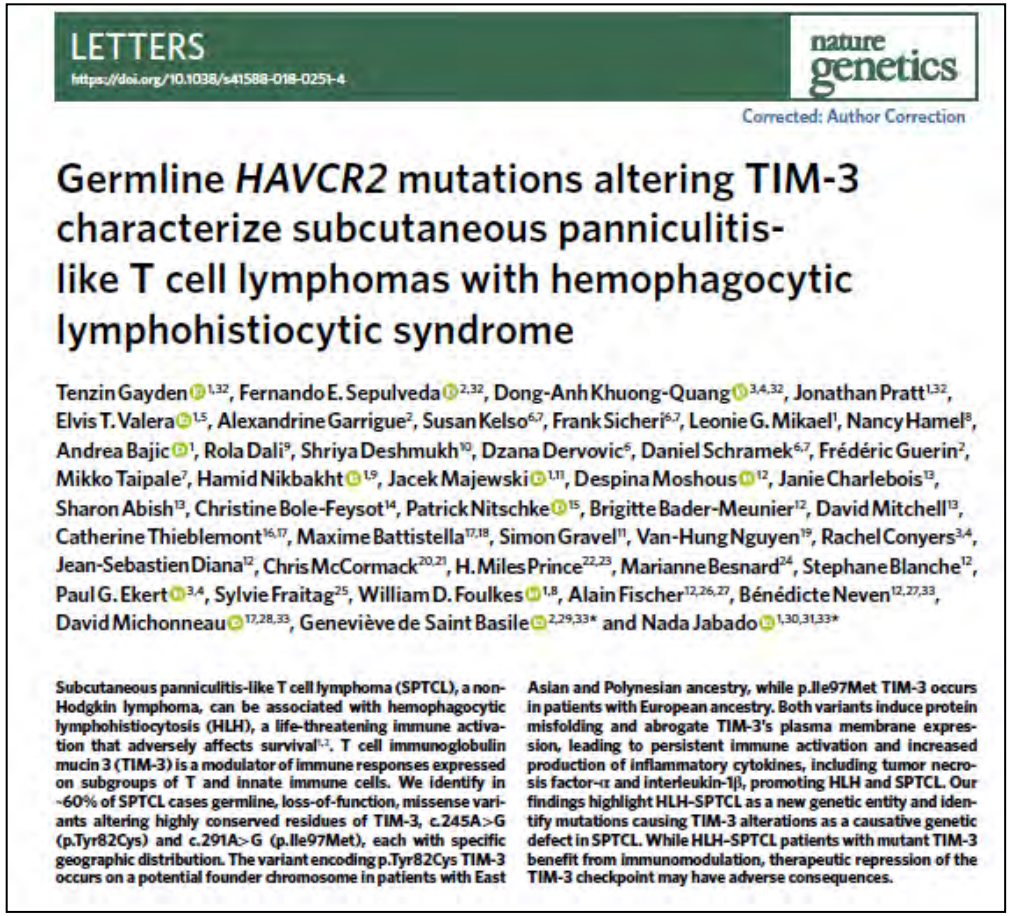
Here we describe the case of an infant who developed multiple subcutaneous nodules after a viral infection and was subsequently diagnosed with histologically confirmed SPTCL. The lymphoid infiltrate regressed after nonaggressive therapy, that is, cyclosporin A (CSA), instead of the aggressive multiagent chemotherapy traditionally used to treat T-cell lymphomas. The significance of these findings for the classification and management of this clonal subcutaneous T-cell lymphoproliferation in children is discussed.

CASE REPORT

A 6-month-old African male infant presented with extensive nodular and infiltrated lesions on the limbs and face 1 week after chickenpox infection. His parents were consanguineous. The other initial clinical findings did not show abnormalities, and the blood cell count was within reference range. Some of the skin nodules became rapidly ulcerated (Fig. 1). The infant presented with a high fever associated with a deteriorating general condition and lymphadenopathy 3.5 months after the onset of the skin disease. The bone marrow aspirate presented a well-characterized HPS, and 2 cutaneous biopsies showed similar findings (Fig. 2). Hematoxylin-eosin staining revealed a superficial and deep cellular infiltrate, changes in the epidermis, and marked lobular panniculitis. Large areas of fat necrosis and karyorrhexis were present in the subcutis. The fat lobules were massively infil-

- **Reactive clonal proliferation** > true lymphoma
  - reported cases in association with immunodeficiencies

(the child was diagnosed with familial lymphohistiocytosis)



LETTERS
https://doi.org/10.1038/s41588-018-0251-4
nature genetics
Corrected: Author Correction

Germline *HAVCR2* mutations altering TIM-3 characterize subcutaneous panniculitis-like T cell lymphomas with hemophagocytic lymphohistiocytic syndrome

Tenzin Gayden[1,32], Fernando E. Sepulveda[2,32], Dong-Anh Khuong-Quang[3,4,32], Jonathan Pratt[1,32], Elvis T. Valera[1,5], Alexandrine Garrigue[2], Susan Kelso[6,7], Frank Sicheri[6,7], Leonie G. Mikael[1], Nancy Hamel[8], Andrea Bajic[1], Rola Dali[9], Shriya Deshmukh[10], Dzana Dervovic[6], Daniel Schramek[6,7], Frédéric Guerin[2], Mikko Taipale[7], Hamid Nikbakht[1,9], Jacek Majewski[1,11], Despina Moshous[12], Janie Charlebois[13], Sharon Abish[13], Christine Bole-Feysot[14], Patrick Nitschke[15], Brigitte Bader-Meunier[12], David Mitchell[13], Catherine Thieblemont[16,17], Maxime Battistella[17,18], Simon Gravel[11], Van-Hung Nguyen[19], Rachel Conyers[3,4], Jean-Sebastien Diana[12], Chris McCormack[20,21], H. Miles Prince[22,23], Marianne Besnard[24], Stephane Blanche[12], Paul G. Ekert[3,4], Sylvie Fraitag[25], William D. Foulkes[1,8], Alain Fischer[12,26,27], Bénédicte Neven[12,27,33], David Michonneau[17,28,33], Geneviève de Saint Basile[2,29,33*] and Nada Jabado[1,30,31,33*]

Subcutaneous panniculitis-like T cell lymphoma (SPTCL), a non-Hodgkin lymphoma, can be associated with hemophagocytic lymphohistiocytosis (HLH), a life-threatening immune activation that adversely affects survival[1,2]. T cell immunoglobulin mucin 3 (TIM-3) is a modulator of immune responses expressed on subgroups of T and innate immune cells. We identify in ~60% of SPTCL cases germline, loss-of-function, missense variants altering highly conserved residues of TIM-3, c.245A>G (p.Tyr82Cys) and c.291A>G (p.Ile97Met), each with specific geographic distribution. The variant encoding p.Tyr82Cys TIM-3 occurs on a potential founder chromosome in patients with East Asian and Polynesian ancestry, while p.Ile97Met TIM-3 occurs in patients with European ancestry. Both variants induce protein misfolding and abrogate TIM-3's plasma membrane expression, leading to persistent immune activation and increased production of inflammatory cytokines, including tumor necrosis factor-α and interleukin-1β, promoting HLH and SPTCL. Our findings highlight HLH-SPTCL as a new genetic entity and identify mutations causing TIM-3 alterations as a causative genetic defect in SPTCL. While HLH-SPTCL patients with mutant TIM-3 benefit from immunomodulation, therapeutic repression of the TIM-3 checkpoint may have adverse consequences.

- Young patients (onset< 22 YO)
- Hemophagocytic lymphohistiocytosis

T cell immunoglobulin mucin 3 (TIM-3) is a modulator of immune responses expressed on subgroups of T and innate immune cells

Practical aspect: Subcutaneous Panniculitis-like T-cell clonal Proliferation rather than Subcutaneous Panniculitis-like T-cell Lymphoma

- **Immunomodulations must be favoured**:
  - Steroids +/-
  - Cyclosporin A
  - Sometimes blood marrow transplantation
- **Avoid cytotoxic chemotherapy**:
  - unnecessary
  - side effects!


PEDIATRICS

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Clonal Cytophagic Histiocytic Panniculitis in Children May Be Cured by Cyclosporine A

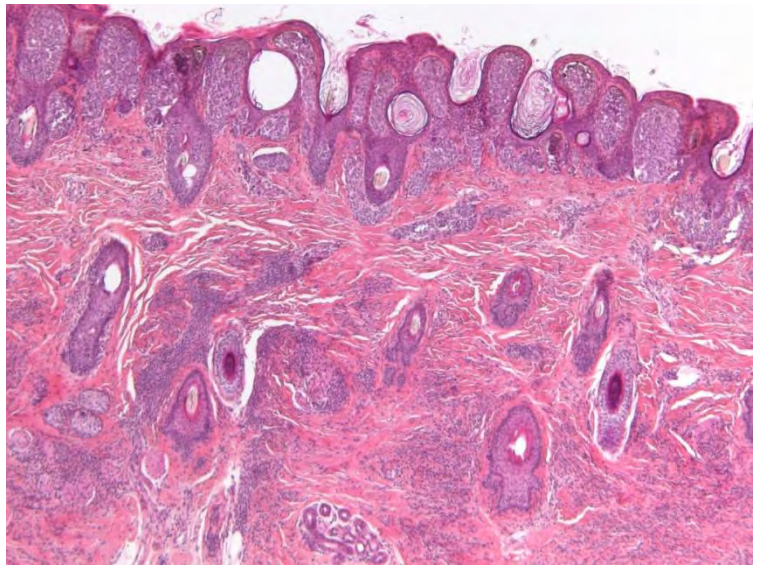
Brigitte Bader-Meunier, Sylvie Fraitag, Carl Janssen, Karine Brochard, Laurence Lamant, Carine Wouters and Christine Bodemer

Pediatrics 2013;132;e545; originally published online July 15, 2013;
DOI: 10.1542/peds.2012-3256

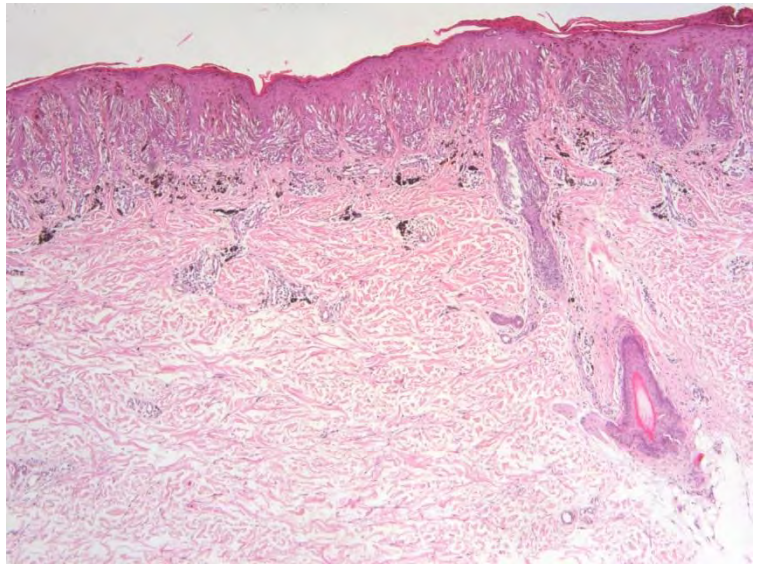
Melanocytic proliferations

Melanocytic proliferations

Congenital nevi



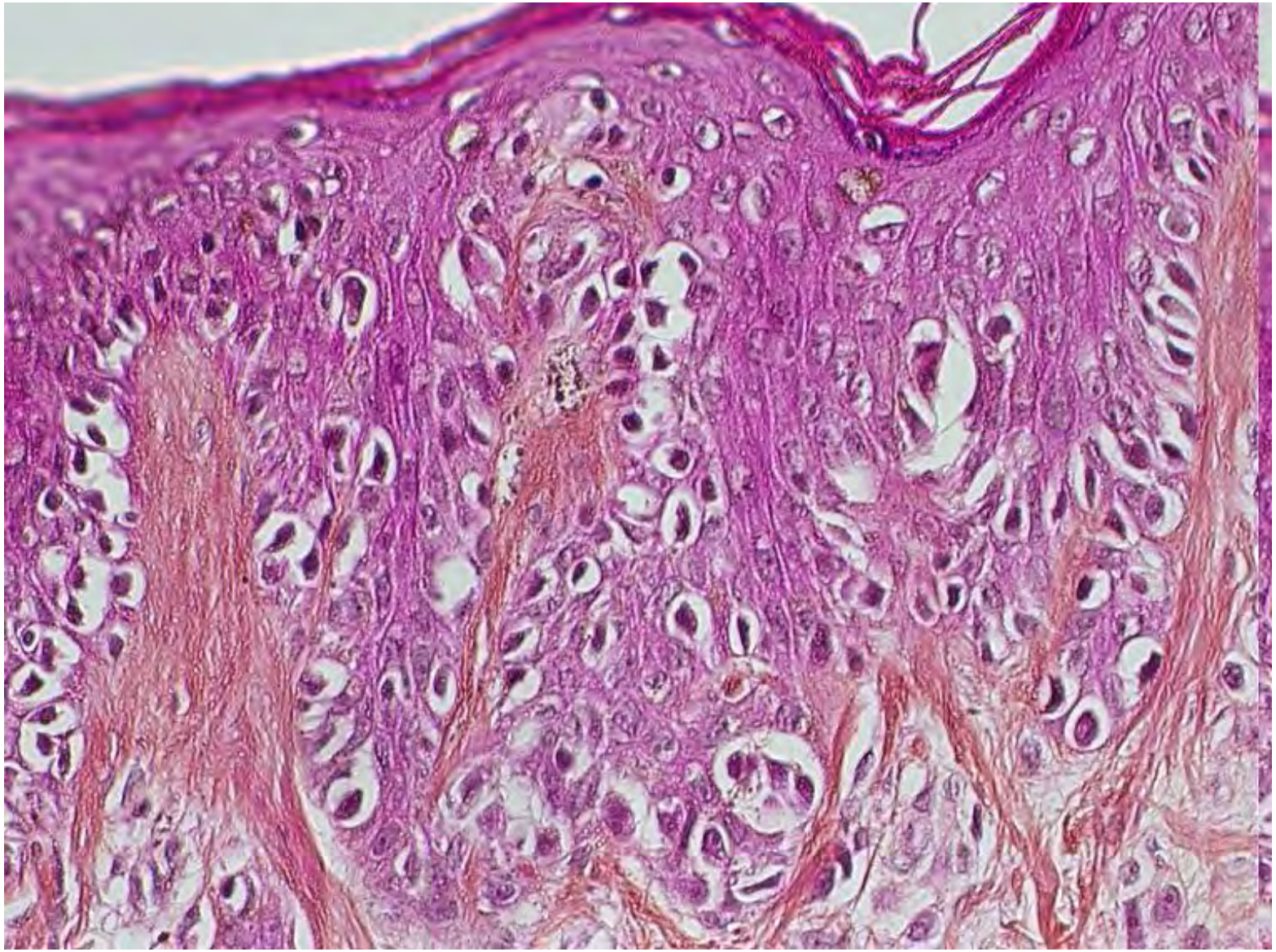
Acquired nevi

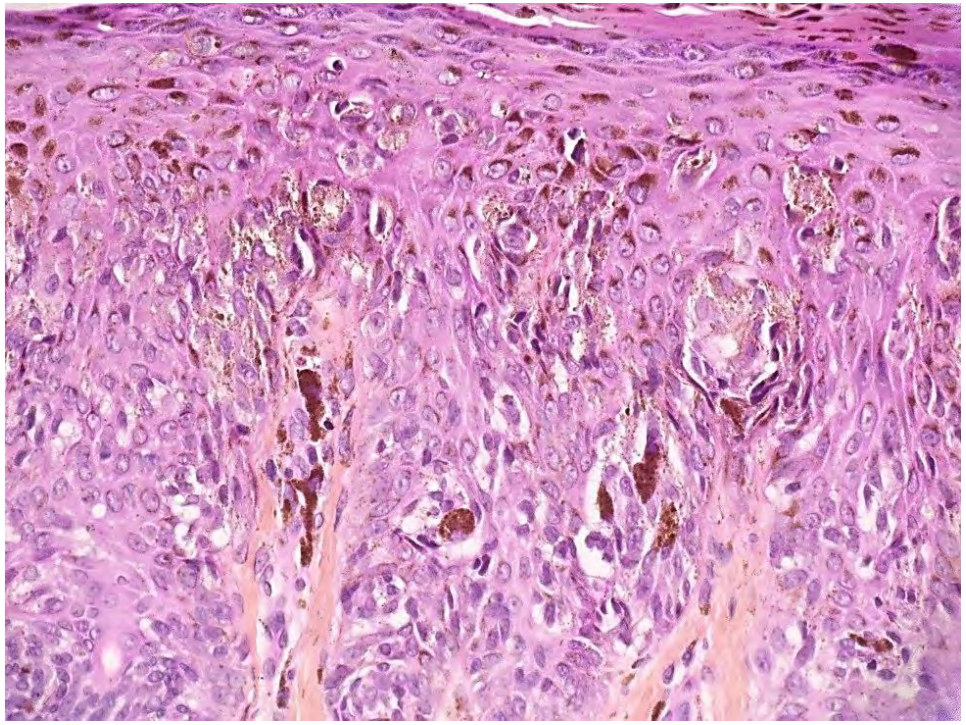


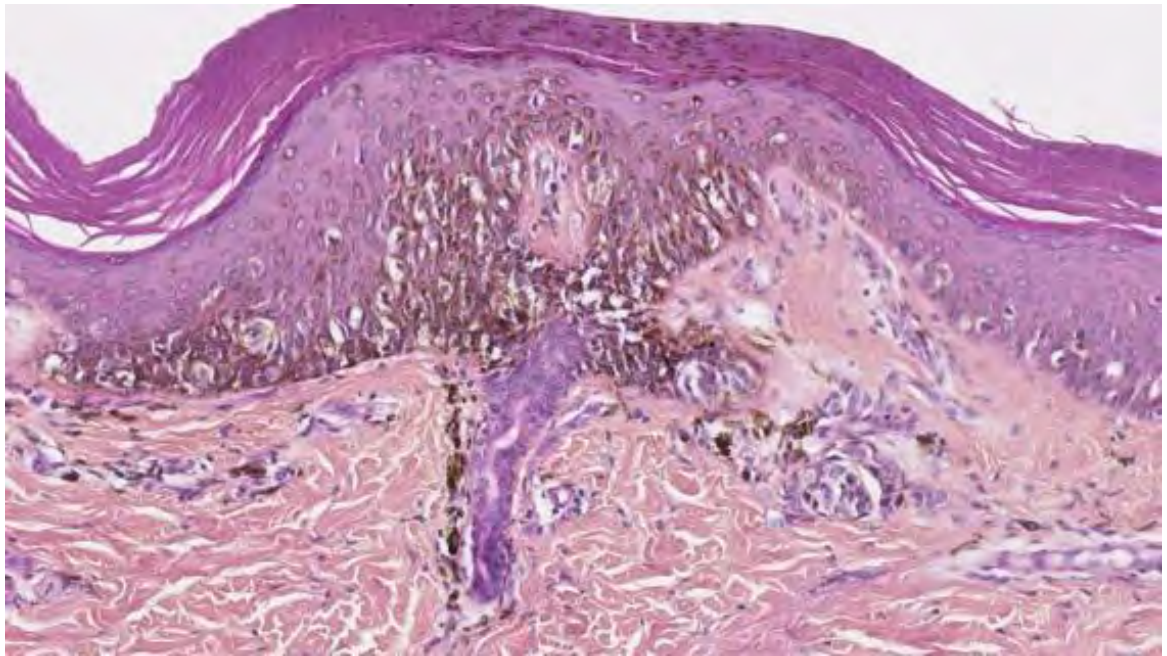
Congenital nevi

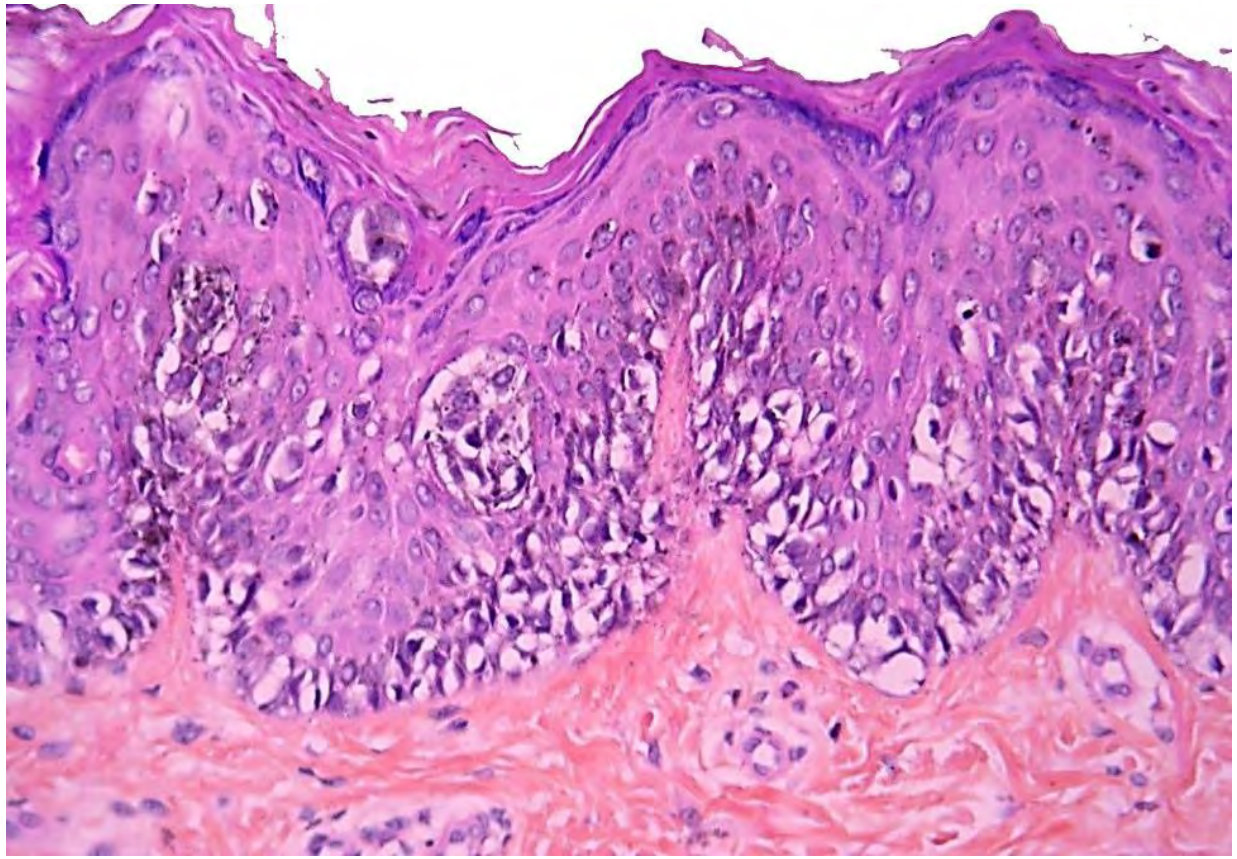
In neonates and small infants congenital nevi may resemble melanomas

Congenital nevi can mimic **Superficial Spreading Melanomas**

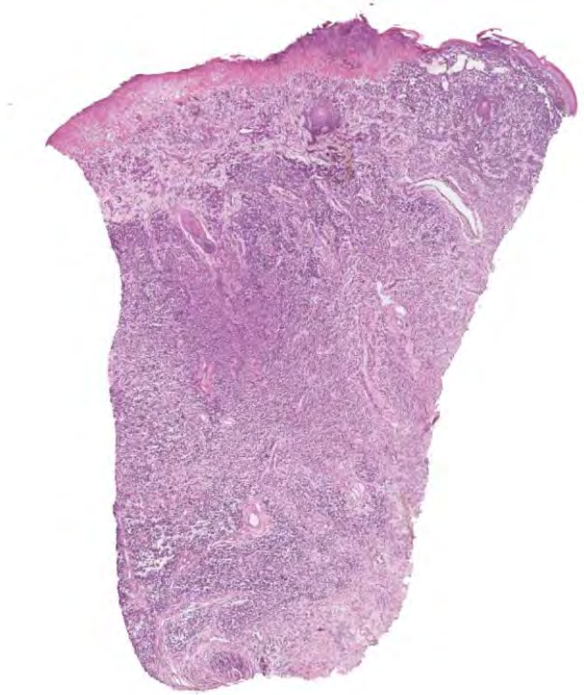


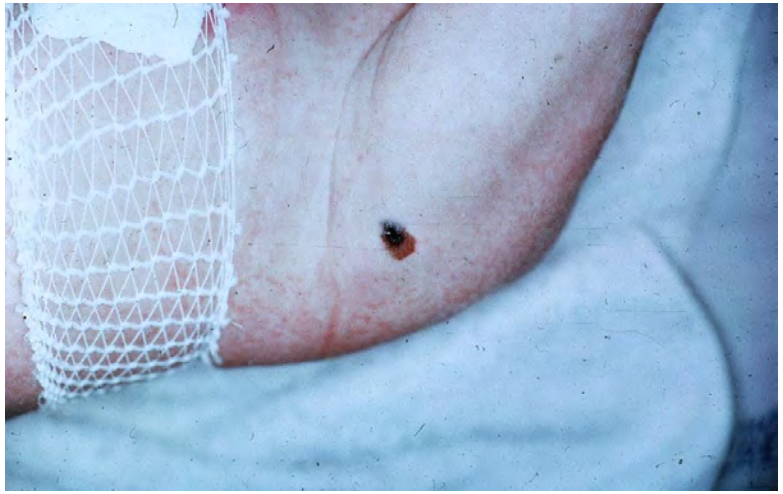


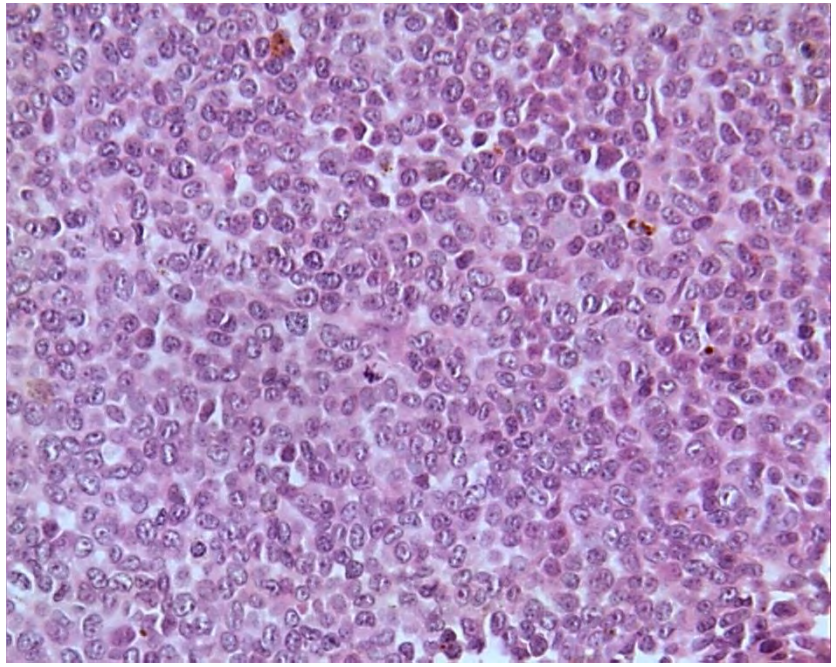




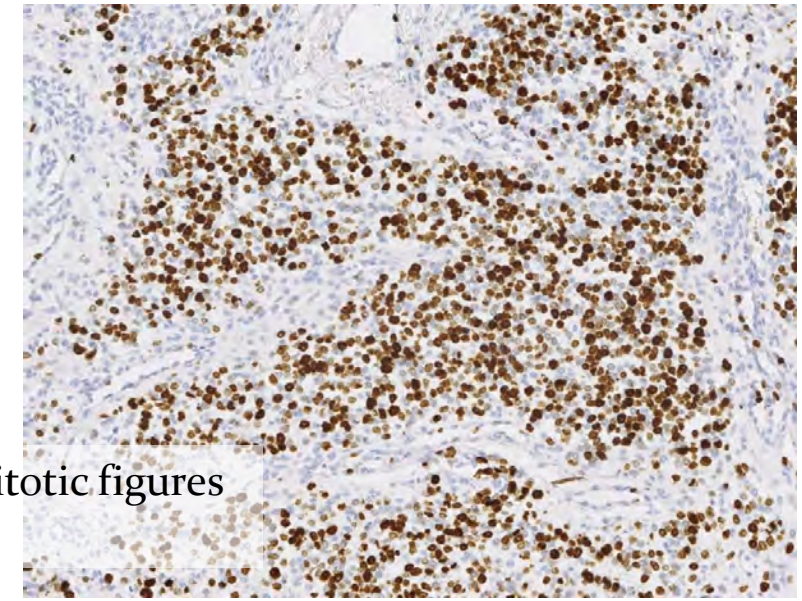
Can mimic **nodular melanomas**



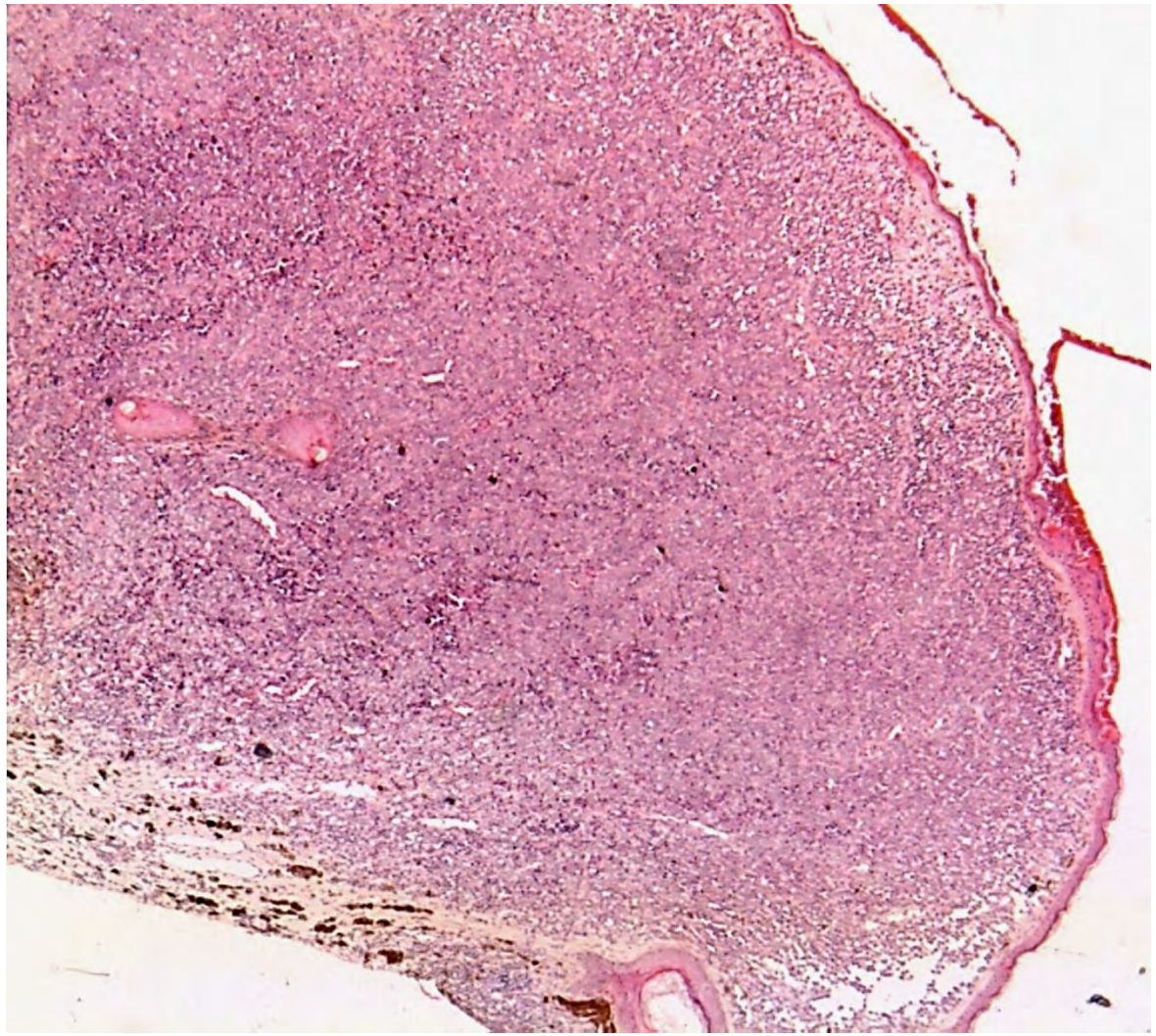




Ki67

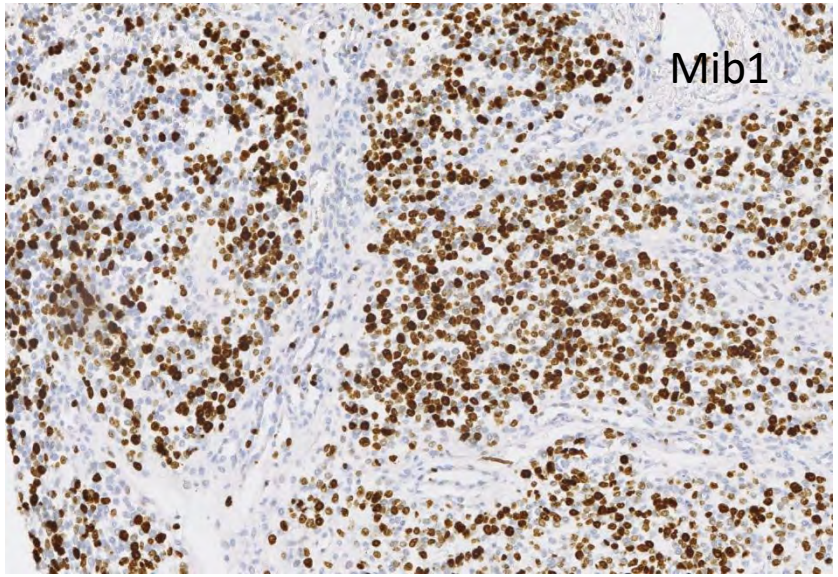


In neonates benign tumours may show mitotic figures
Ki67 index may reach about 70 % !



Don't interprete a melanocytic tumour early in life!

Be careful!

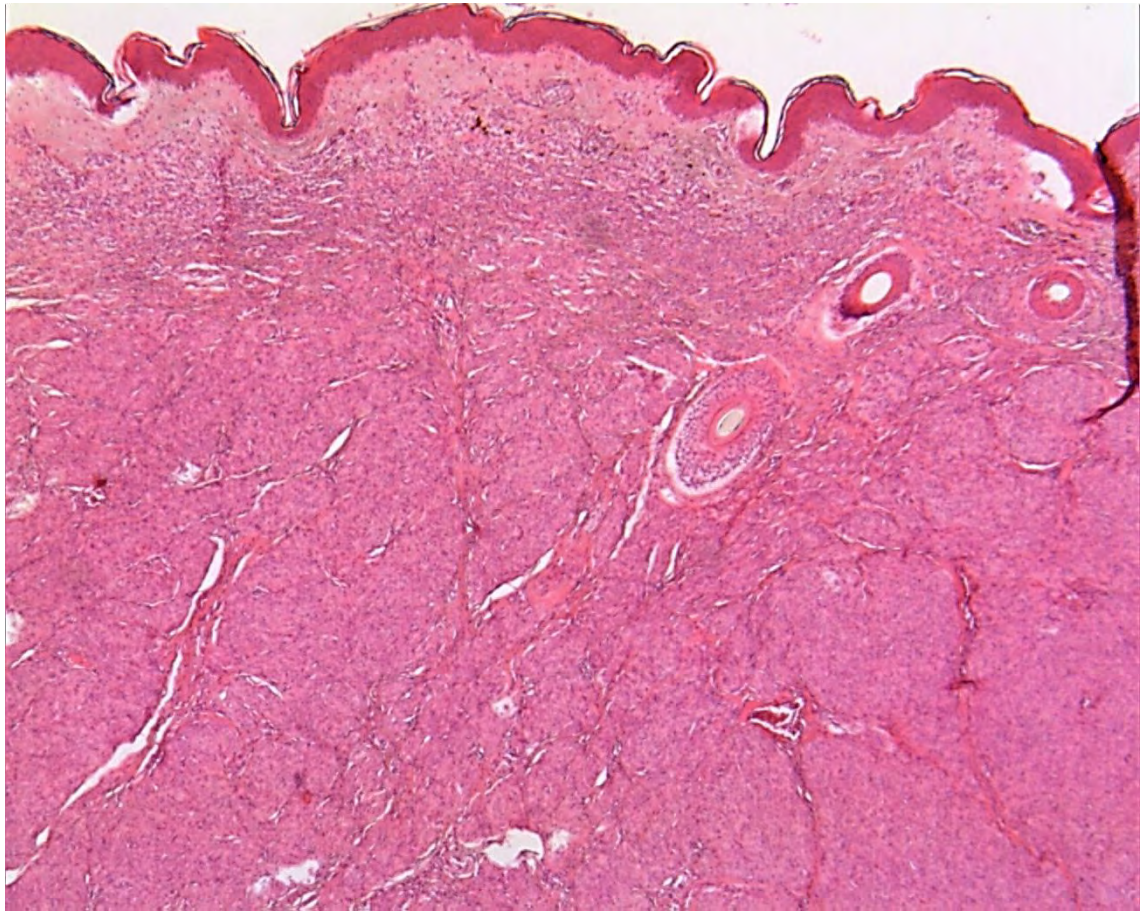


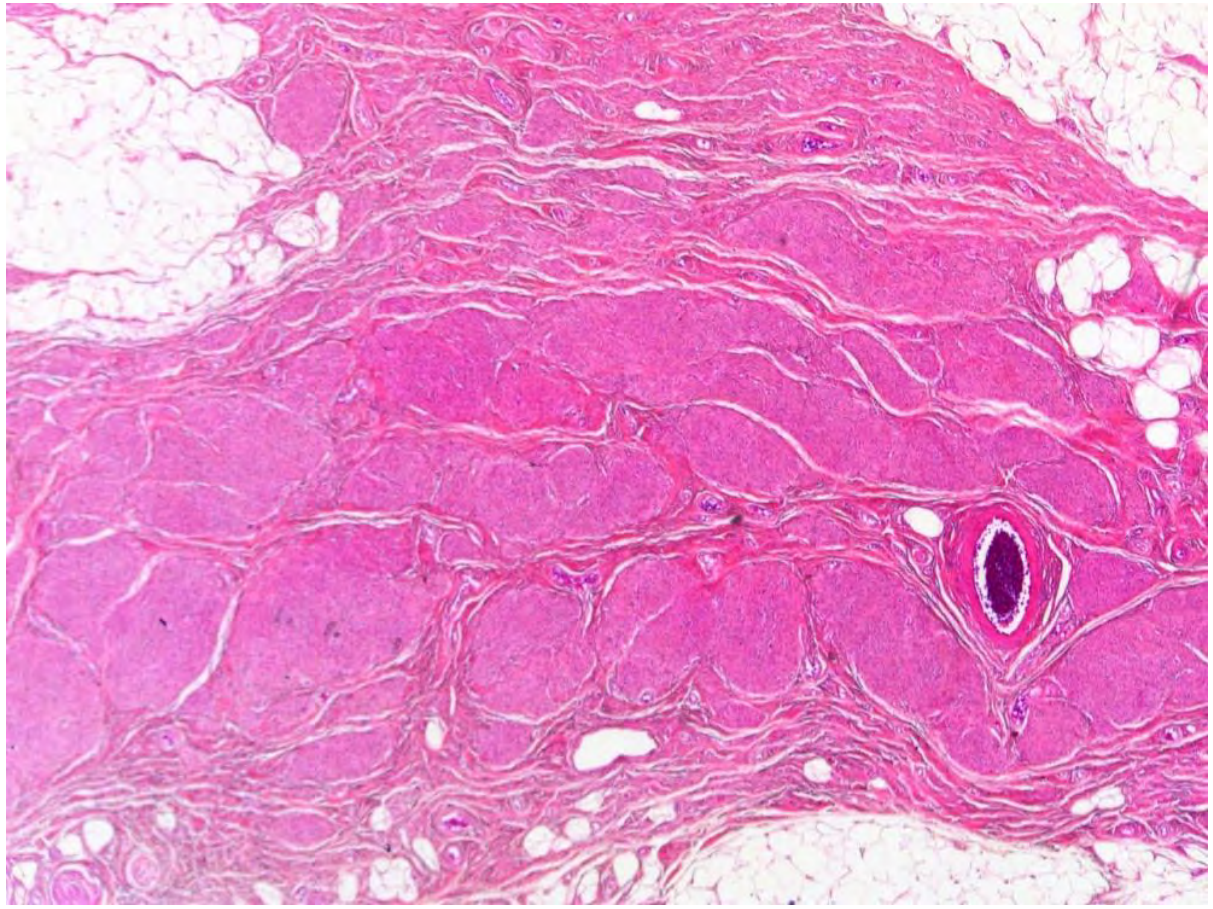
Congenital melanoma is extremely rare!
Less than 30 cases in the littérature!

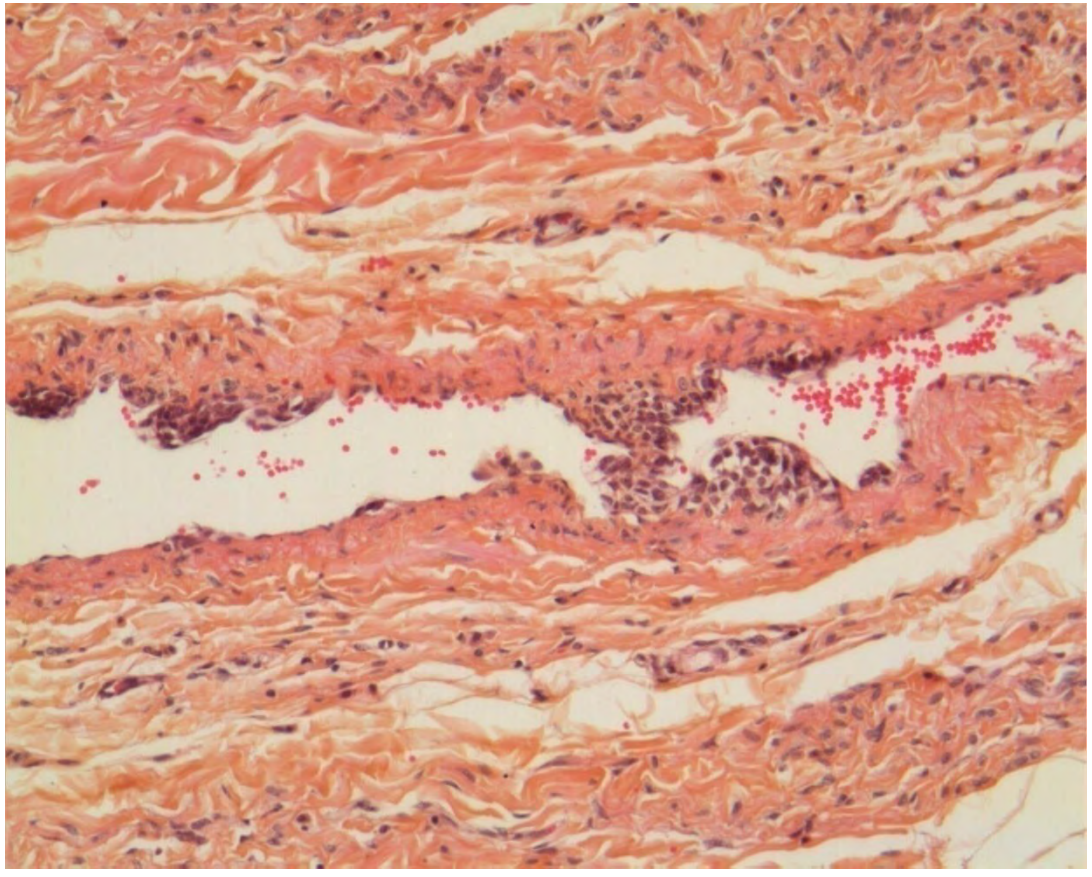
Large congenital melanocytic nevi (>20 cm)

may mimic melanomas later as well

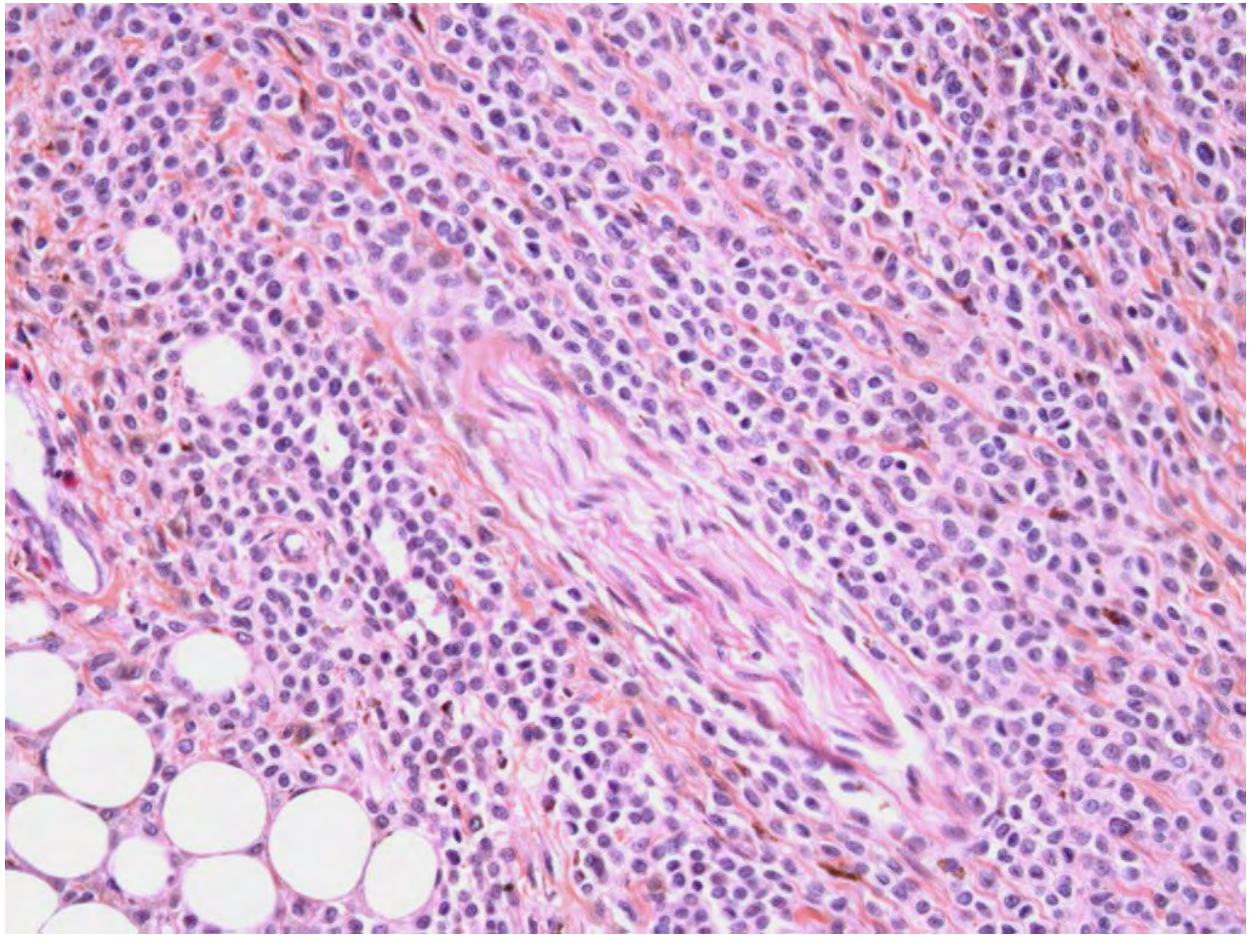
Inversion of the maturation gradient (schwannian maturation)

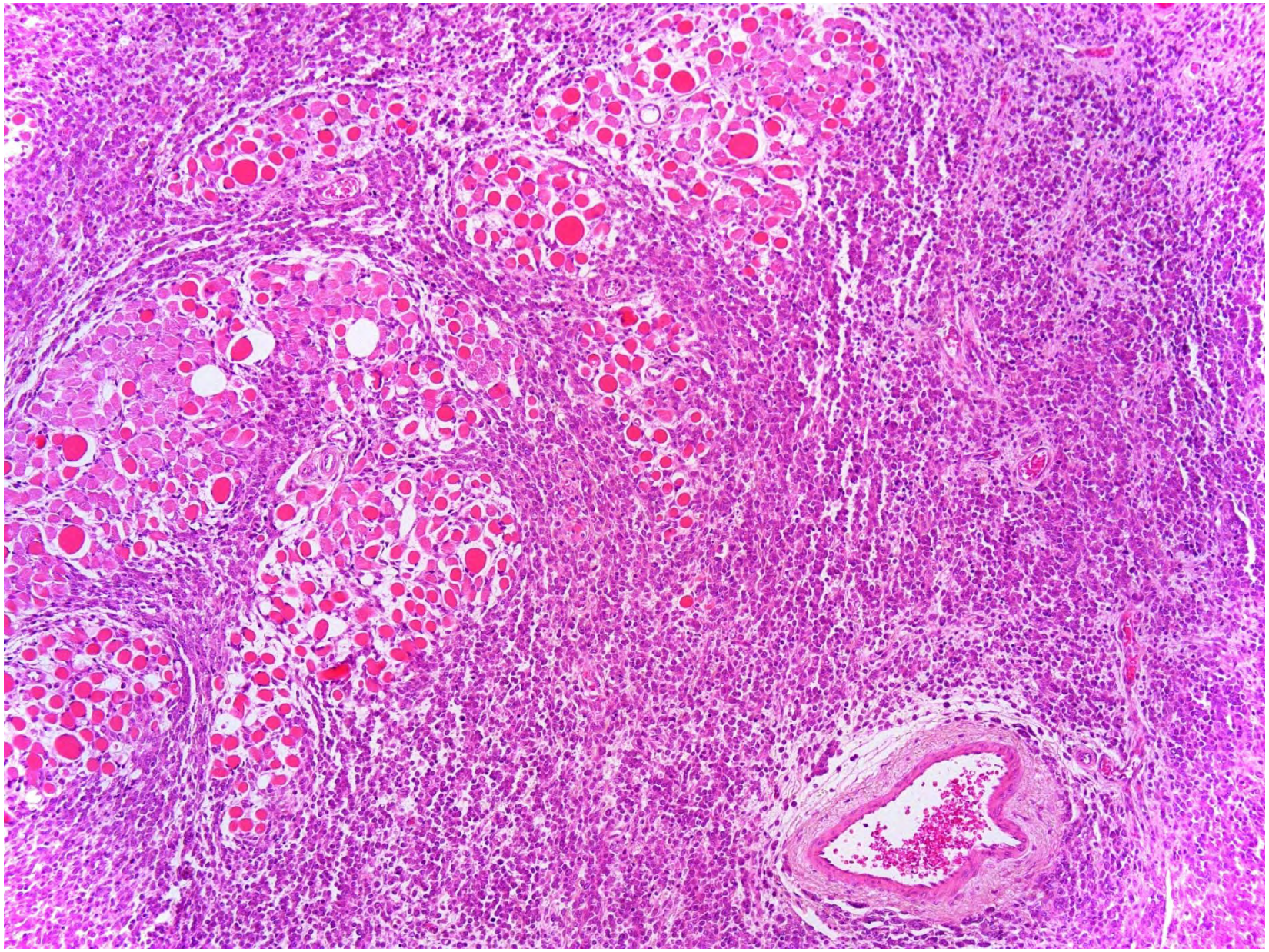






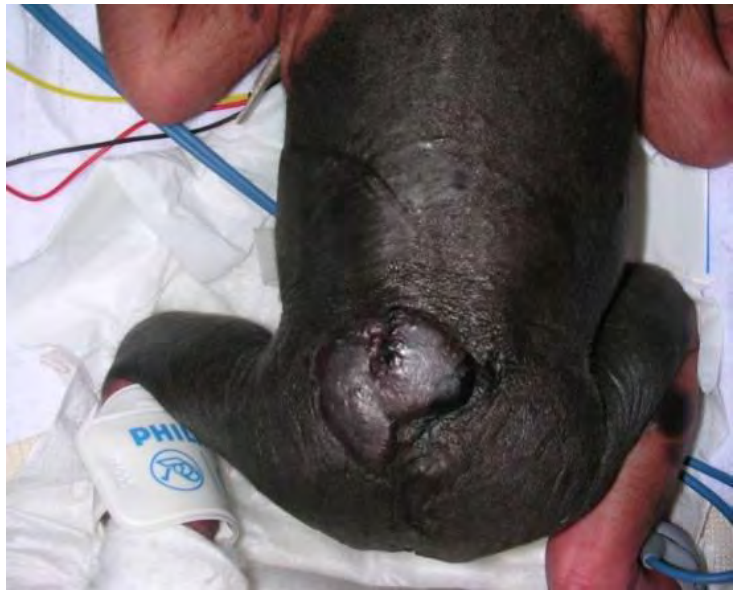
Melanocytic infiltration of the vessel walls and the small nerves



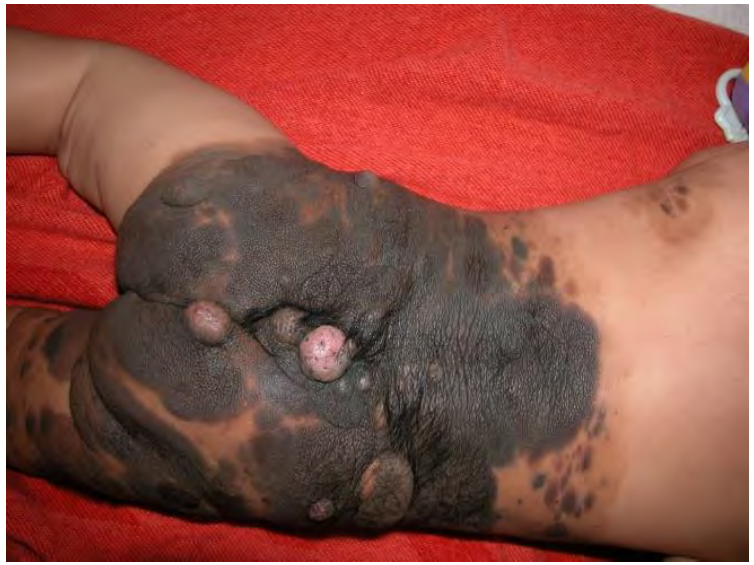


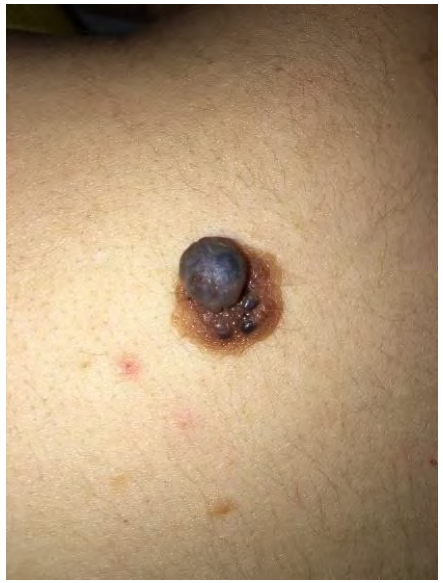
.....the muscle

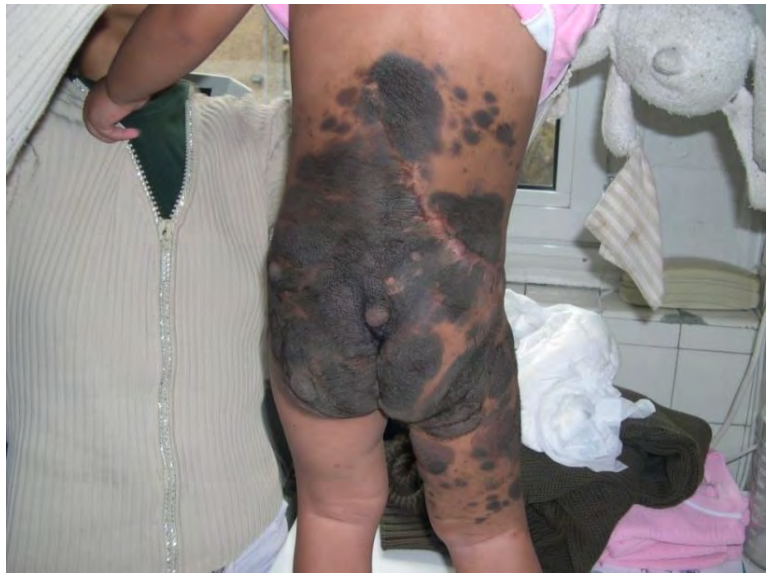
CMN with « Proliferative Nodules »



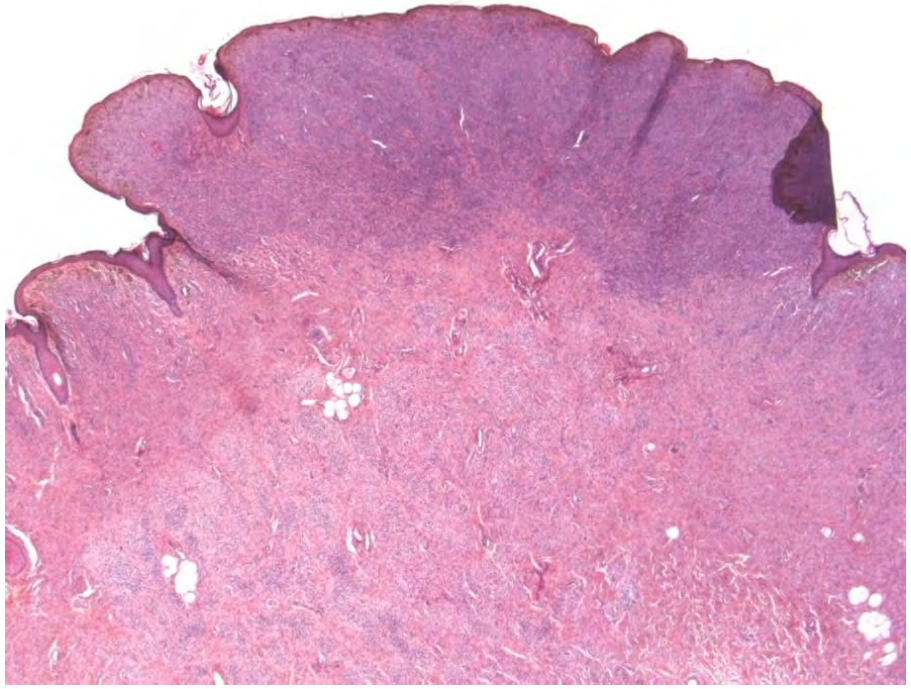
- **Are usually present at birth**, but may appear later, even in adulthood
- Single, several, multiple
- **Stable** or develop slowly
- Are always benign (recently appearing nodule: caution!)

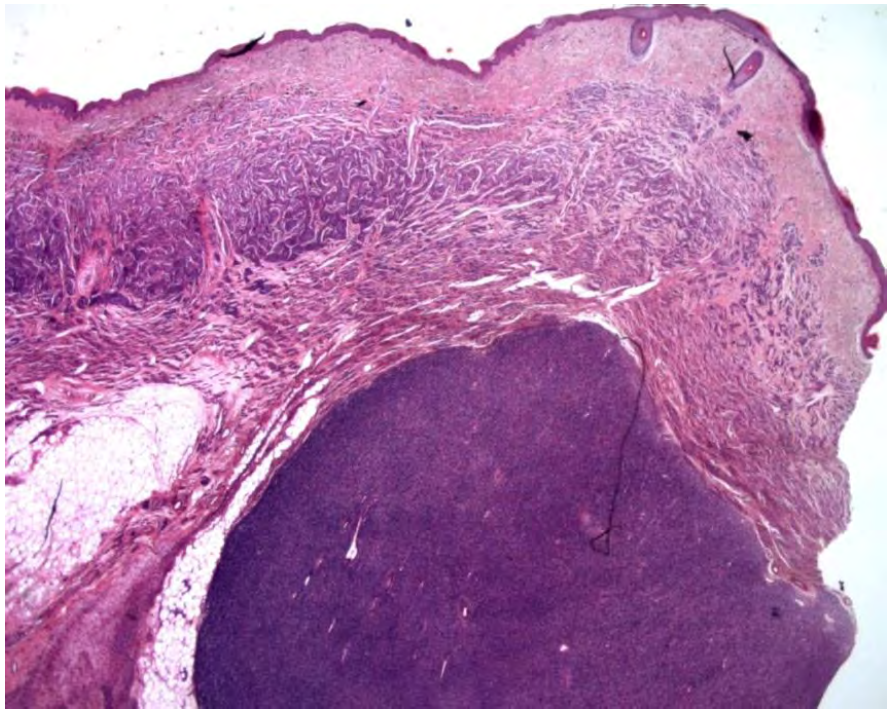




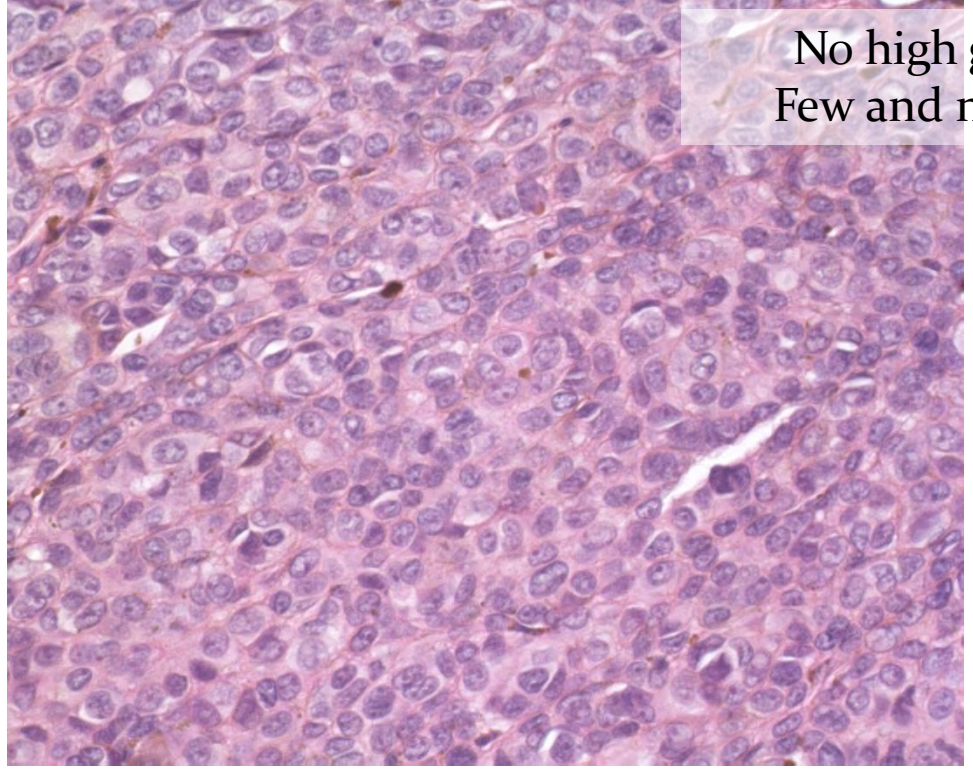


- Characterized by **increased cellularity** and **distinct morphology** compared with the background naevus
- May be:
  - **superficial**
  - **deep**

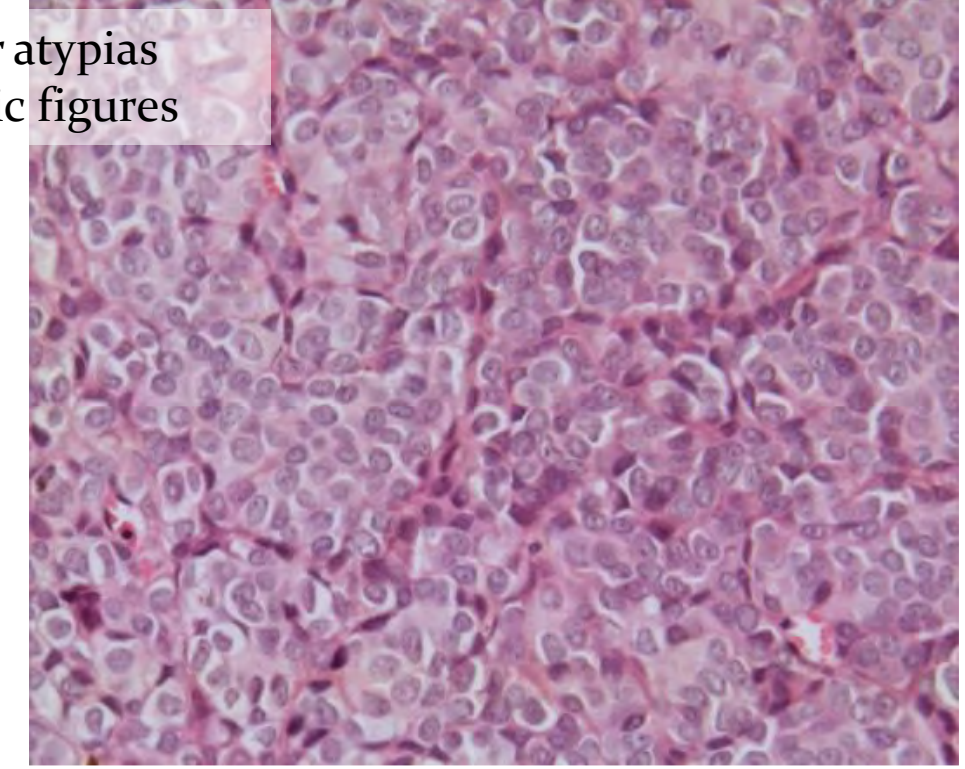




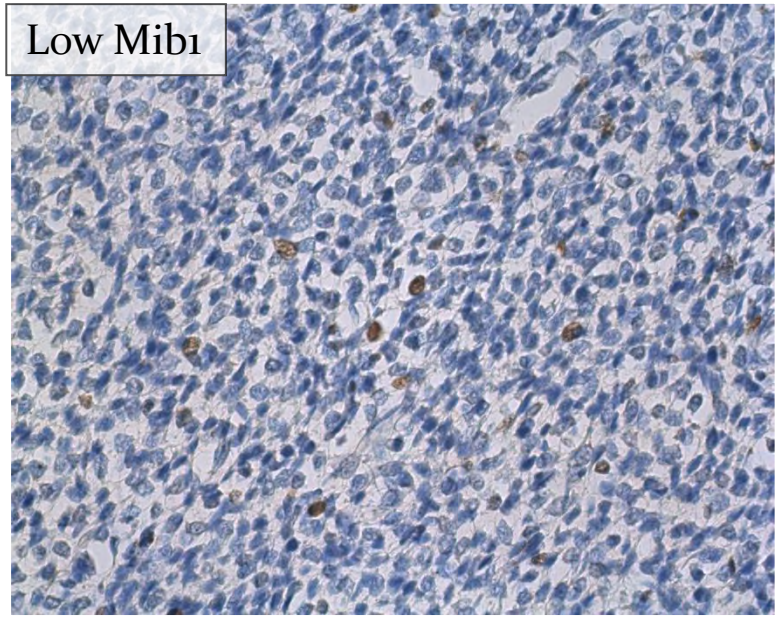
Menzinger S, Fraitag S. Pseudomalignancies in Children: Histological Clues, and Pitfalls to Be Avoided. Dermatopathology (Basel). 2021 Aug 14;8(3):376-389.

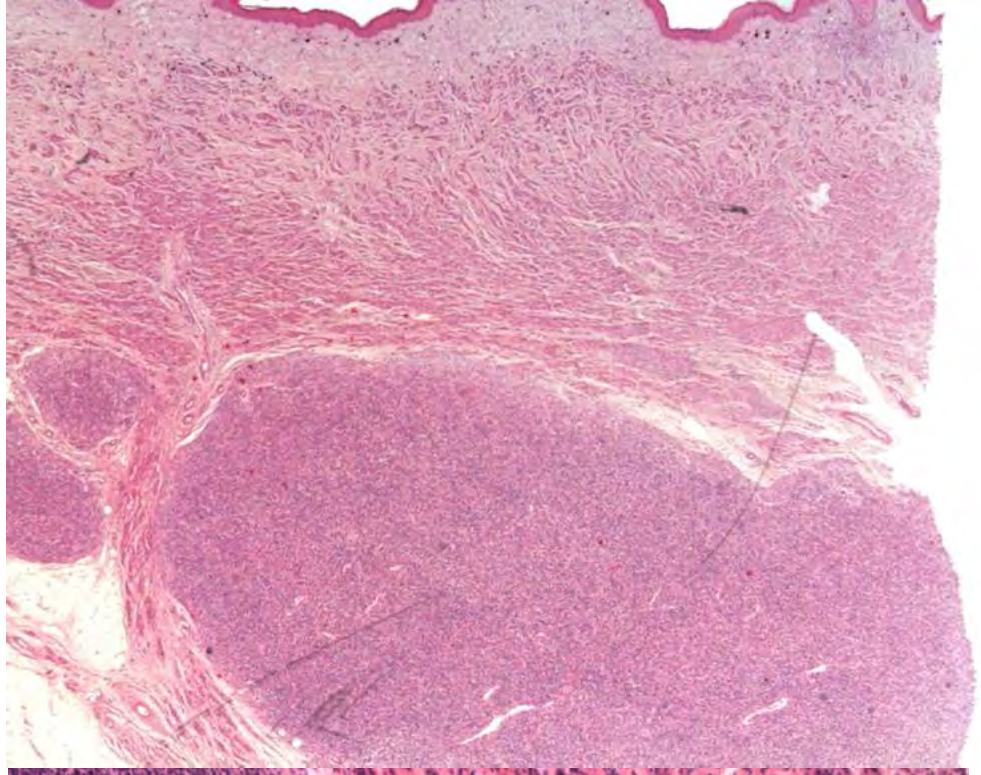


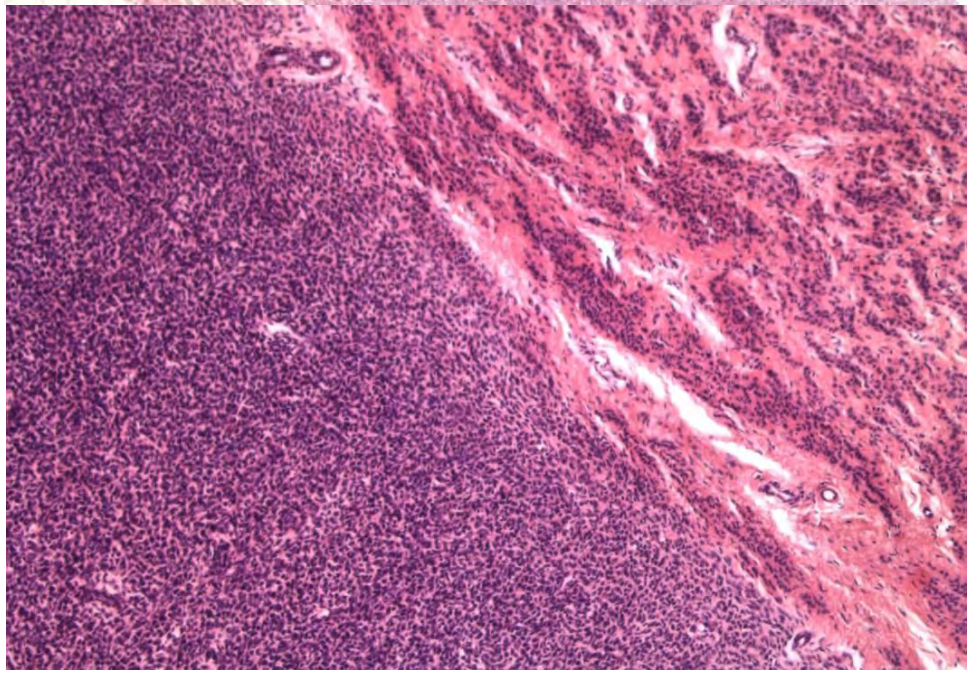
No high grade cellular atypias
Few and normal mitotic figures



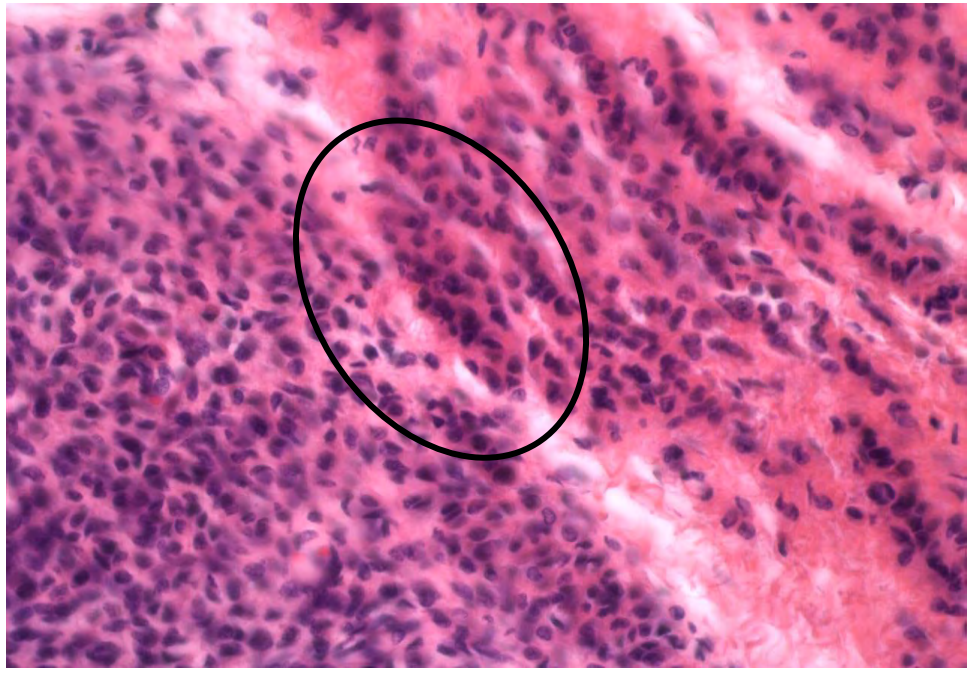
Low Mib1



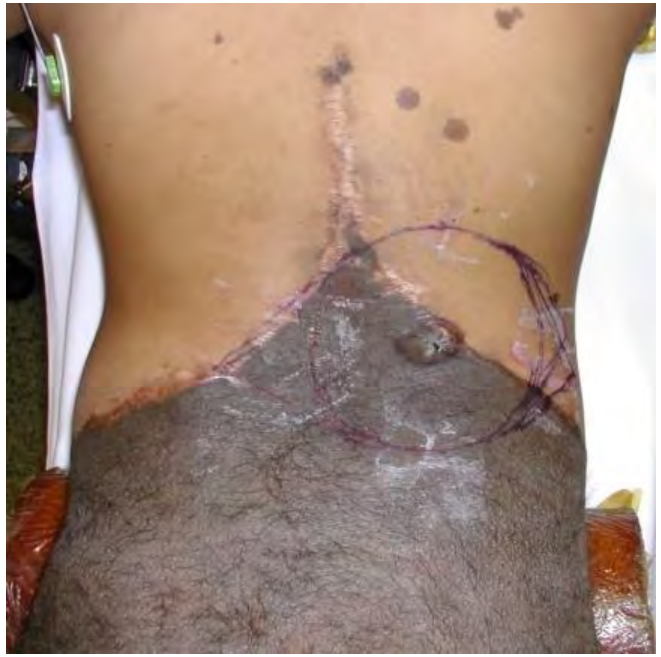


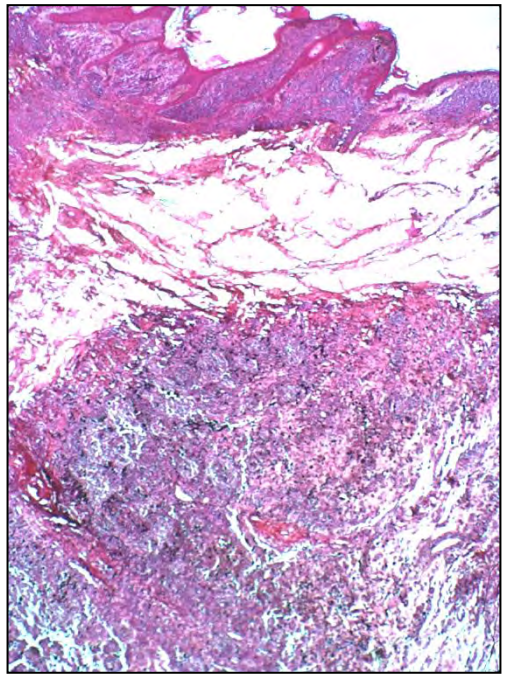


Blending



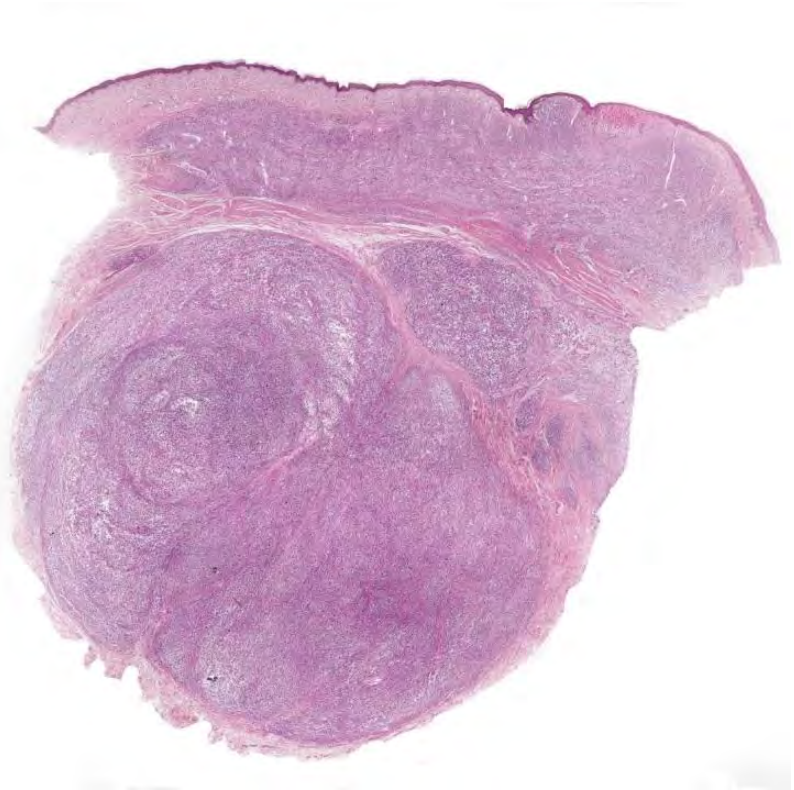
Malignant melanoma can occur in a CMN!





Melanoma associated with congenital melanocytic nevi

- Risk: overestimated for a long time
- All sizes taken together: **0.7% - 1.25%**
  - large/giant CN: 3 to 6 %, **proportional to the size**,
  - localized to the *trunk*,
  - ≥2 *medium* CN or multiple satellites
  - abnormal screening MRI of the *CNS*
- Many MM are extra-cutaneous:
  meningeal MM, brain (1/3)
- Mostly **before puberty**



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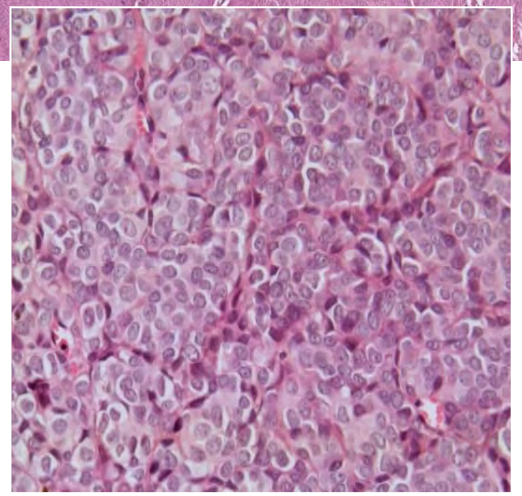
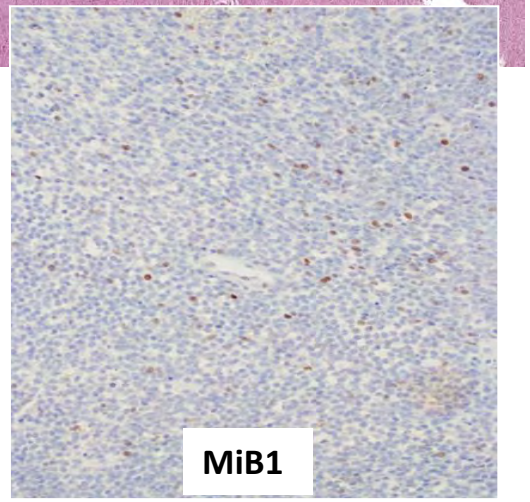
Lacoste C, Avril MF, Frassati-Biaggi A, Dupin N, Chrétien-Marquet B, Mahé E, Bodemer C, Vergier B, de la Fouchardière A, Fraitag S. Acta Derm Venereol. 2015 Jul;95(6):686-90.

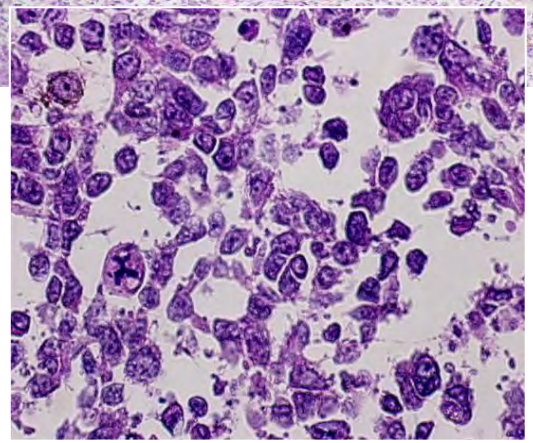
Proliferative nodule

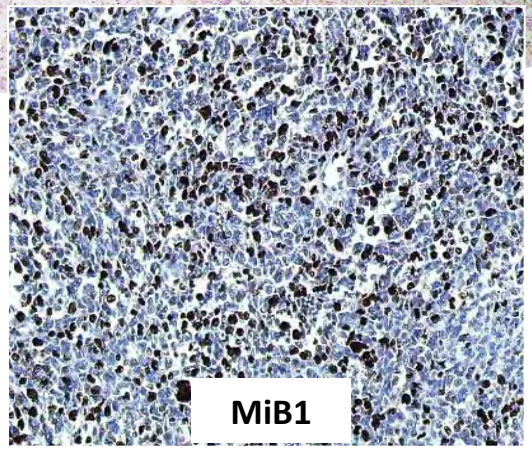




- **Neonate, stable**
- Blending with adjacent naevus
- Slight atypias
- Few, normal mitoses, MiB1 < 10%

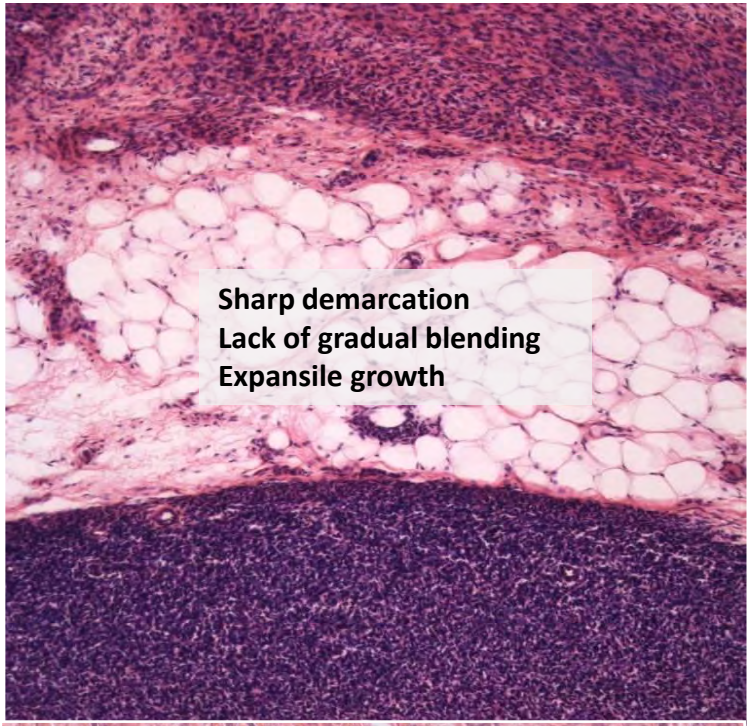
Melanoma

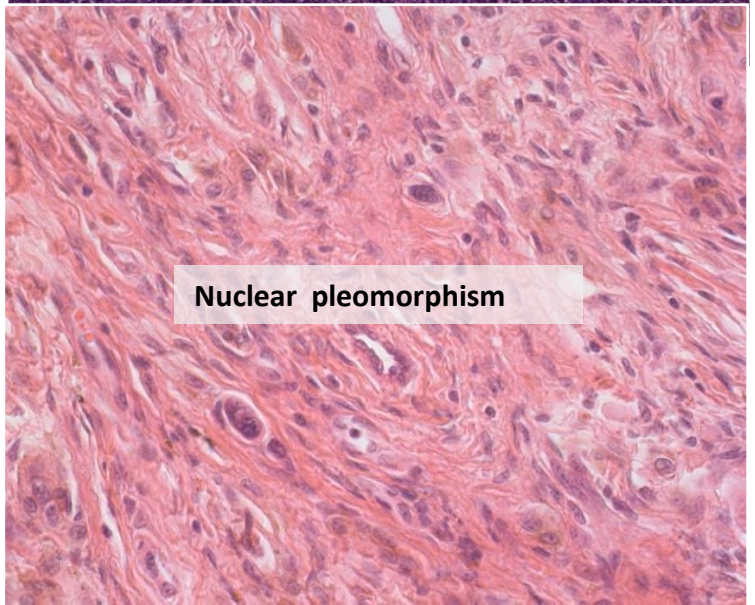


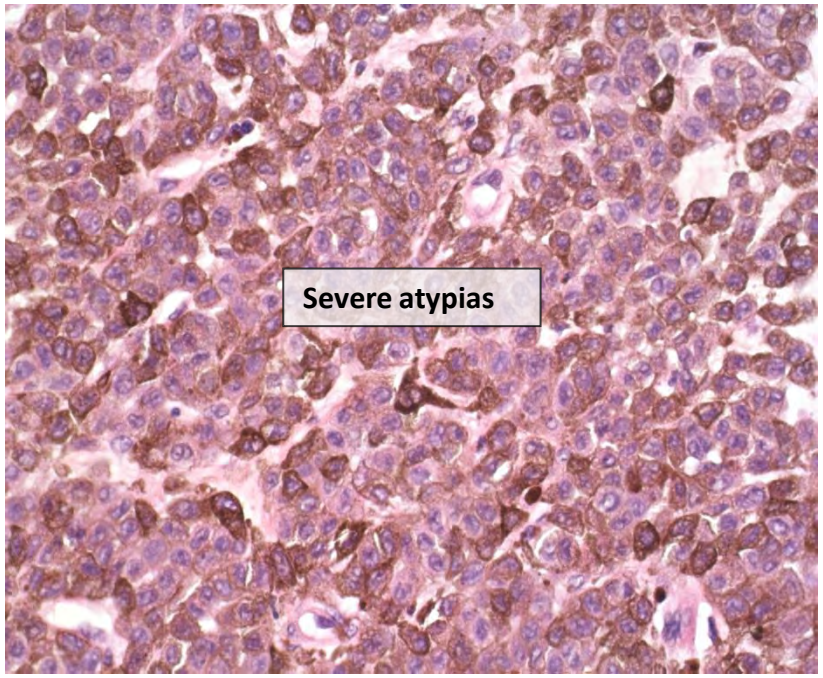


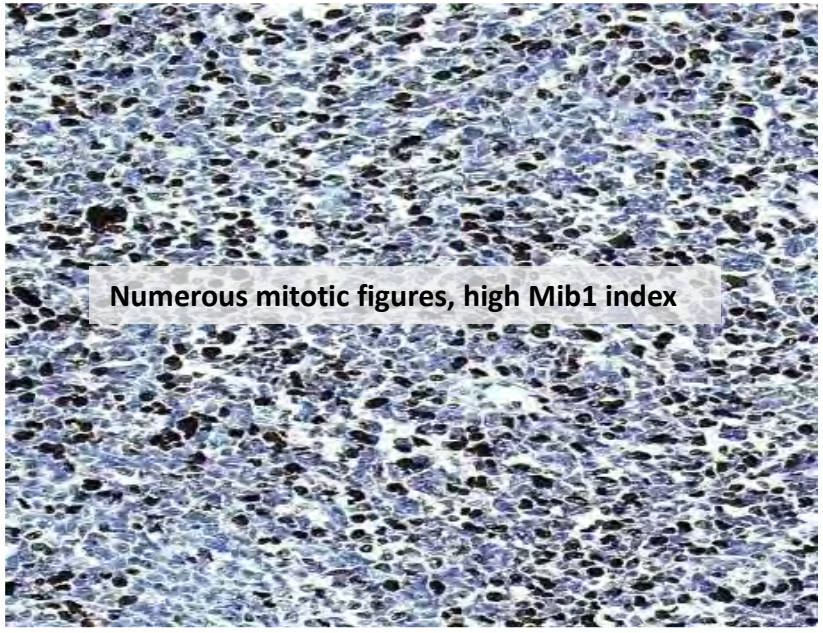
- **New nodule or nodule modification (ulceration, enlargement..)**
- Sharp demarcation, no blending
- **Necrosis**, atypias ++,
- **Atypical mitoses** ++, MiB1 > 40%

« Atypical » proliferative nodule







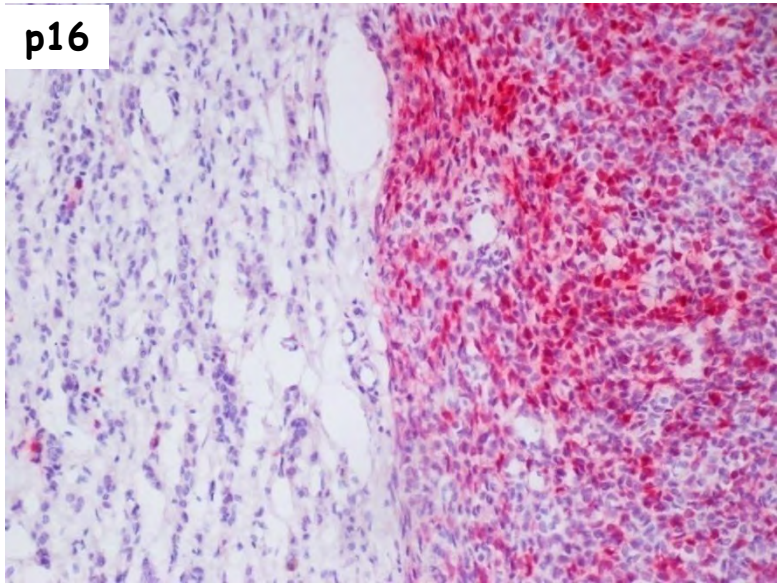


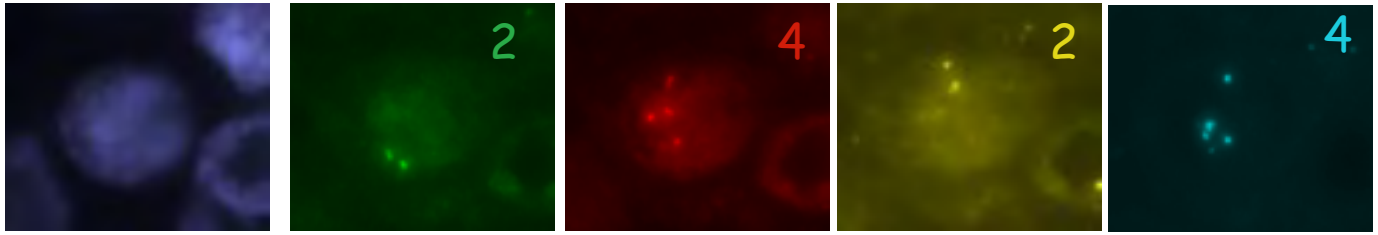
Ambiguous cases!

HELP!

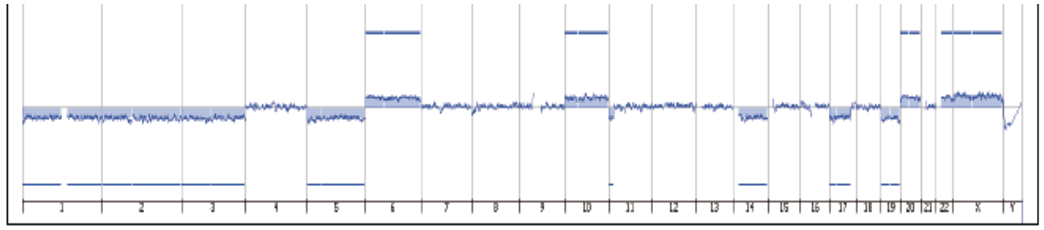
?

- immunohistochemistry
- cytogenetic





FISH



CGH

Figure2G

Can immunohistochemistry be helpful?

~~*P16*~~

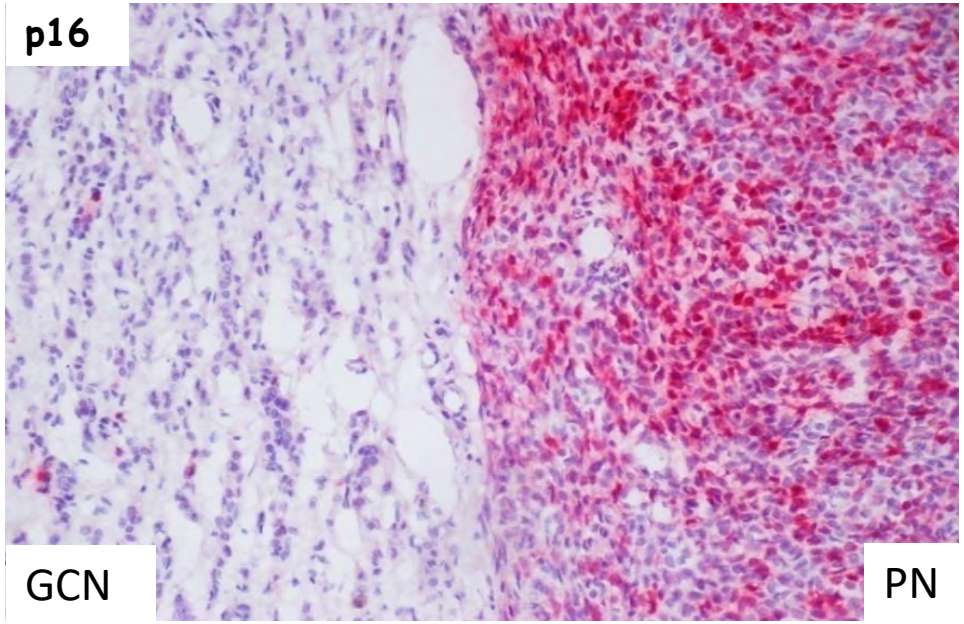
JAMA Dermatology | Brief Report

Proliferative Nodules vs Melanoma Arising in Giant Congenital Melanocytic Nevi During Childhood

Bèatrice Vergier, MD, PhD; Elodie Laharanne, PhD; Martina Prochazkova-Carlotti, PhD; Arnaud de la Fouchardière, MD; Jean-Philippe Merlio, MD, PhD; Natacha Kadlub; Marie-Françoise Avril, MD; Christine Bodemer, MD; Caroline Lacoste, MD; Franck Boralevi, MD, PhD; Alain Taieb, MD, PhD; Khaled Ezzedine, MD, PhD; Sylvie Fraitag, MD

Béatrice (not Bèatrice)

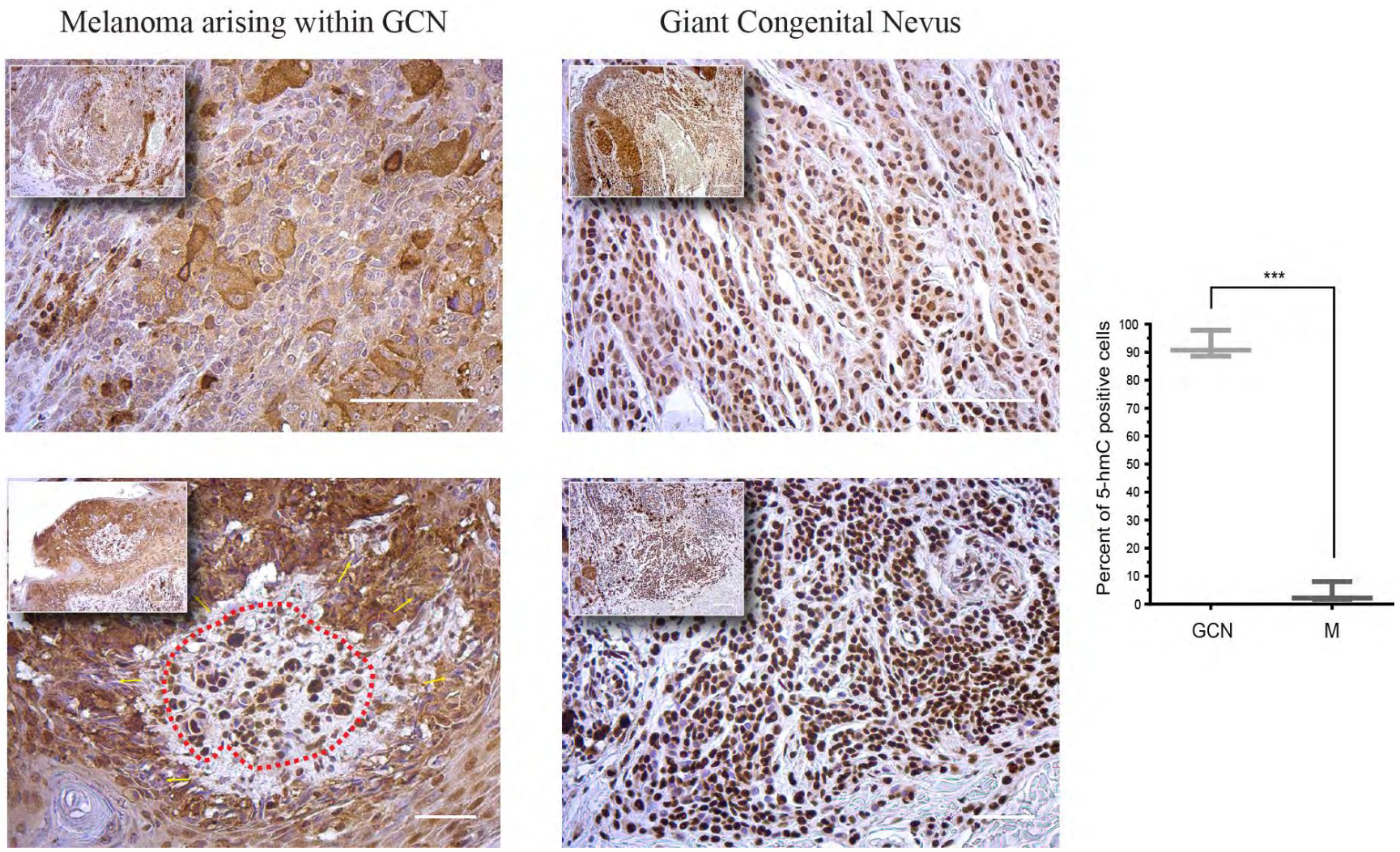
MD after Kadlub



JAMA Dermatol. 2016 Oct 1;152(10):1147-1151

5-HMC

Loss of 5-hmC (5-hydroxymethylcytosine): an epigenetic hallmark of melanoma

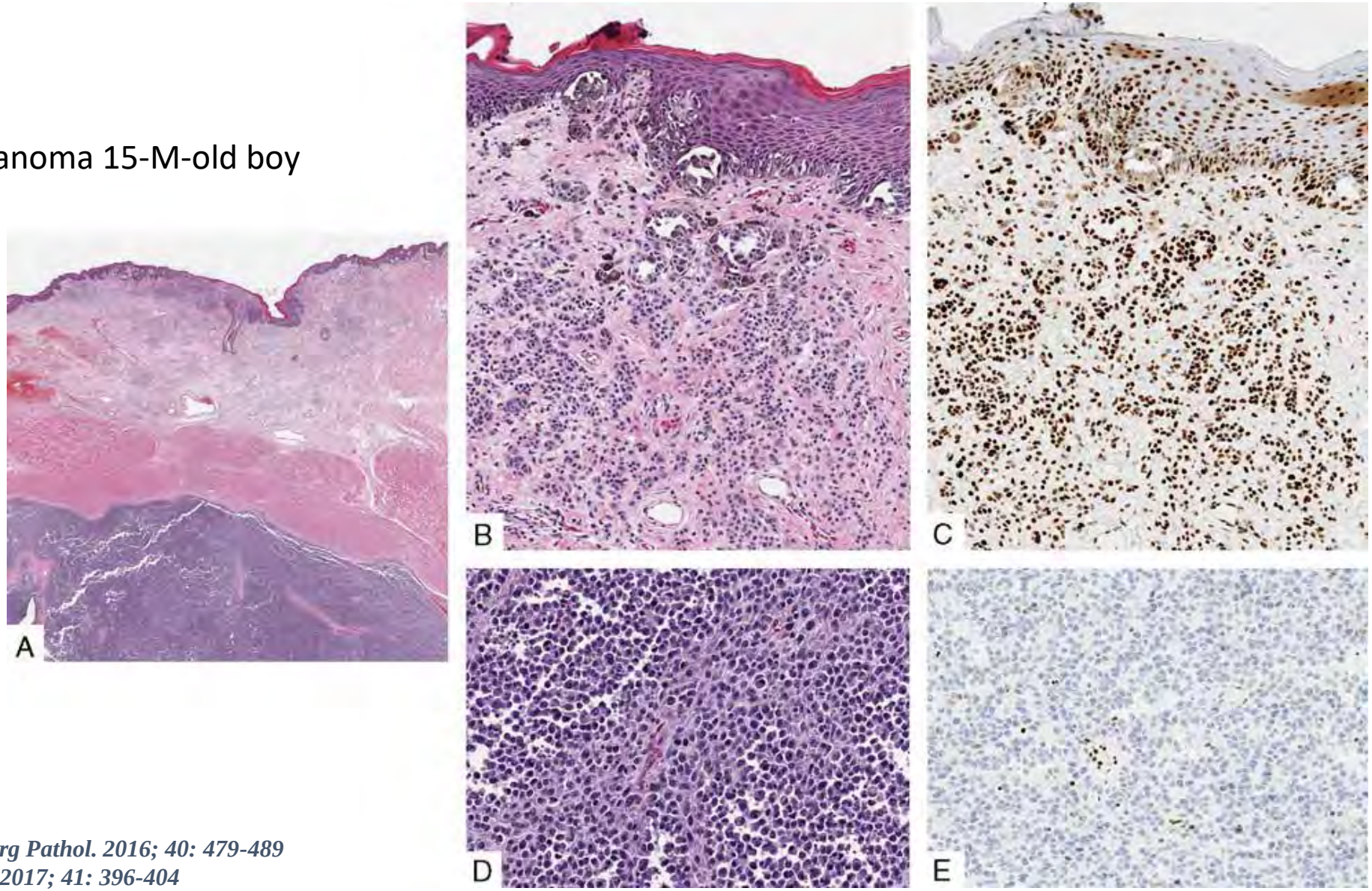


Pavlova O, Fraitag S, Hohl D. J Invest Dermatol. 2016 Dec;136(12):2453-2461.

H3K27me3

Another epigenetic hallmark of melanoma

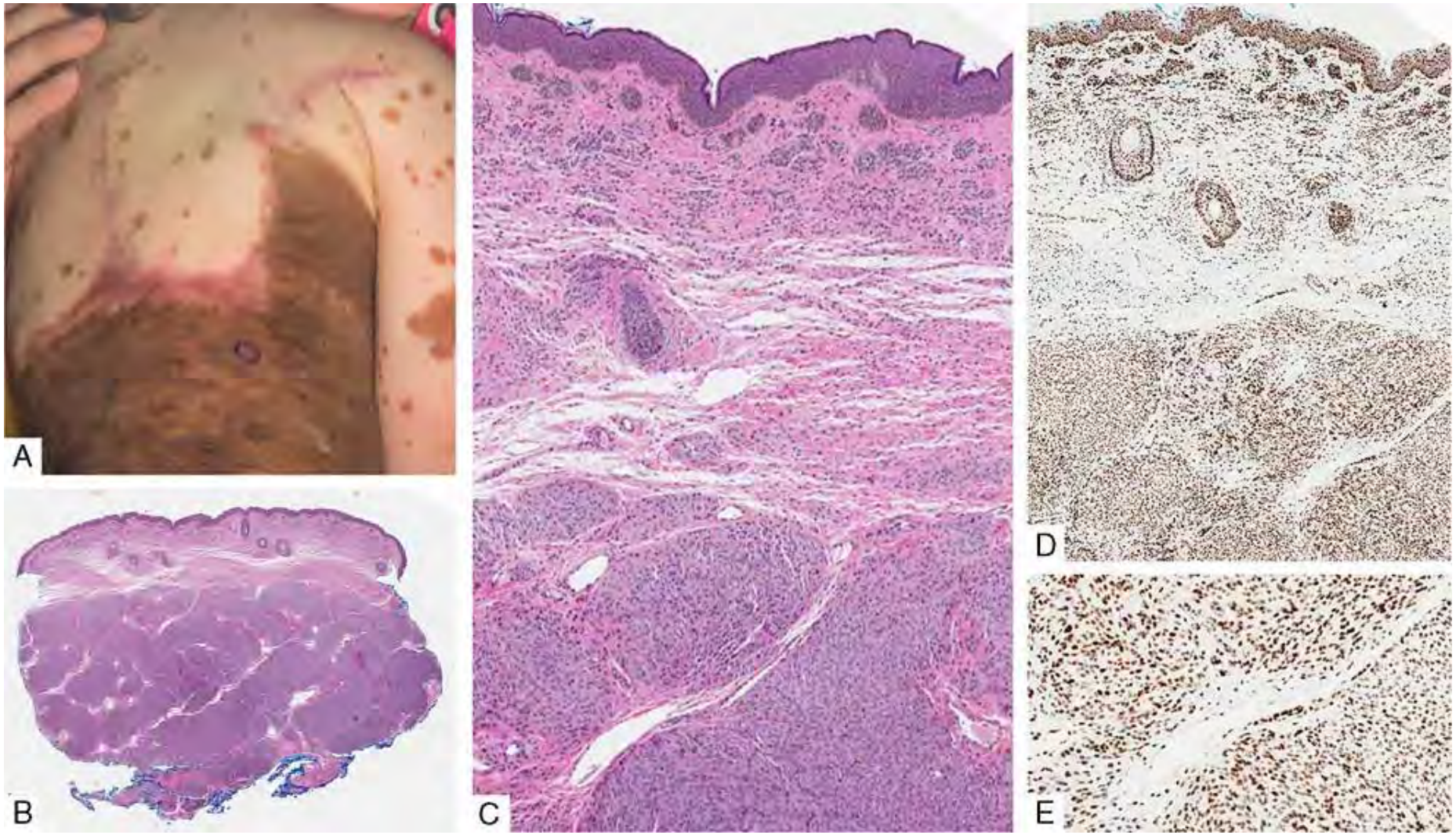
Lethal melanoma 15-M-old boy



Prieto-Granada CN et al. Am J Surg Pathol. 2016; 40: 479-489
Busam K et al. Am J Surg Pathol. 2017; 41: 396-404

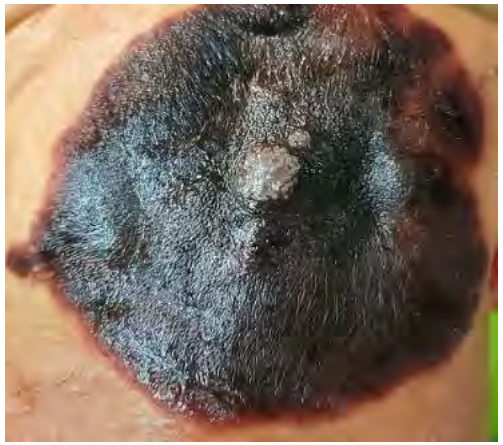
H3K27me3

Benign proliferative nodule



Busam K et al. Am J Surg Pathol. 2017; 41: 396-404

PRAME ? PReferentially expressed Antigen in MElanoma



Anti-PRAME: diffusely positive within the congenital nevus while negative within the larger proliferating cells!

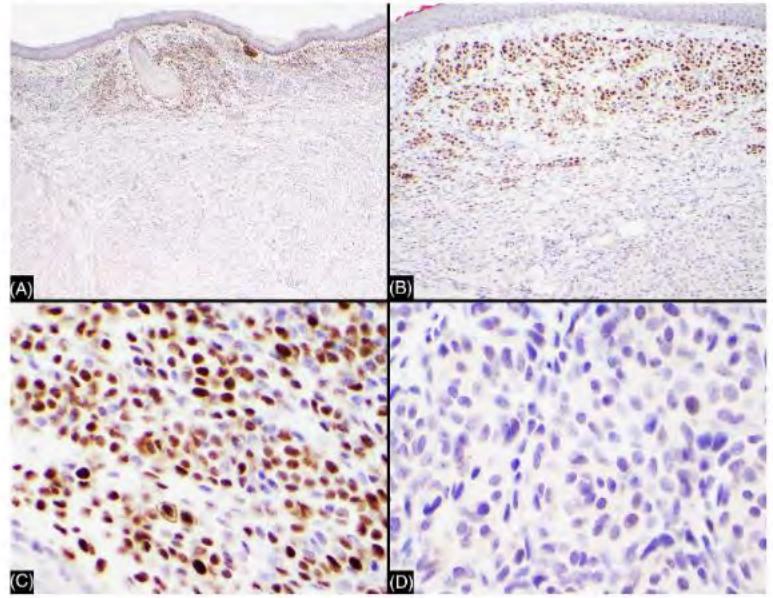
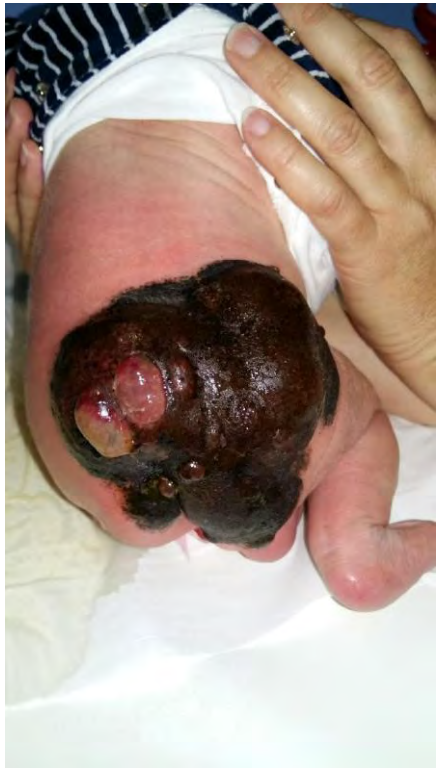
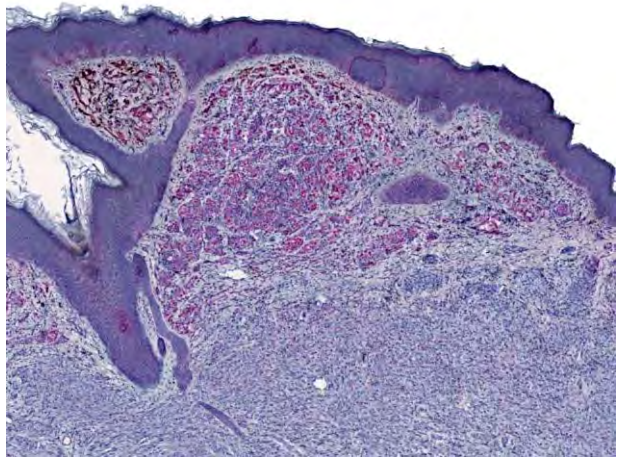


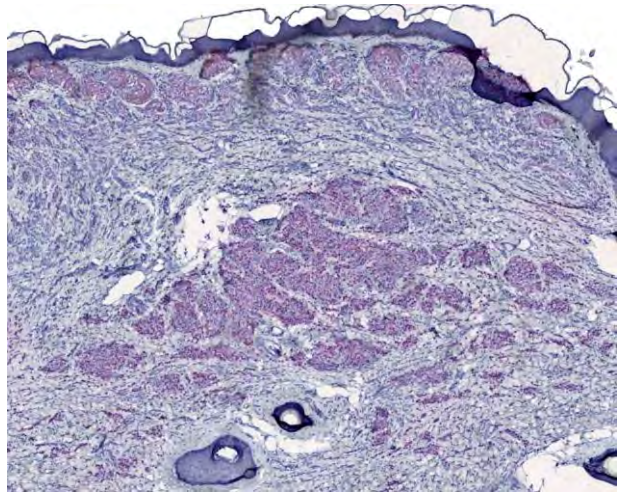
FIGURE 5 A,B, An immunohistochemical study with PReferentially expressed Antigen in MElanoma (PRAME) showed differential patterns of staining within the nevus and proliferative nodule (PRAME, ×40 and ×100). C, Melanocytes within the giant congenital melanocytic nevus were diffusely positive (PRAME, ×400), D, while the larger proliferating cells were essentially negative (PRAME, ×400)

Gill P, Prieto VG, Austin MT, Giubellino A, Torres-Cabala CA. Diagnostic utility of PRAME in distinguishing proliferative nodules from melanoma in giant congenital melanocytic nevi. J Cutan Pathol. 2021 Nov;48(11):1410-1415.

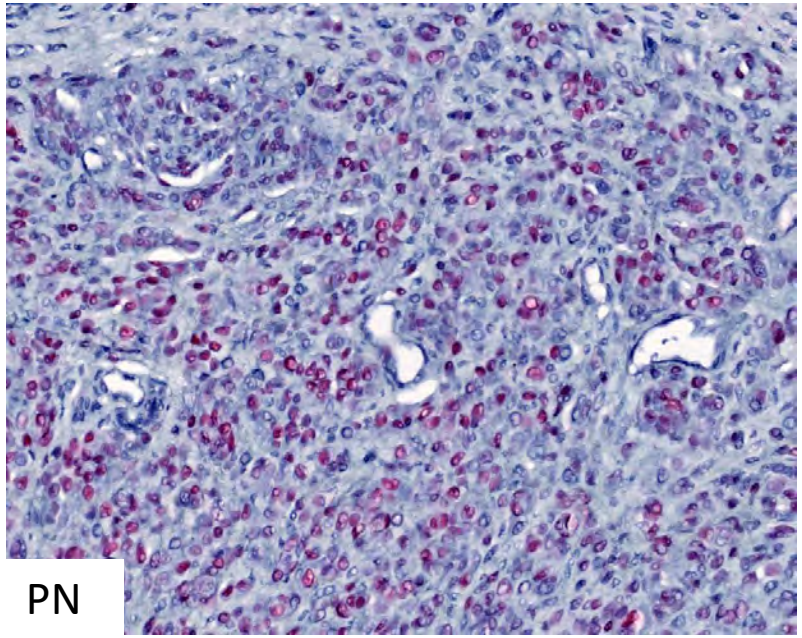


Anti-PRAME: **negative** within the congenital nevus while **positive** within the larger proliferating cells!

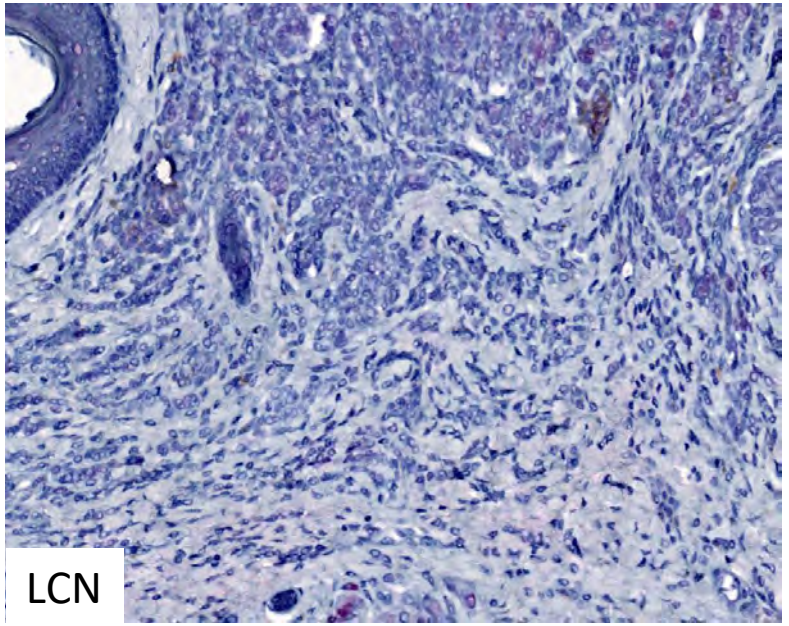




~~PRAME~~



PN



LCN

FISH?

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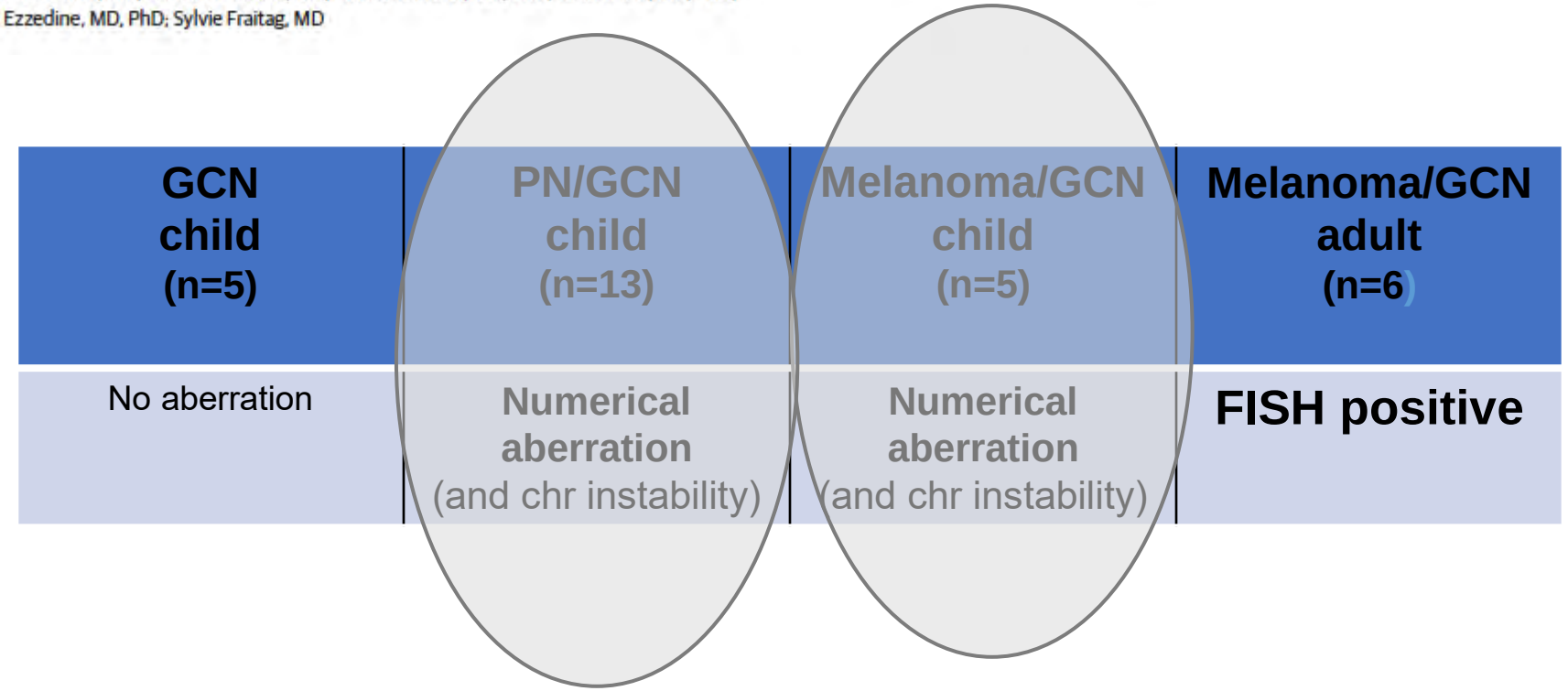


Vergier et al. JAMA Dermatol. 2016 Oct 1;152(10):1147-1151

CGH/ RNAseq

- numerous chromosomal aberrations

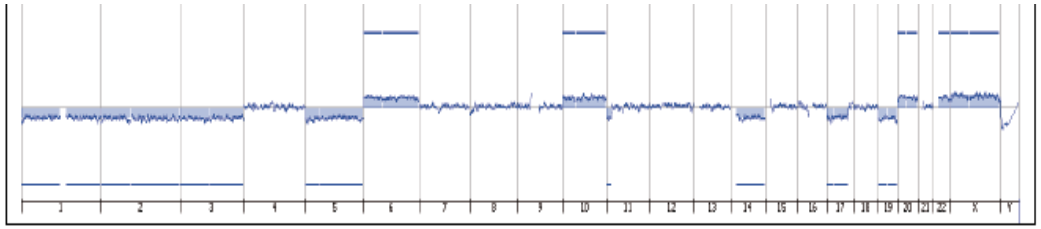
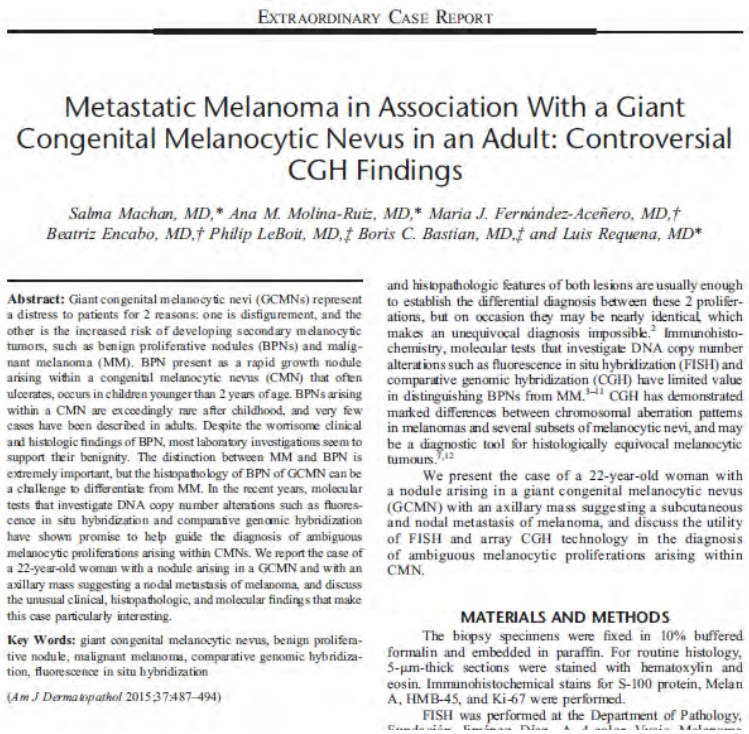


Figure2G A De la Fouchardière

Lacoste C et al. Acta Derm Venereol. 2015 Jun 24;95(6):686-90



EXTRAORDINARY CASE REPORT

Metastatic Melanoma in Association With a Giant Congenital Melanocytic Nevus in an Adult: Controversial CGH Findings

Salma Machan, MD, Ana M. Molina-Ruiz, MD,* Maria J. Fernández-Aceñero, MD,† Beatriz Encabo, MD,† Philip LeBoit, MD,‡ Boris C. Bastian, MD,‡ and Luis Requena, MD**

Abstract: Giant congenital melanocytic nevi (GCMNs) represent a distress to patients for 2 reasons: one is disfigurement, and the other is the increased risk of developing secondary melanocytic tumors, such as benign proliferative nodules (BPNs) and malignant melanoma (MM). BPN present as a rapid growth nodule arising within a congenital melanocytic nevus (CMN) that often ulcerates, occurs in children younger than 2 years of age. BPNs arising within a CMN are exceedingly rare after childhood, and very few cases have been described in adults. Despite the worrisome clinical and histologic findings of BPN, most laboratory investigations seem to support their benignity. The distinction between MM and BPN is extremely important, but the histopathology of BPN of GCMN can be a challenge to differentiate from MM. In the recent years, molecular tests that investigate DNA copy number alterations such as fluorescence in situ hybridization and comparative genomic hybridization have shown promise to help guide the diagnosis of ambiguous melanocytic proliferations arising within CMNs. We report the case of a 22-year-old woman with a nodule arising in a GCMN and with an axillary mass suggesting a nodal metastasis of melanoma, and discuss the unusual clinical, histopathologic, and molecular findings that make this case particularly interesting.

Key Words: giant congenital melanocytic nevus, benign proliferative nodule, malignant melanoma, comparative genomic hybridization, fluorescence in situ hybridization

(*Am J Dermatopathol* 2015;37:487–494)

and histopathologic features of both lesions are usually enough to establish the differential diagnosis between these 2 proliferations, but on occasion they may be nearly identical, which makes an unequivocal diagnosis impossible.[2] Immunohistochemistry, molecular tests that investigate DNA copy number alterations such as fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH) have limited value in distinguishing BPNs from MM.[3–11] CGH has demonstrated marked differences between chromosomal aberration patterns in melanomas and several subsets of melanocytic nevi, and may be a diagnostic tool for histologically equivocal melanocytic tumours.[7,12]

We present the case of a 22-year-old woman with a nodule arising in a giant congenital melanocytic nevus (GCMN) with an axillary mass suggesting a subcutaneous and nodal metastasis of melanoma, and discuss the utility of FISH and array CGH technology in the diagnosis of ambiguous melanocytic proliferations arising within CMN.

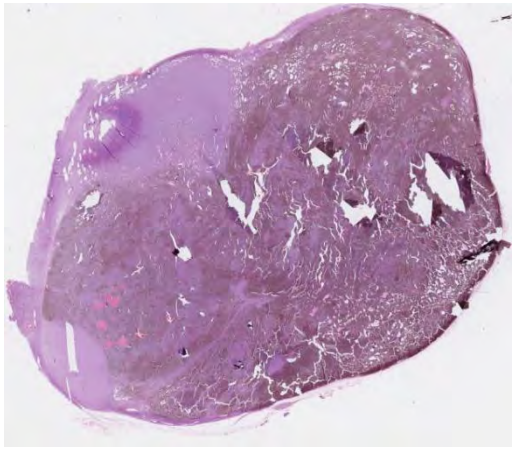
MATERIALS AND METHODS

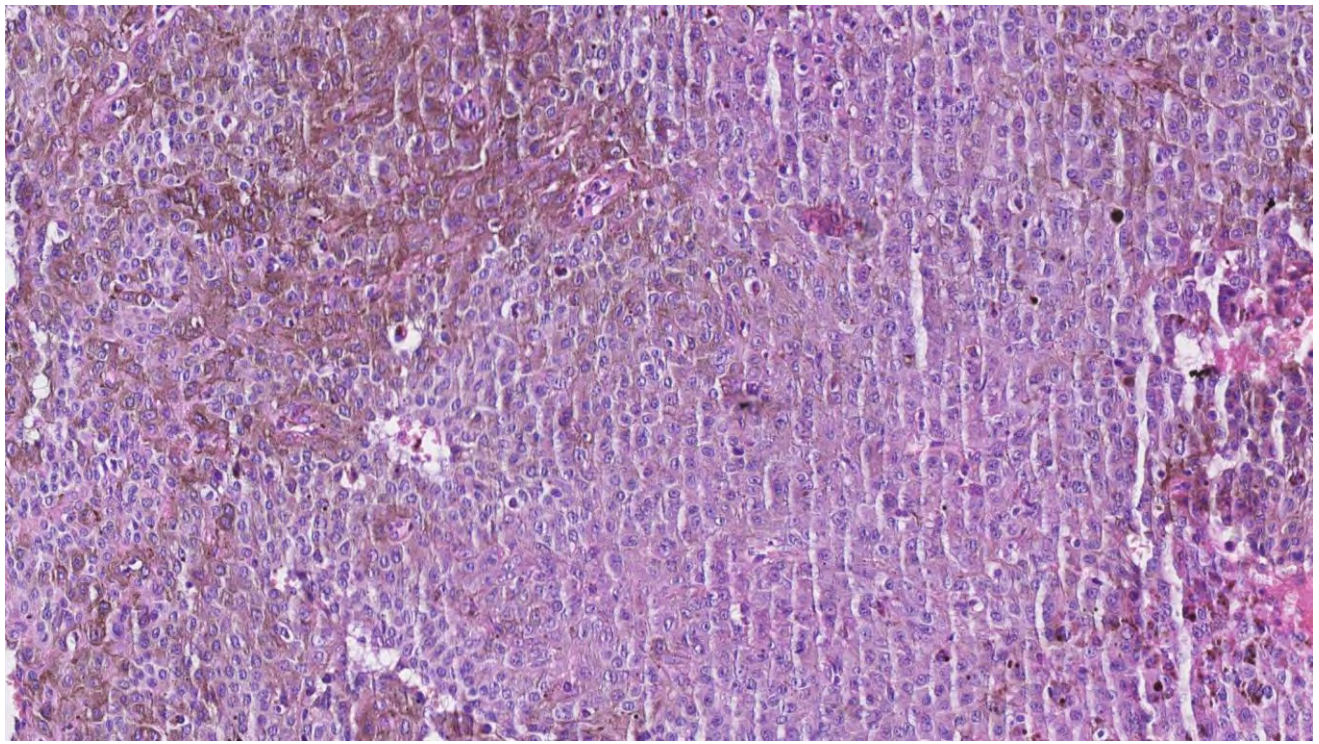
The biopsy specimens were fixed in 10% buffered formalin and embedded in paraffin. For routine histology, 5-μm-thick sections were stained with hematoxylin and eosin. Immunohistochemical stains for S-100 protein, Melan A, HMB-45, and Ki-67 were performed.

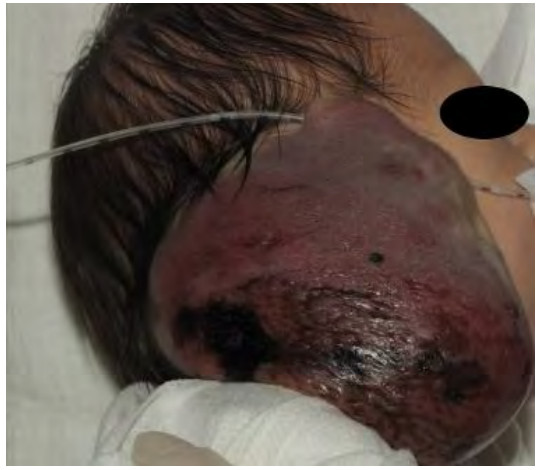
FISH was performed at the Department of Pathology,

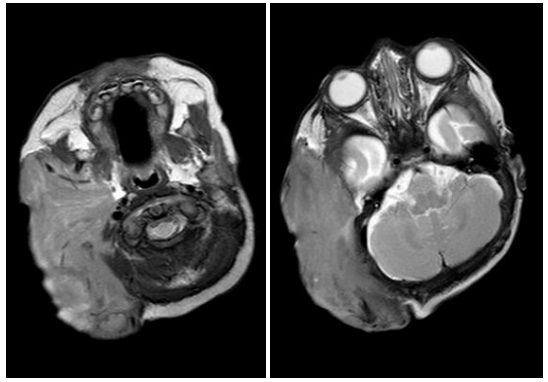
Quiz

7 MO female
Enormous tumour on the lateral side of the neck, 15 cm in diameter present since birth
Histo: marked cytological atypias, necrosis, high mitotic index (8/HPF)

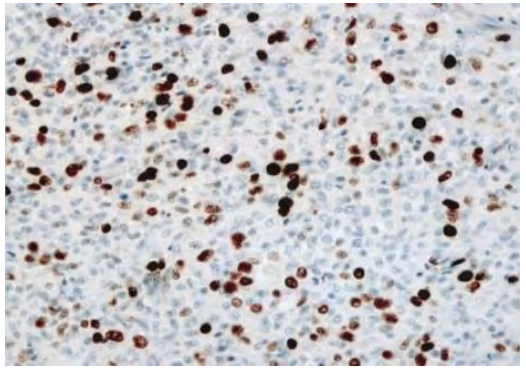








Melanoma>proliferative nodule
Work up negative
Surgery and close follow-up



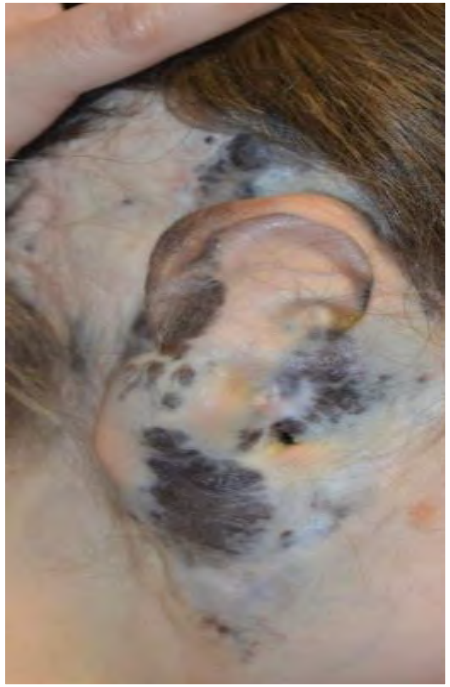
Mib1:40 %

Pr J Mazereeuw , Toulouse

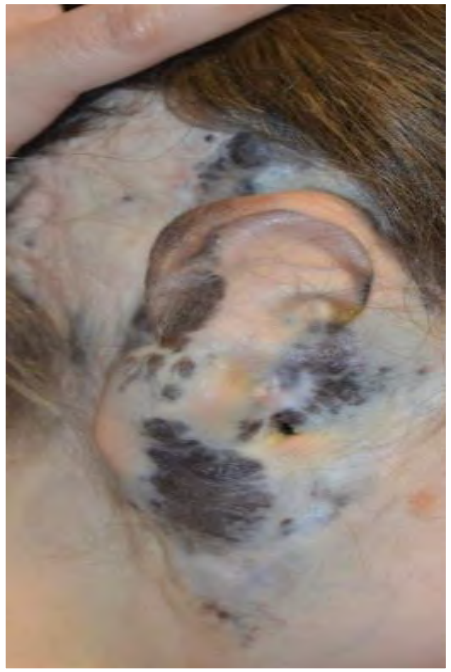
Only part of the tumour was removed

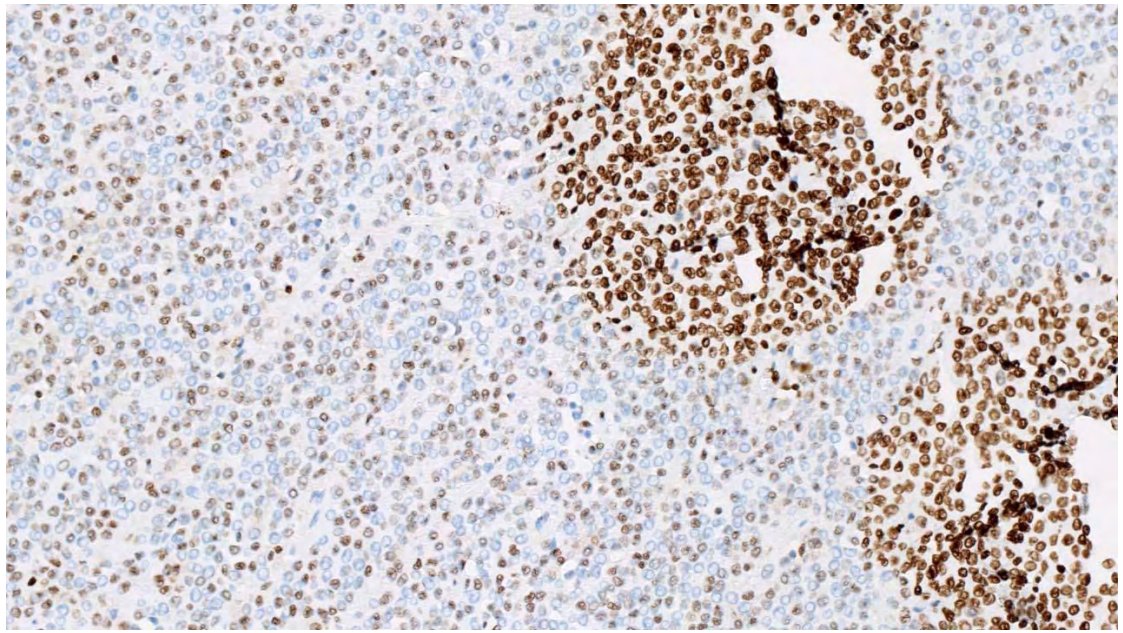
At 6 years of age
No secondaries, in good health

Benign?

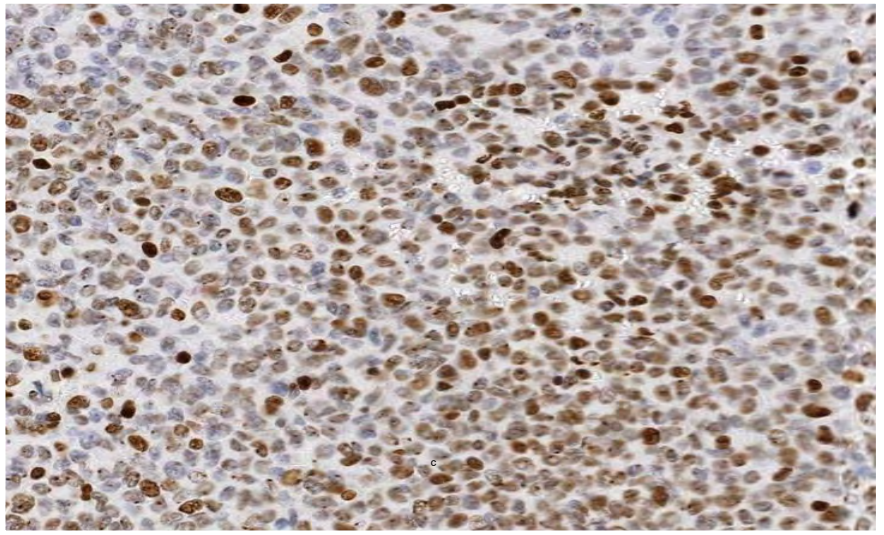


Immunohistochemistry





5HMC

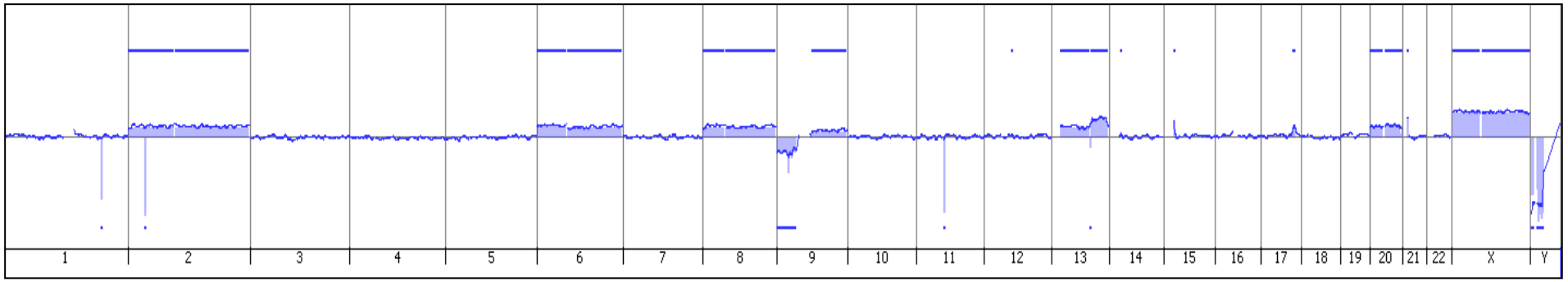


H3K27me3

Dr Busam

CGH

(Dr Arnaud De La Fouchardière)



Gains of **whole** chr. 2,6,8,13,20, instabilities
Homozygous deletion of 9p21 (CDKN2A, p16)

In the process of « turning into » malignant tumour?...

Mass spectrometry imaging
(Dr Lazova)

EXTRAORDINARY CASE REPORT

Mass Spectrometry Imaging Can Distinguish on a Proteomic Level Between Proliferative Nodules Within a Benign Congenital Nevus and Malignant Melanoma

Rossitza Lazova, MD,† Zhe Yang, MD, PhD,‡ Constantin El Habr, MD,§ Young Lim, BS,* Keith Adam Choate, MD, PhD,*†¶ Erin H. Seeley, PhD,‖ Richard M. Caprioli, PhD,** and Li Yangqun, MD‡*

Abstract: Histopathological interpretation of proliferative nodules occurring in association with congenital melanocytic nevi can be very challenging due to their similarities with congenital malignant melanoma and malignant melanoma arising in association with congenital nevi. We hereby report a diagnostically challenging case of congenital melanocytic nevus with proliferative nodules and ulcerations, which was originally misdiagnosed as congenital malignant melanoma. Subsequent histopathological examination in consultation by one of the authors (R.L.) and mass spectrometry imaging analysis rendered a diagnosis of congenital melanocytic nevus with proliferative nodules. In this case, mass spectrometry imaging, a novel method capable of distinguishing benign from malignant melanocytic lesions on a proteomic level, was instrumental in making the diagnosis of a benign nevus. We emphasize the importance of this method as an ancillary tool in the diagnosis of difficult melanocytic lesions.

Key Words: congenital melanocytic nevus, proliferative nodule, congenital melanoma, malignant melanoma, mass spectrometry imaging, mass spectrometry, proteomics

(*Am J Dermatopathol* 2017;39:689–695)

INTRODUCTION

Congenital melanocytic nevi are present in 1%–2% of newborns. Changes in its morphology are common and are usually divided into 2 main groups. The first group, which development of nodular melanocytic lesions and ulcerations within the congenital melanocytic nevi, could signify de novo malignant melanoma arising within the nevus.[1–3] Proliferative nodules are sometimes difficult to differentiate from malignant melanoma due to the many clinical and histopathological similarities.[4,5]

Several recent studies have shown that mass spectrometry imaging (MSI) can be used to differentiate between histologically difficult lesions. Although there may be morphological features that look similar between benign and malignant lesions[6,7] or between diseases of similar tissue origin,[8,9] the underlying biology including proteomics between these samples is different. MSI is a natural match for pathology as the same type of thin tissue sections used for pathology are used for MSI to determine the protein composition in the tissue with the spatial information within the sample being preserved. In a recent study, we determined that 5 proteins were differentially expressed in the melanocytes of Spitz nevi and Spitzoid melanomas.[6] In a subsequent large study, MSI proved to be helpful in the classification of diagnostically challenging atypical Spitzoid neoplasms when the previously determined molecular signature was applied.[10] Furthermore, the diagnosis rendered by MSI correlated better with the clinical outcome than the histopathological diagnosis. MSI determines differences in the expression of proteins within benign and malignant melanocytic lesions of any type, which allows for their correct classification and diagnosis.

Mass spectrometry was consistent with a melanoma.

Finally, after the age of 7 years, hepatic and pulmonary metastastatic involvement occured and led to the death 5 months later

Masson Regnault M, Fraitag S, Lamant L, Maza A, De la Fouchardière A, Tournier E, Lauwers F, Carfagna L, Meyer N, De Berail A, Busam KJ, Lazova R, Mazereeuw-Hautier J. Ann Dermatol Venereol. 2020 Nov;147(11):746-754.

Nodule in a congenital naevus

Pathological examination

Non atypical nodule

↓

Excision, nothing else

Nodule in a congenital naevus

Pathological examination

Non atypical nodule

↓

Excision, nothing else

Atypical nodule

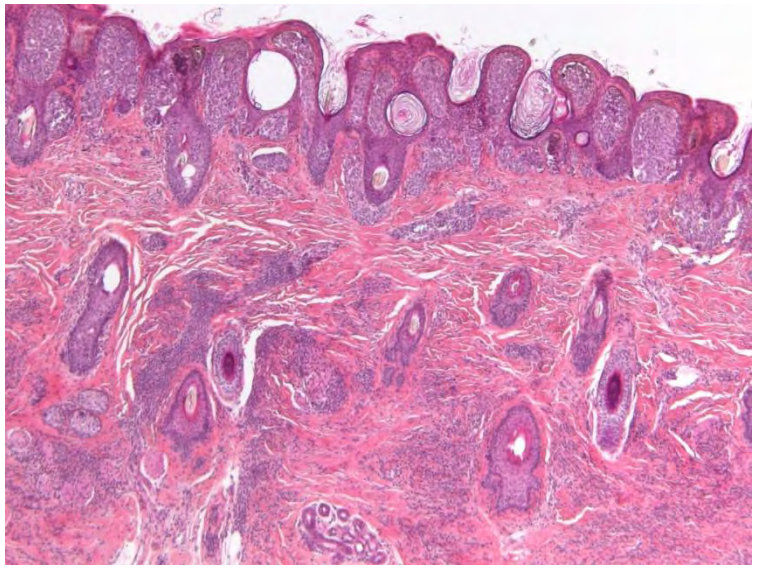
- atypias, necrosis, mitoses
- IHC : ↗Ki67, 5-hmC, H3K27me3, *PRAME (?)*

↓

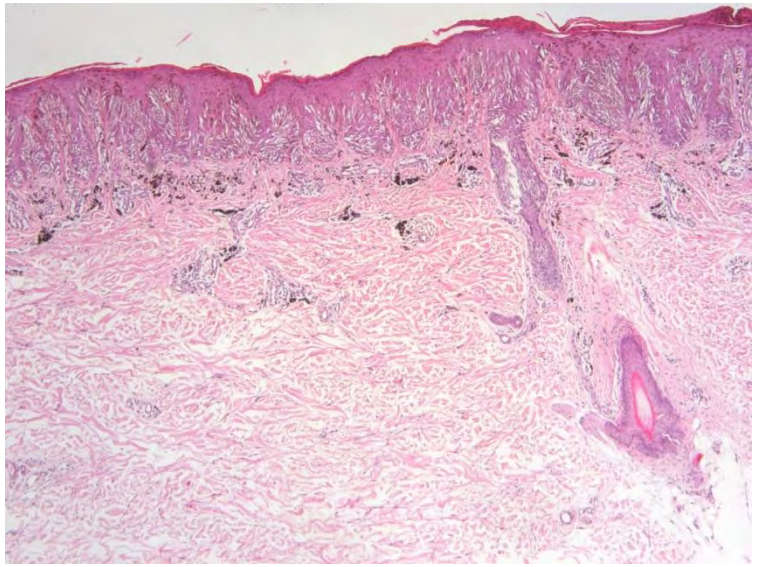
Cytogenetic, mass spectrophotometry imaging
Large excision
Follow-up

Melanocytic proliferations

Congenital melanocytic nevi

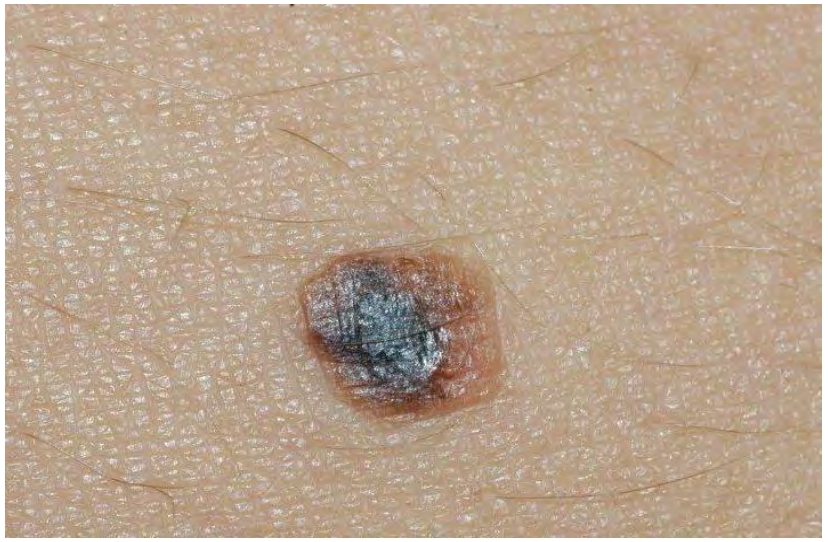


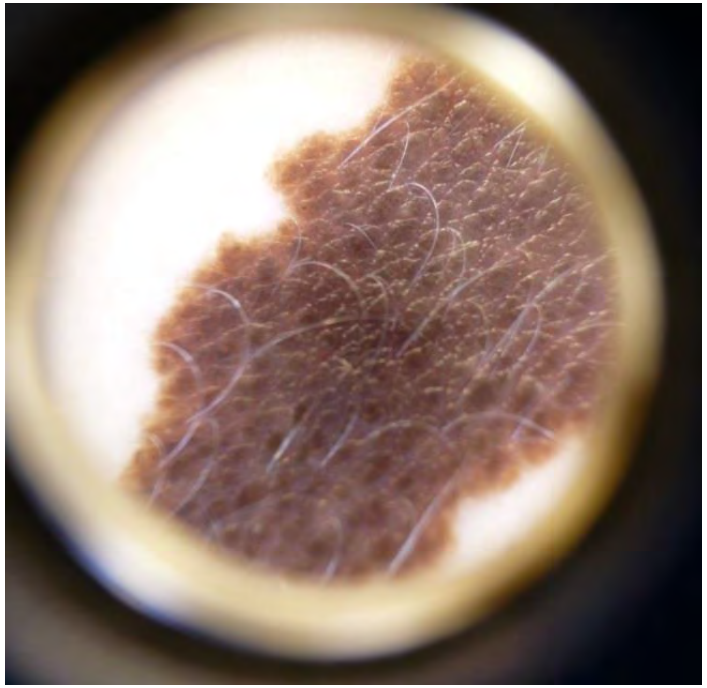
Aquired melanocytic nevi

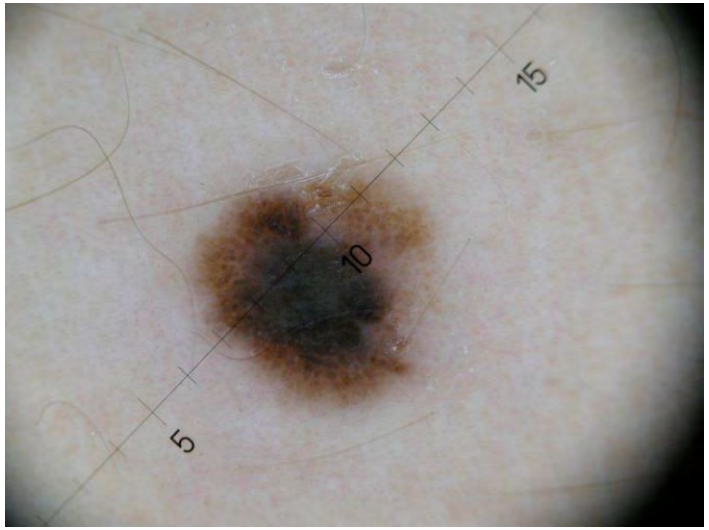


Aquired common nevi in children

Can mimic SSM:
-clinically and in dermoscopy

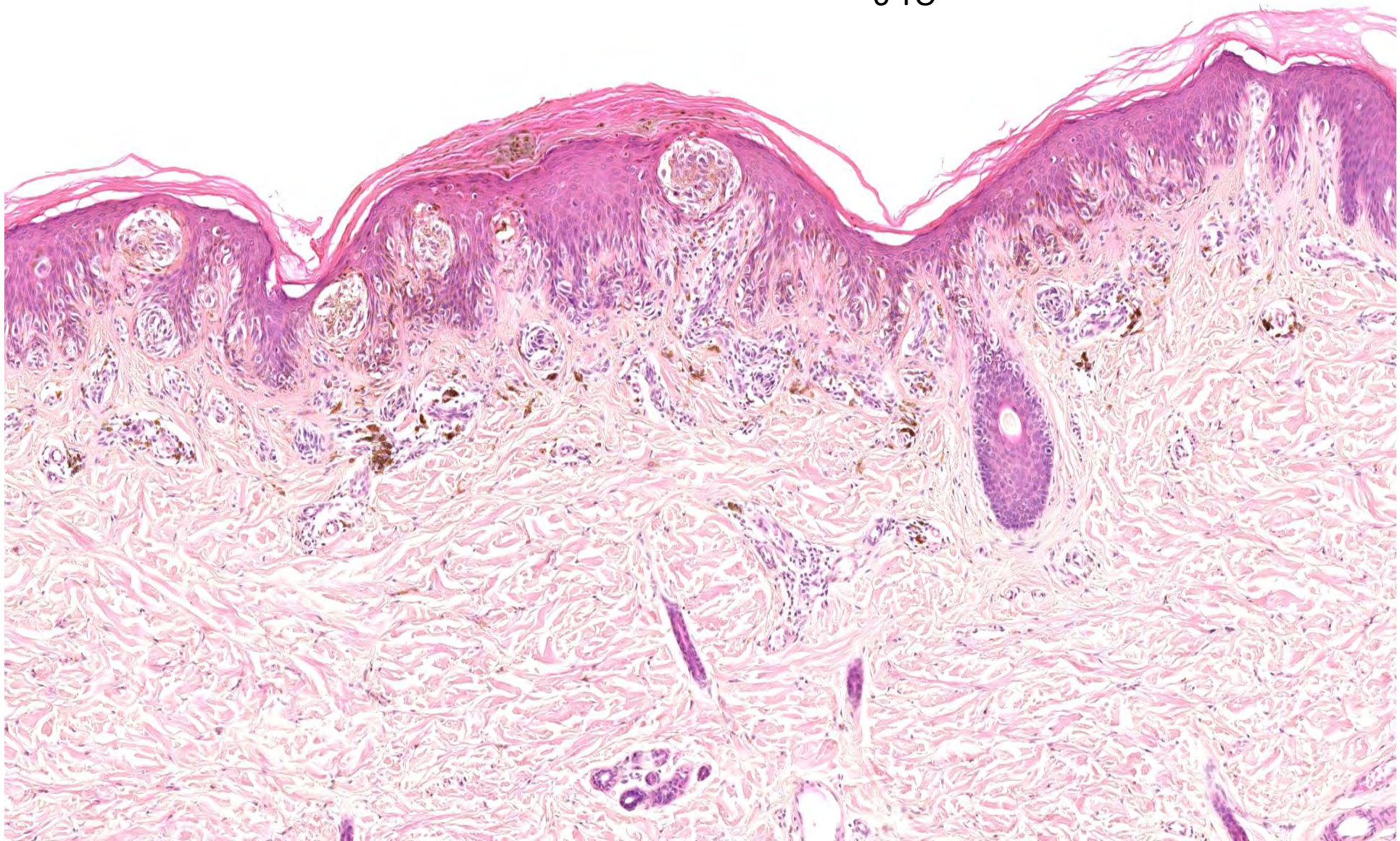






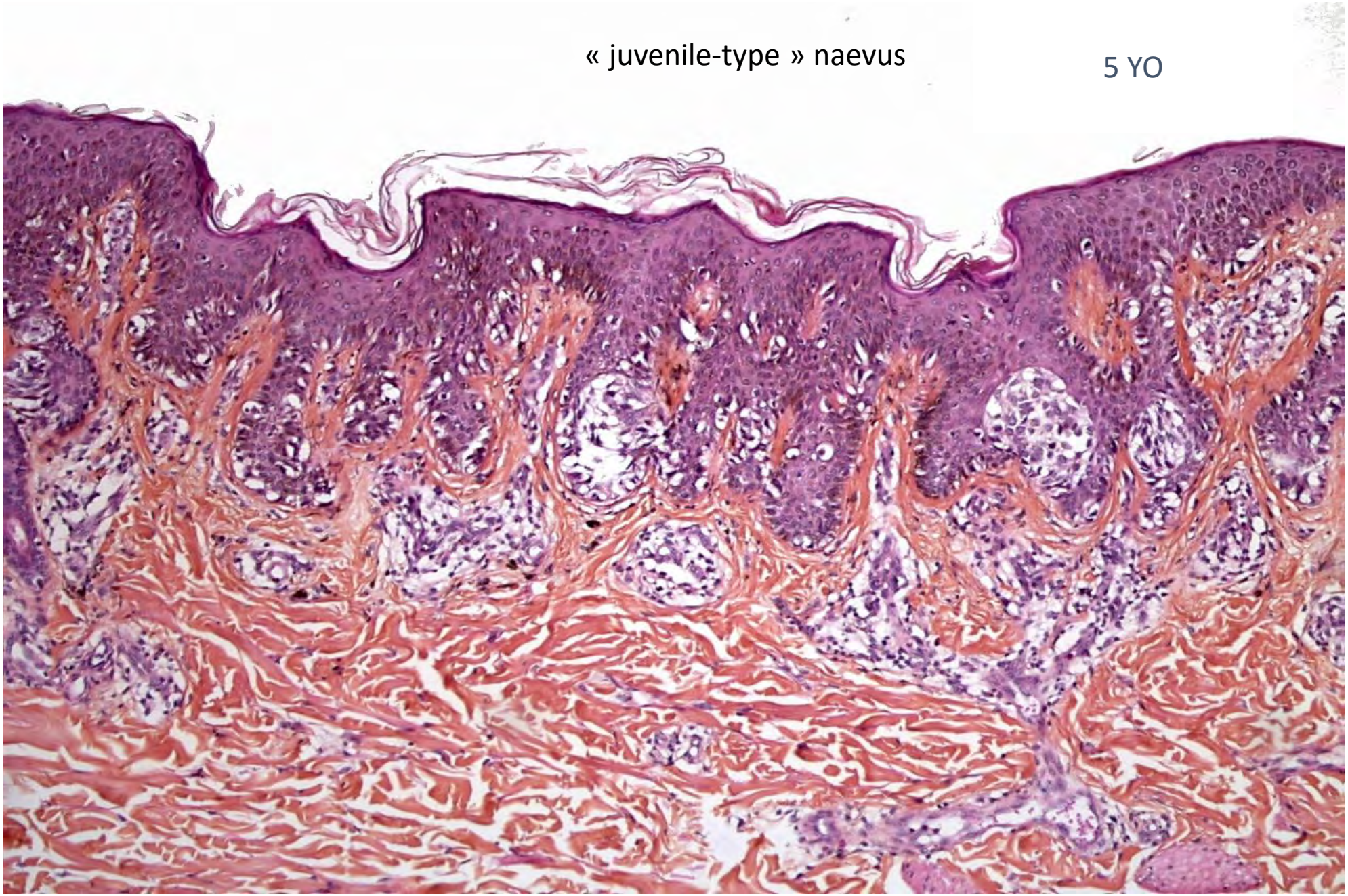
Can also mimic SSM histologically

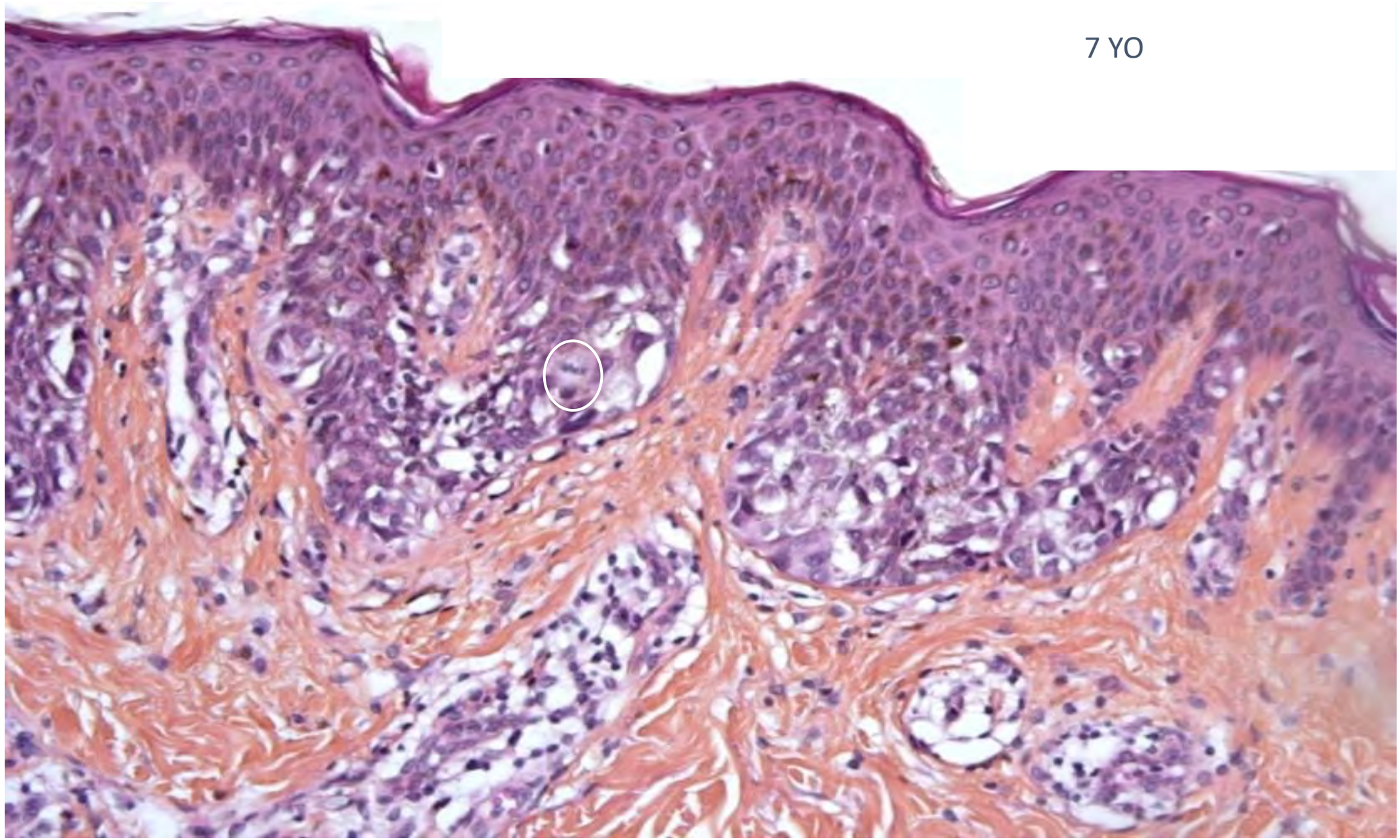
6 YO

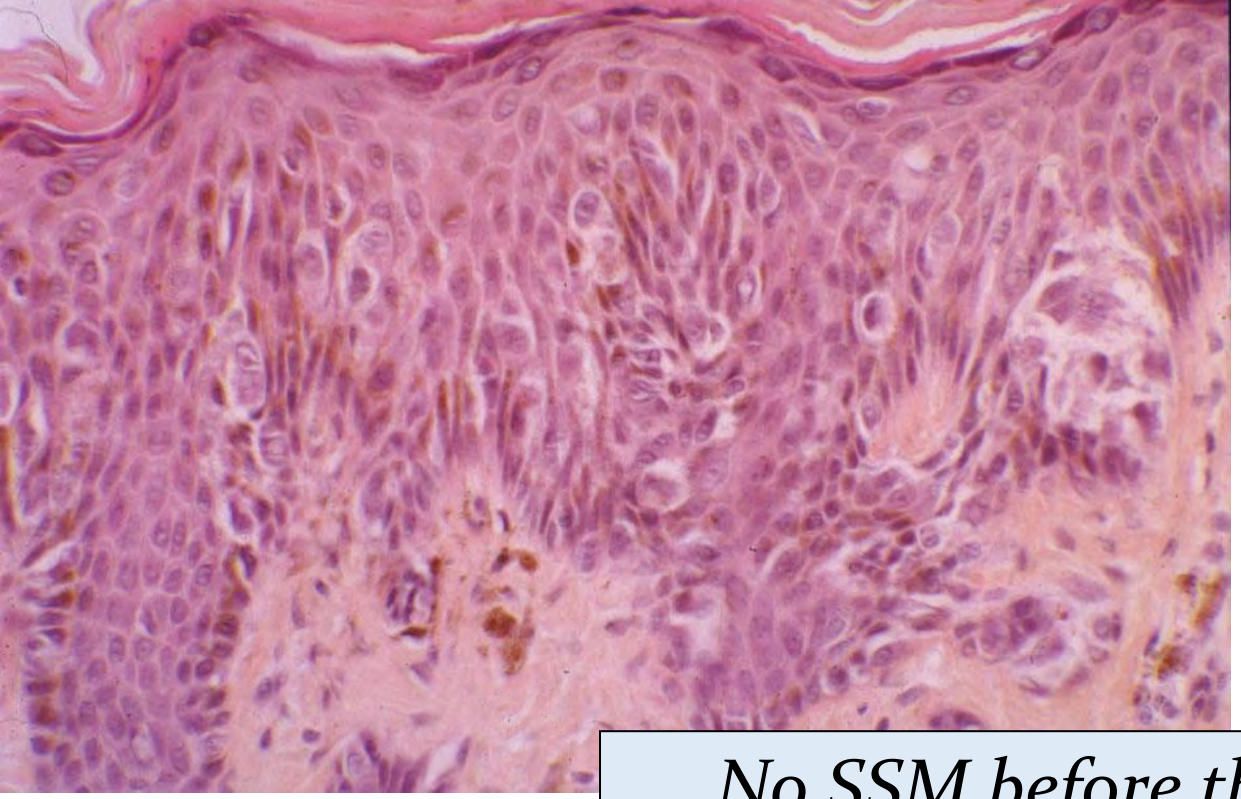


« juvenile-type » naevus

5 YO




7 YO



4 YO

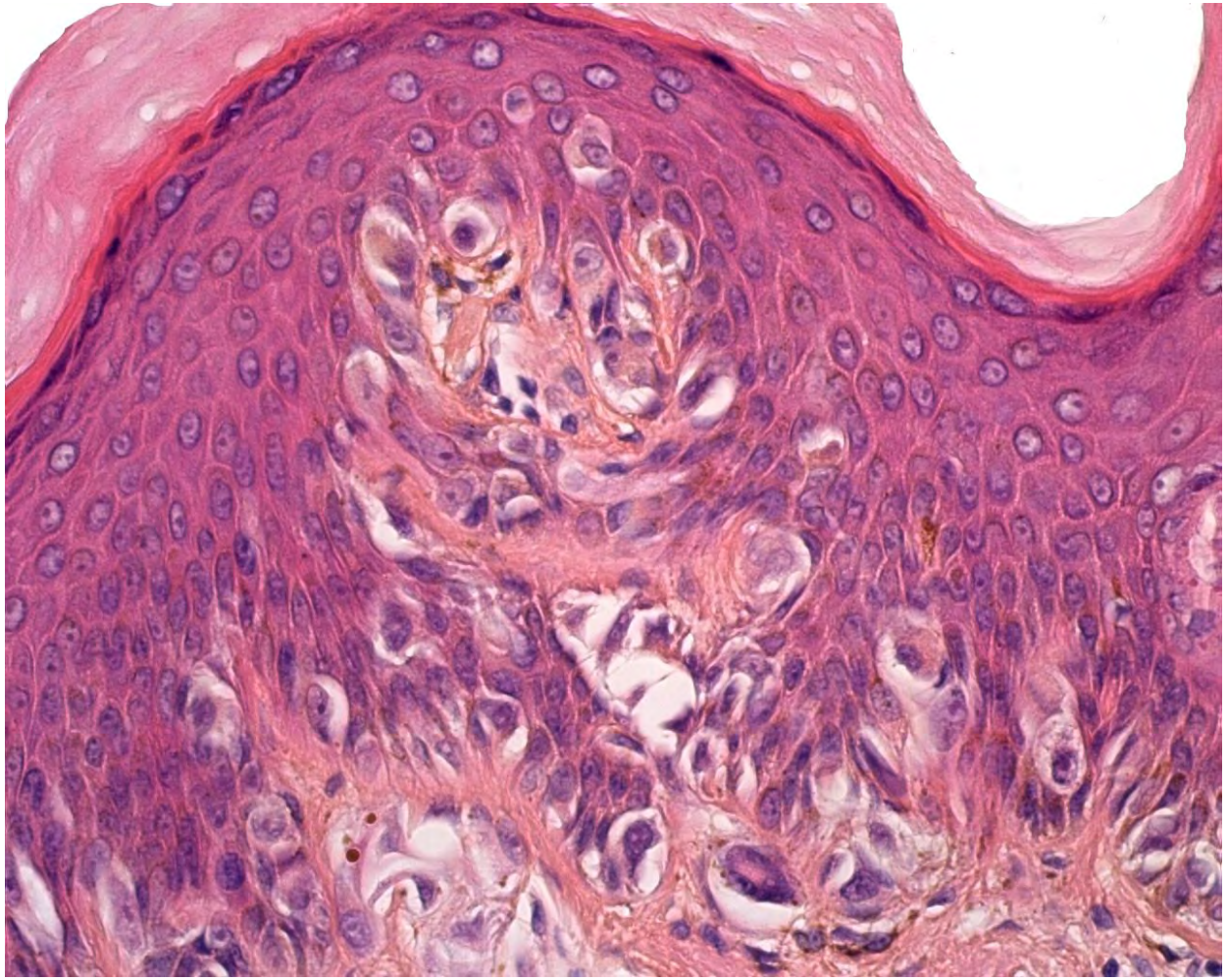
No SSM before the prepubertal period!

Overdiagnoses!

- Anxiety
- Unesthetic scar
- Follow-up
- Insurance
- Trials

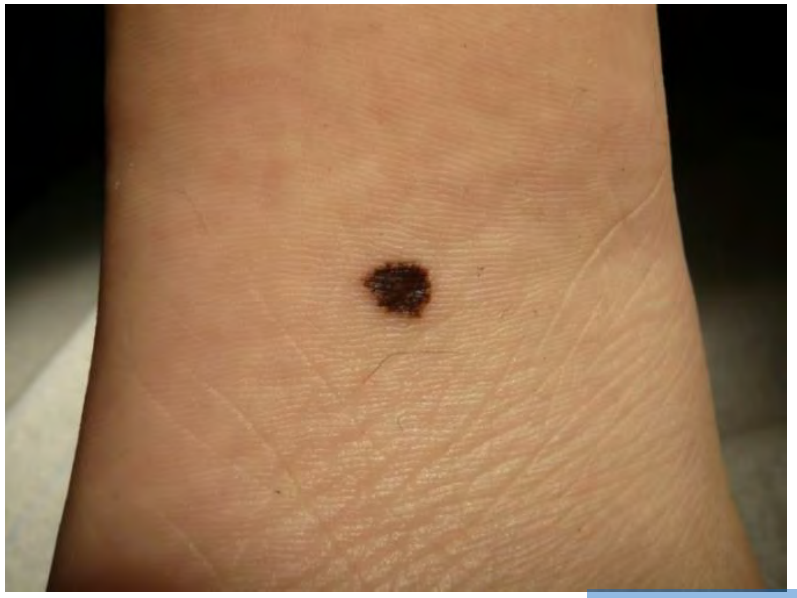
Spatz A et al, Int J Cancer 1996, 68, 317-24

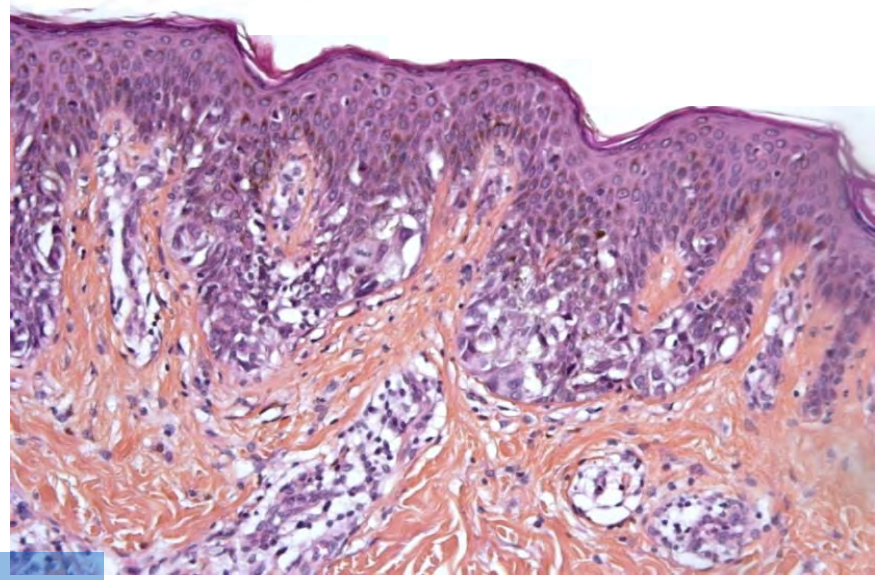
- But numerous nevi observed in children may mimic a SSM histologically
- **Always consider the age**



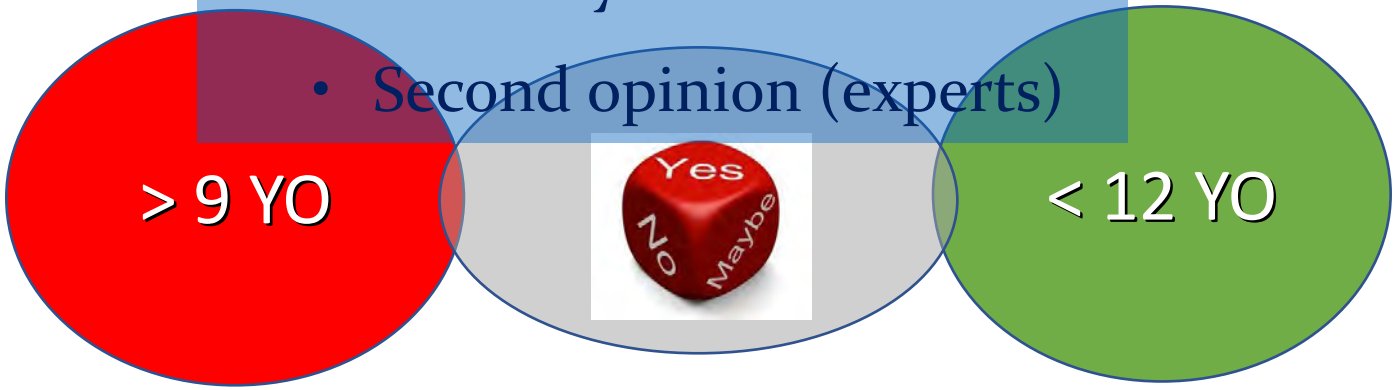
Ask for a second opinion if any doubt (experts)

Atypical/ambiguous nevi versus SSM

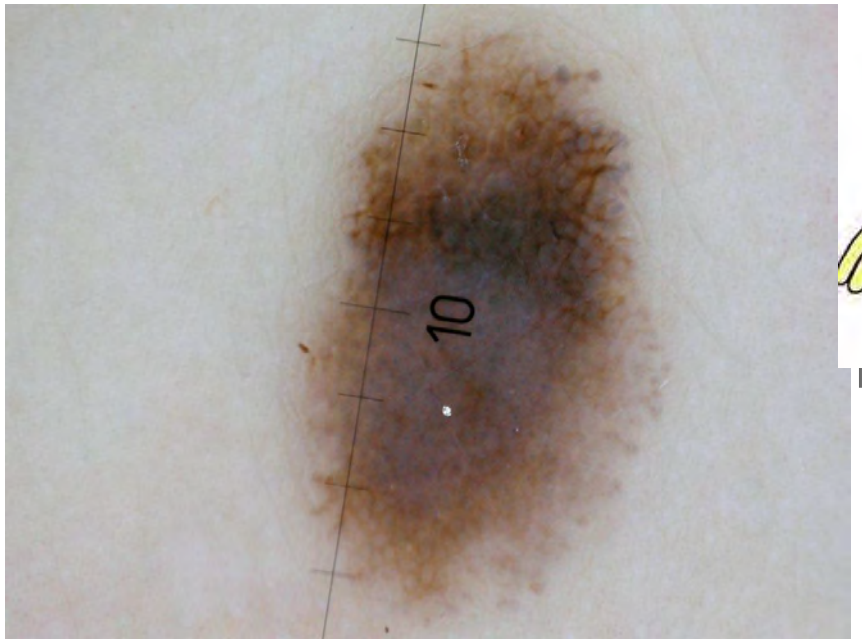


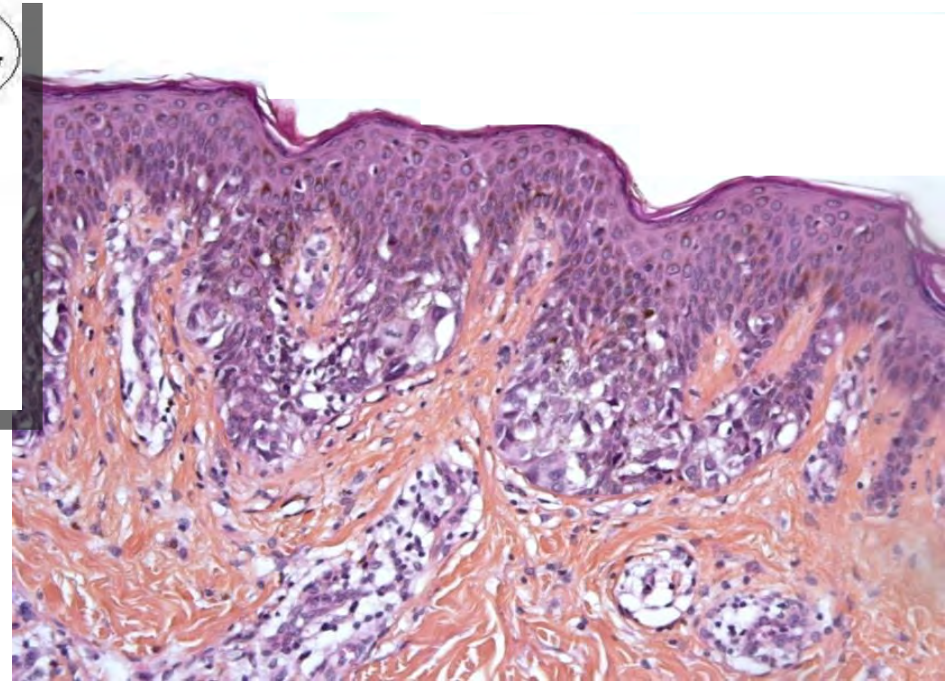


- Risk factors?
- Ancillary tests
- Second opinion (experts)

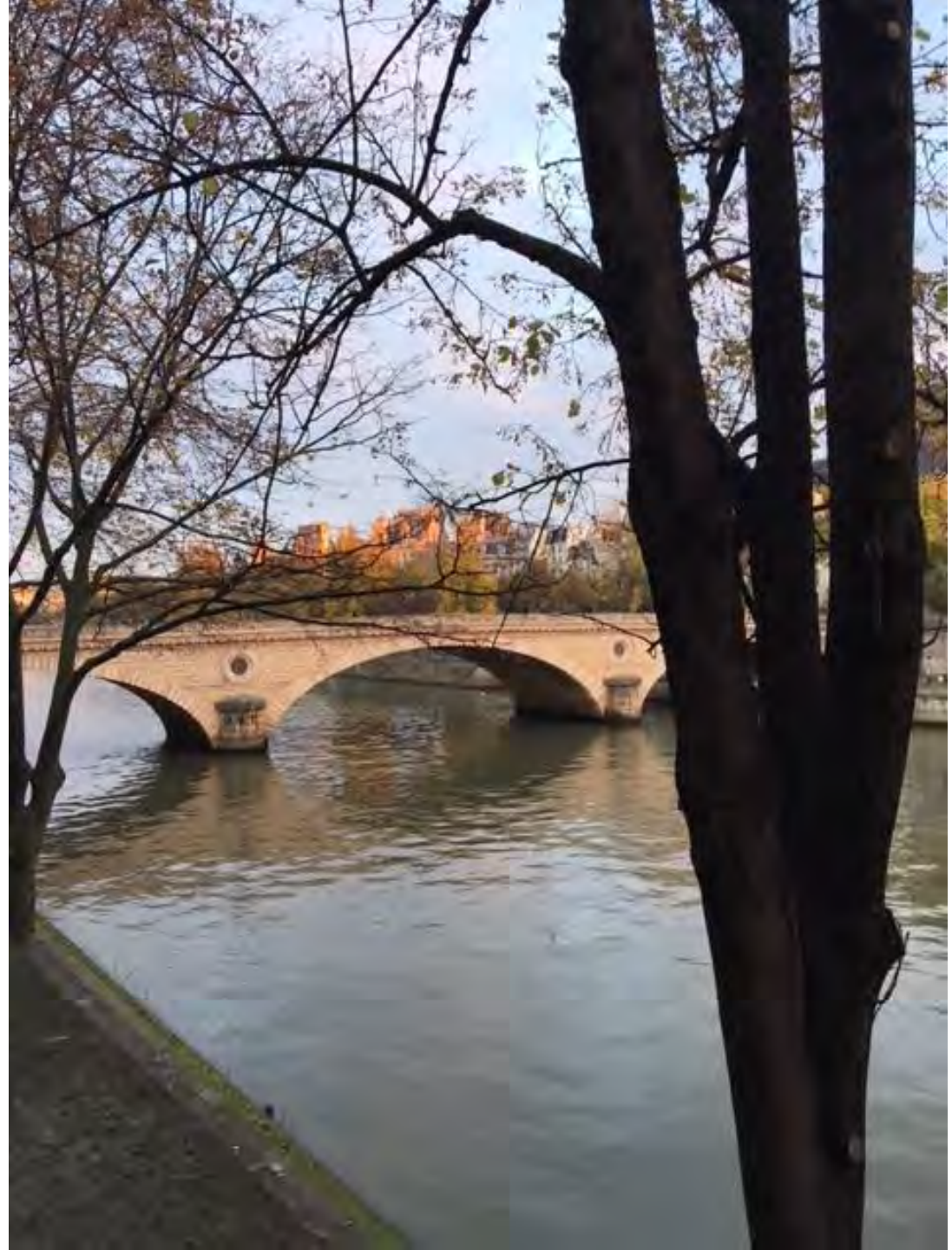


Ambiguous naevus versus SSM





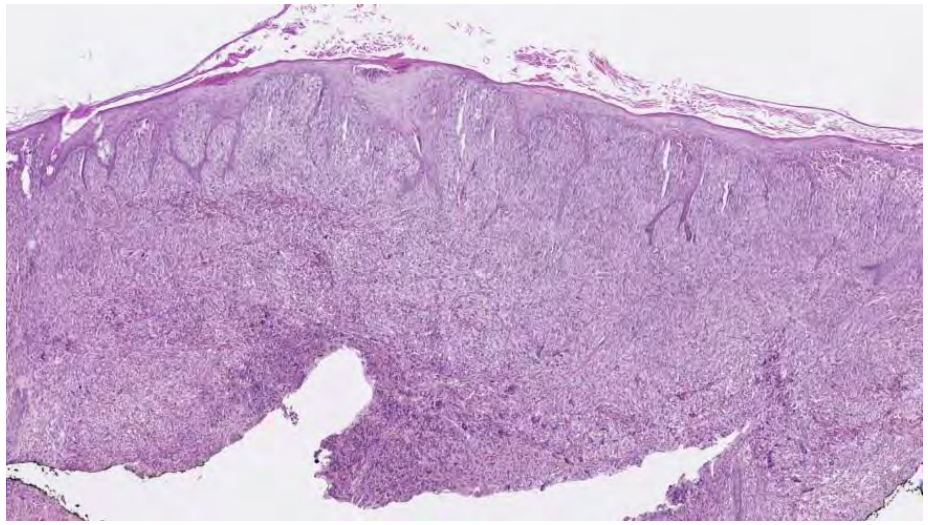
If we can't tell: **better say « probably benign »** than « probably malignant » but ask for re-excision and follow-up to be save



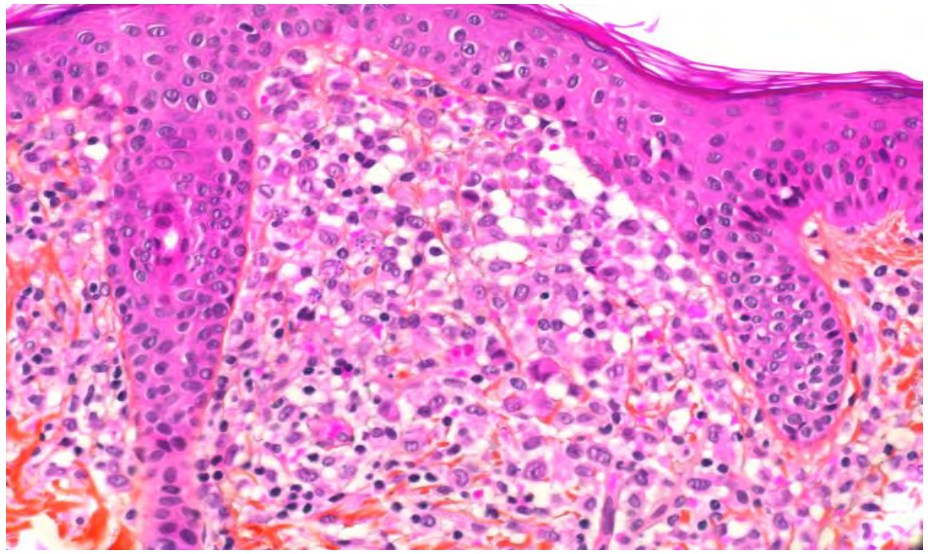
Histiocytic infiltrates

Histiocytic infiltrates

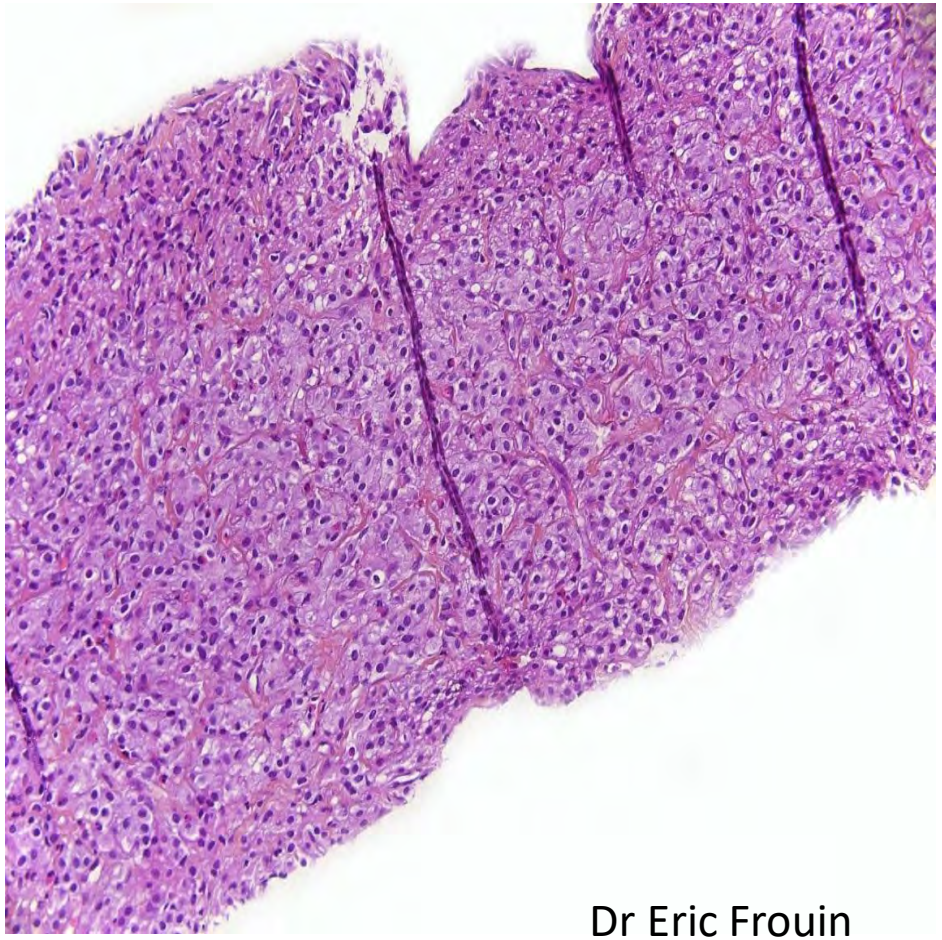
CD1a negative histiocytic infiltrates



CD1a positive histiocytic infiltrates

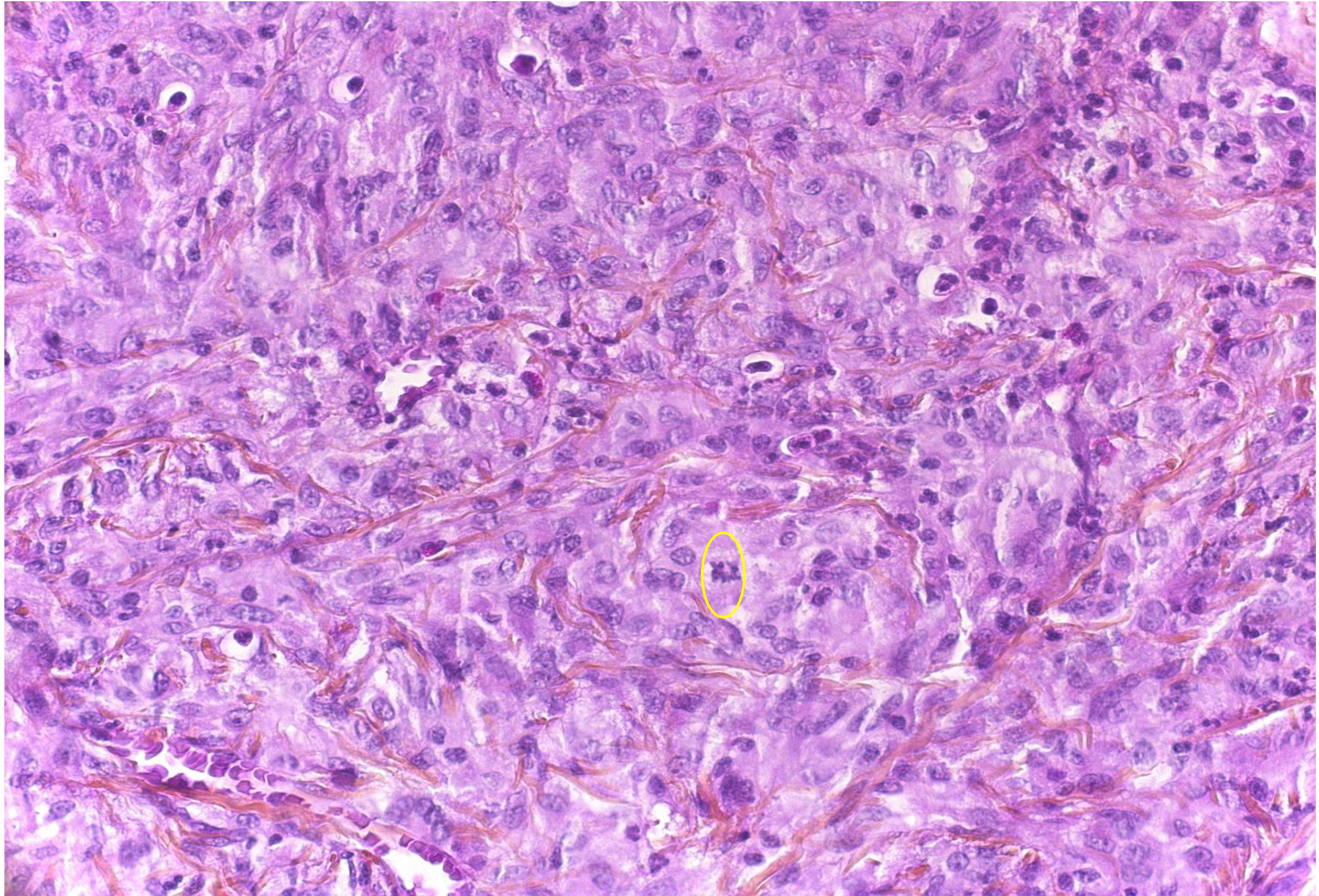


Quiz

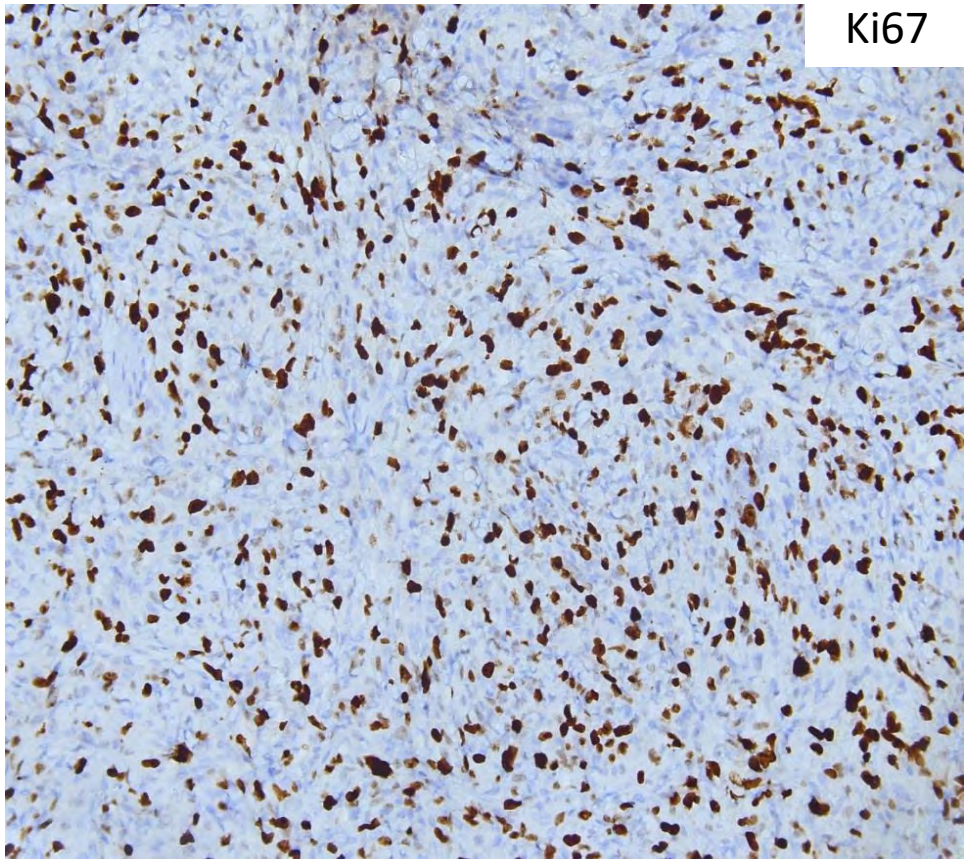


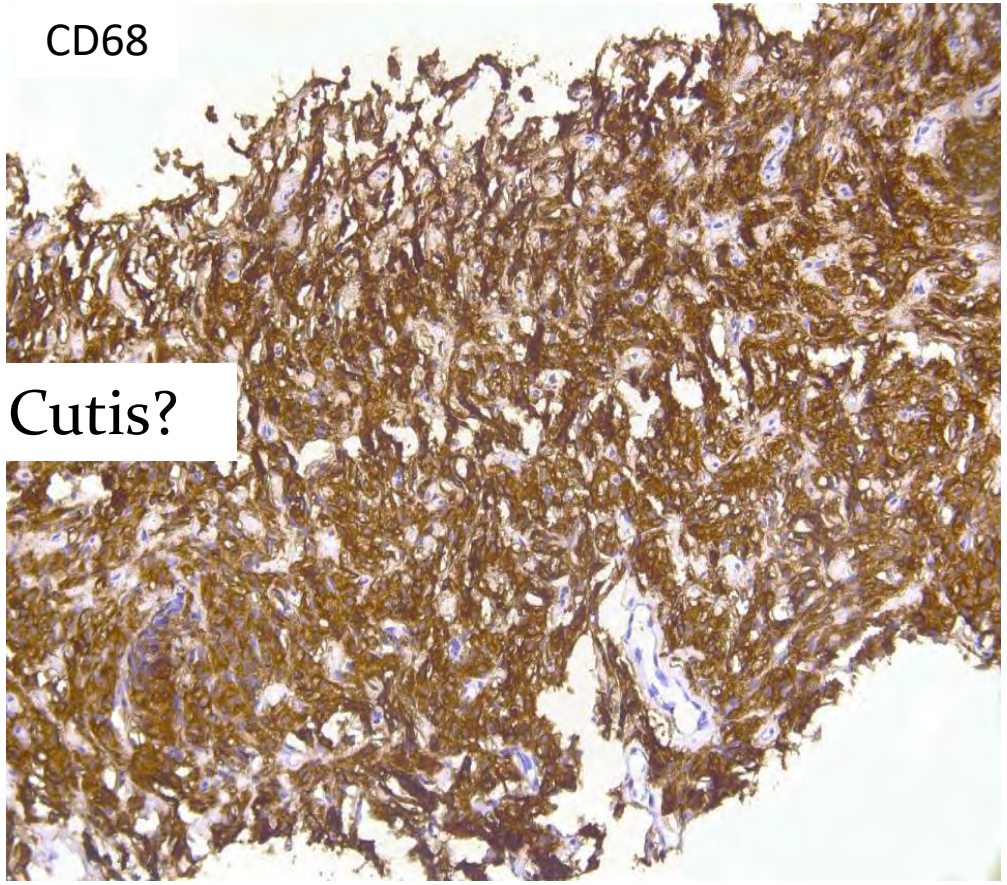
Dr Eric Frouin
Poitiers

- Neonate
- Three nodules present at birth: 2 on the nose, one on the neck
- Biopsy: rule out malignant tumour. **Urgent**



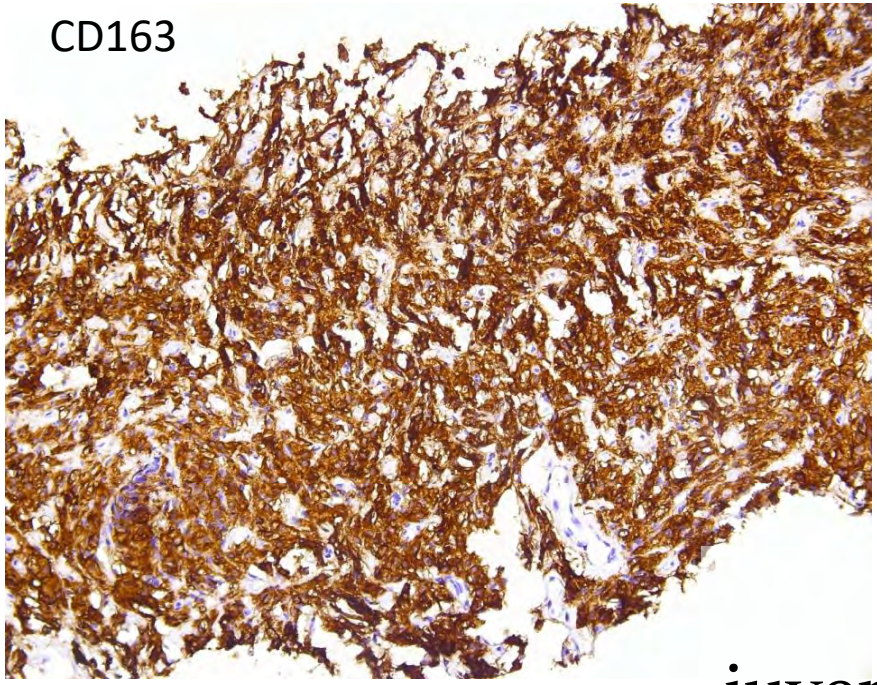
Immunohistochemistry





Monoblastic Leukemia Cutis?

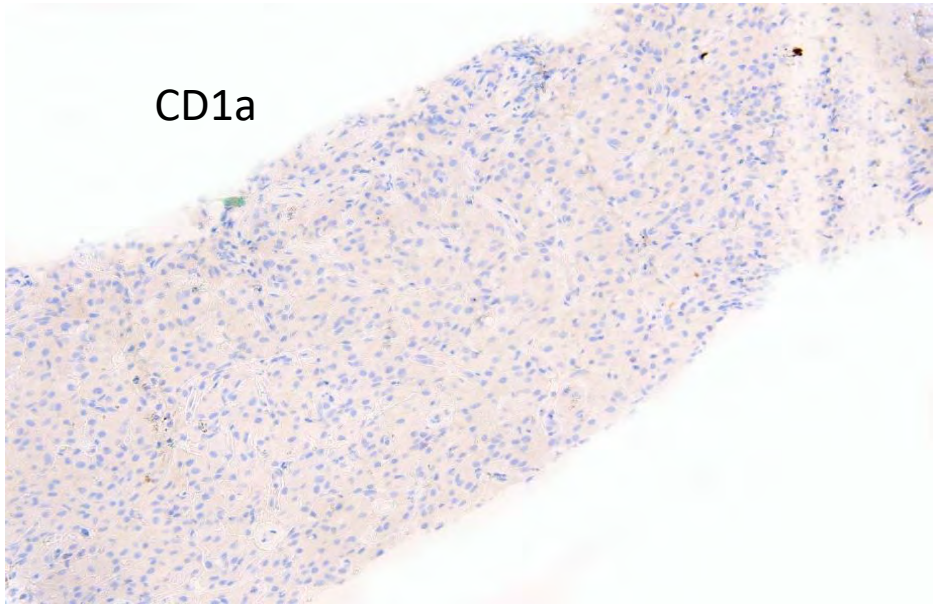
CD163



FXIIIa

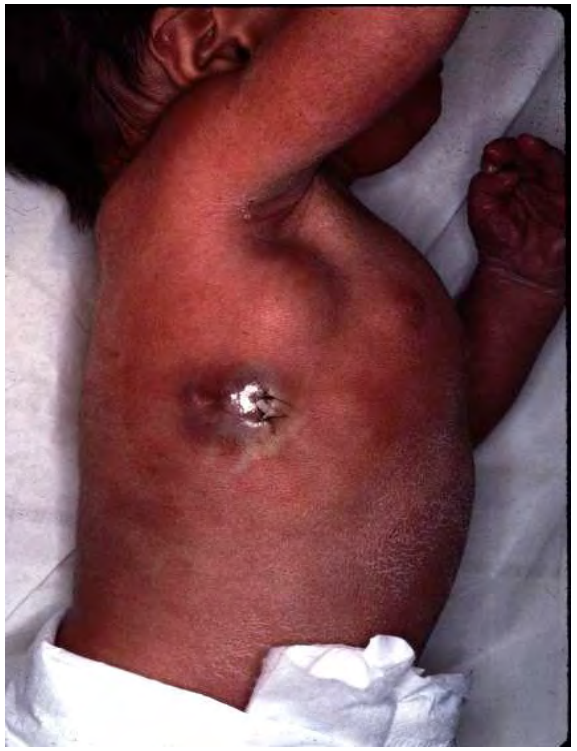
Early tumoral juvenile xanthogranuloma

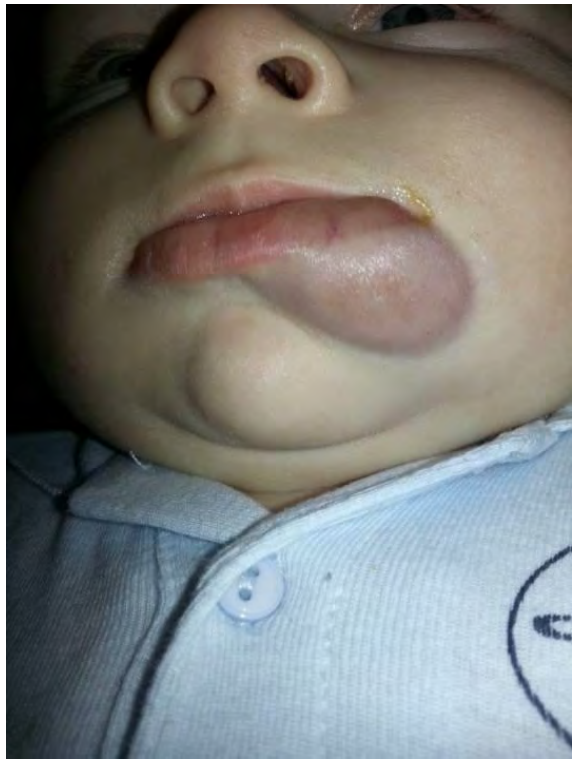
CD1a

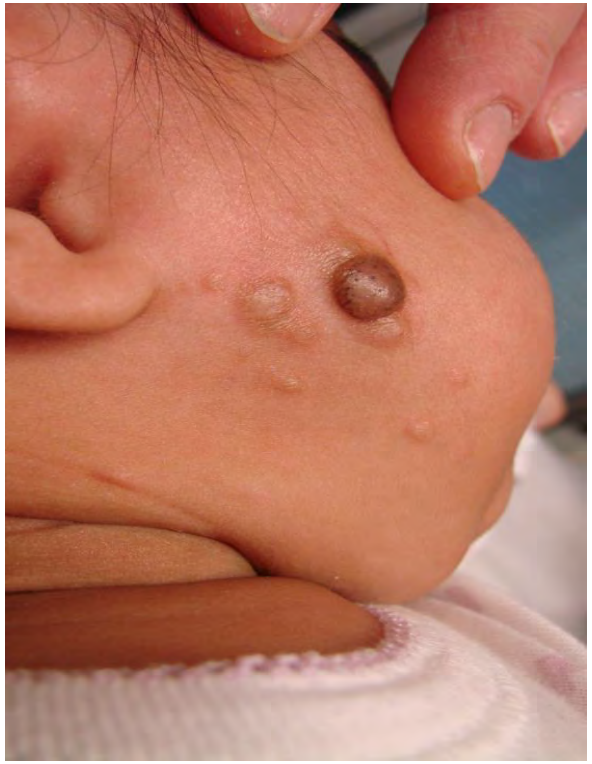


Tumoral juvenile xanthogranuloma

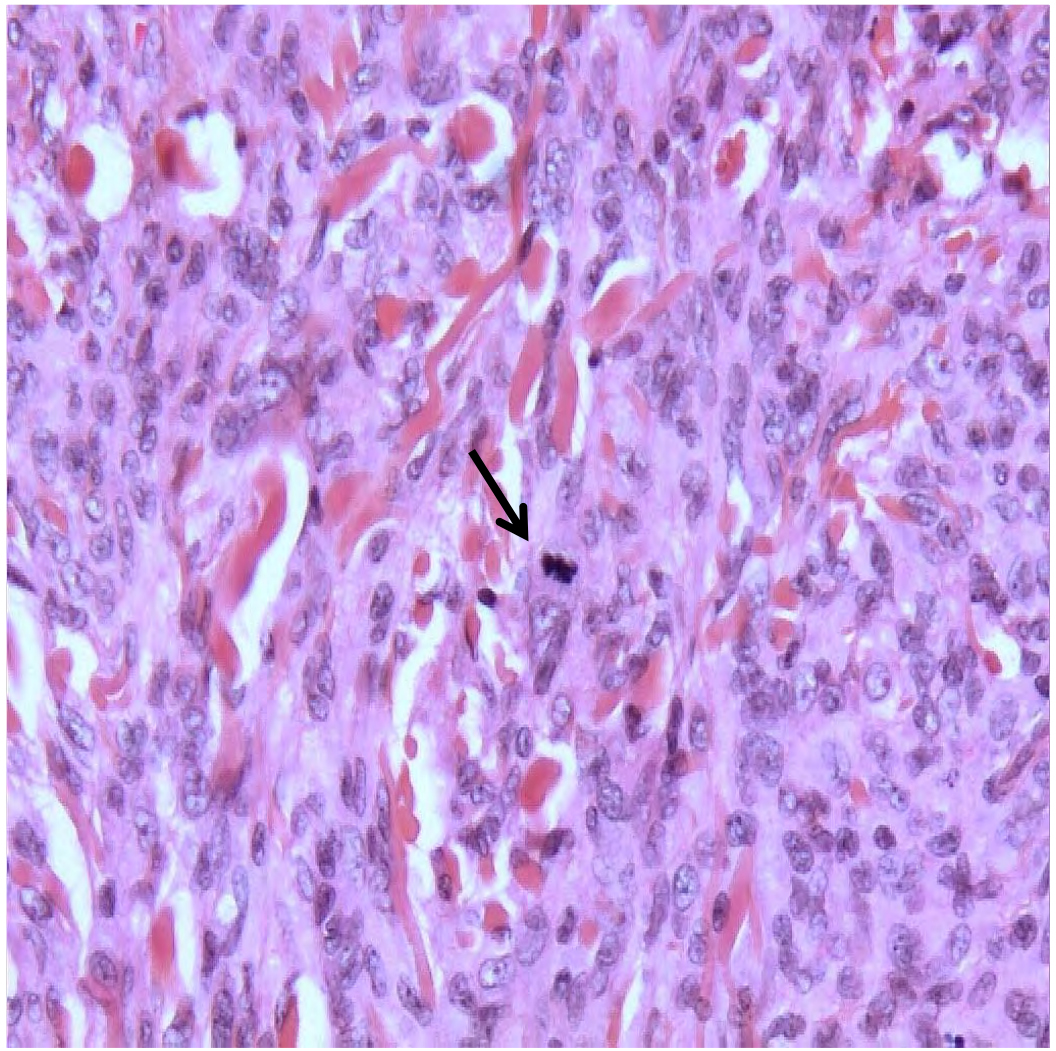
- Very misleading and worrying ⇨ always biopsied
- Can reach several cm in size
- Occurs *always in the neonatal period*



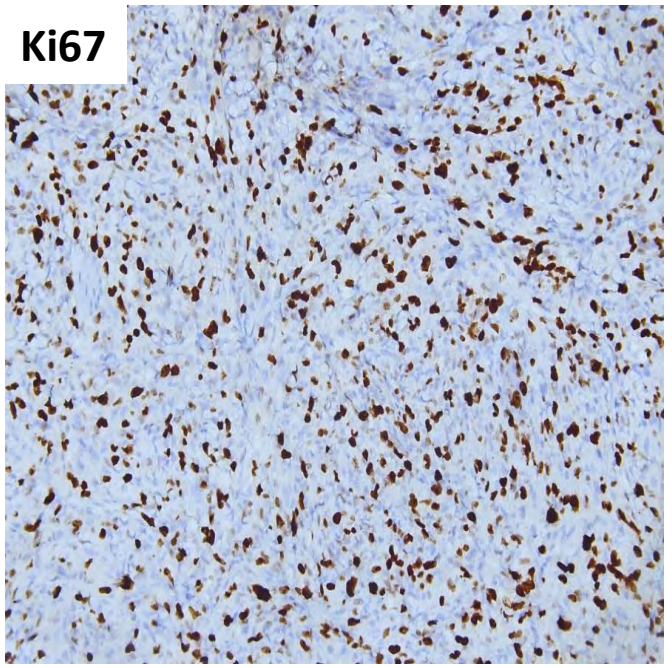




Early JXG: **not yet xanthomized**, numerous mitotic figures, **Ki67++!**

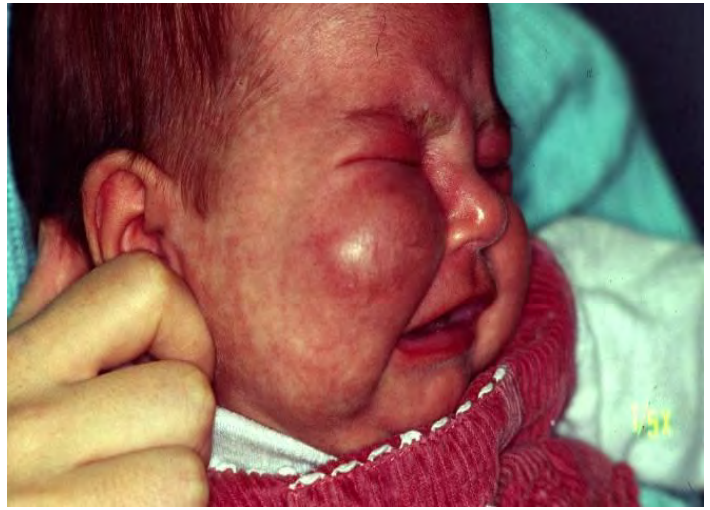


Pitfall!



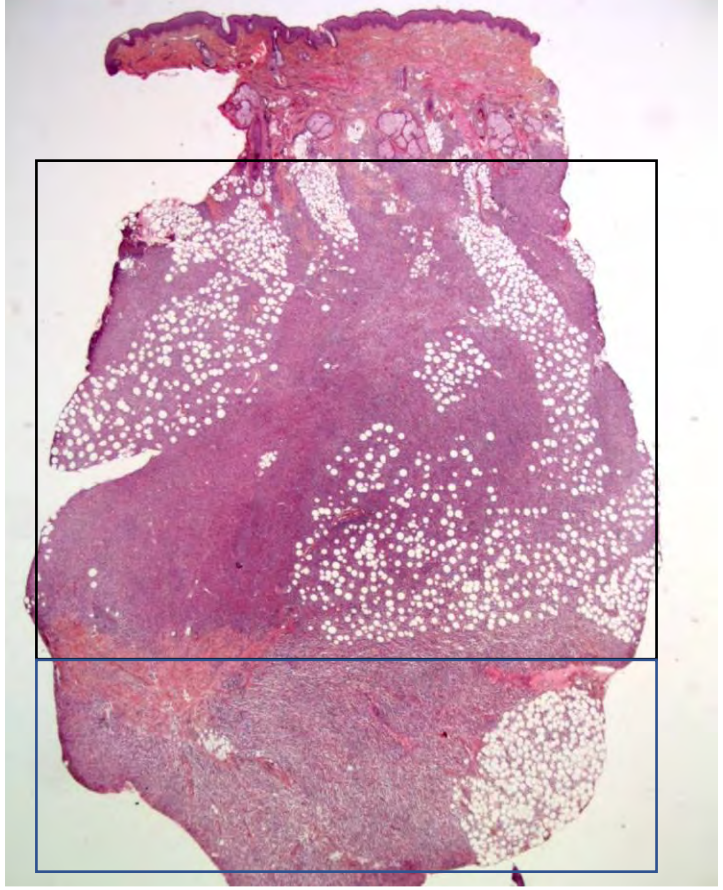
≠ Hematological tumour, sarcoma

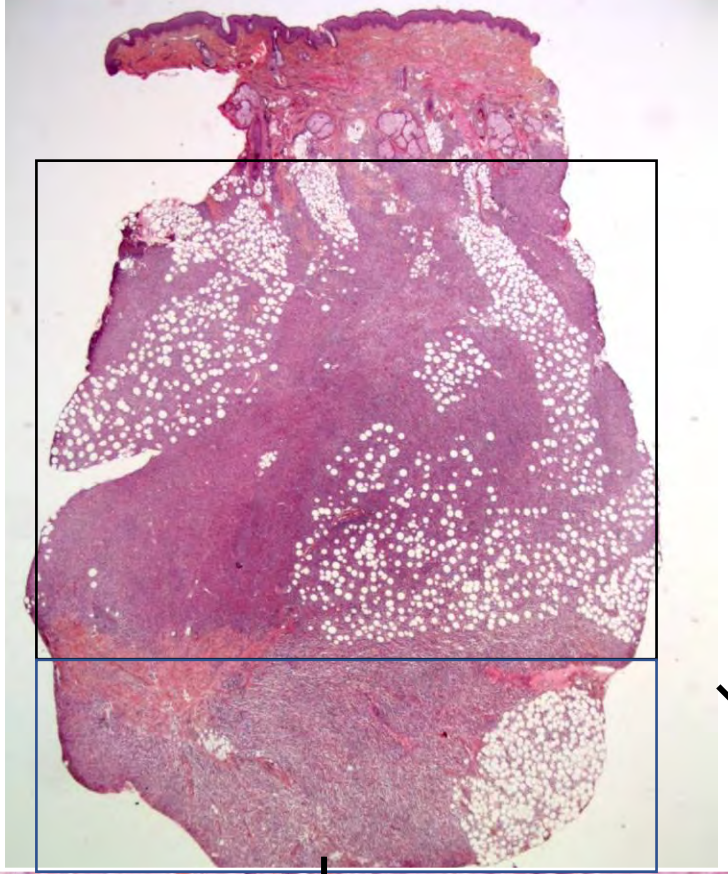
Quiz

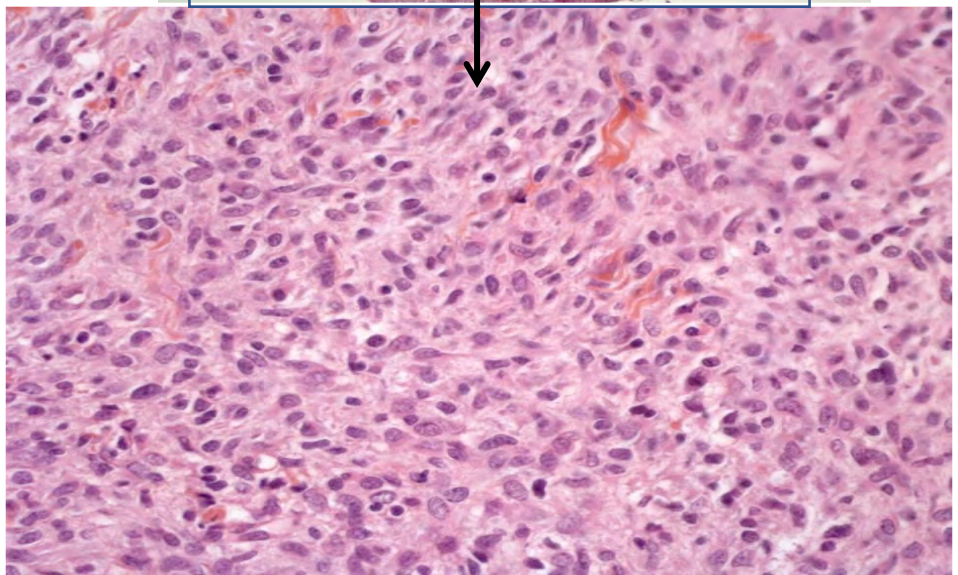


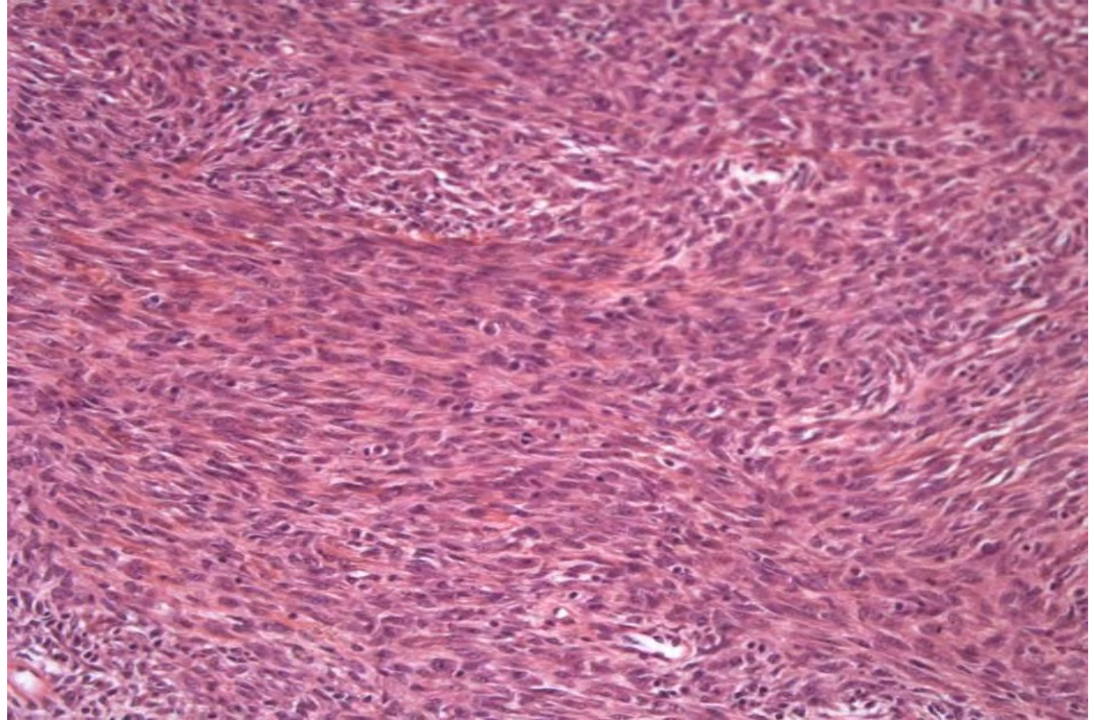
Dr C Eschard, Reims

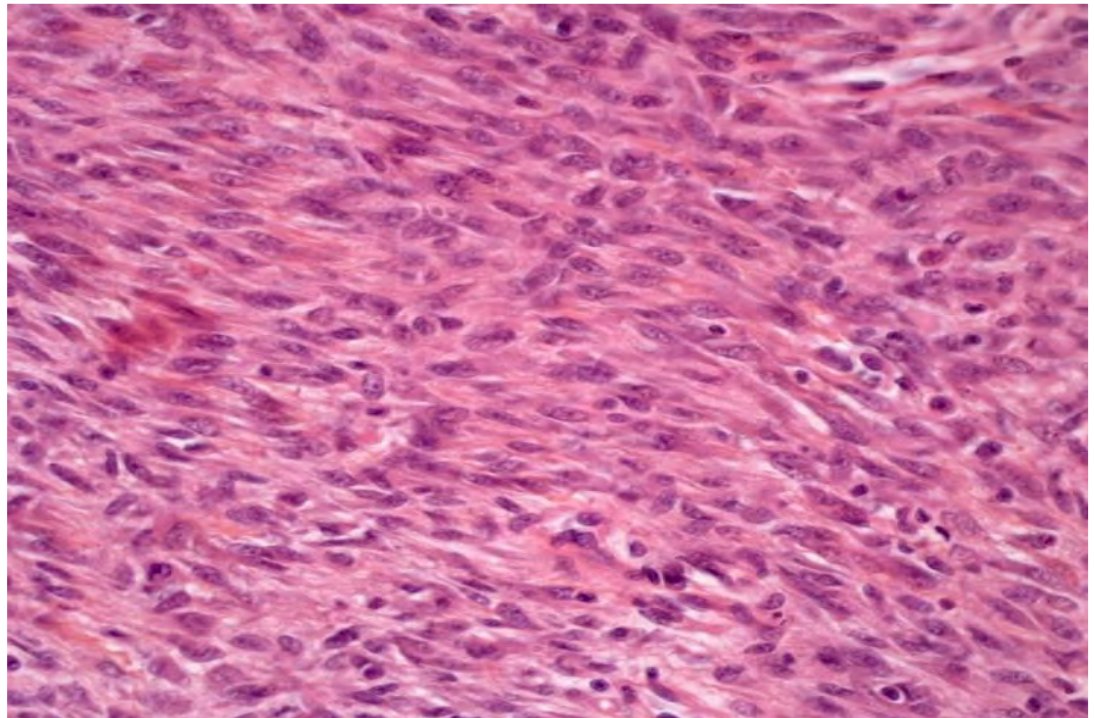
- Newborn. Deep mass on the cheek.
- RMI: infiltration of the fat but not the underlying muscle
- First fine needle biopsy: spindle cells. Sarcoma, fibromatosis ?

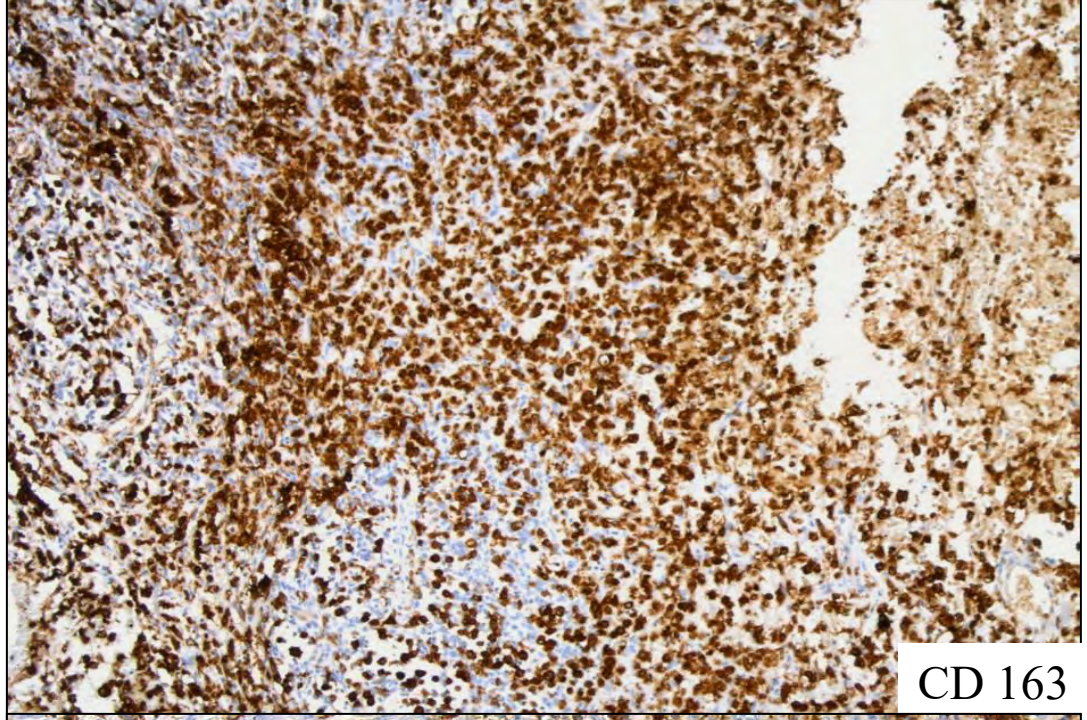




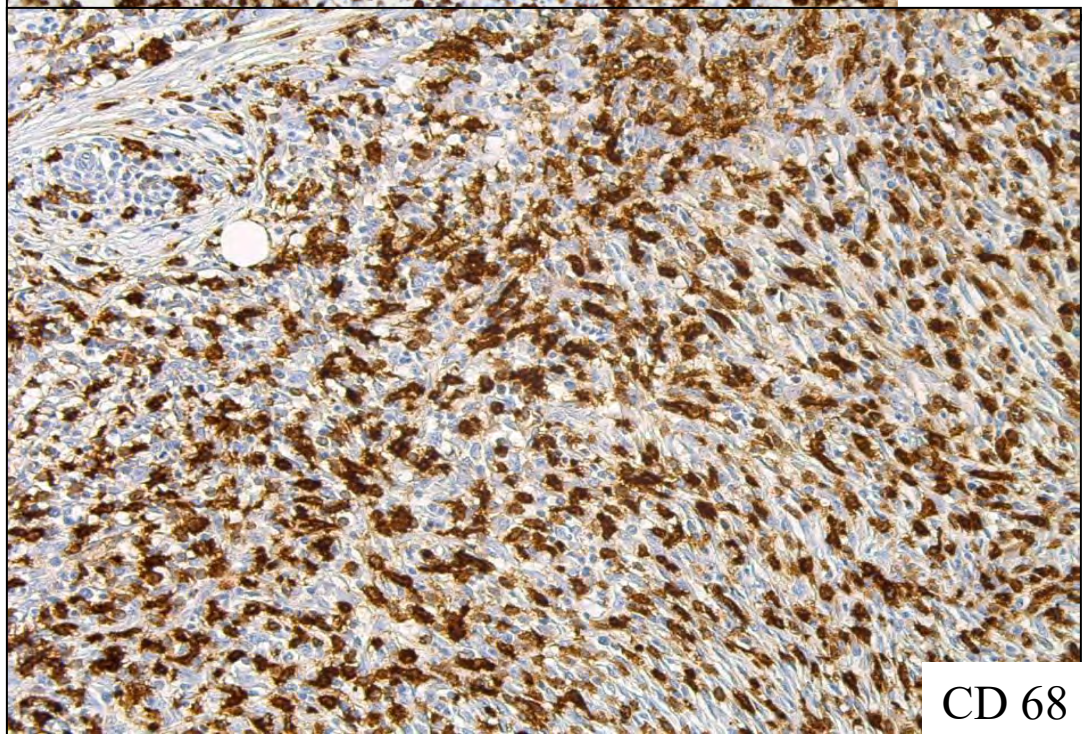




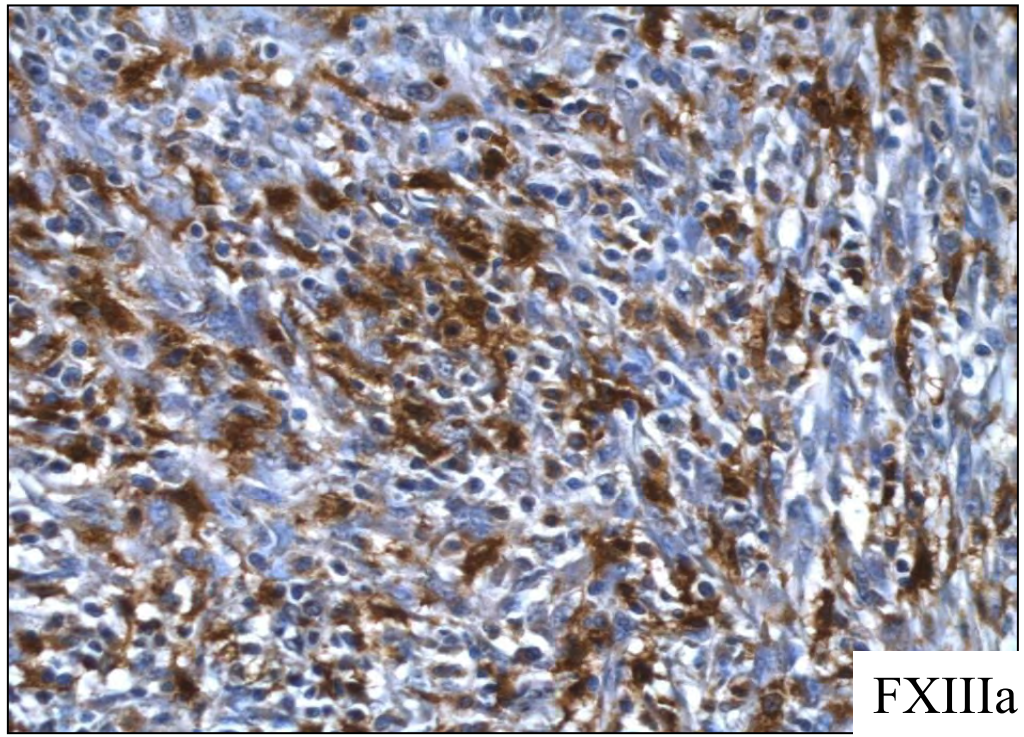




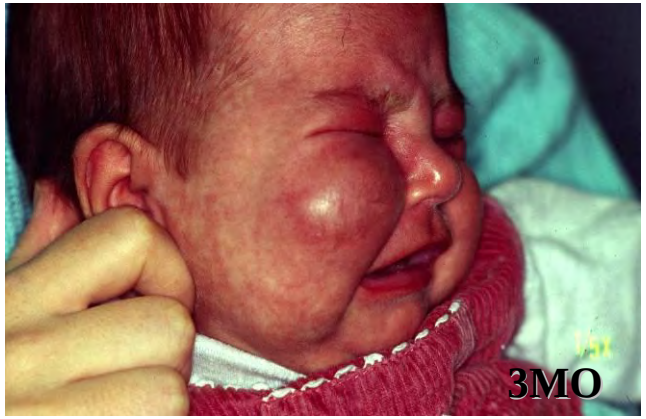
CD 163

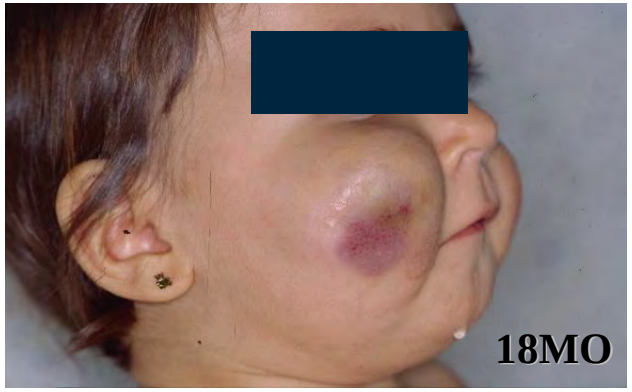


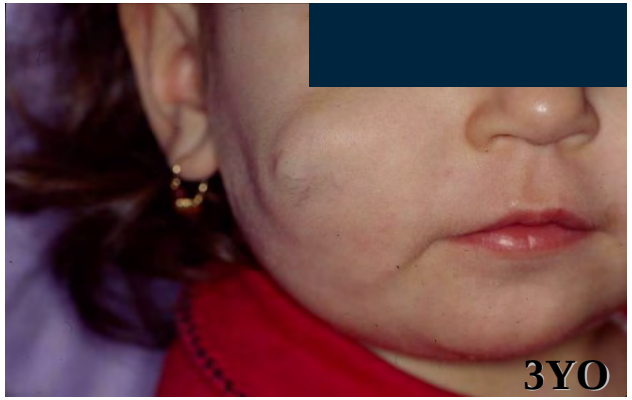
CD 68

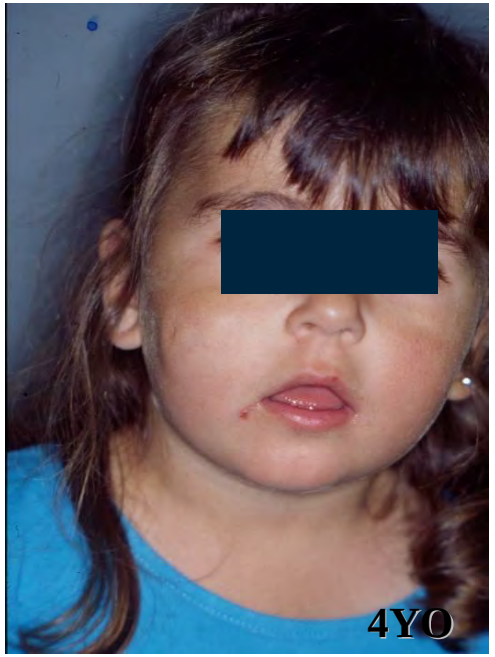


FXIIIa



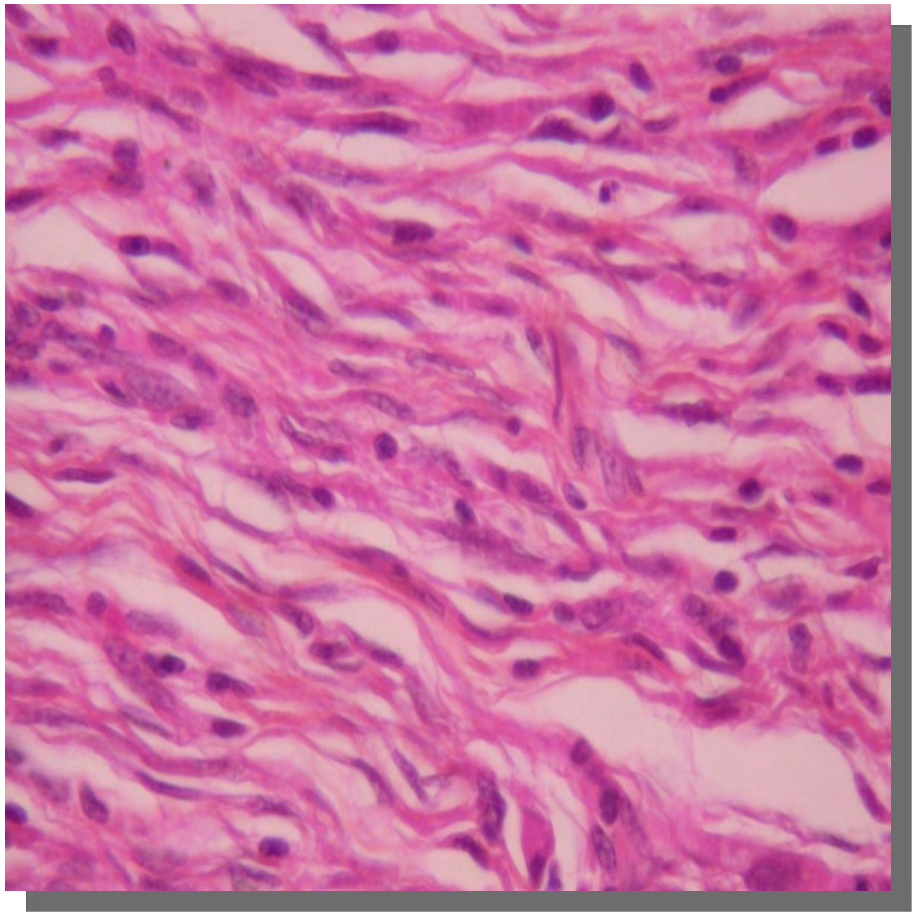






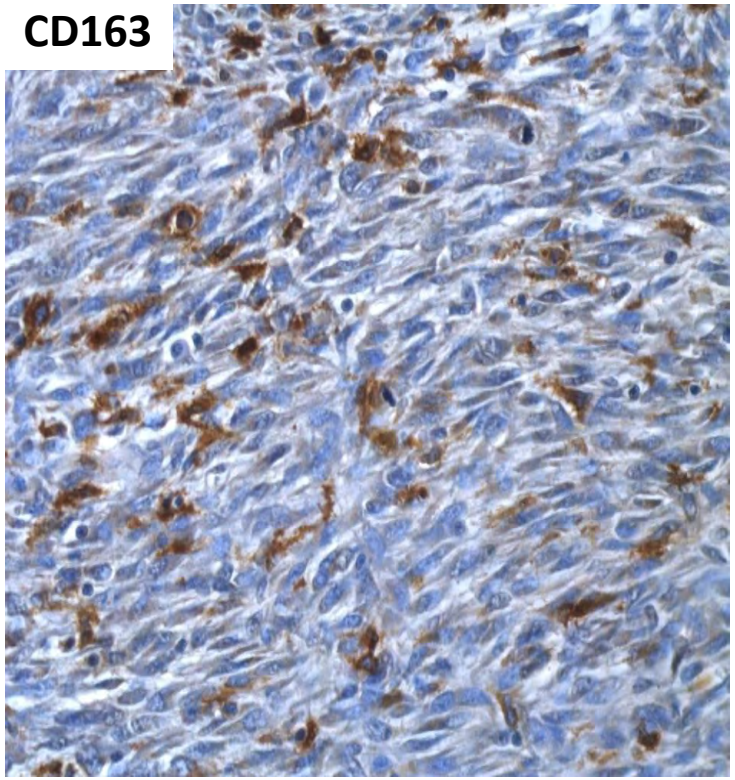
Early tumoral
juvenile xanthogranuloma
with spindle-shaped cells

JXG with **spindle-shaped cells!**



Misleading!!

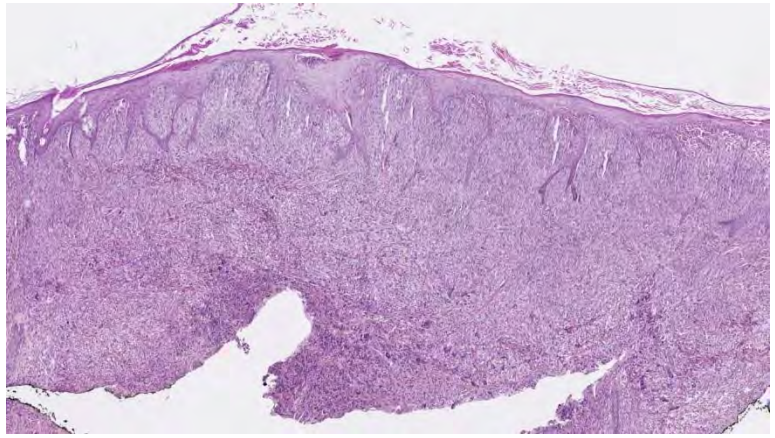
CD163



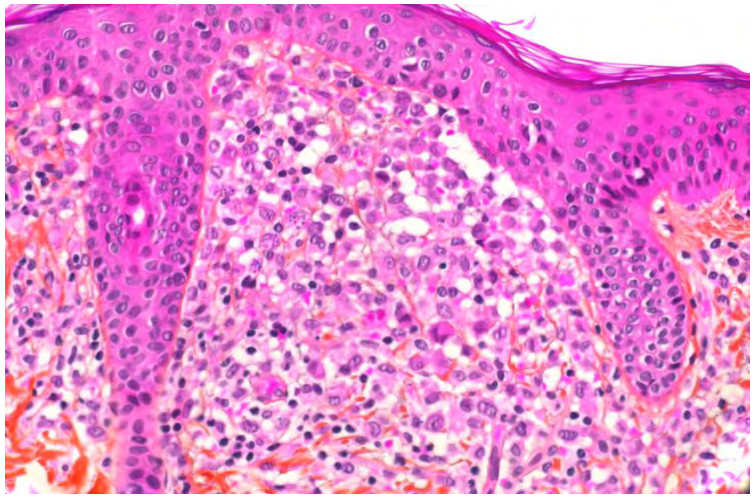
- Spindle cell tumour

Histiocytic infiltrate

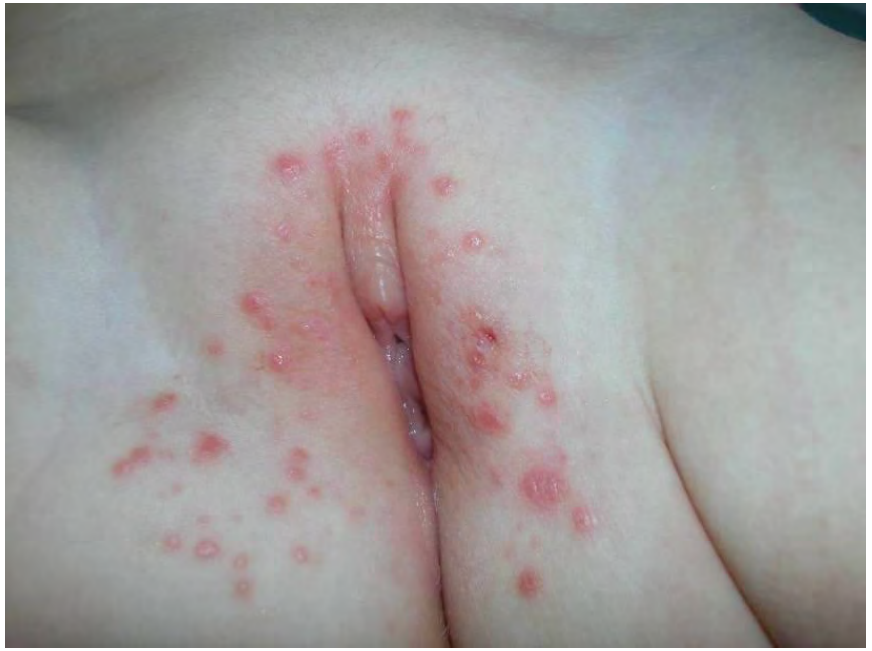
CD1a negative histiocytic infiltrate



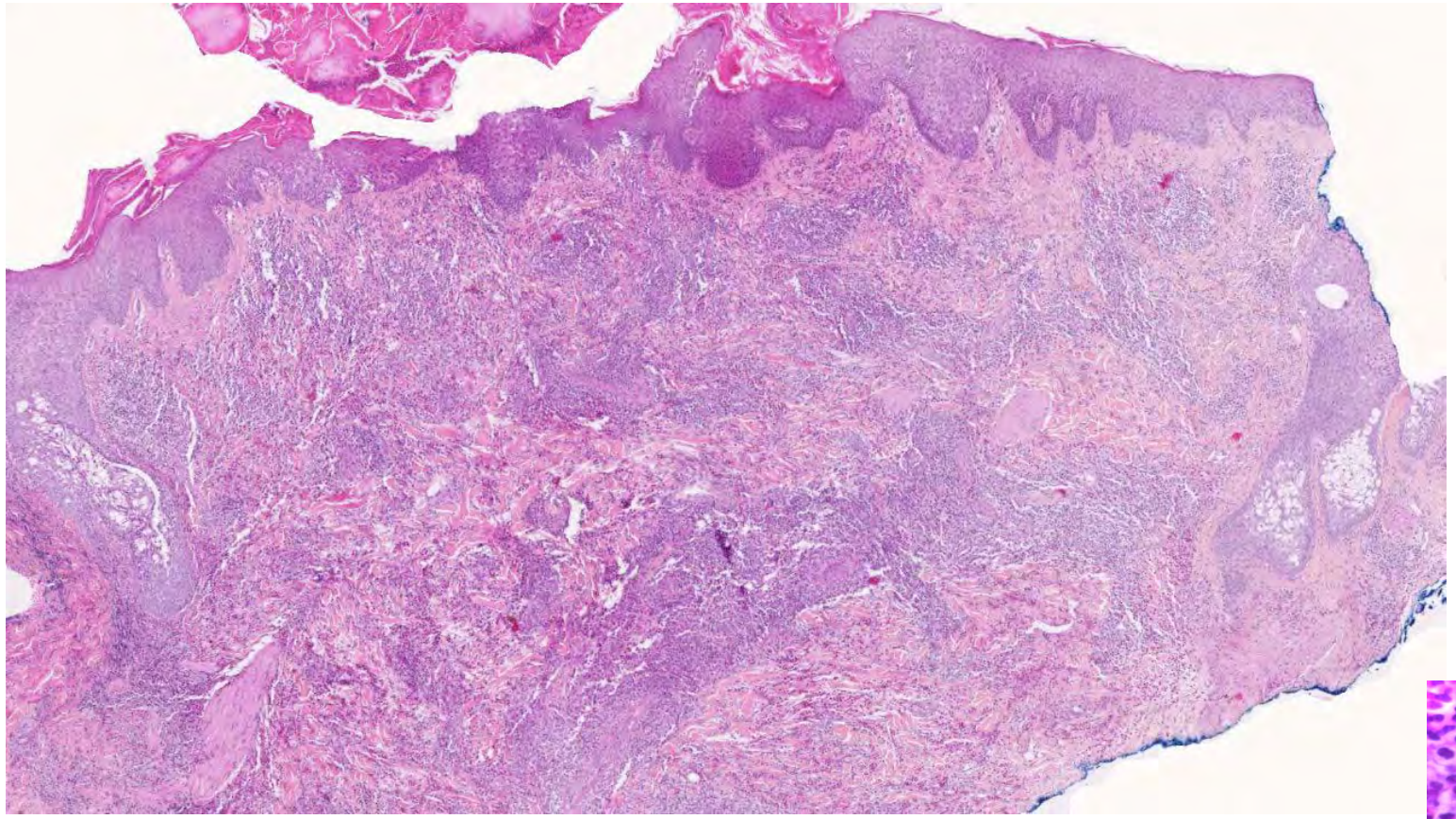
CD1a positive histiocytic infiltrate

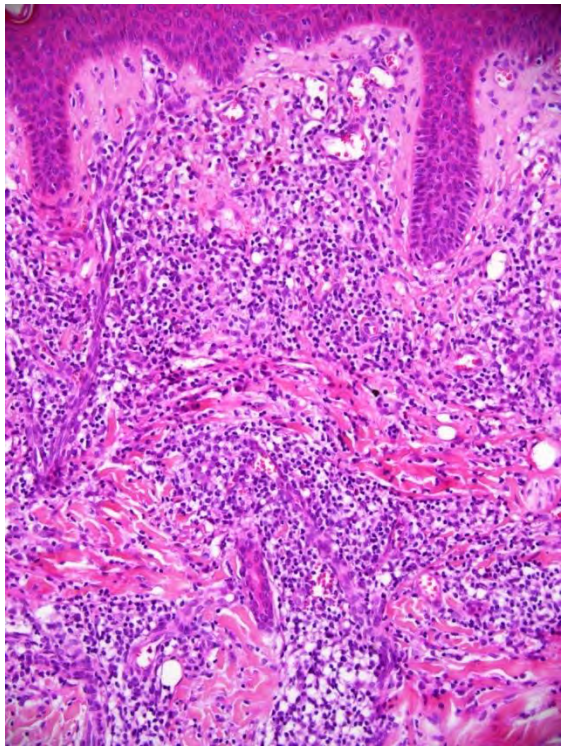


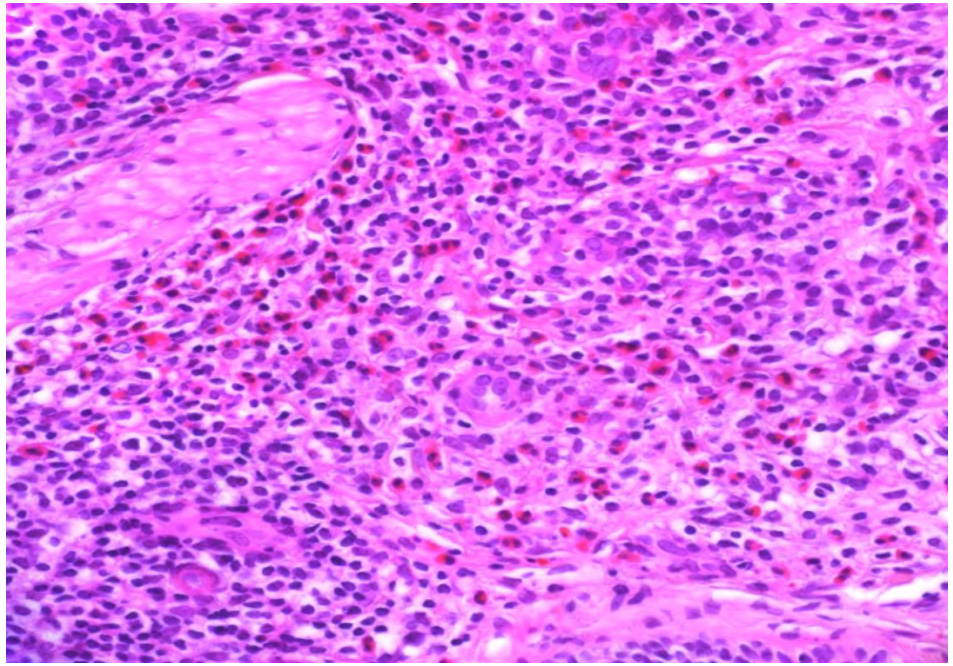
Quiz



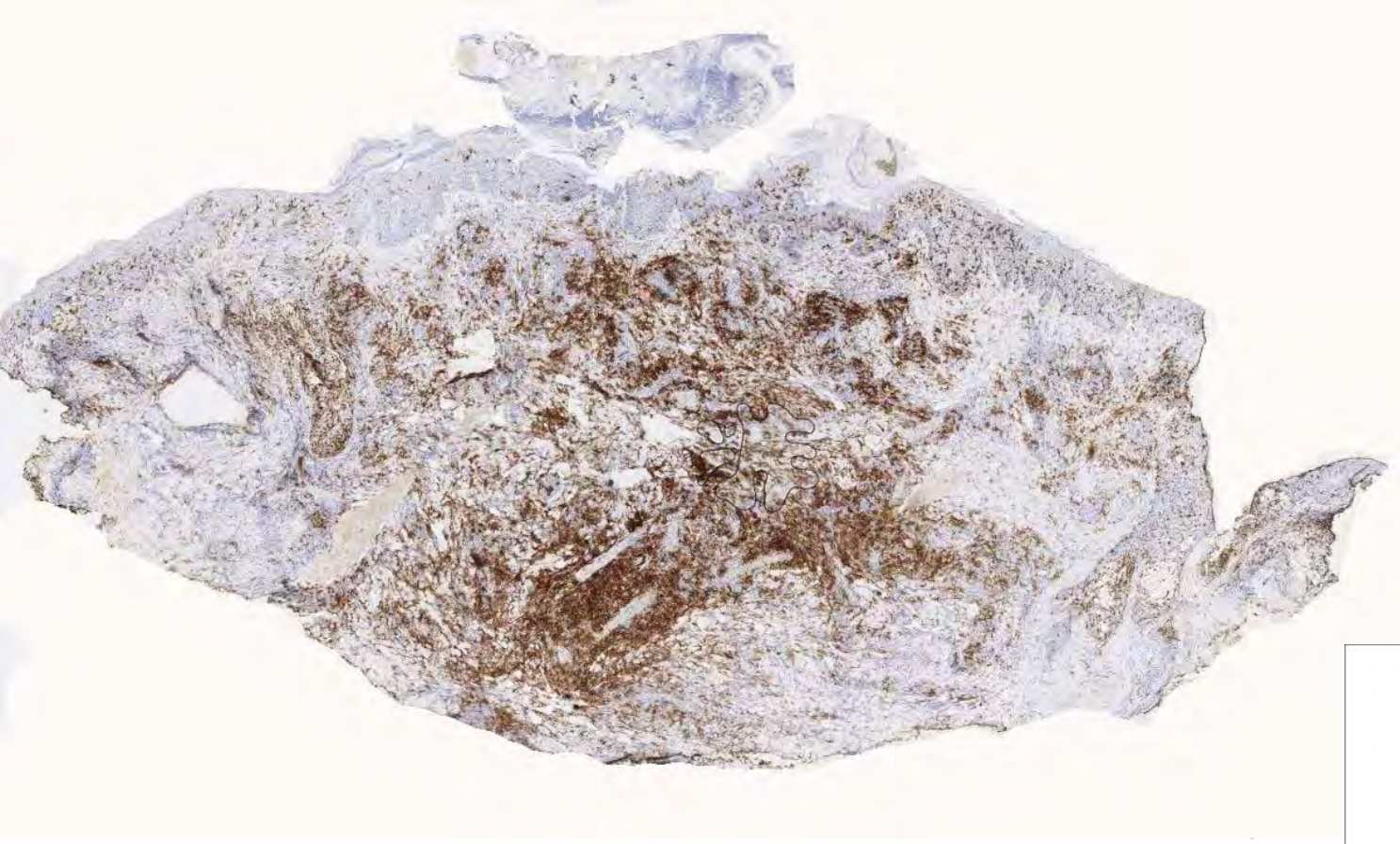
- 3 YO girl
- Slightly itchy papular lesions in the vulvar area
- Langerhans cell histiocytosis?



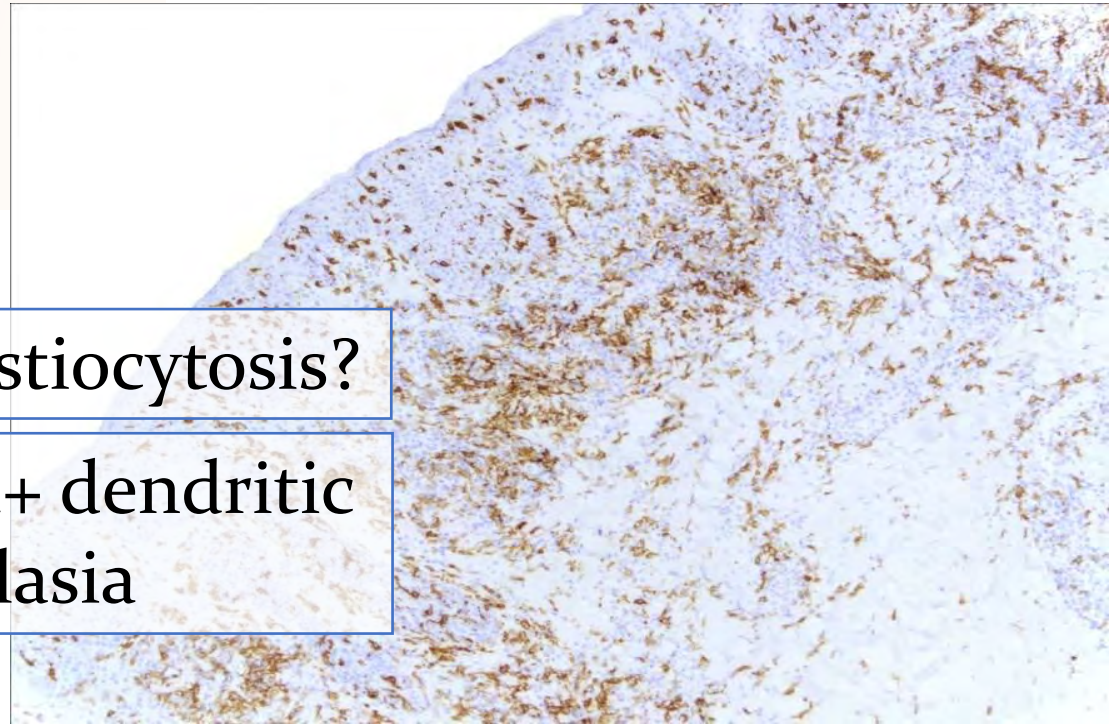




- Epidermal hyperplasia
- Peri-vascular and interstitial infiltrate
- Lymphocytes, histiocytes and eosinophils



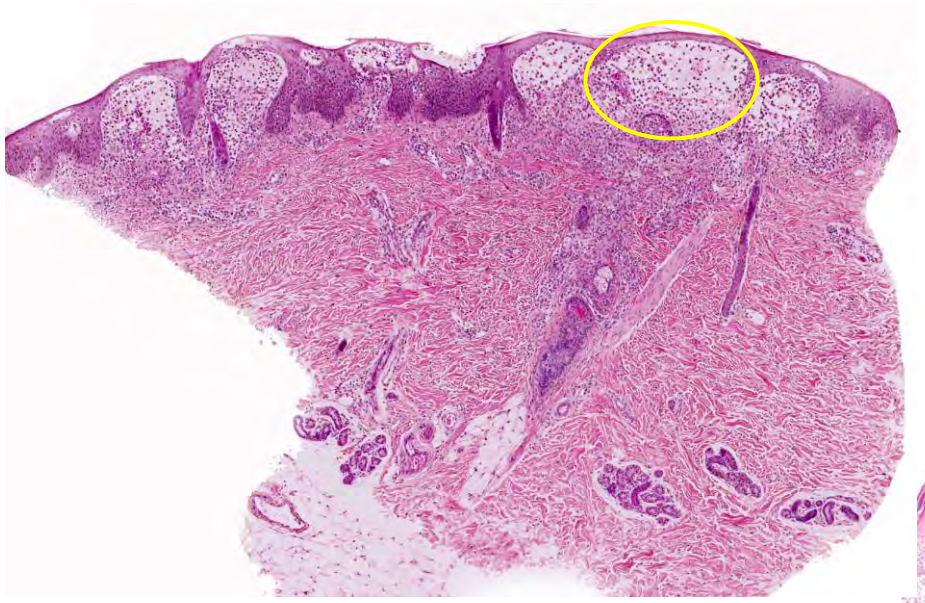
CD1a

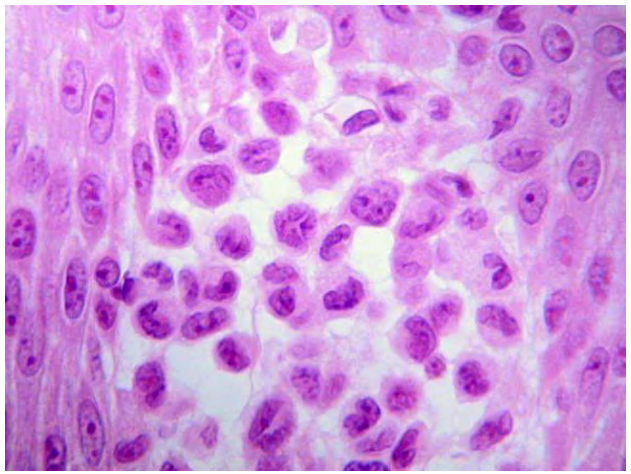


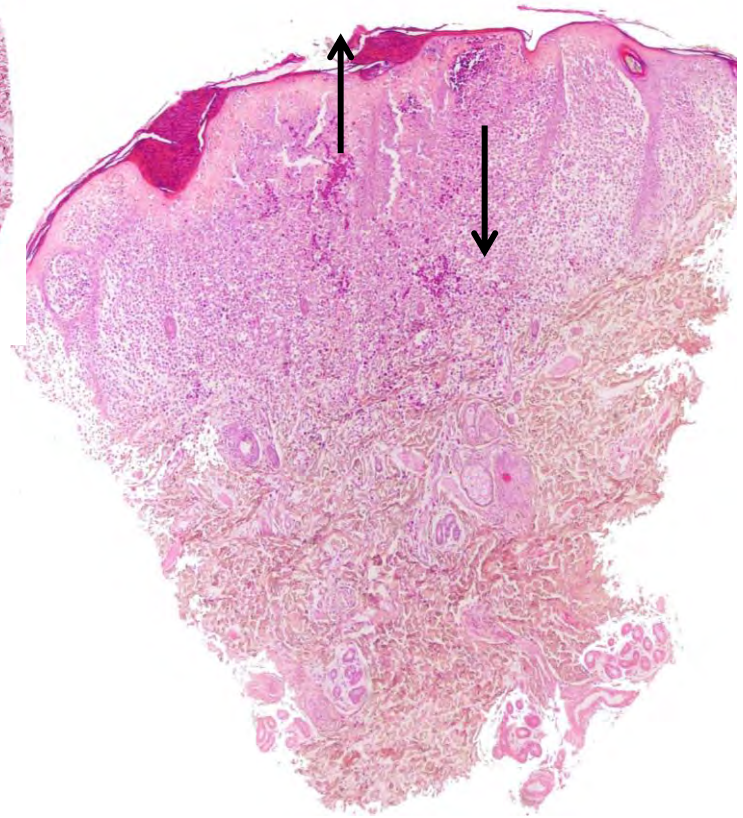
Langerhans cell histiocytosis?

Prurigo with CD1a+ dendritic cell hyperplasia

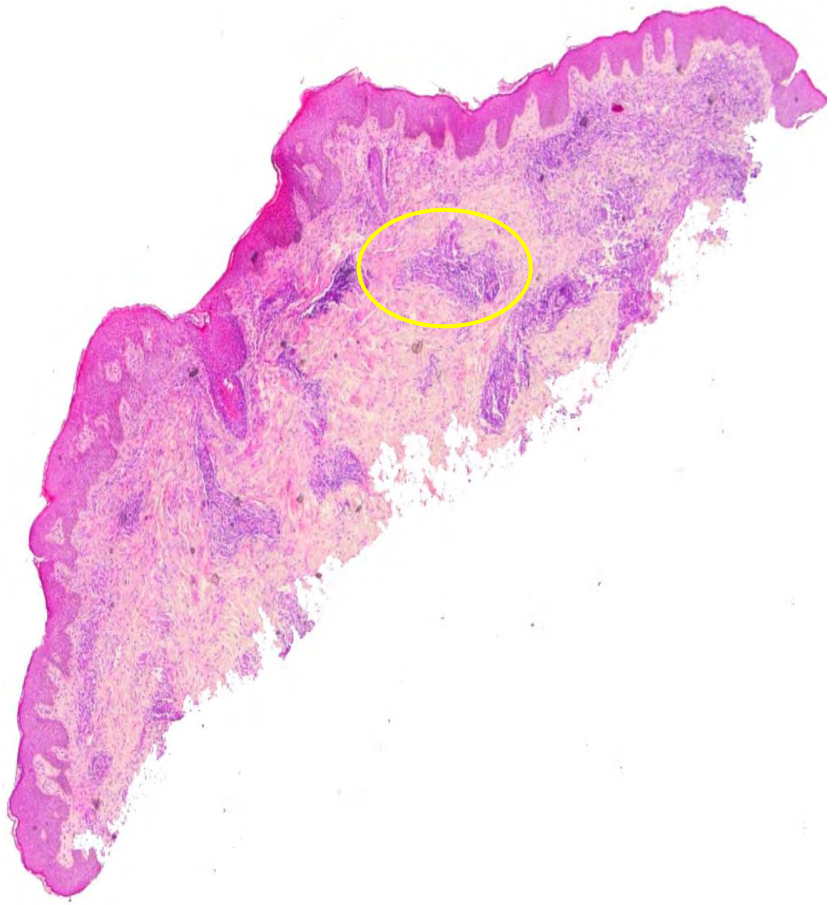
CD1a dendritic cell hyperplasia ≠ Langerhans cell histiocytosis







LCH



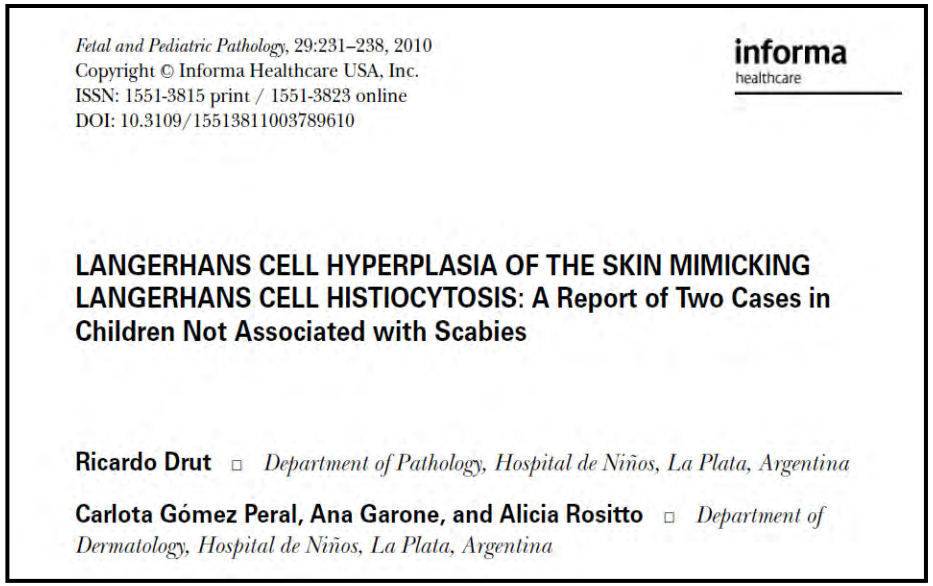
CD1a dendritic cell hyperplasia

« Langerhans cell » hyperplasia

- Arthropod bite reactions (scabies)/ prurigo
- Regressive lesions (warts, molluscum contagiosums….)
- Spongiotic dermatoses (atopic dermatitis, contact…)
- Erythematous-squamous diseases (psoriasis, pityriasis lichenoïdes)
- Interface dermatitis (lichen, erythema multiforme..)
- Regressive melanocytic nevi
- Lymphoproliferative disorders
- Stroma of various tumors

Pitfall !

Clinico-pathological correlations !



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informa
healthcare

LANGERHANS CELL HYPERPLASIA OF THE SKIN MIMICKING LANGERHANS CELL HISTIOCYTOSIS: A Report of Two Cases in Children Not Associated with Scabies

Ricardo Drut □ *Department of Pathology, Hospital de Niños, La Plata, Argentina*

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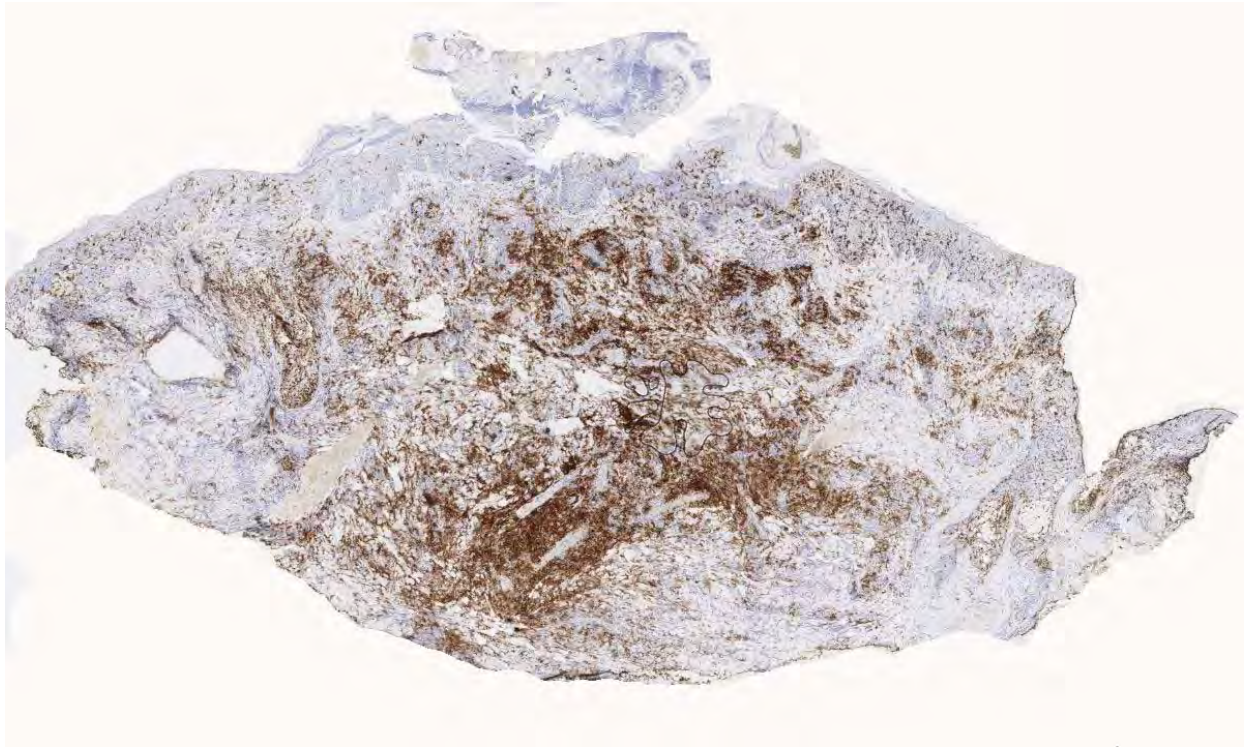
« ~~Langerhans cell hyperplasia~~ »
= CD1a+ dendritic cell hyperplasia

CD1a

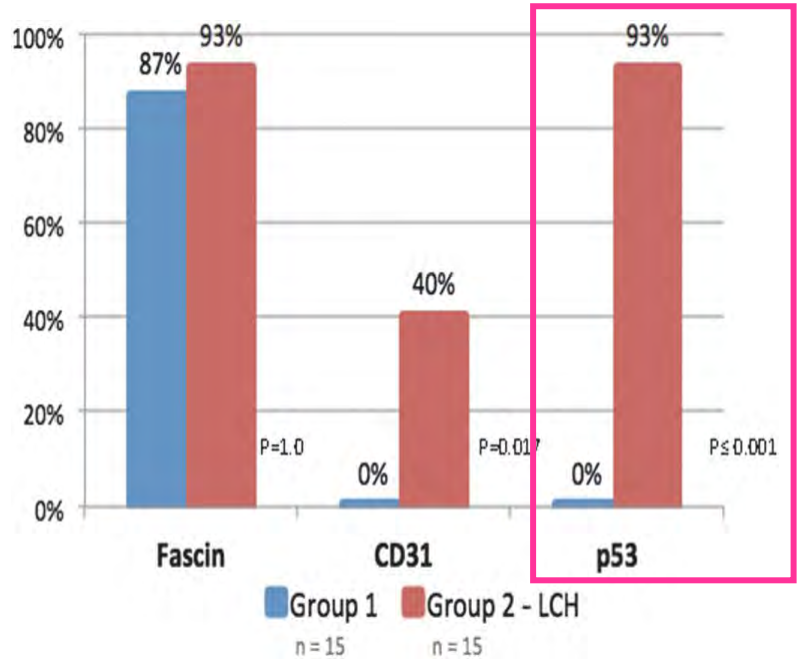


CD207 (Langerin)

p53 Is a Helpful Marker in Distinguishing Langerhans Cell Histiocytosis From Langerhans Cell Hyperplasia

Shane A. Grace, BS, Angela M. Sutton, DO,† Eric S. Armbrecht, PhD,‡ Claudia I. Vidal, MD, PhD,† Ilana S. Rosman, MD,§ and Maria Y. Hurley, MD†*

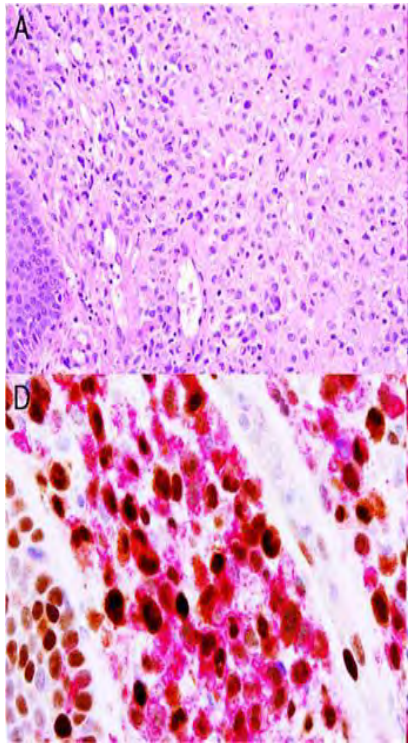
Am J Dermatopathol 2017; 39(10):726-730

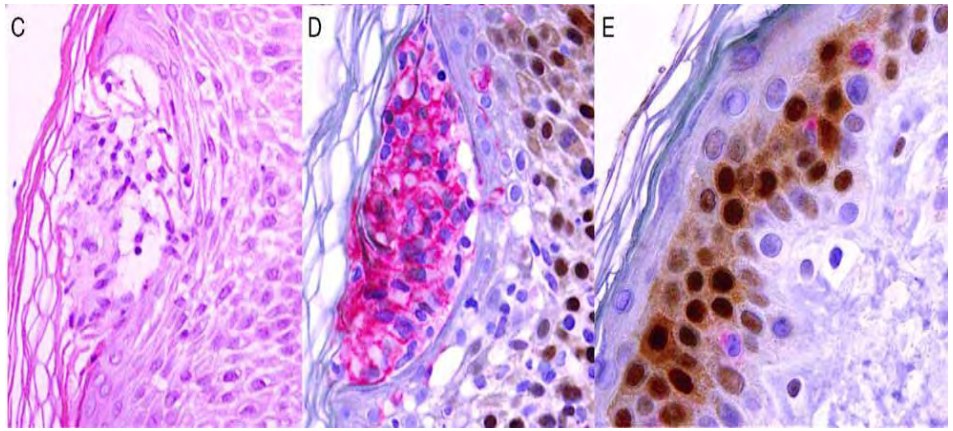


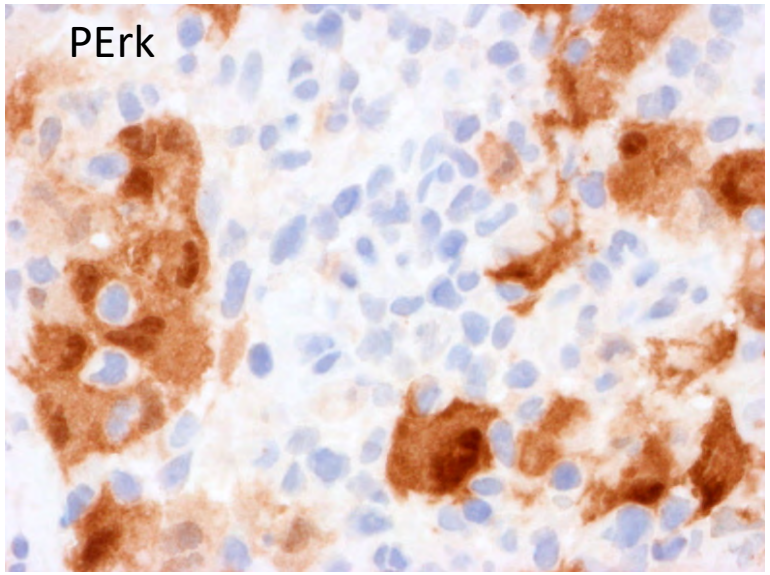
Cyclin D1 Is Expressed in Neoplastic Cells of Langerhans Cell Histiocytosis but Not Reactive Langerhans Cell Proliferations

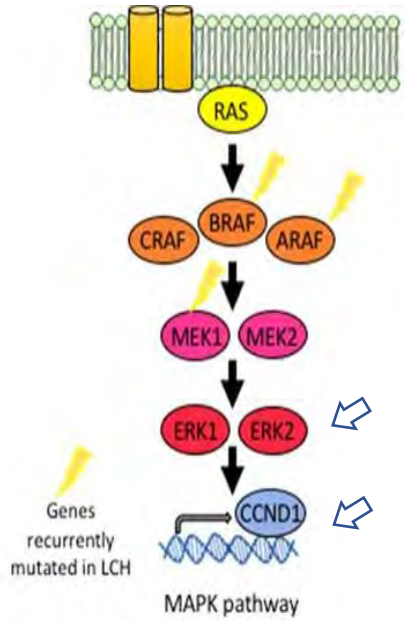
Vignesh Shanmugam, MD, Jeffrey W. Craig, MD, PhD, Jason L. Hornick, MD, PhD, Elizabeth A. Morgan, MD, Geraldine S. Pinkus, MD, and Olga Pozdnyakova, MD, PhD

Am J Surg Pathol 2017; 41:1390-1396



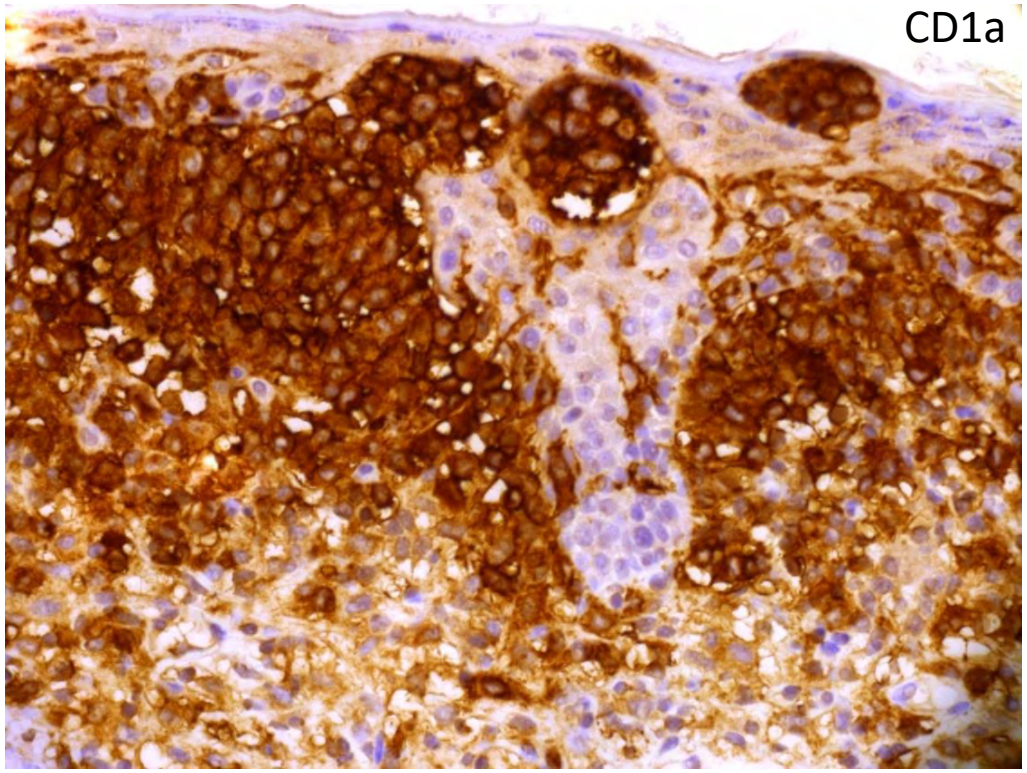


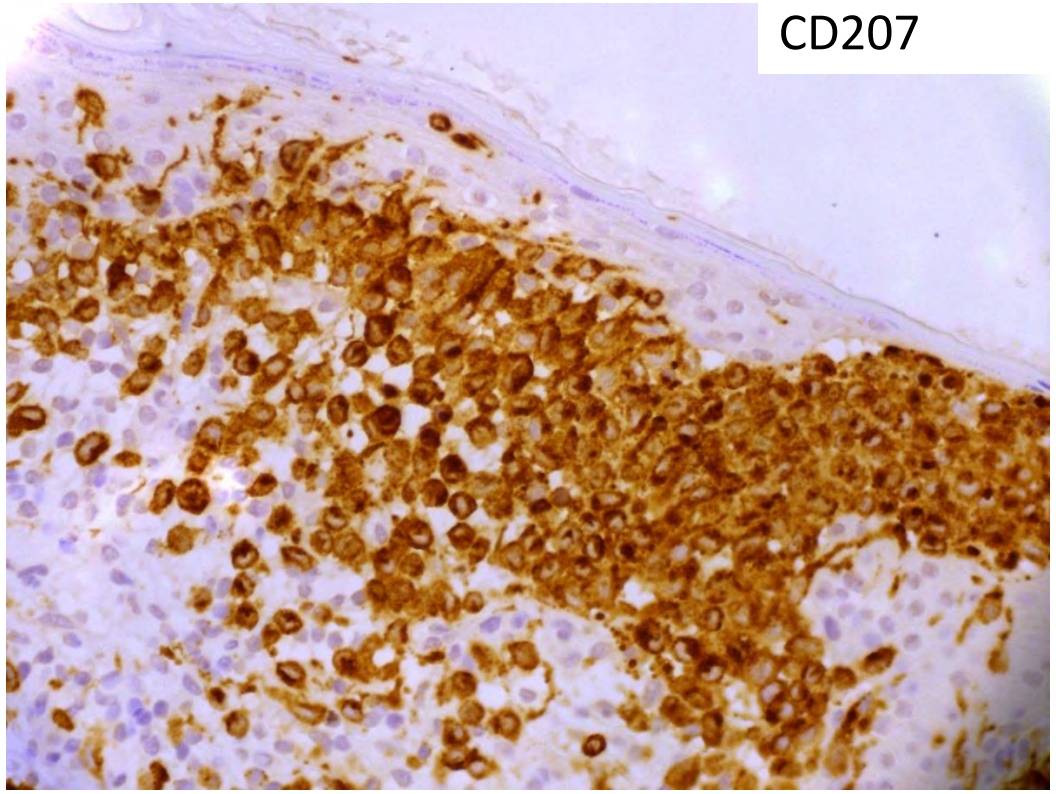




Fraitag S, Emile JF. Cutaneous histiocytoses in children. Histopathology. 2022 Jan;80(1):196-215.

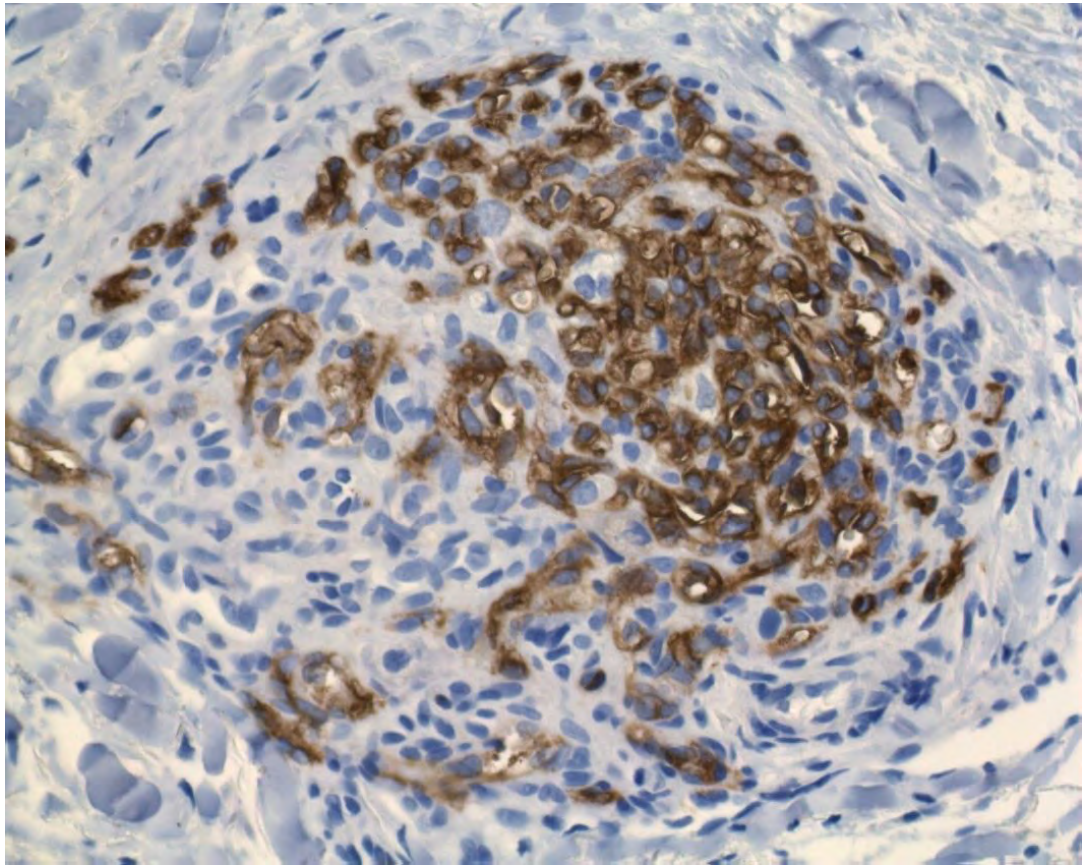
- **Langerin (anti-CD207):** very sensible and specific for Birbeck granules





LCH

Vascular anomalies



D2-40

2018

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ISSVA

Appendix 4

vascular anomalies

possibly associated with platelet count / coagulation disorders

Type Alt ← for previous view

Anomalies	Hematological disorders
Tufted angioma Kaposiform hemangioendothelioma	Profound and sustained thrombocytopenia with profound hypofibrinogenemia, consumptive coagulopathy and elevated D-dimer (Kasabach-Merritt phenomenon)
Rapidly involuting congenital hemangioma	Transient mild/moderate thrombocytopenia, +/- consumptive coagulopathy and elevated D-dimer
Venous malformations / Lymphatic-venous malformations	Chronic localized intravascular coagulopathy with elevated D-dimer, +/- hypofibrinogenemia, and +/- moderate thrombocytopenia (may progress to DIC after trauma or operation)
Lymphatic malformations	Chronic localized intravascular coagulopathy with elevated D-dimer and +/- mild to moderate thrombocytopenia *(consider Kaposiform lymphangiomatosis)* (may progress to DIC after trauma or operation)
Multifocal lymphangioendotheliomatosis with thrombocytopenia / Cutaneovisceral angiomatosis with thrombocytopenia	Sustained, fluctuating, moderate to profound thrombocytopenia with gastrointestinal tract bleeding or pulmonary hemorrhage
Kaposiform lymphangiomatosis	Mild/moderate thrombocytopenia, +/-hypofibrinogenemia, and D-dimer elevation

Back to overview

Appendix 4
vascular anomalies
possibly associated with platelet count / coagulation disorders

Type Alt ← for previous view

Anomalies	Hematological disorders
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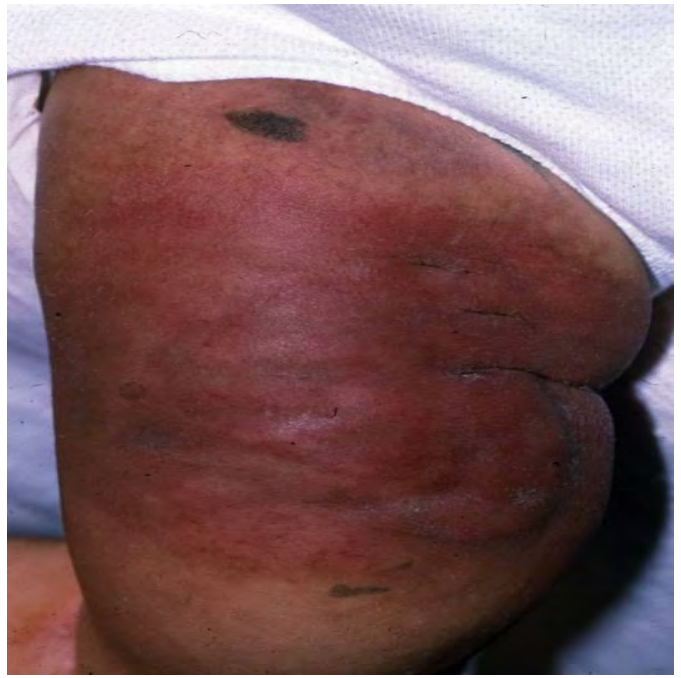
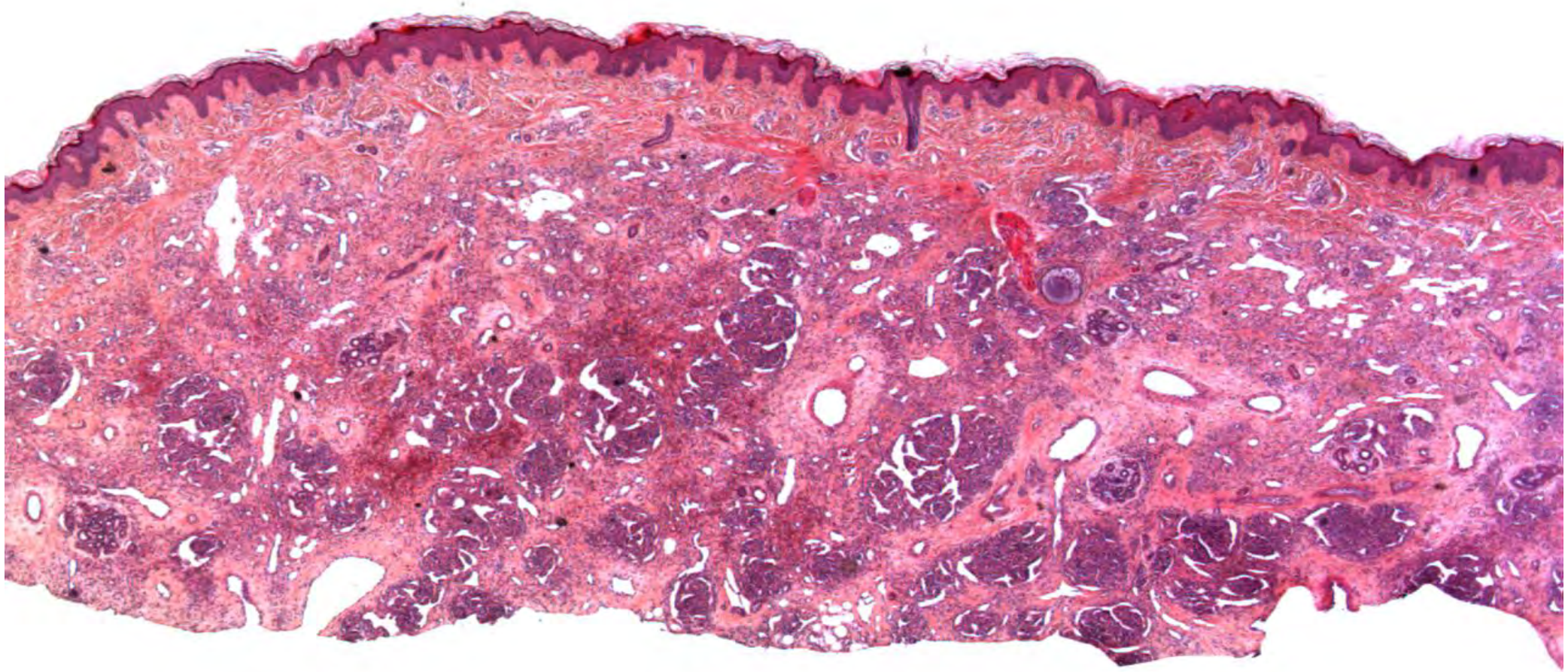
Kaposiform lymphangiomatosis	Mild/moderate thrombocytopenia, +/-hypofibrinogenemia, and D-dimer elevation

Clinical history

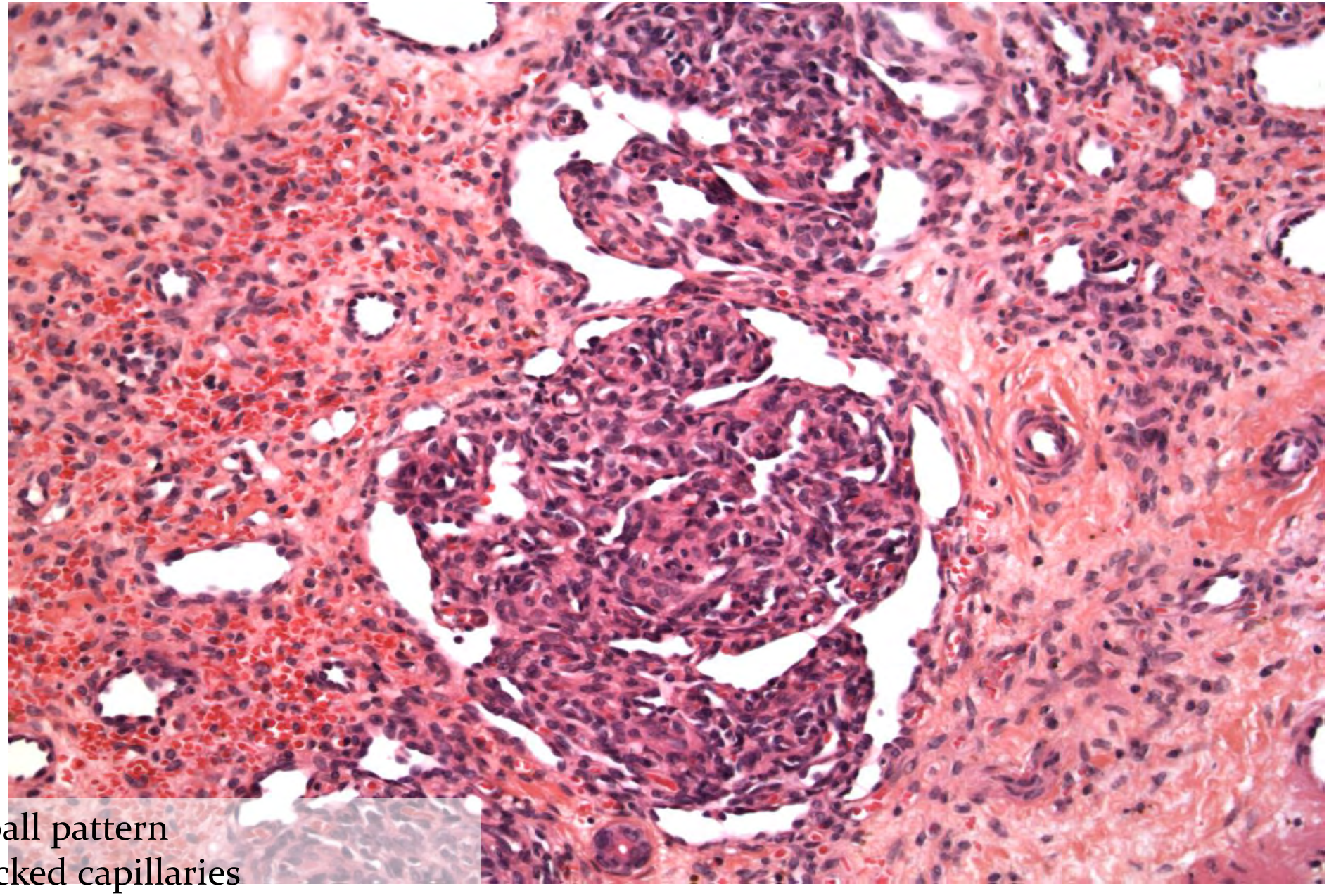
- 2-month-old male infant
- Violaceous lesion of the right thigh
- **Severe trombocytopenia**, from 15 000 to 30 000/mm3
- Hypofibrinogenemia (0,5 à 1 g/l)
- Two biopsies



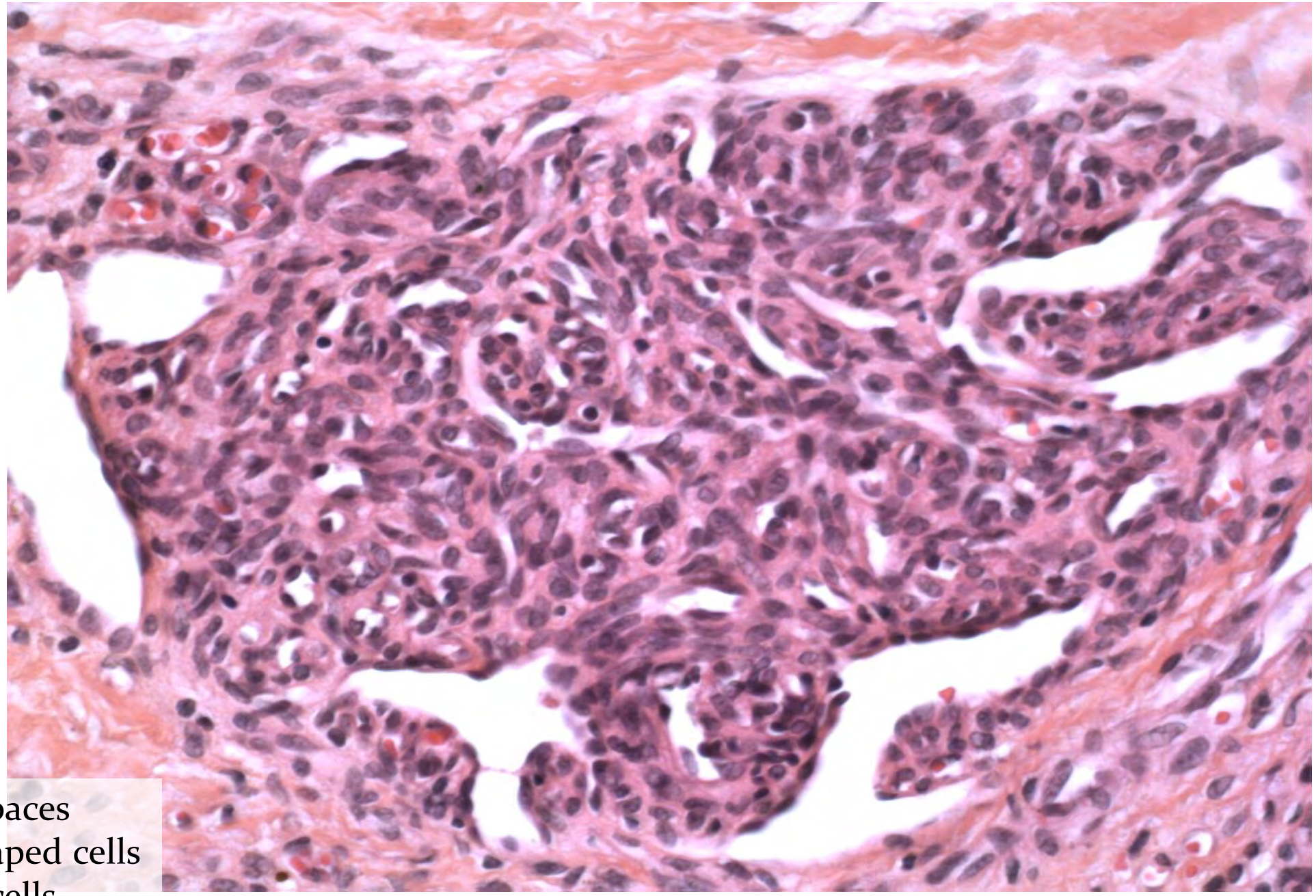
First biopsy



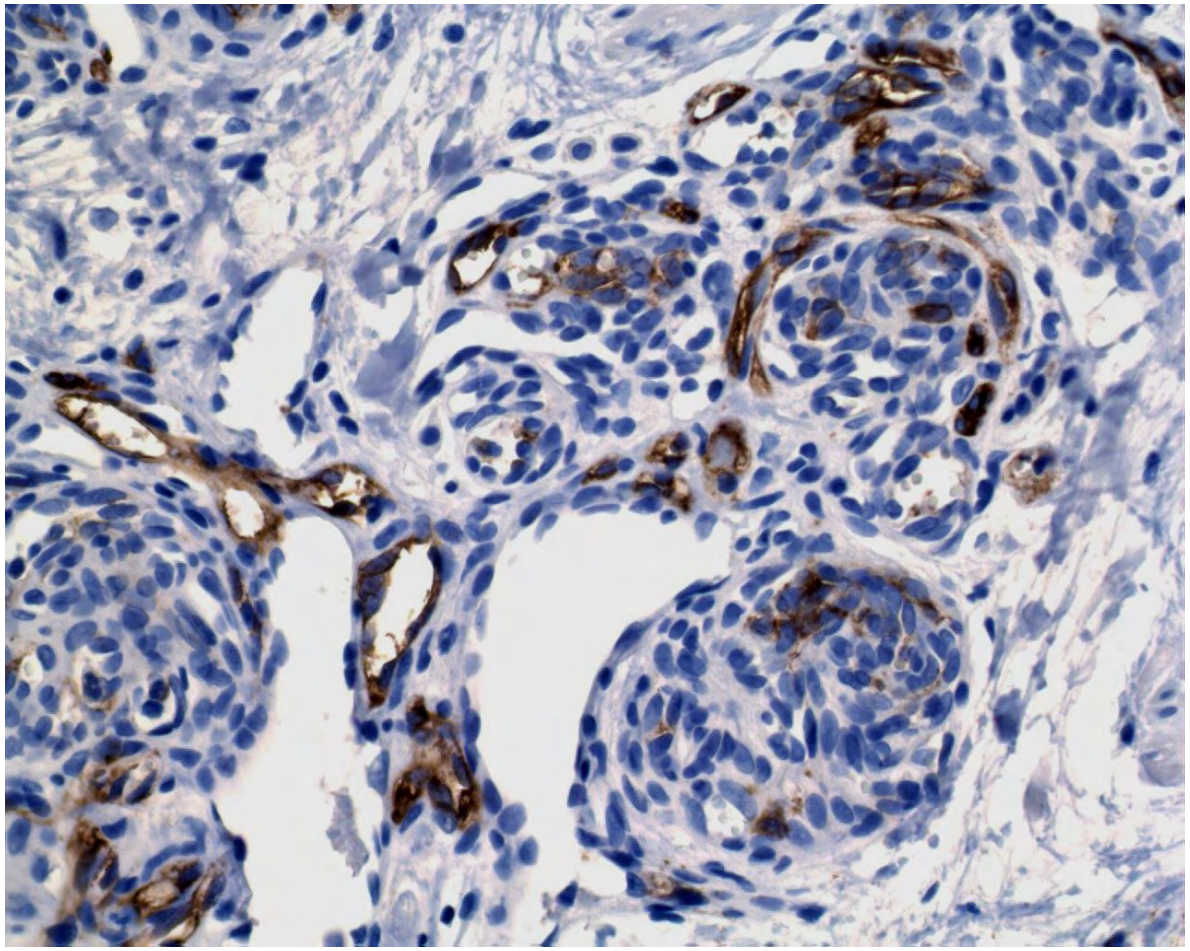
•Sharply circumscribed small lobules
•Thin-walled large vessels



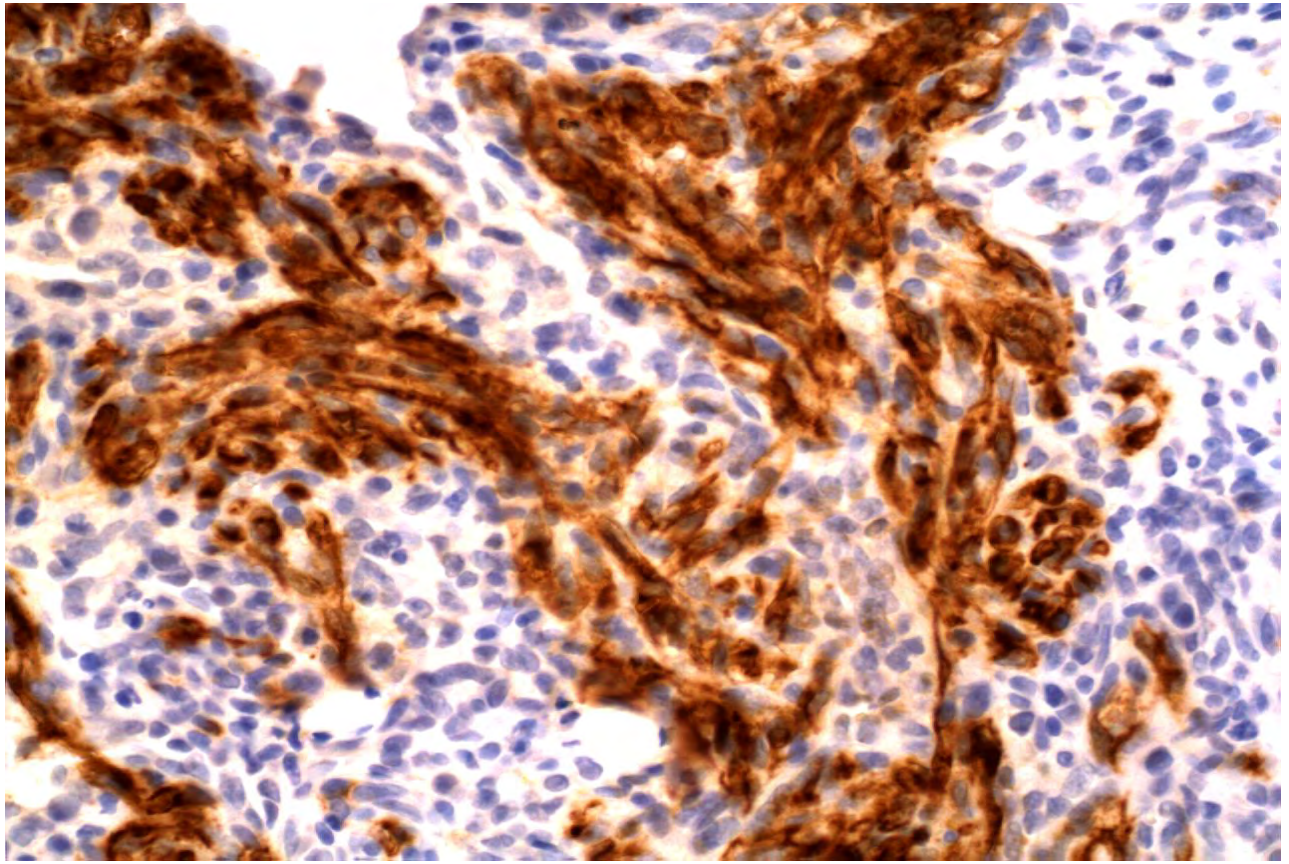
- Cannonball pattern
- Small packed capillaries
- Crescent-shaped vascular spaces



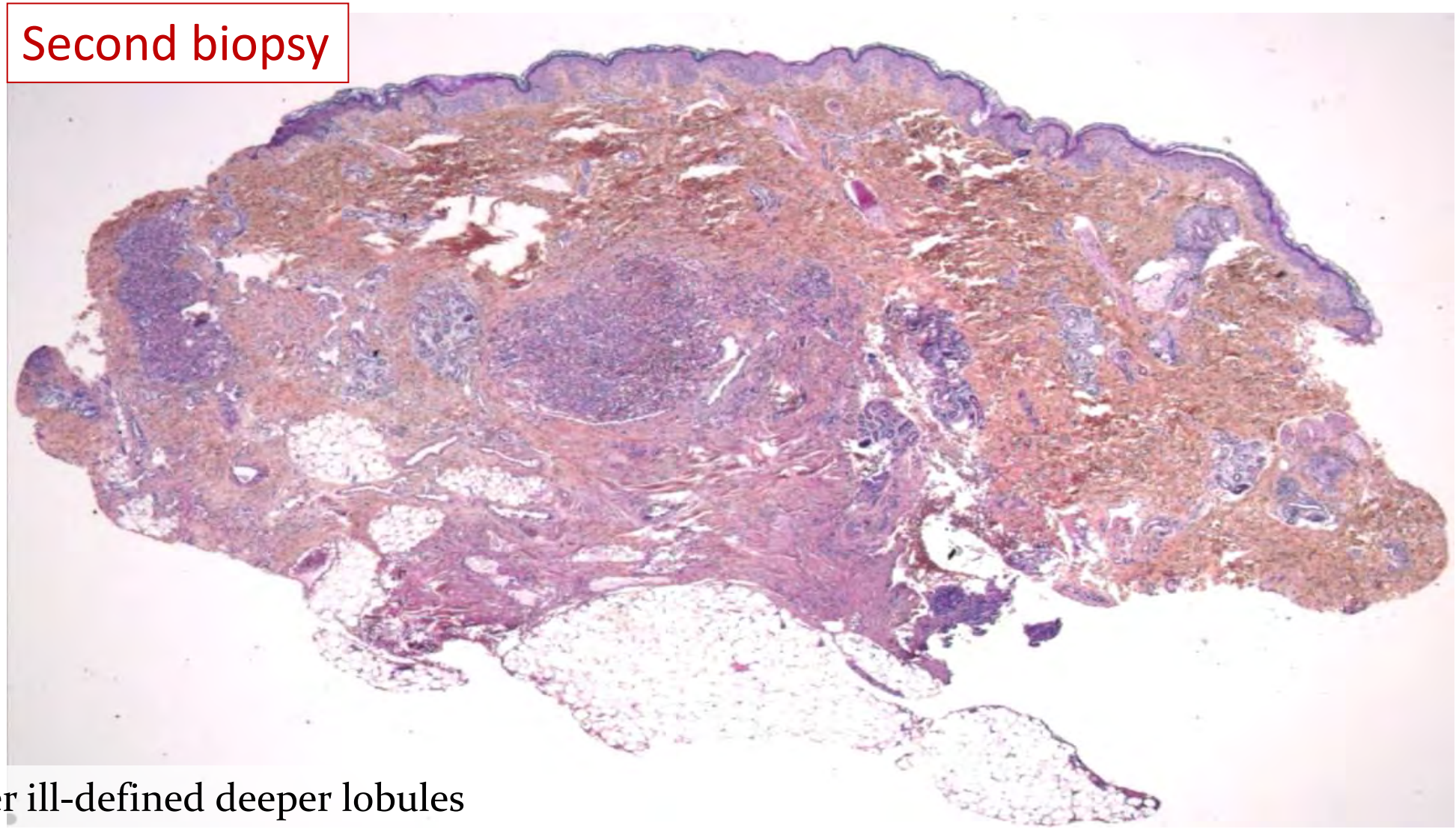
- Split-like spaces
- Spindle-shaped cells
- Red blood cells



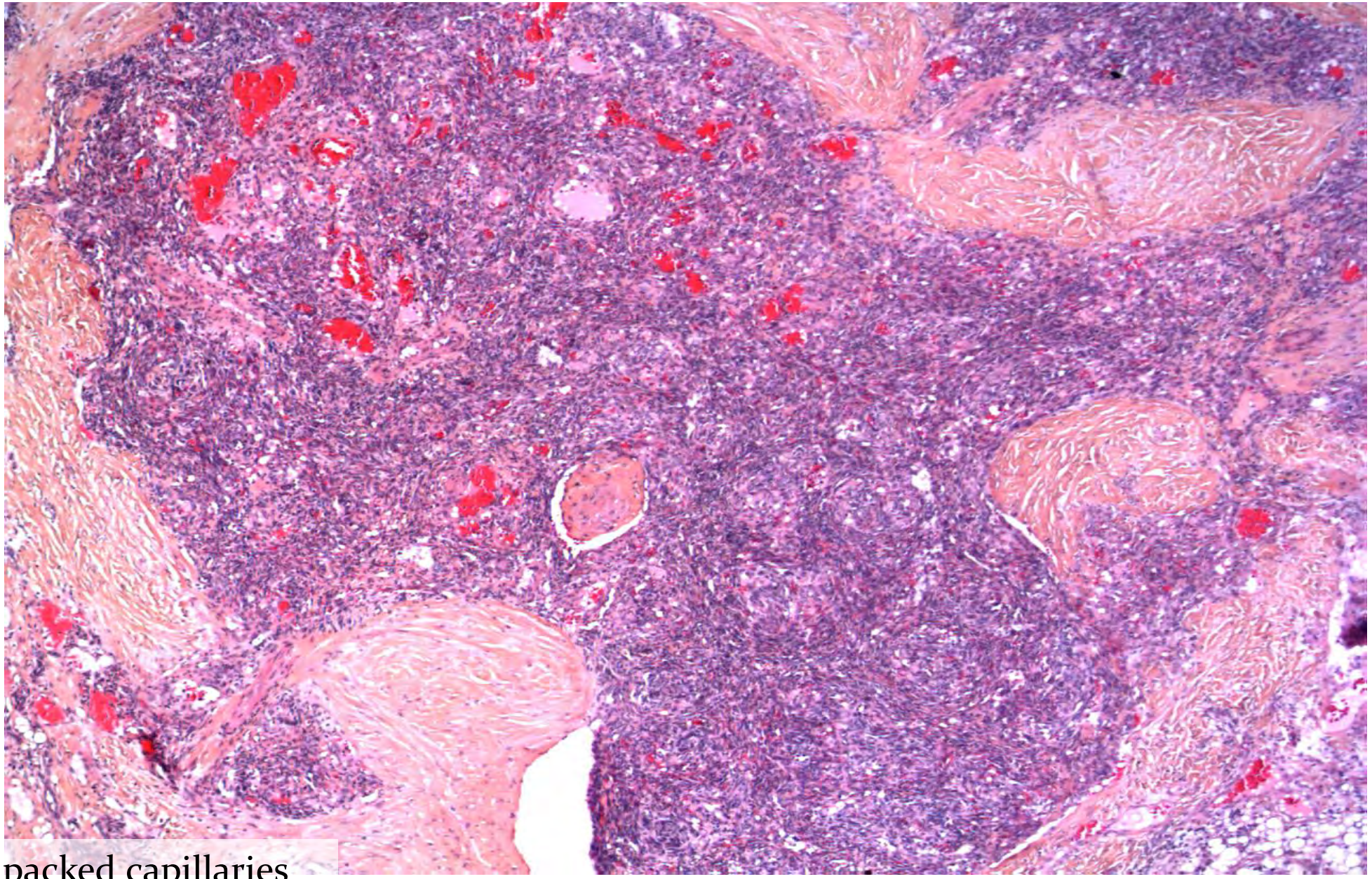
D2-40



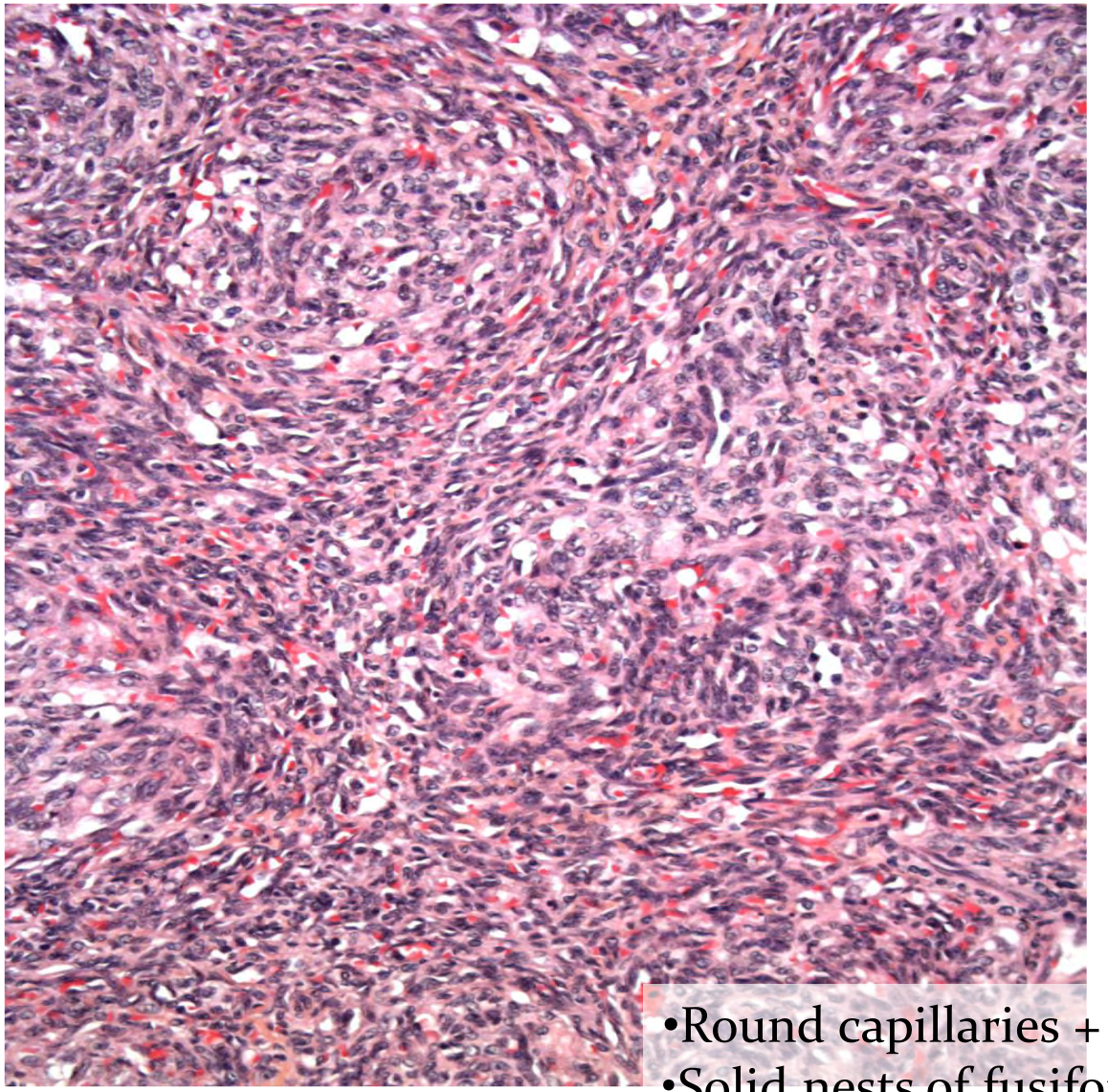
Second biopsy

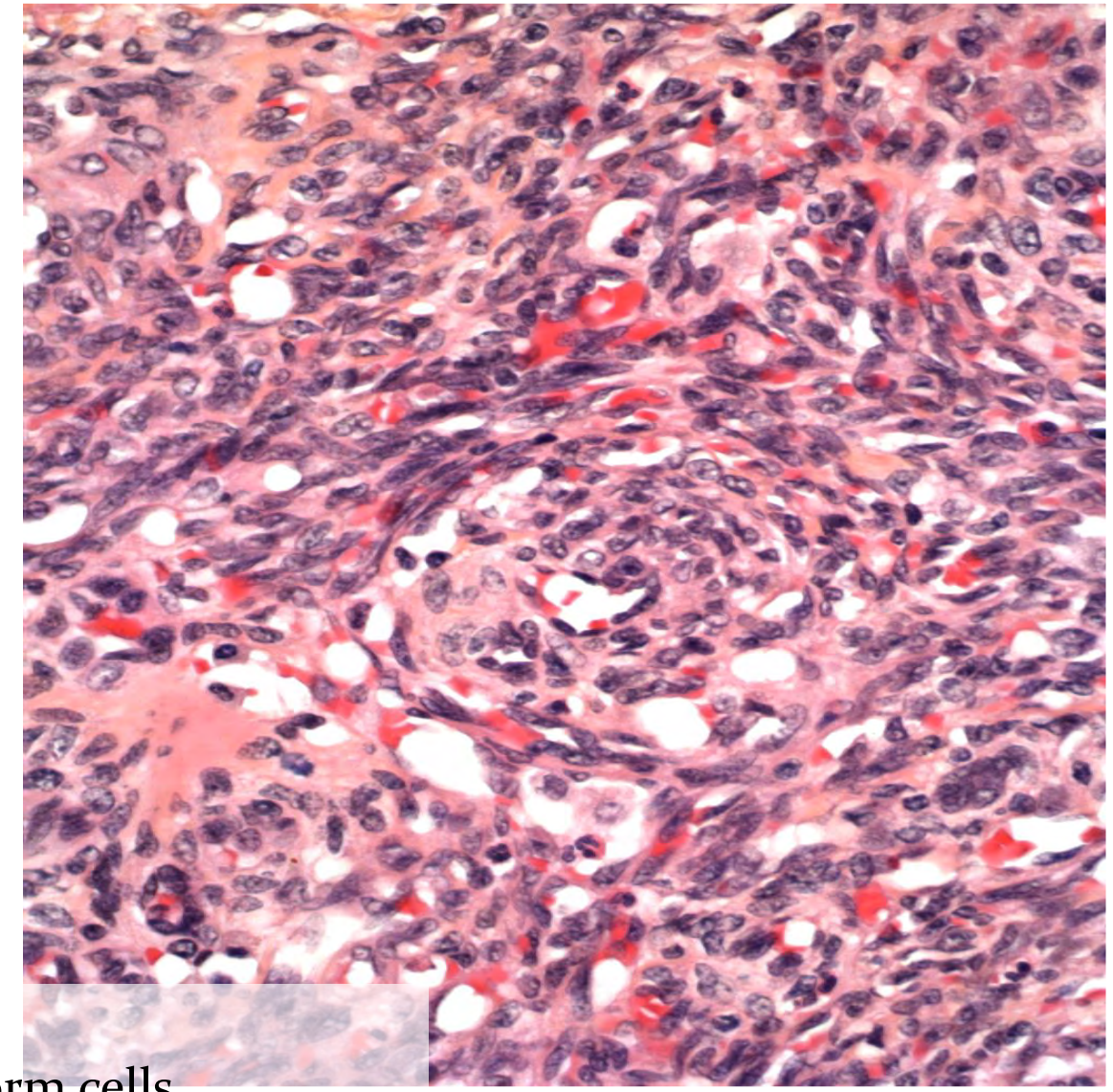


- Larger ill-defined deeper lobules
- Thin-walled large vessels

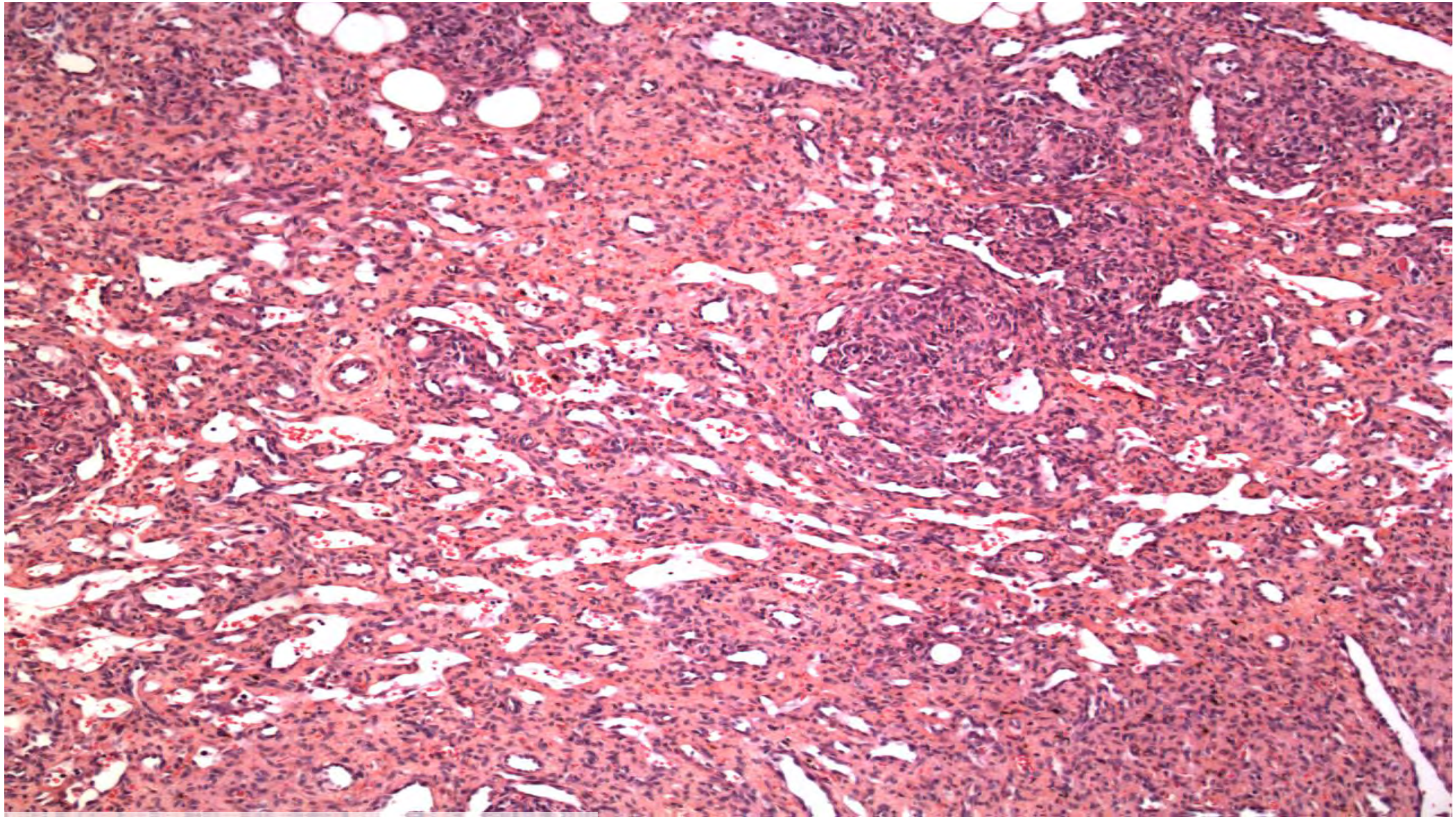


•Small packed capillaries



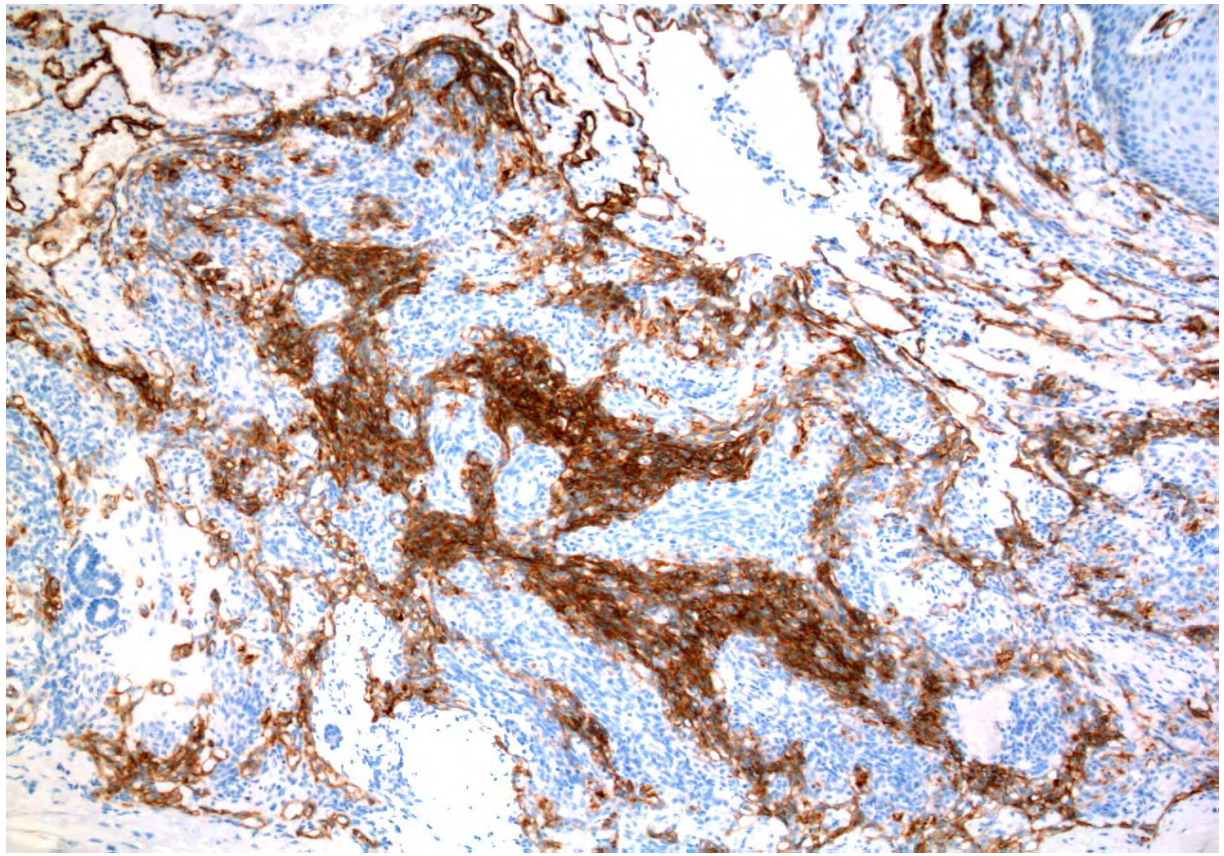


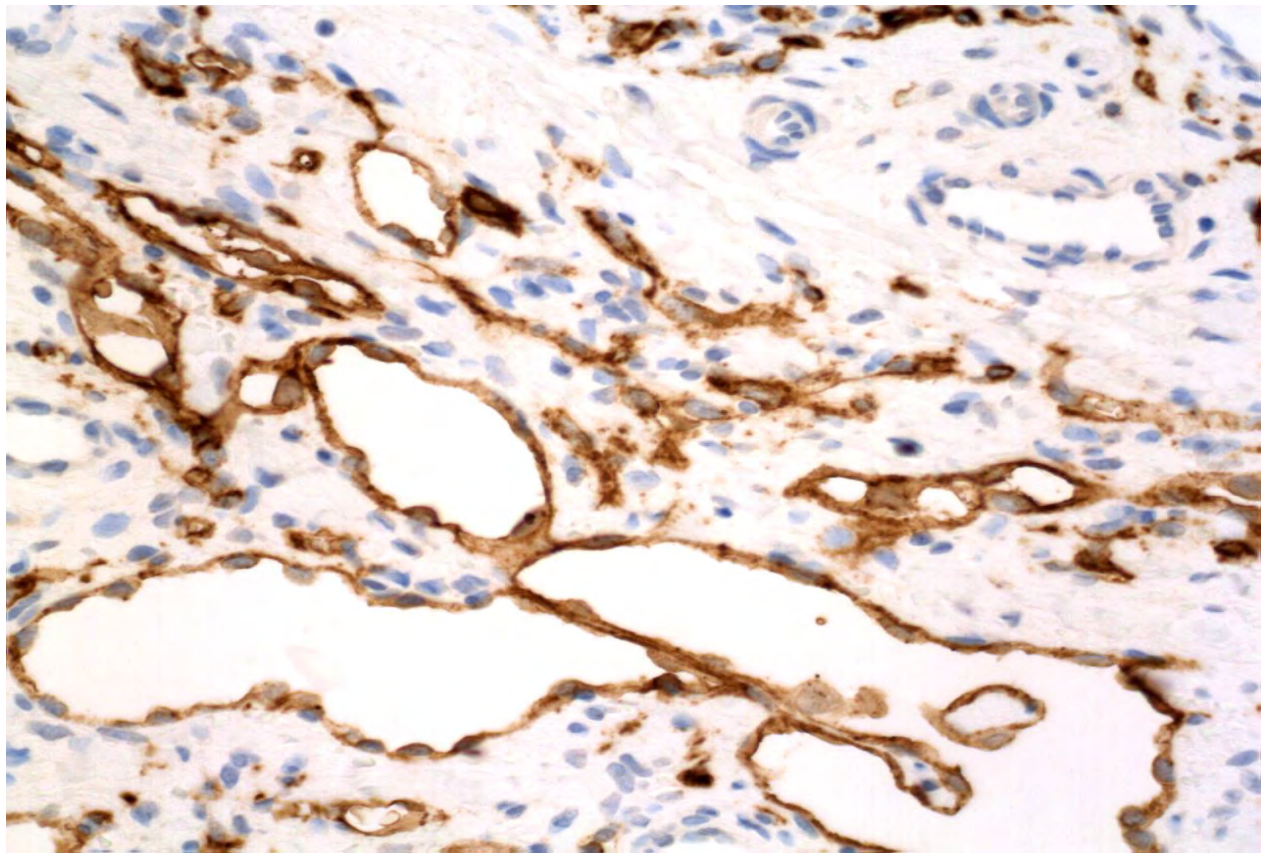
- Round capillaries +
- Solid nests of fusiform cells
- Slit-like spaces containing RBC



•Thin-walled vessels, irregular lumina, lined by flattened endothelial cells

D2-40





Diagnostic

Kasabach-Merritt syndrome

+

tufted angioma?

kaposiform hemangioendothelioma?

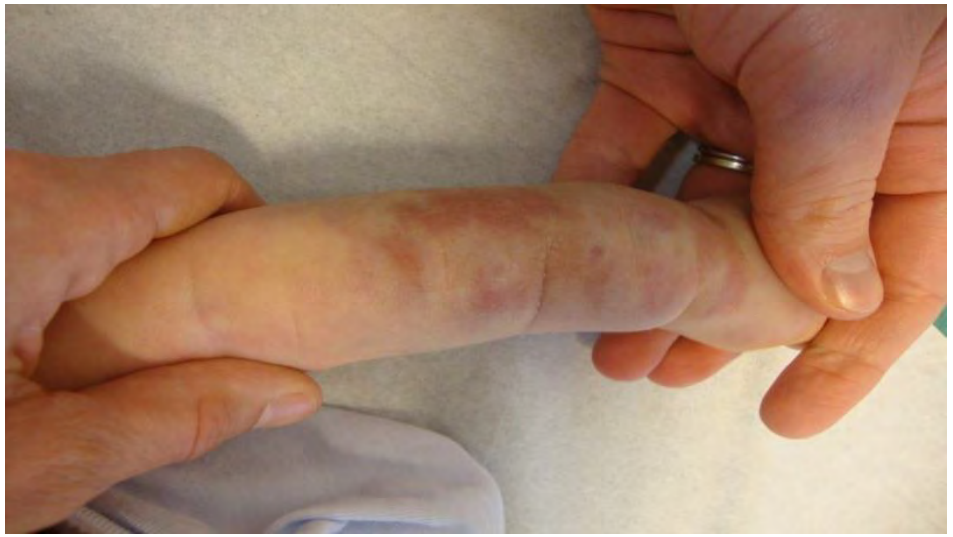
Kasabach-Merritt syndrome

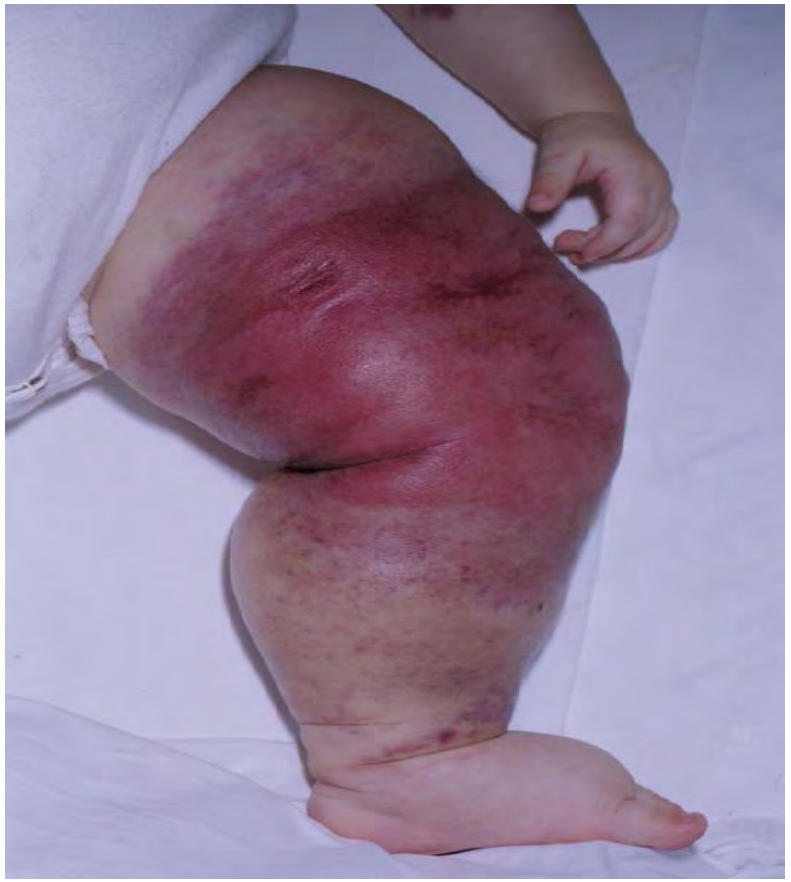
Severe potentially lethal syndrome:

- profound and sustained thrombocytopenia
- low fibrinogen levels
- elevated D-dimer

Specifically associated with:

- kaposiform hemangioendothelioma
- tufted angioma

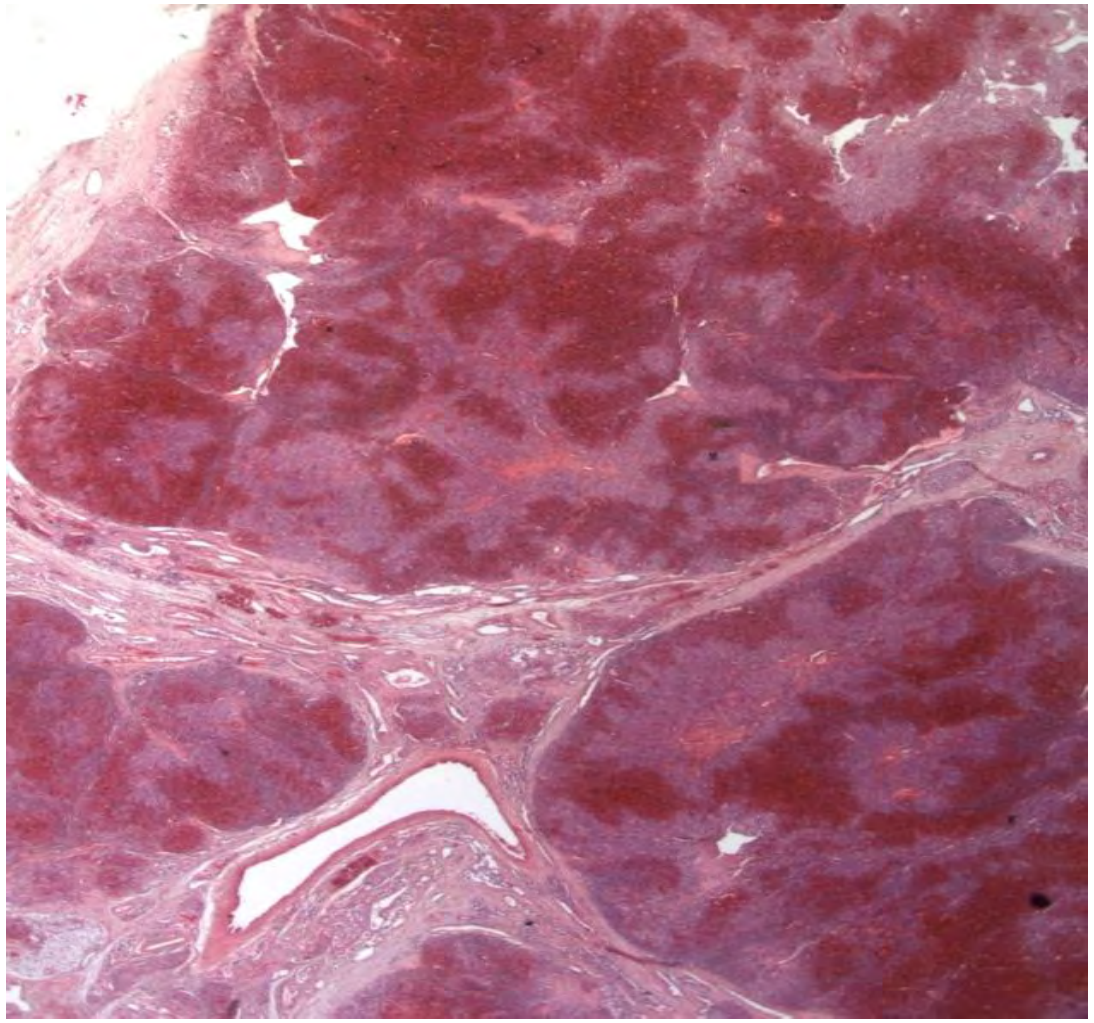


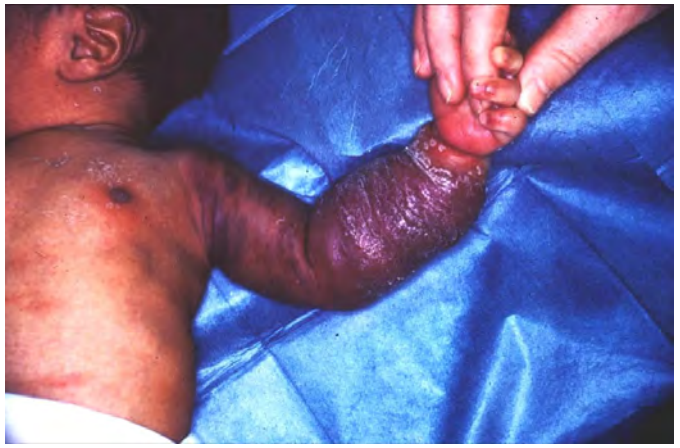


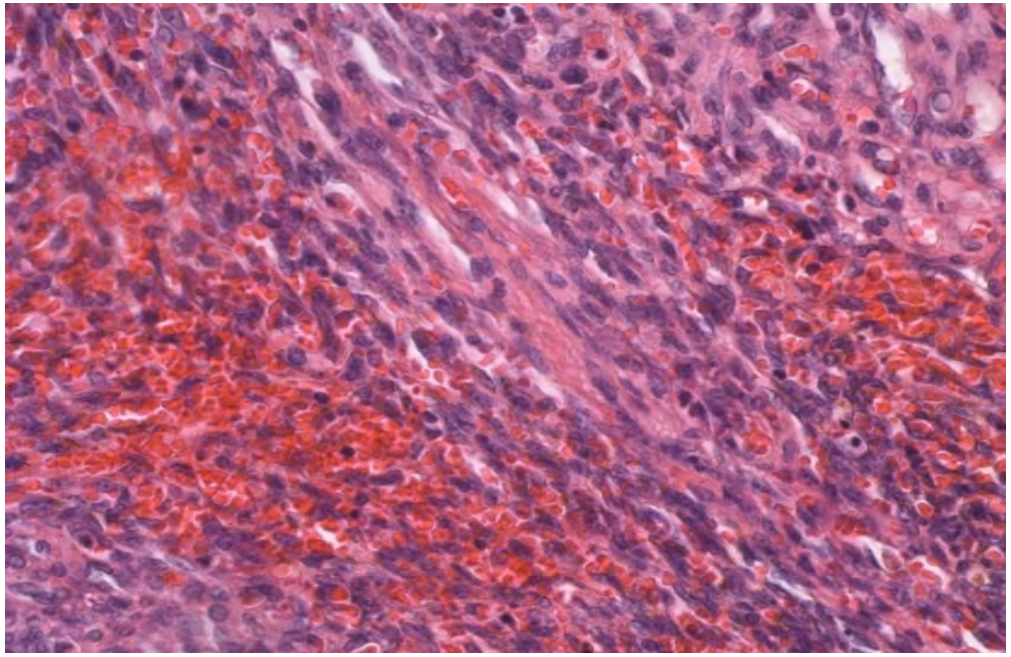
Enjolras O et al. J Pediatr. 1997, 130 (4): 631-40

Kasabach-Merritt syndrome

Platelets are trapped into the tumor
Becomes tender and voluminous

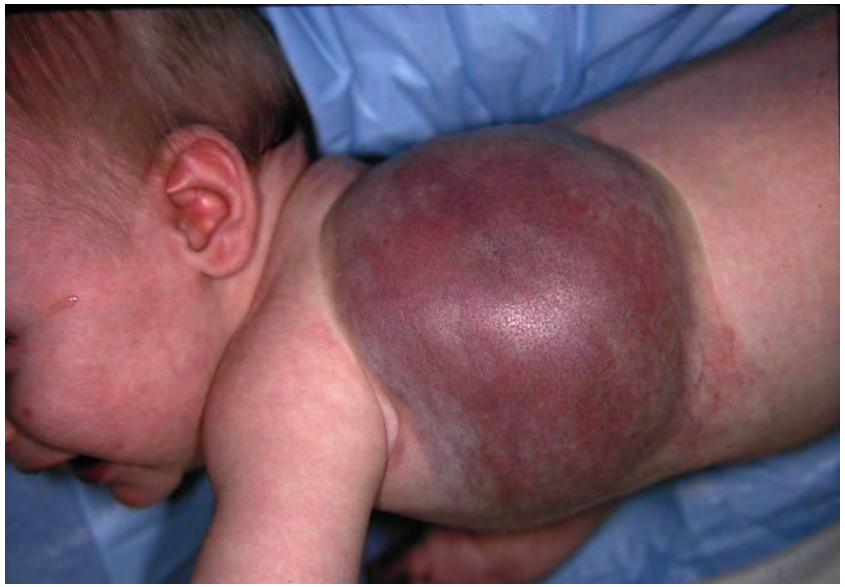


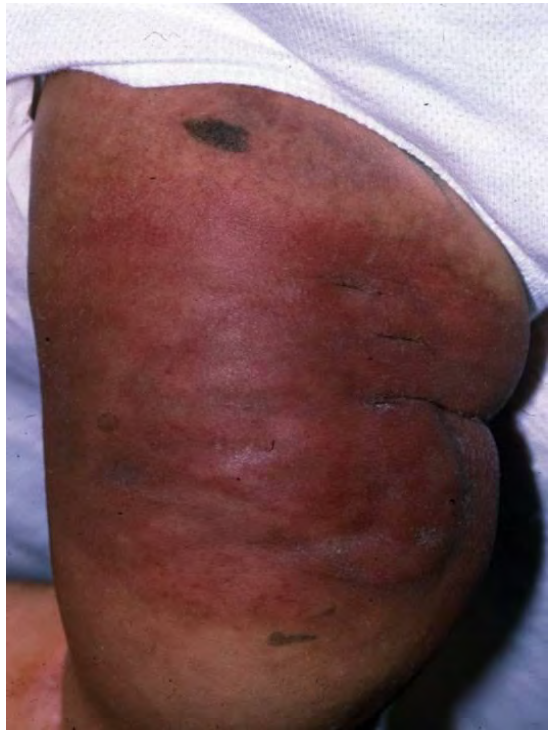




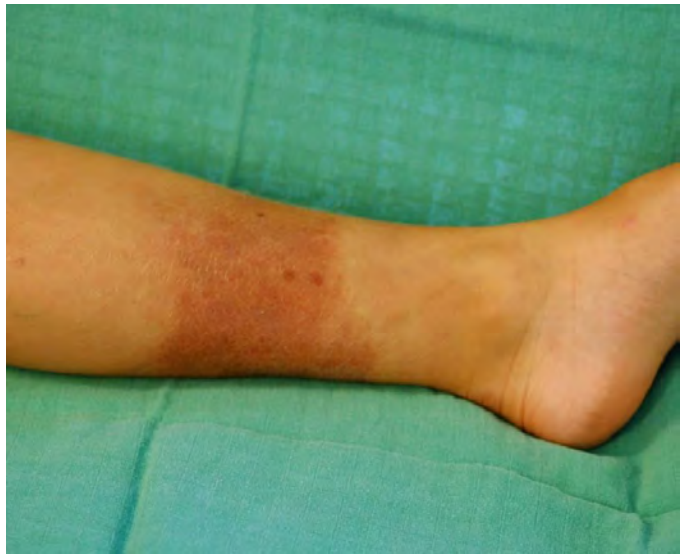
Kaposiform hemangioendothelioma

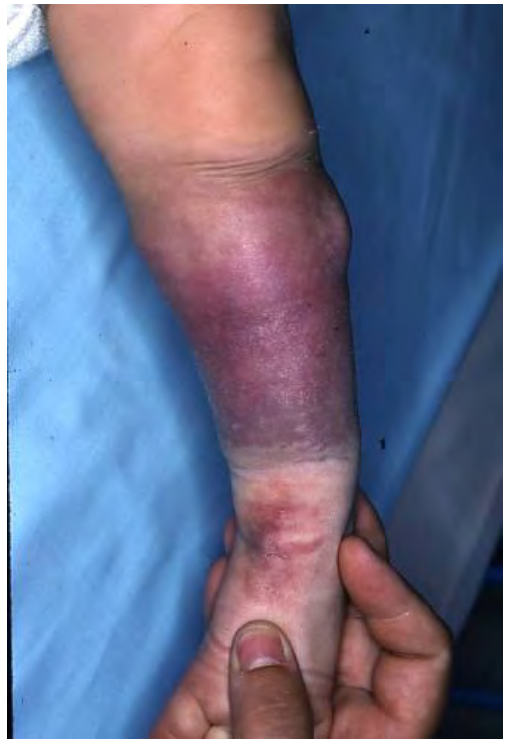
- **Infiltrative** vascular tumor
- Firm, erythematous-violaceous « aubergine coloured » plaque or tumour
- **Almost always associated with Kasabach-Merritt syndrome**



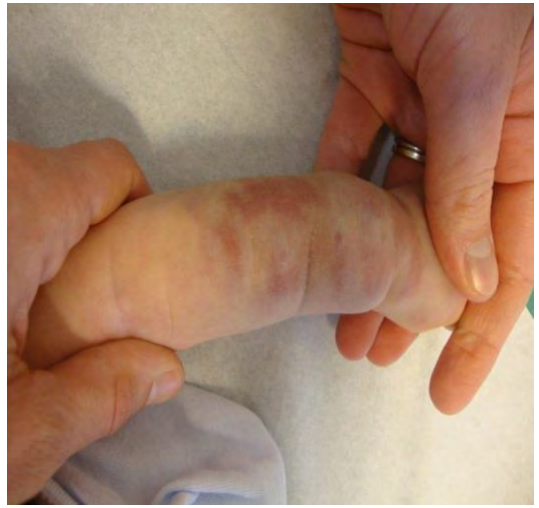


Tufted angioma



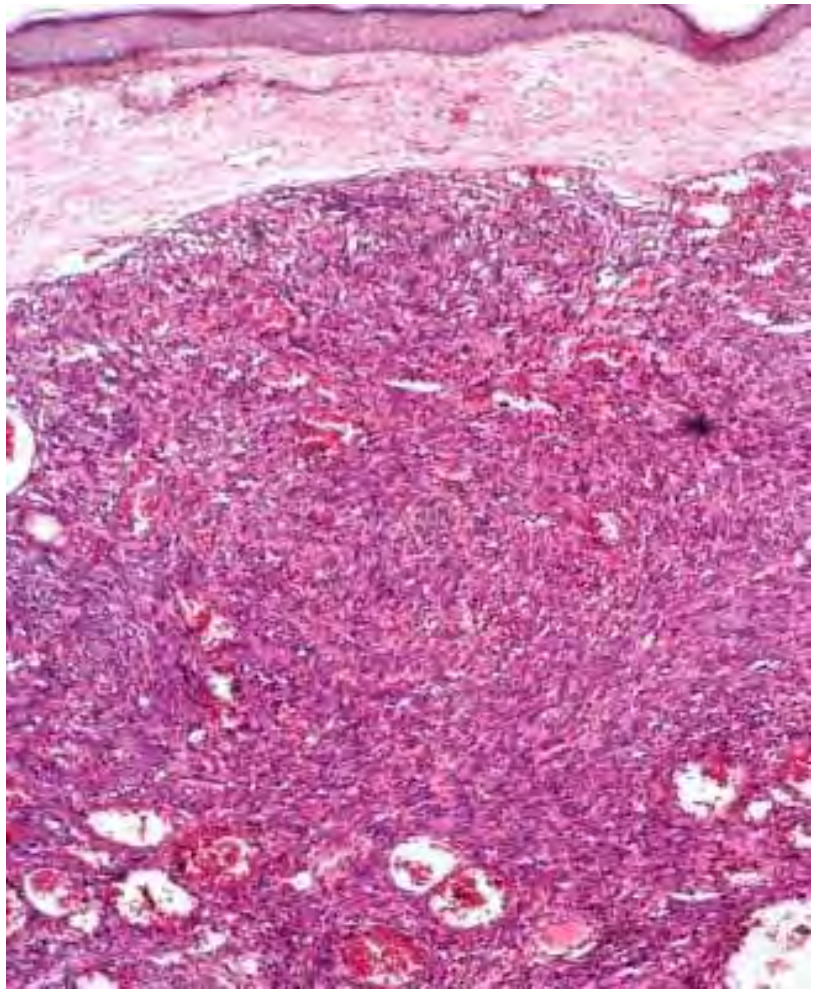


- less infiltrative solitary plaque,
- slightly firm at palpation,
- violaceous or brown, warm,
- commonly located on the proximal areas of limbs
- risk of Kasabach-Merritt syndrome



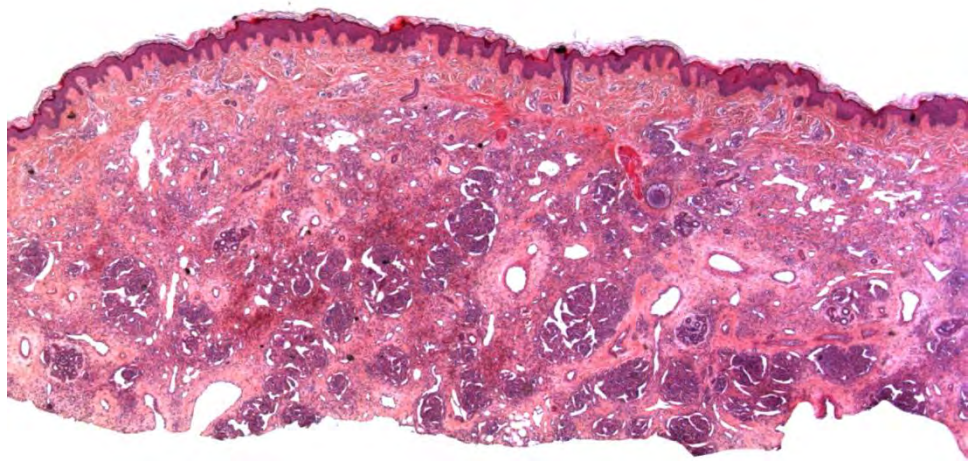
Boccara O, Fraitag S, Lasne D et al. Acta Derm Venereol. 2016 Jan;96(1):77-81

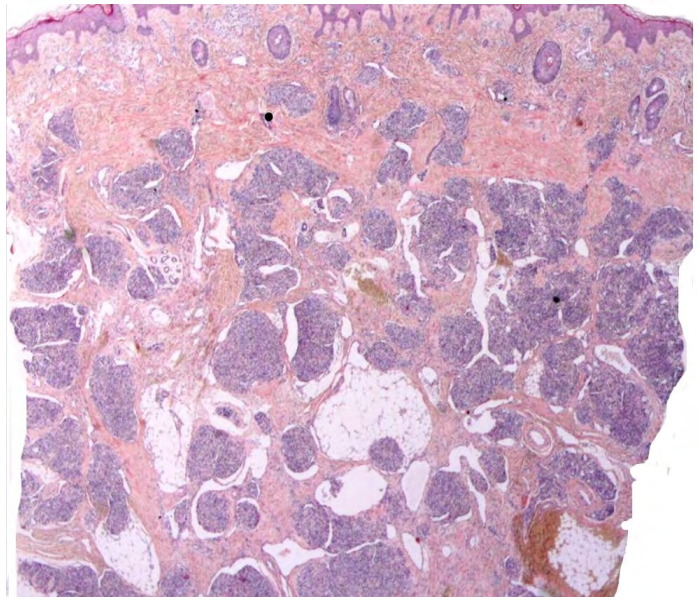
KHE



- Mainly located in the subcutis
- Ill-defined capillary lobules
- Large vessels

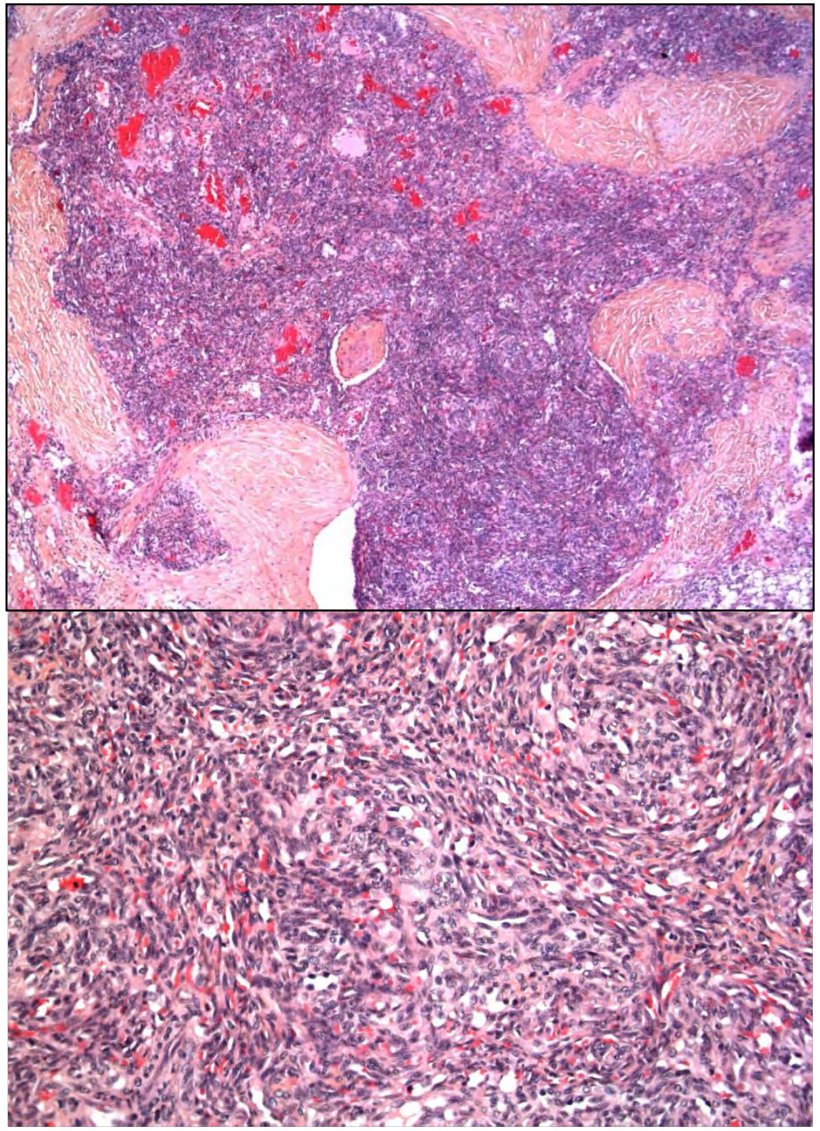
Tufted angioma





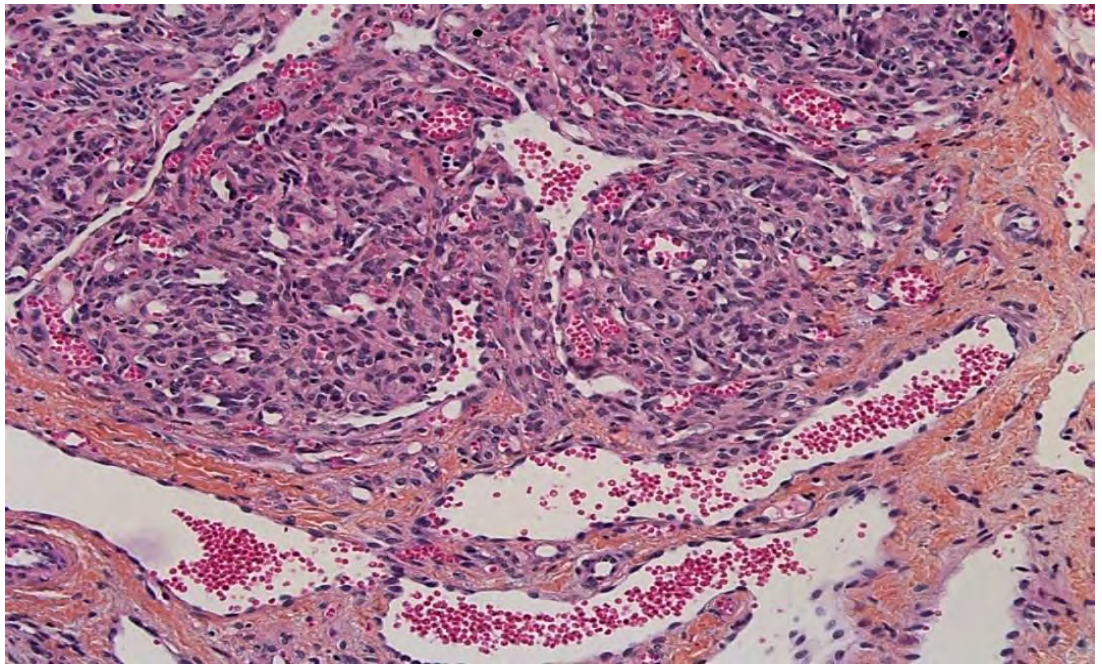
- Intra-dermal lesion
- Well defined “cannonball” lobules
- Some dilated vascular spaces

KHE



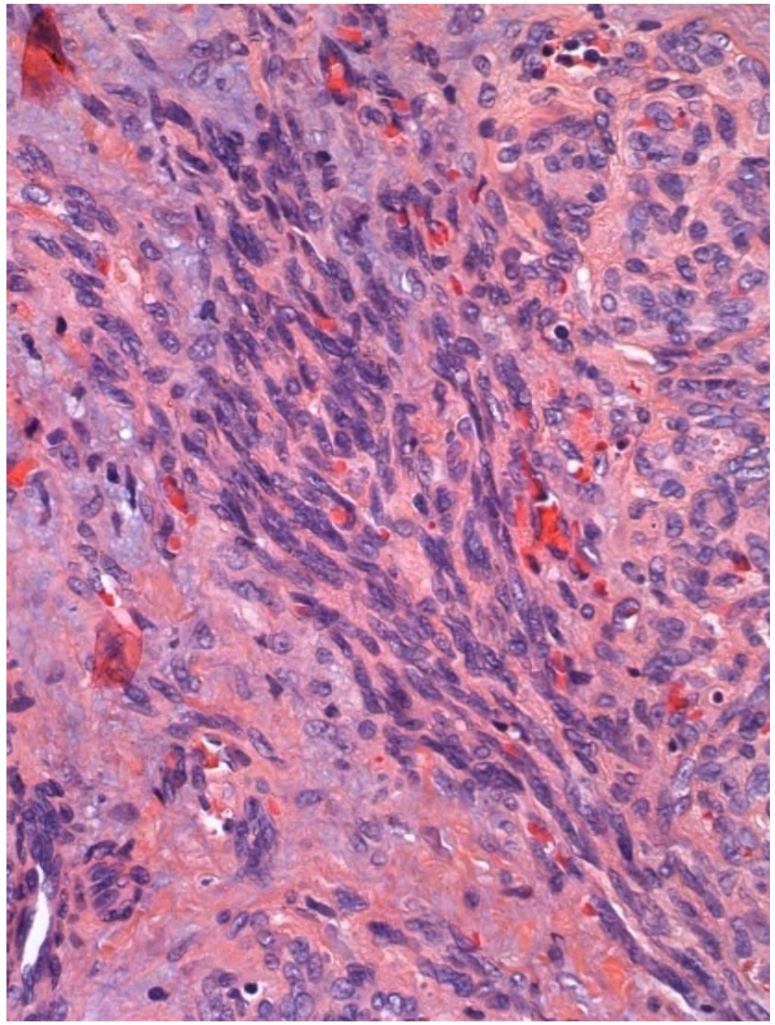
•Small packed capillaries
•Hemorrhagic areas

Tufted angioma

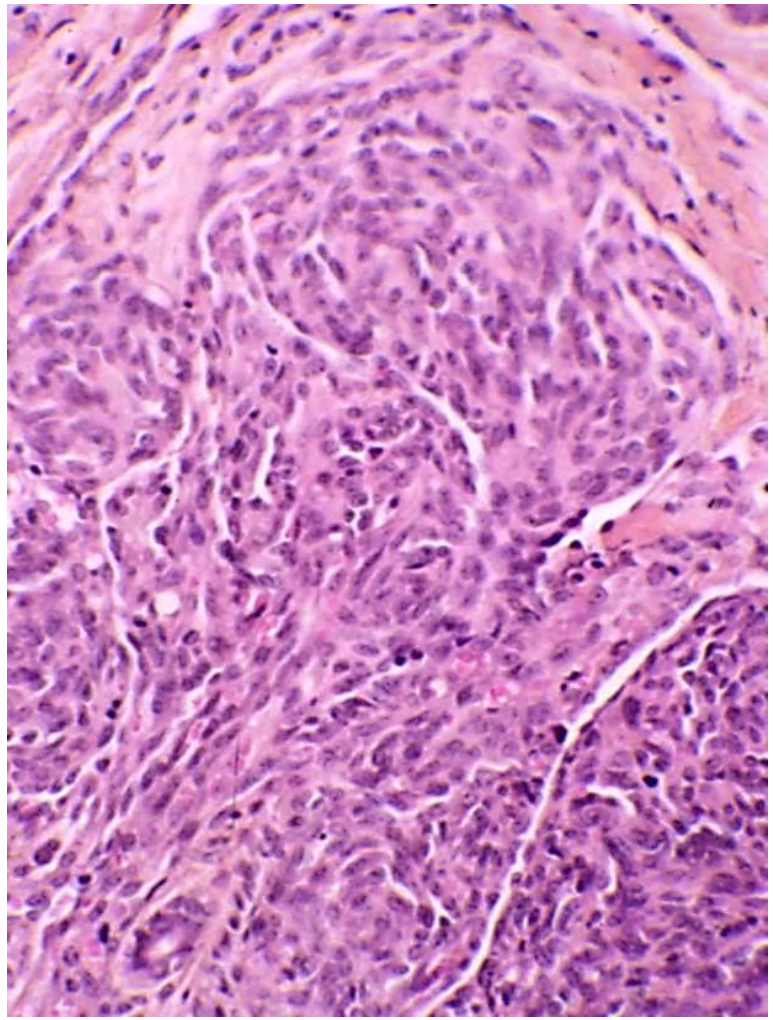


•Small packed capillaries
•Crescent-shaped vascular spaces

KHE

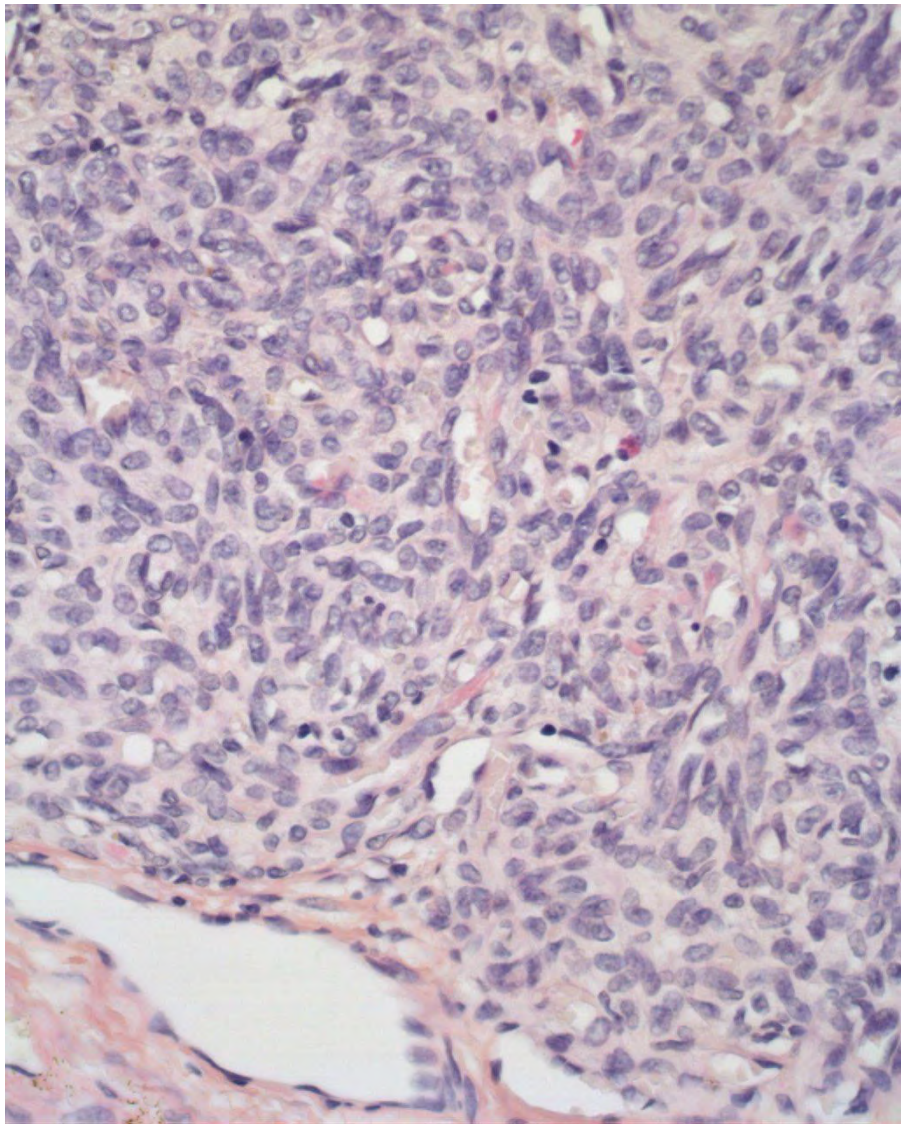


Tufted angioma

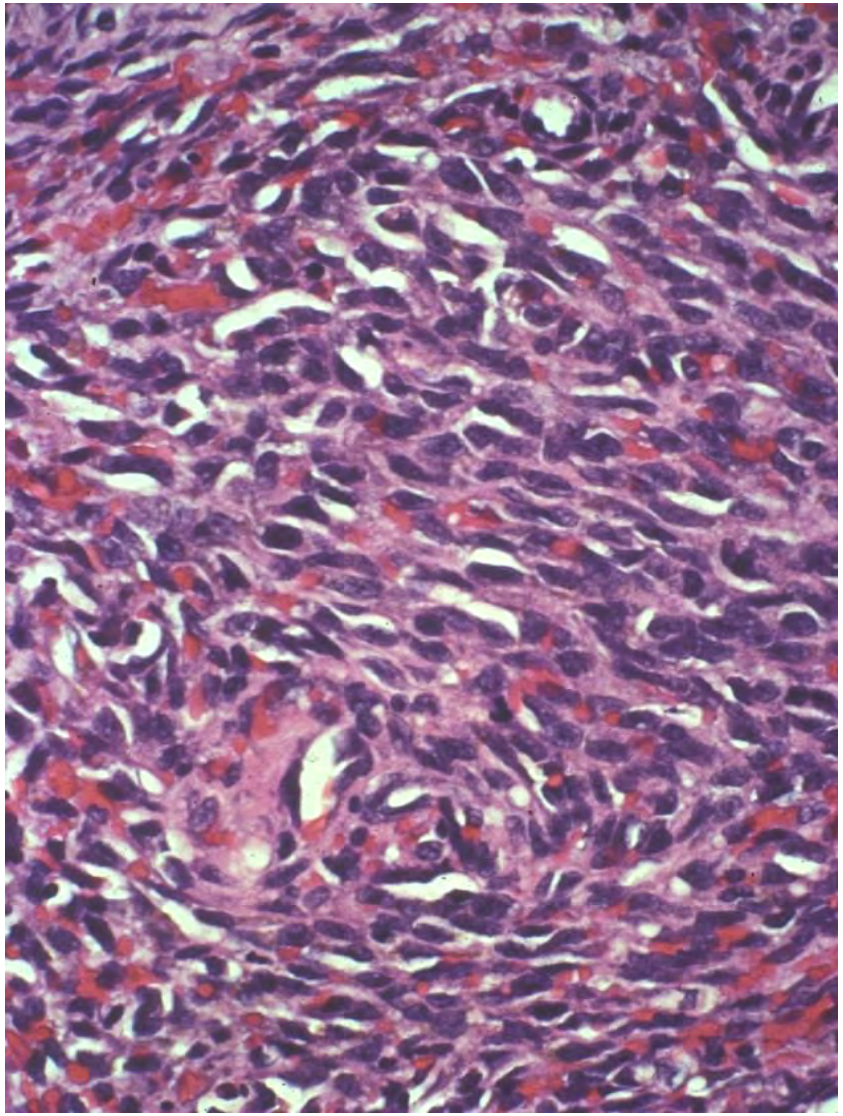


- Spindled endothelial cells
- Slit-like spaces containing red blood cells
- +/- thrombi

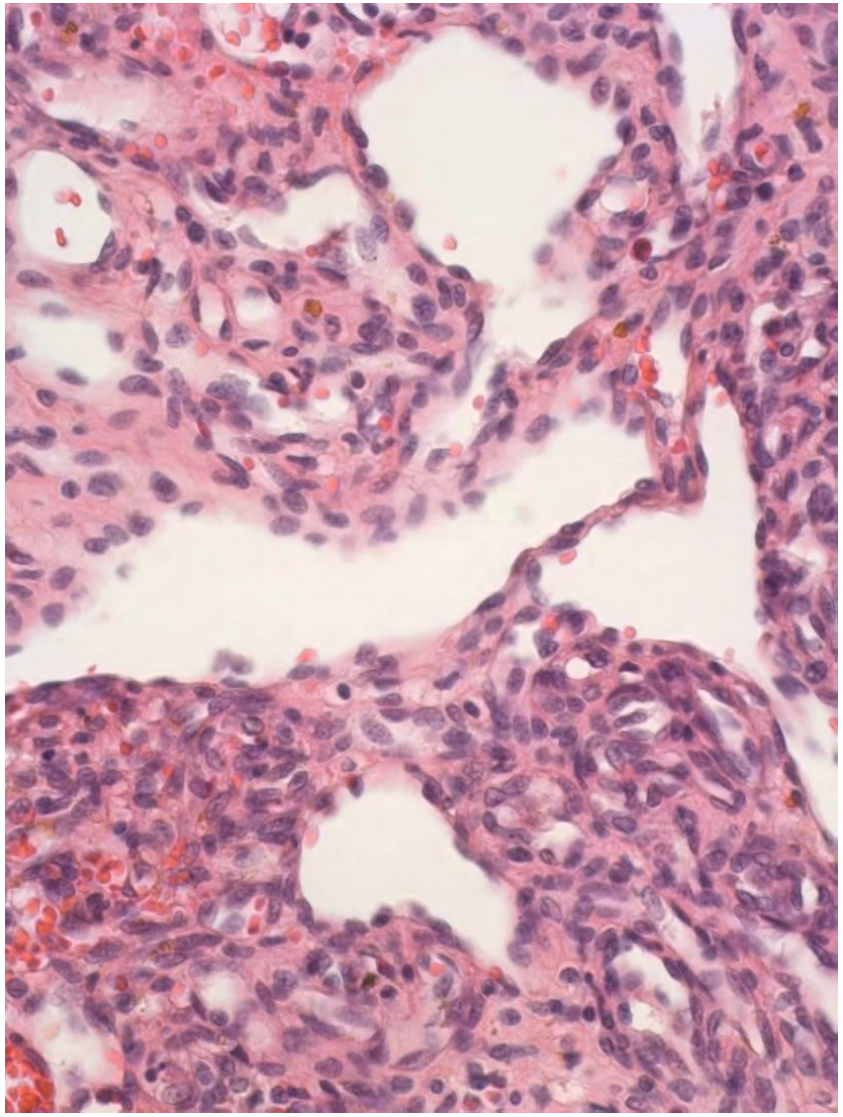
KHE



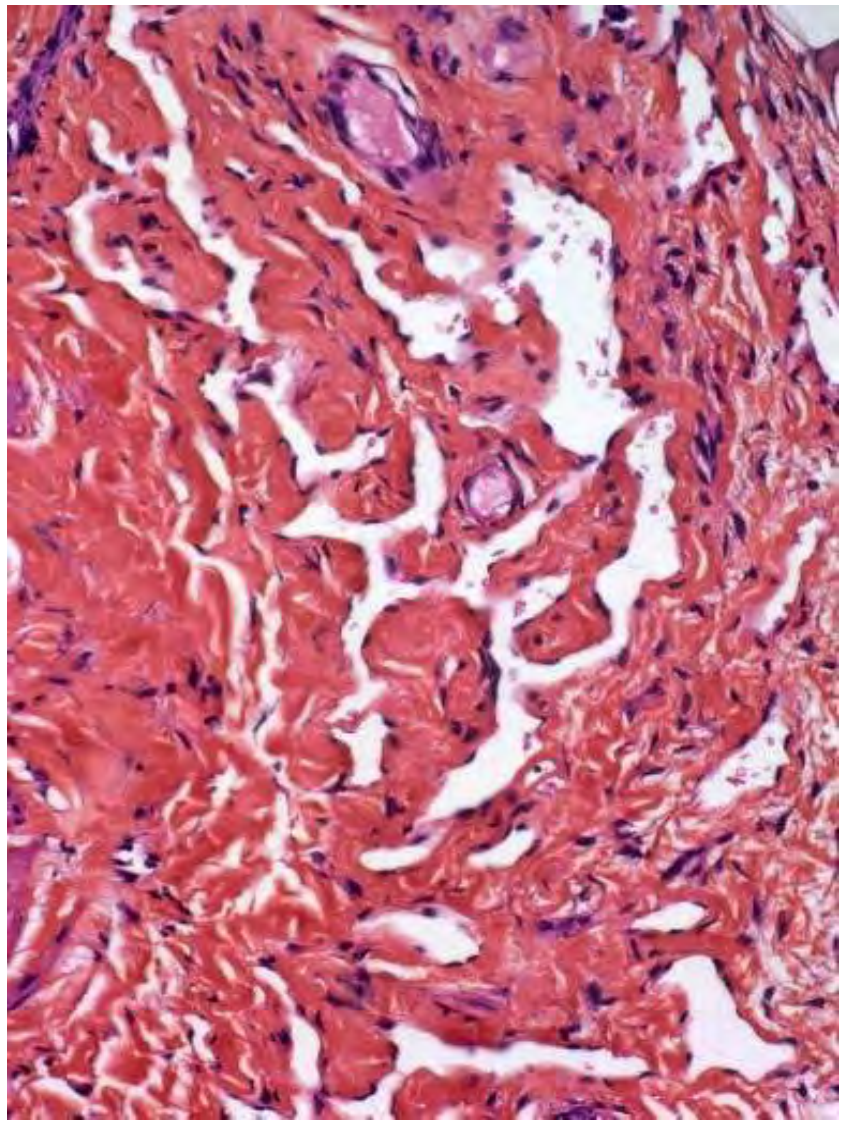
Tufted angioma



KHE



Tufted angioma

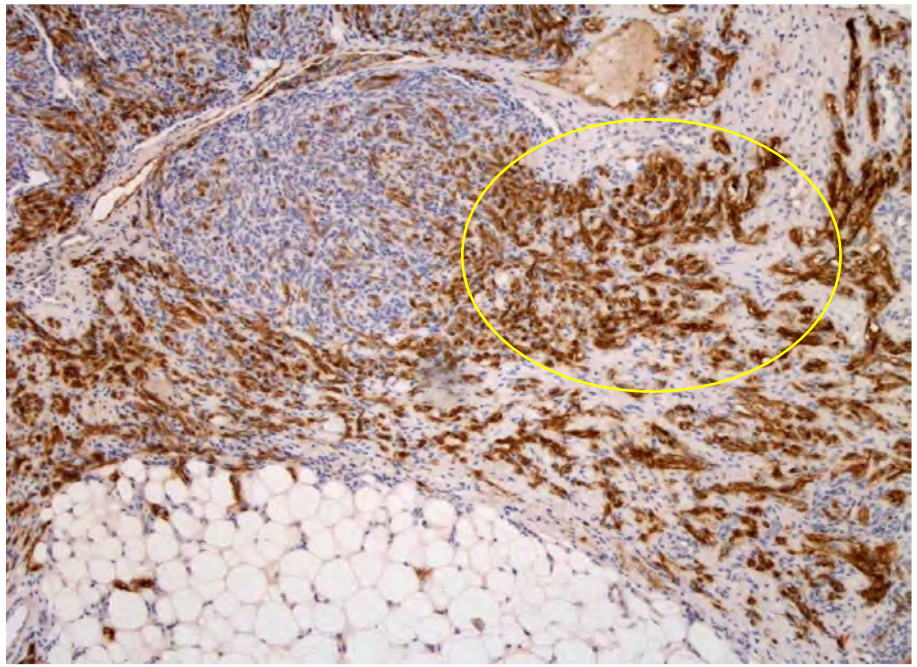


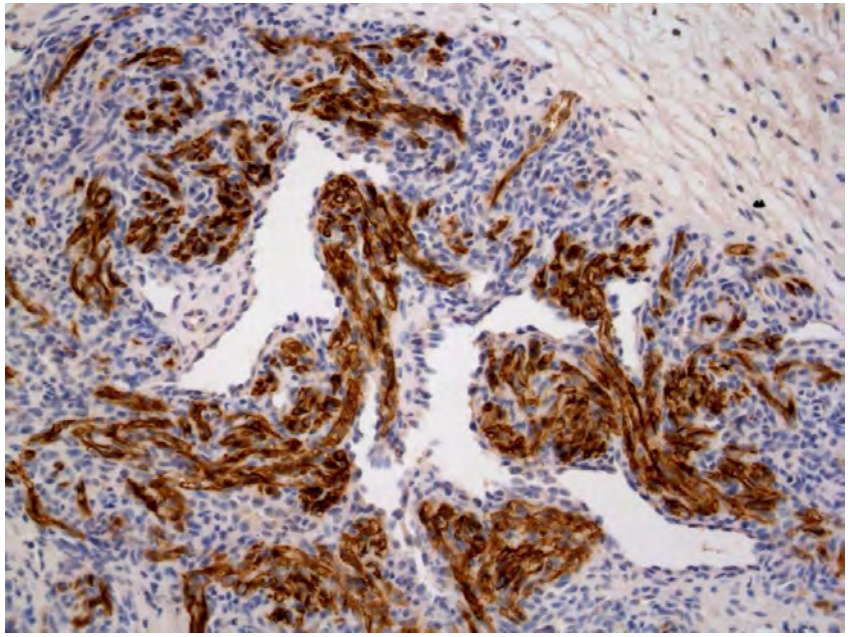
- Thin-walled lymphatic-like structures

KHE

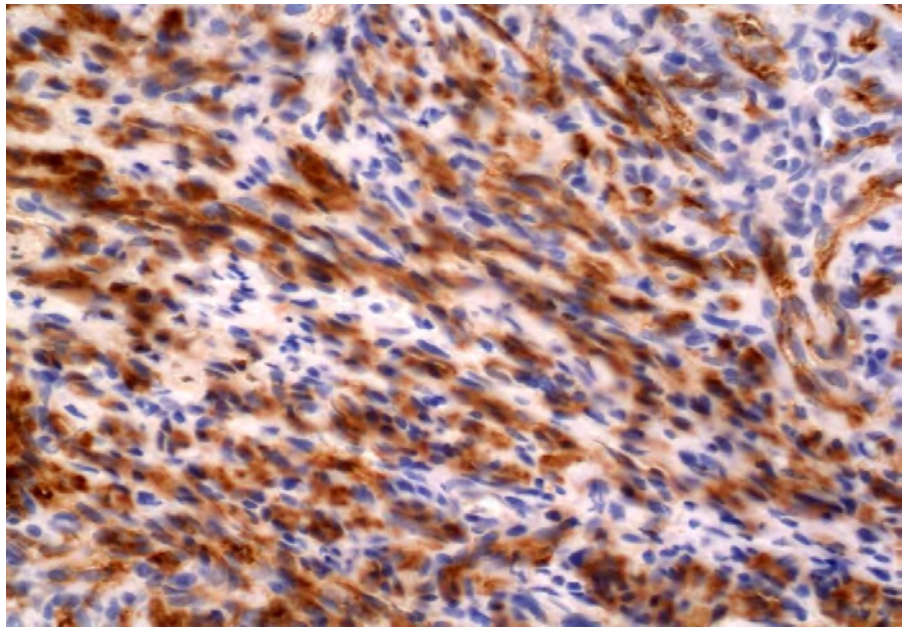
Tufted angioma

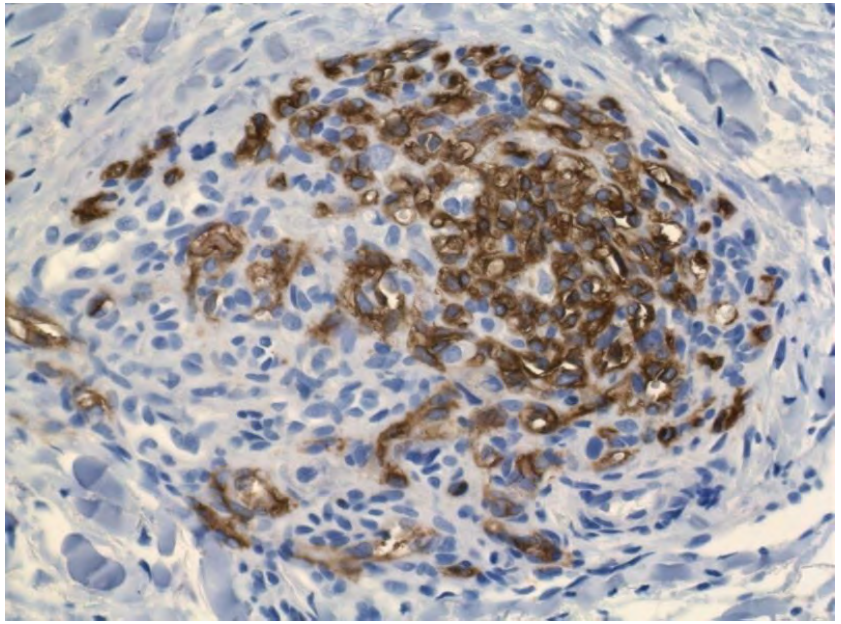
D2-40 +
Lyve 1 +
Prox 1 +





GNA14

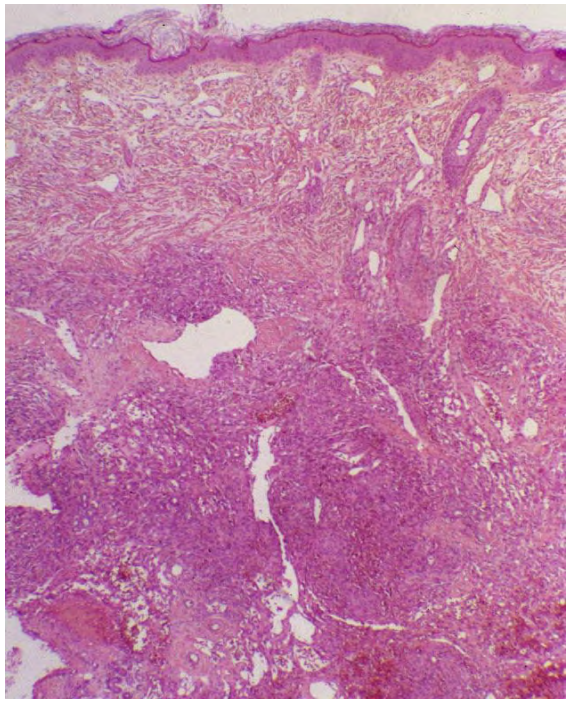


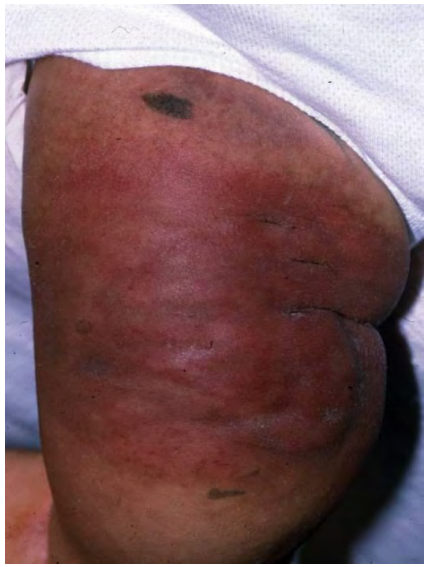


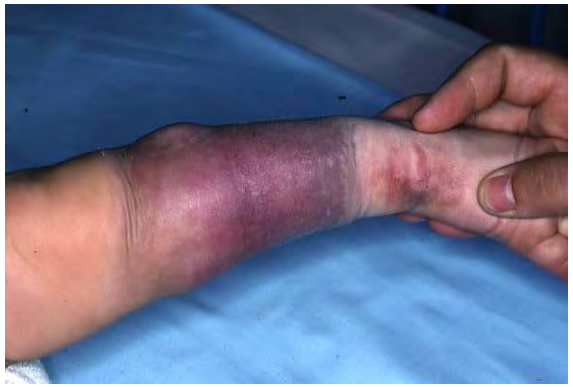
- Many tumors exhibit gradation between TA and KHE

  ⇨ **these two tumors represent 2 ends of the same tumor spectrum**

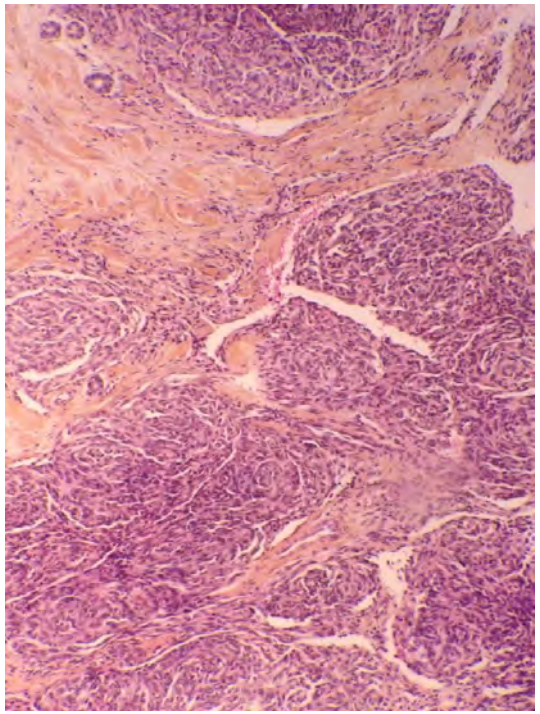
KHE







TA



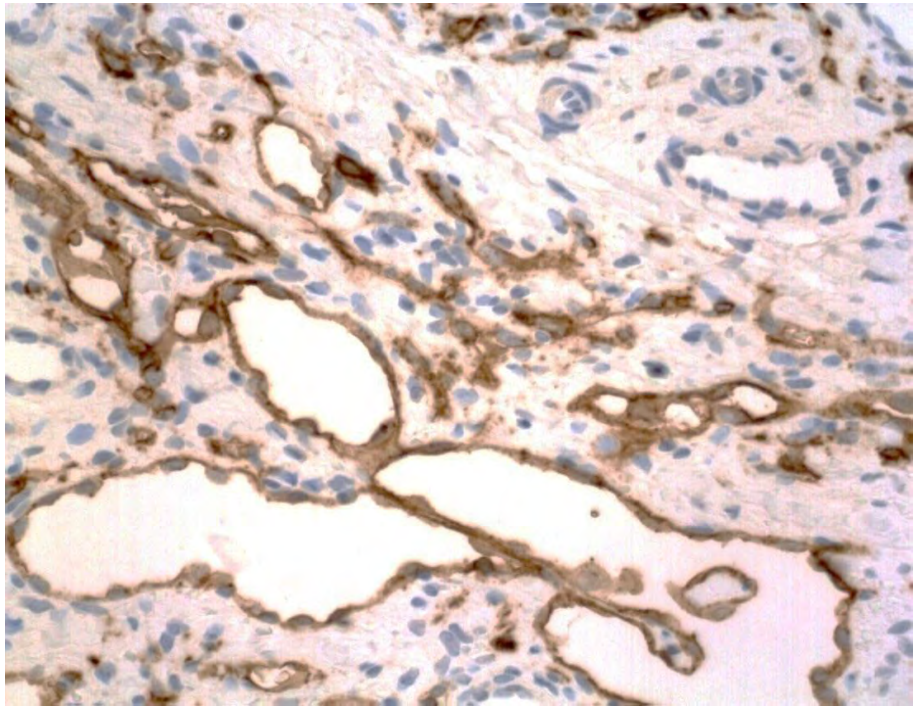
Chu CY et al. Dermatology 2003; 206: 334-337
Rimella Le Huu A et al. Am J Surg Pathol. 2010; 34: 1563-73
Osio A et al. Arch Dermatol.2010; 146: 758-763

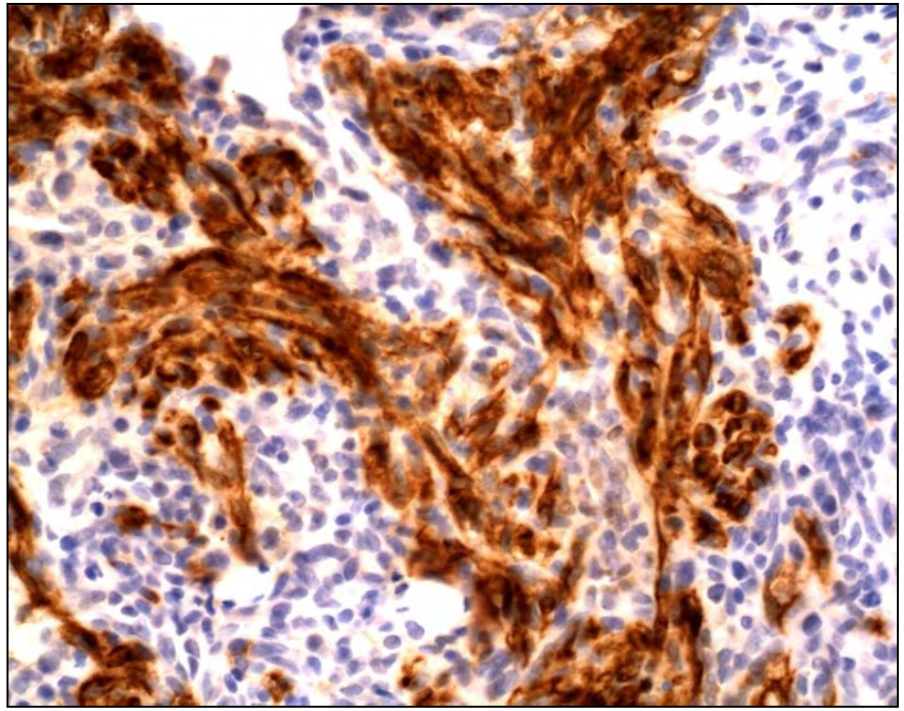
Diagnostic

Vascular tumour potentially associated with Kasabach-Merritt syndrome

Lymphatic phenotype is very helpful (even essential)

- to confirm the diagnosis of KHE/TA
- distinguish from other vascular tumors: congenital hemangiomas or pyogenic granulomas





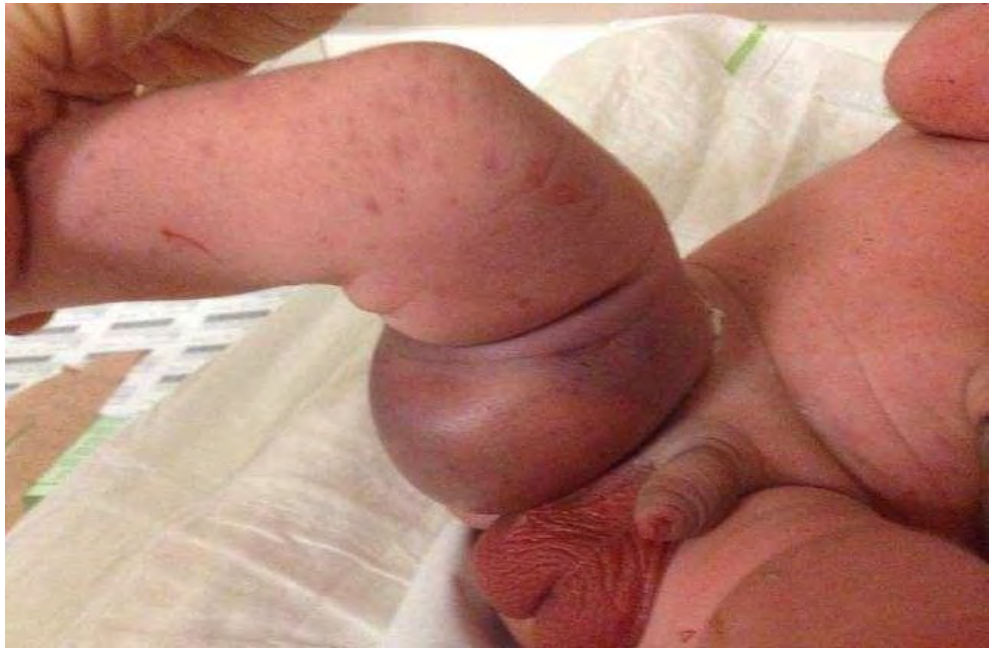
Treatment of choice: Sirolimus!

Boccara O, Puzenat E, Proust S, Leblanc T, Lasne D, Hadj-Rabia S, Bodemer C. The effects of sirolimus on Kasabach-Merritt phenomenon coagulopathy. Br J Dermatol. 2018 Feb;178(2):e114-e116

Clinical history

Quiz

- Full term male neonate
- 3 normal prenatal ultrasounds
- Purple mass on the right thigh, hard at palpation, slightly painful but mobile, extending toward the groin
- Purpuric spots on the overlying skin and scattered throughout the body
- Thrombocytopenia (6000/mm3)

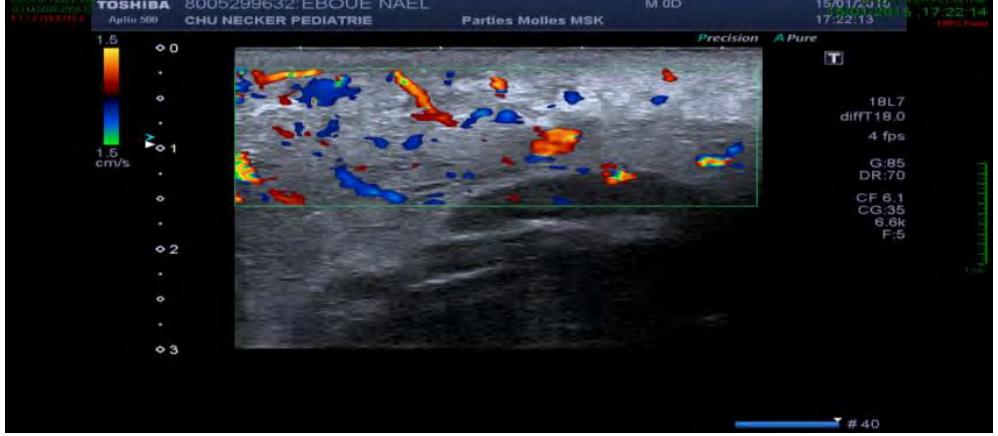


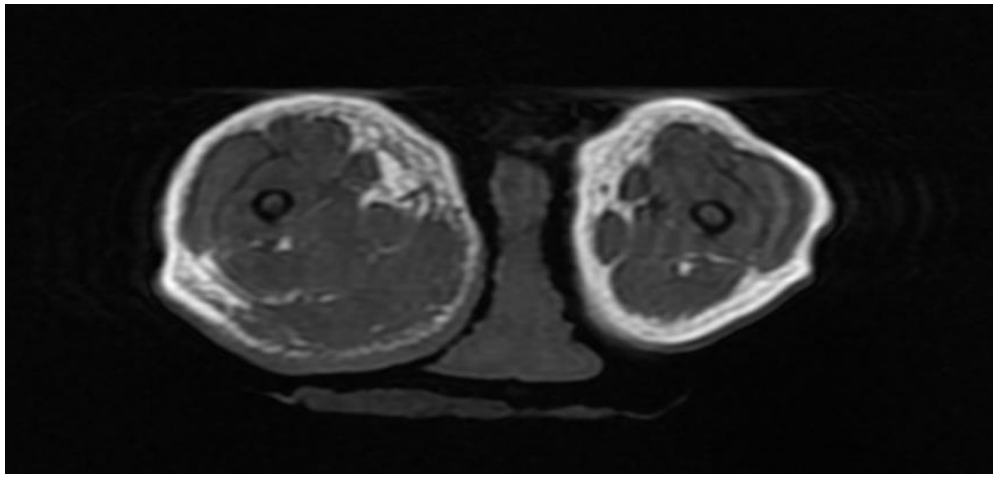
Presumptive diagnoses

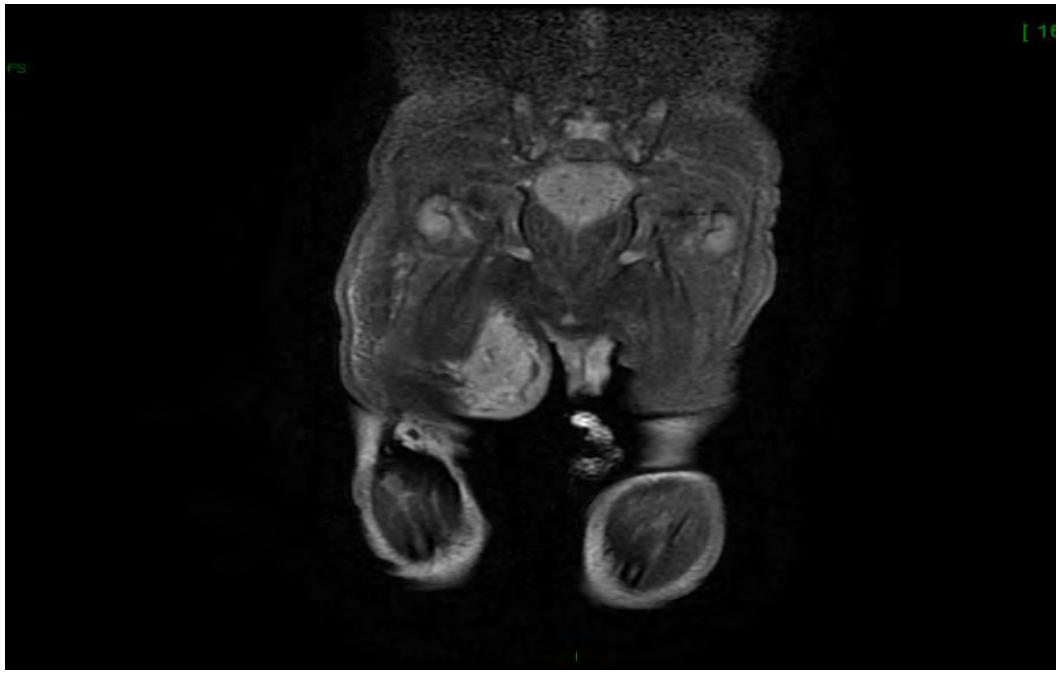
- Sarcoma
- Kaposiform hemangioendothelioma
- Congenital hemangioma (RICH)

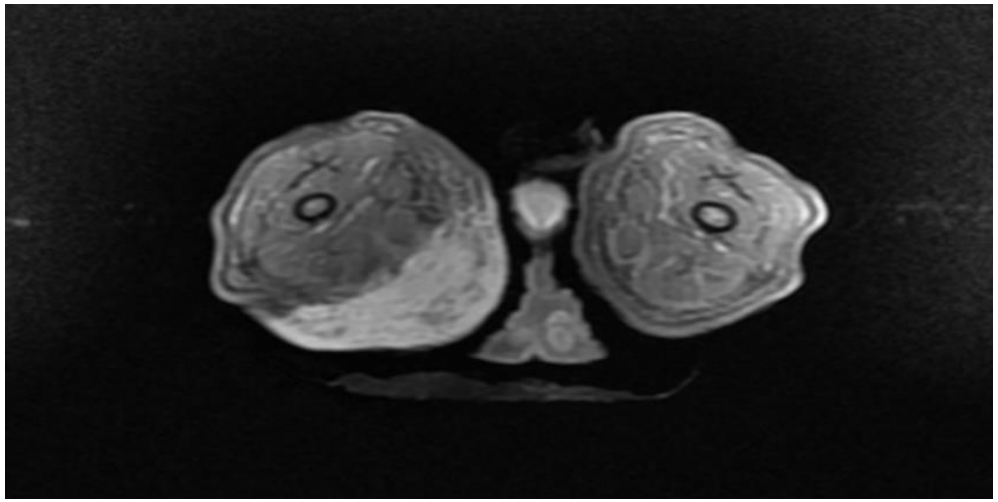
Imaging

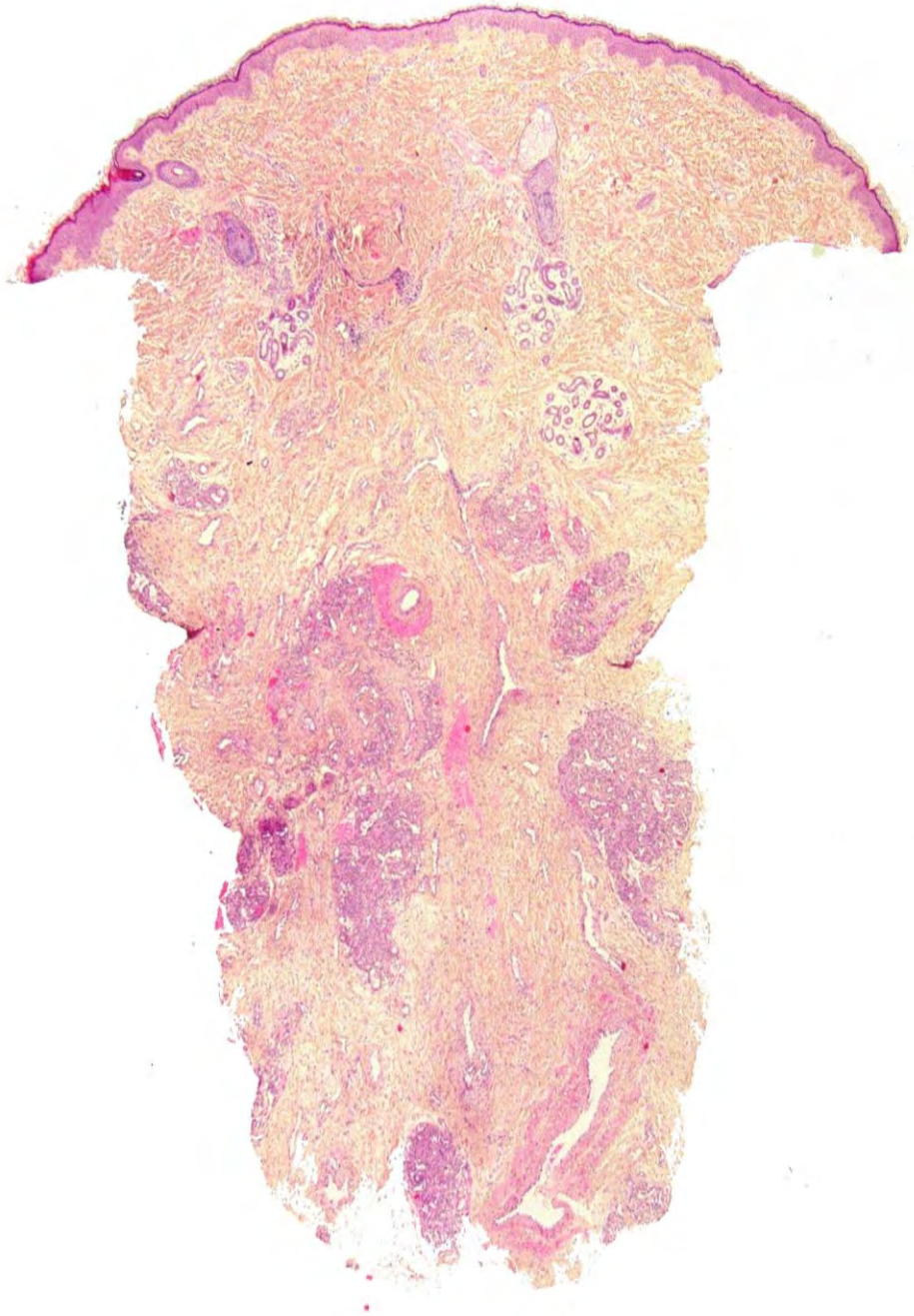
- Ultrasound at D1: KHE
- MRI at D2 : subcutaneous lesion, no bone extension: sarcoma or vascular tumor

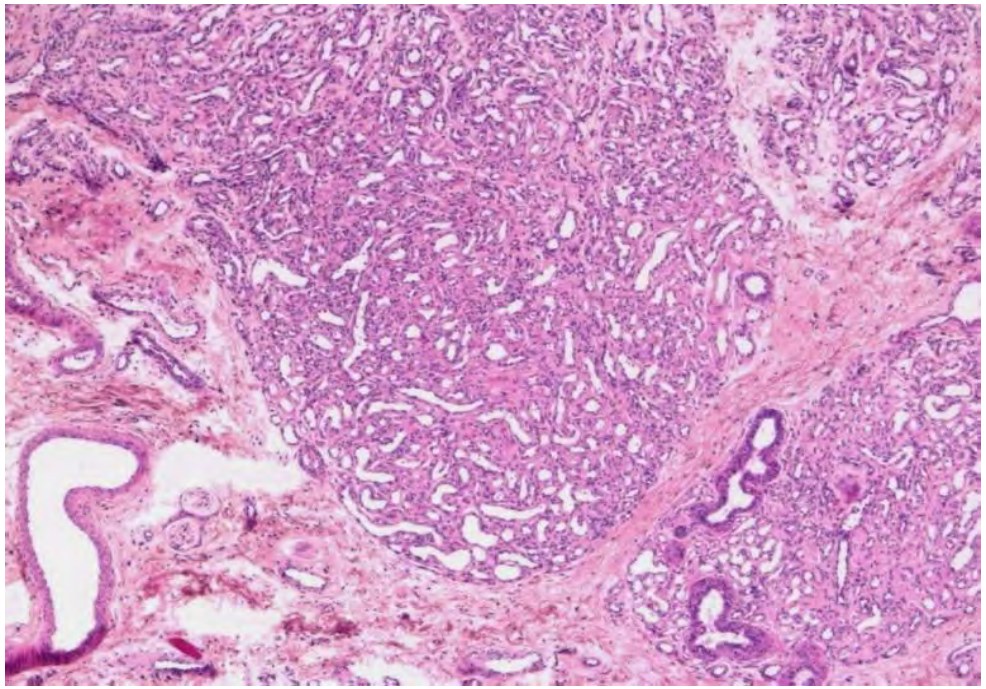






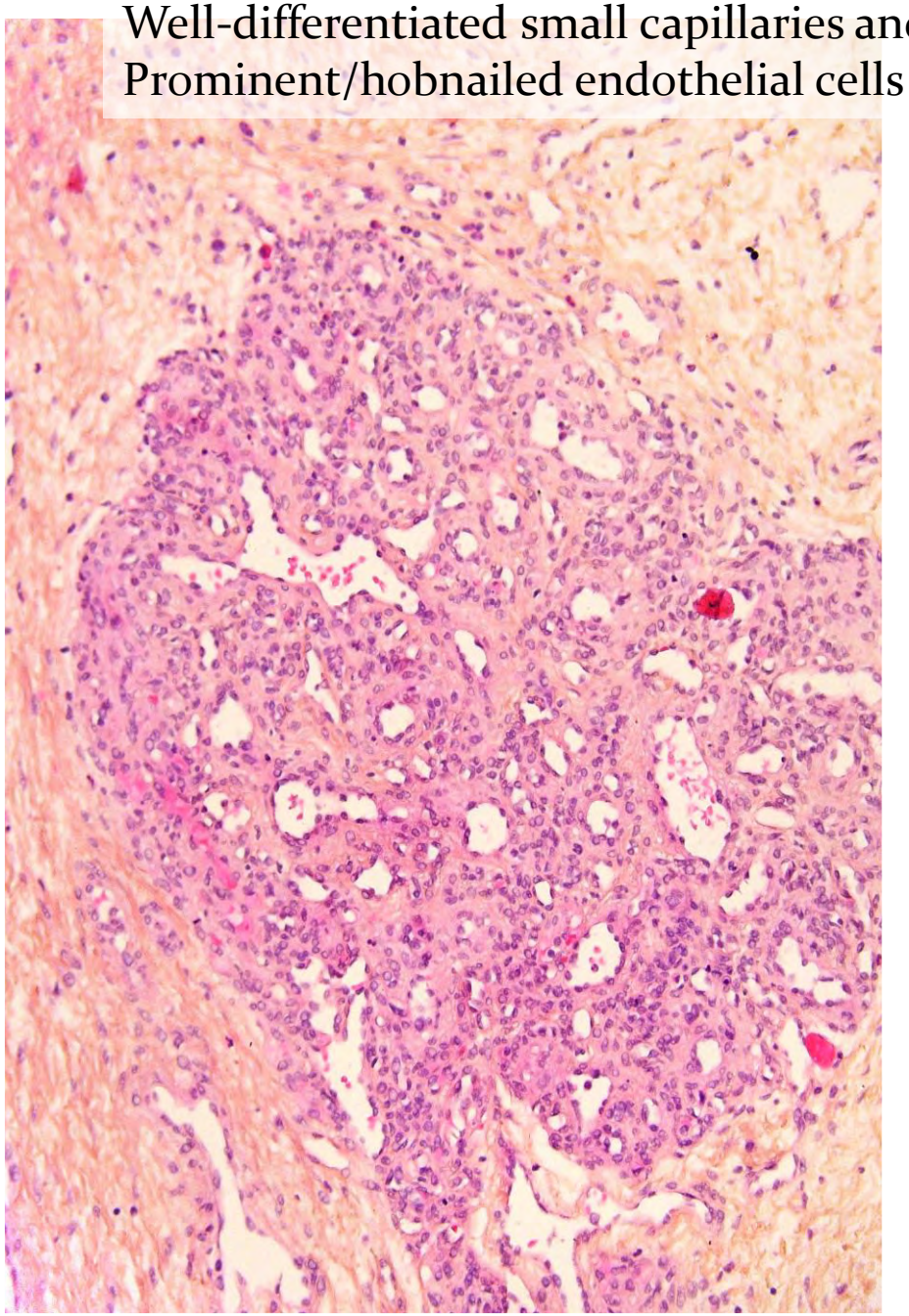


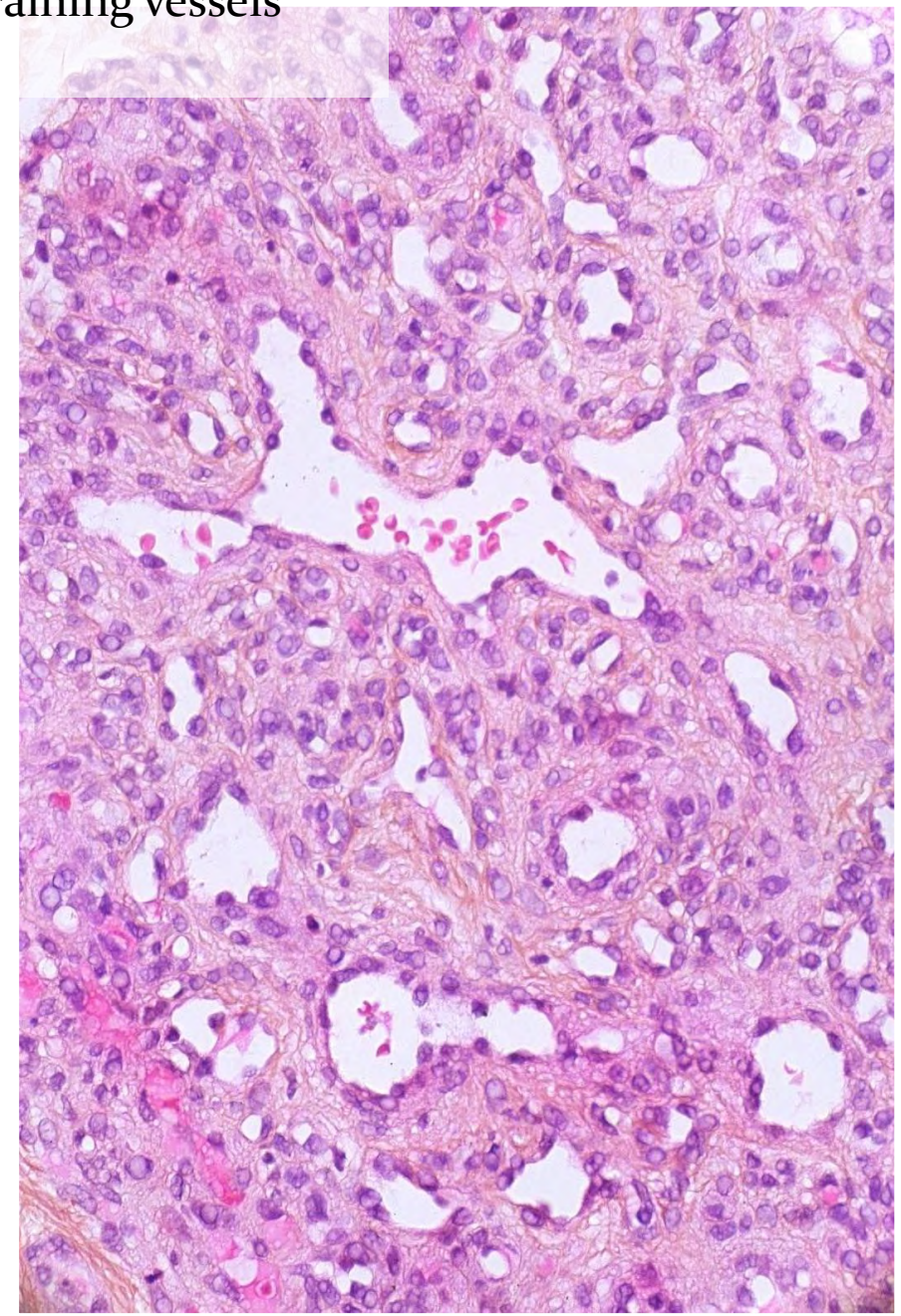




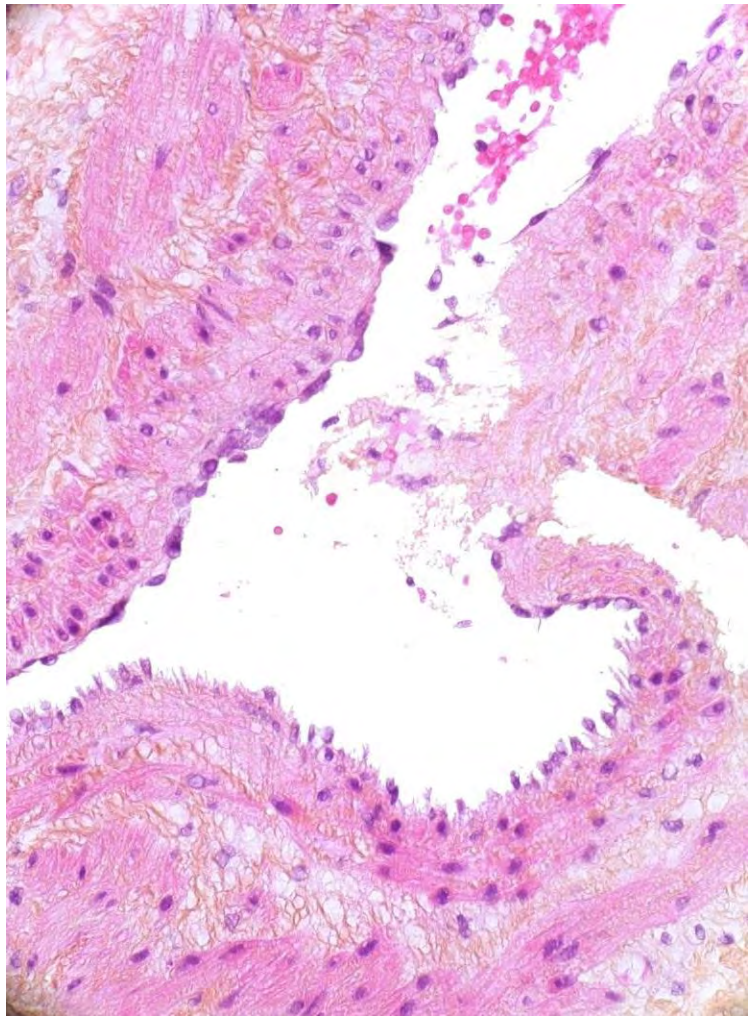
- Well-defined, small and large lobules
- Large vessels
- Dense fibrous tissue

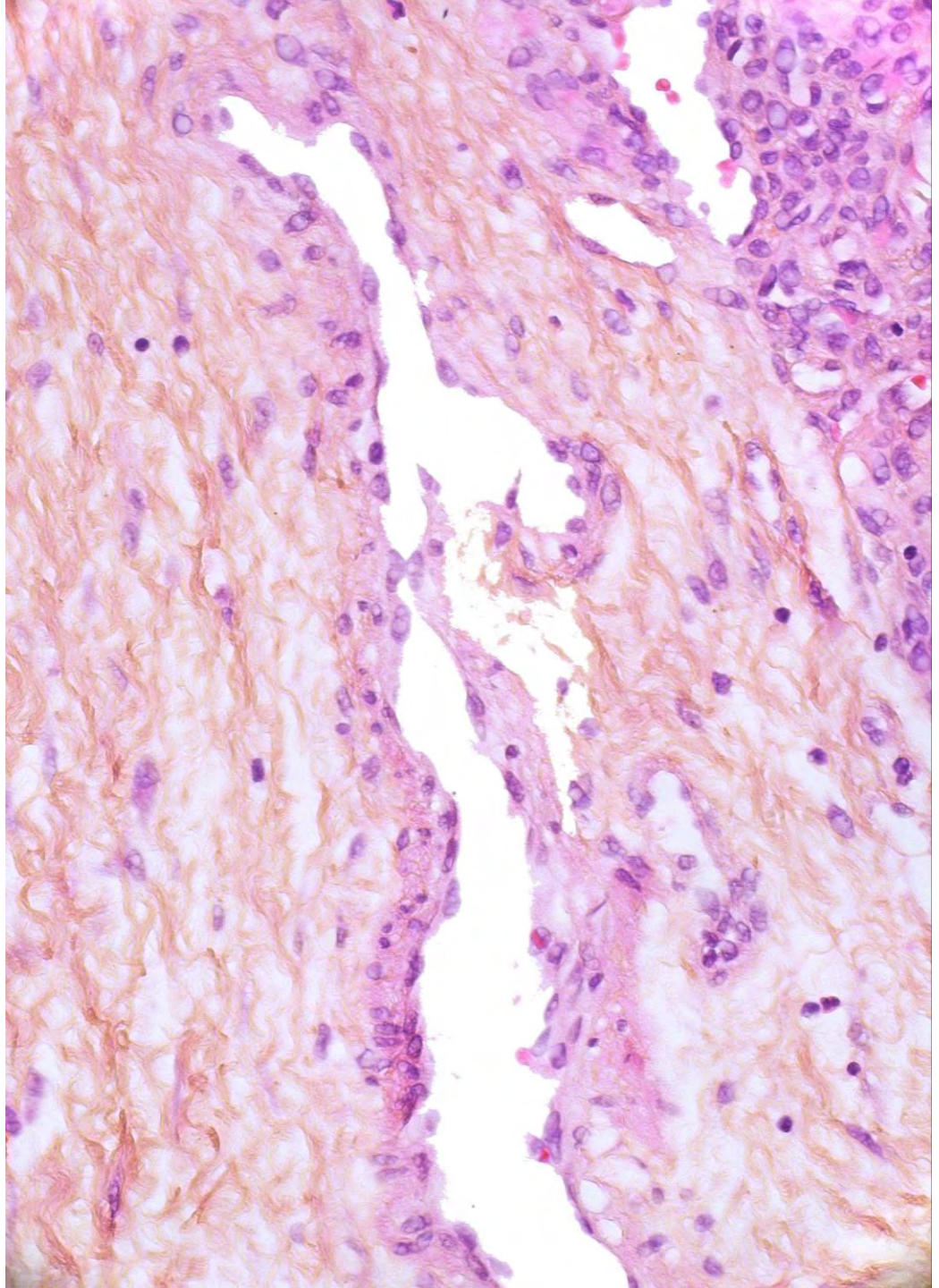
Well-differentiated small capillaries and prominent draining vessels
Prominent/hobnailed endothelial cells



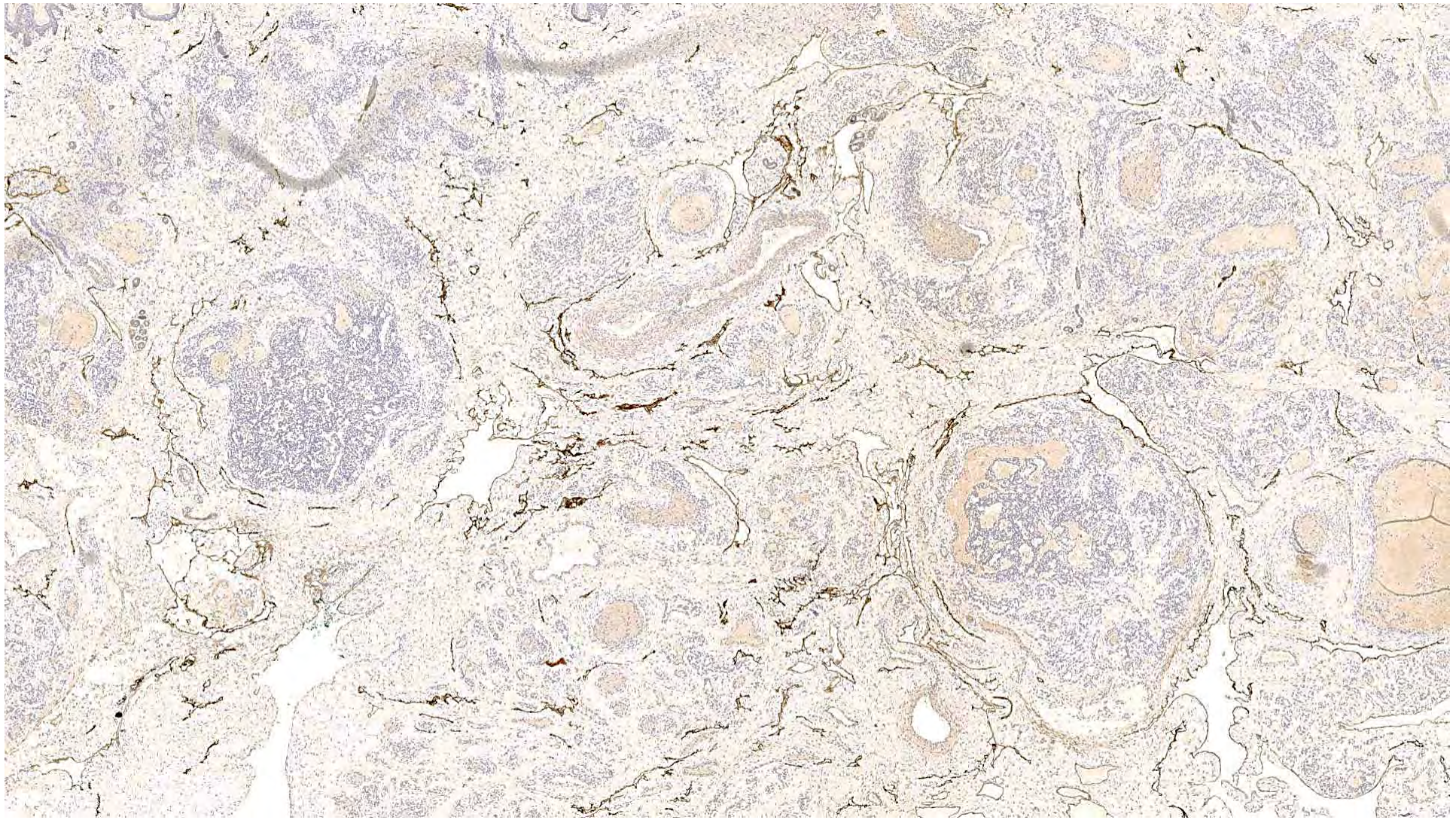


Large, abnormal, vessels





D2-40



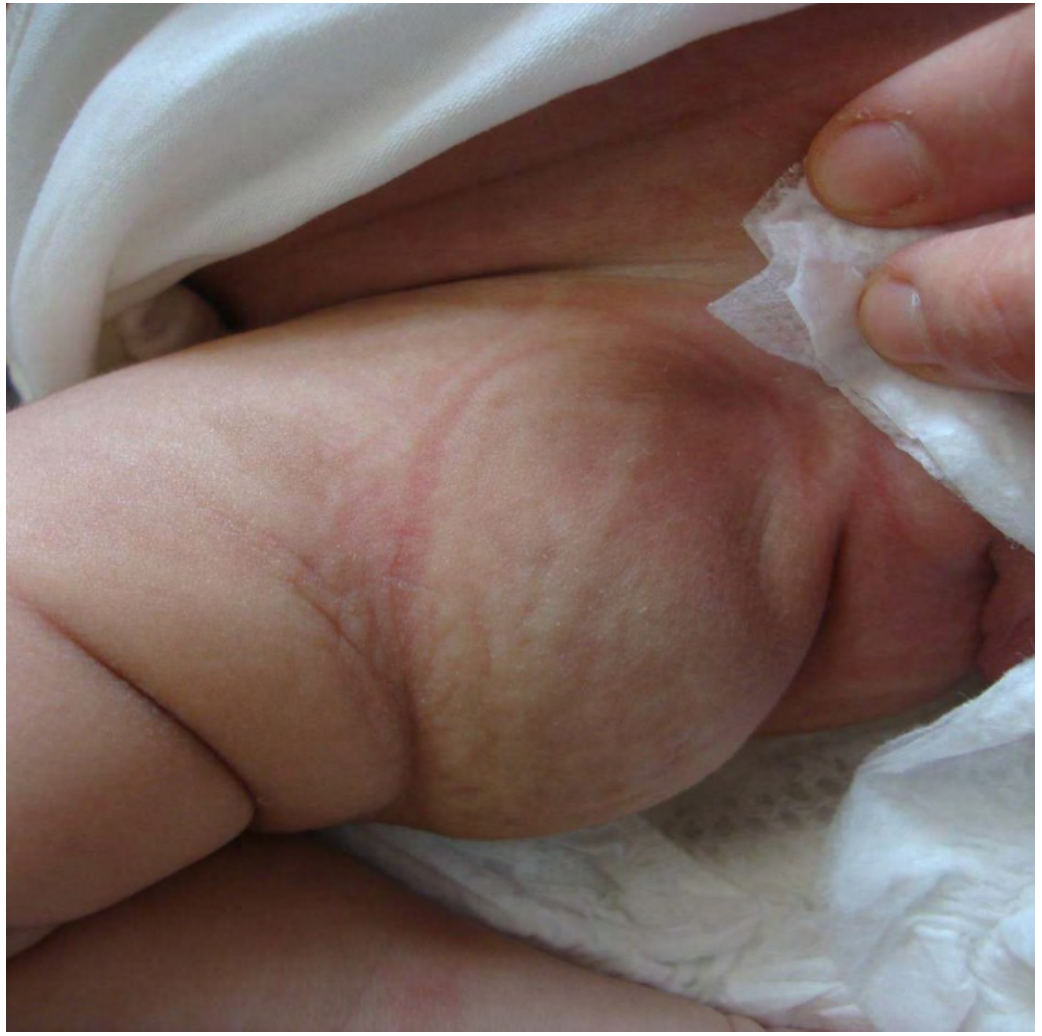
Diagnostic

Congenital hemangioma

Outcome

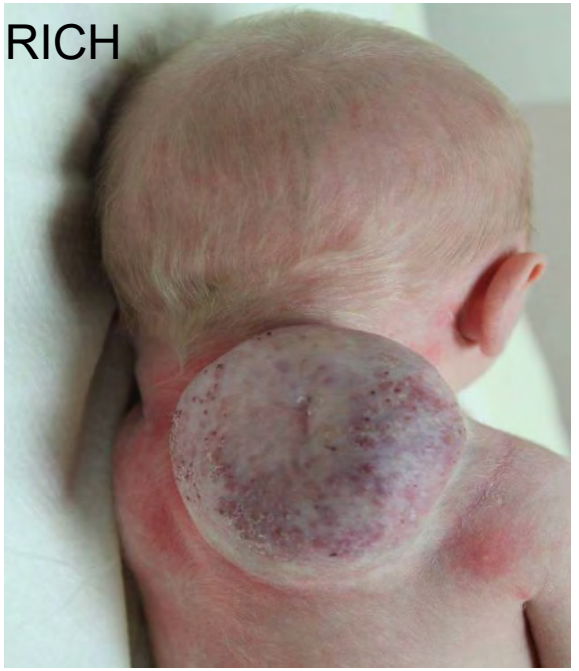
- At 1 month of age: partial spontaneous regression, shrinking and collapsing of the tumor ➡ RICH-type

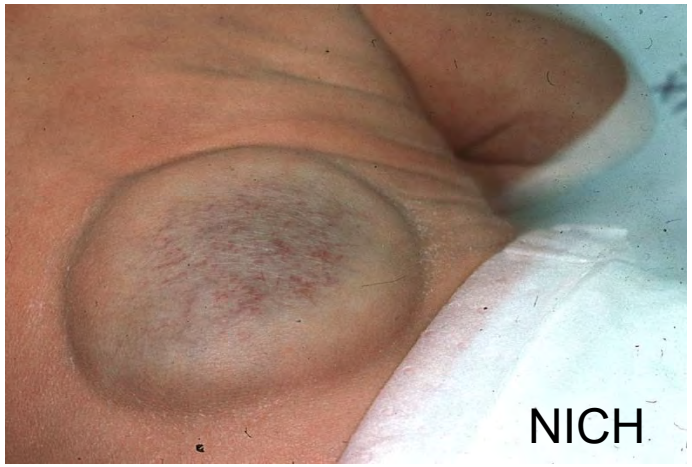
- Progressive improvement of thrombopenia:
  - platelets at D4: 49.000/mm3
  - then at D6: 180.000/mm3



Congenital hemangiomas

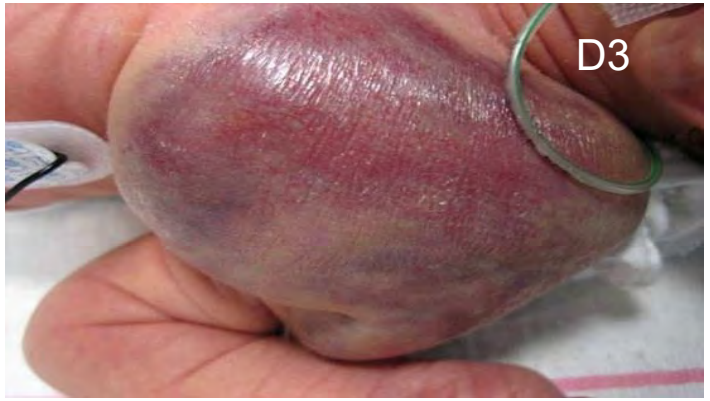
- Intra-uterine onset (UltraSound)
- Present and **fully developed at birth**
- Never grow after birth
- G = B, 5 to 6 cm in diameter
- Head and neck = extremities, rare on the trunk
- Three subtypes:
  - **Rapidly** Involuting Congenital Hemangioma **RICH**
  - **Non** Involuting Congenital Hemangioma **NICH**
  - **Partially** Involuting Congenital Hemangioma **PICH**

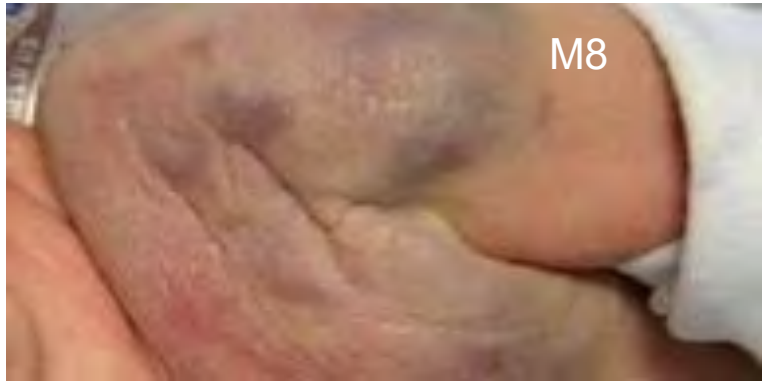




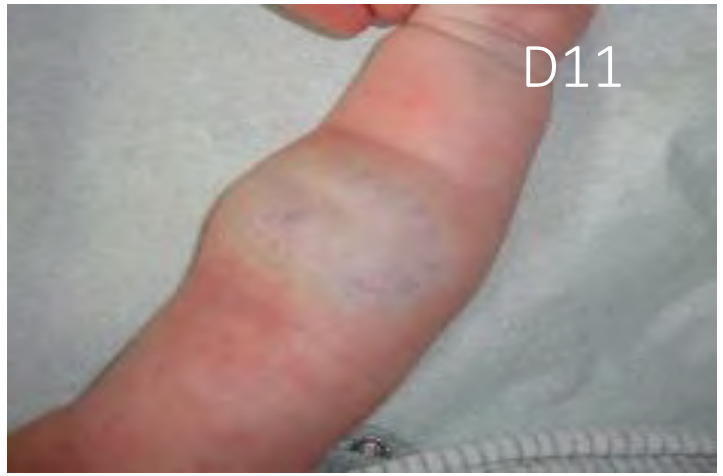
Enjolras O et al. Plast Reconstr Surg 2001;107(7):1647-54
Berenguer B et al. Pediatr Dev Pathol 2003 Pediatr Dev Pathol 6(6):495-510

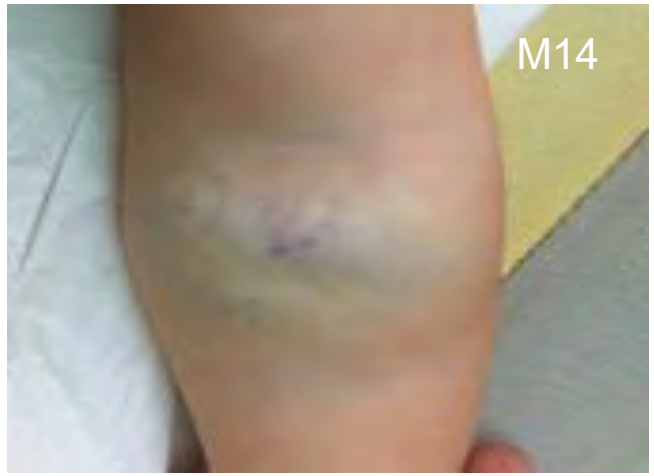
RICH



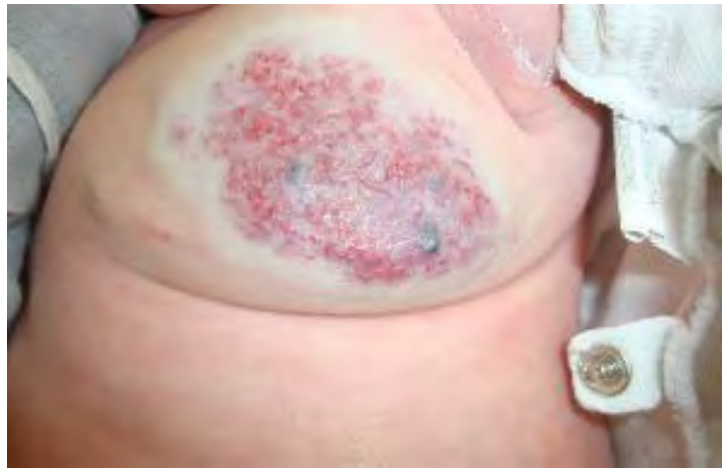


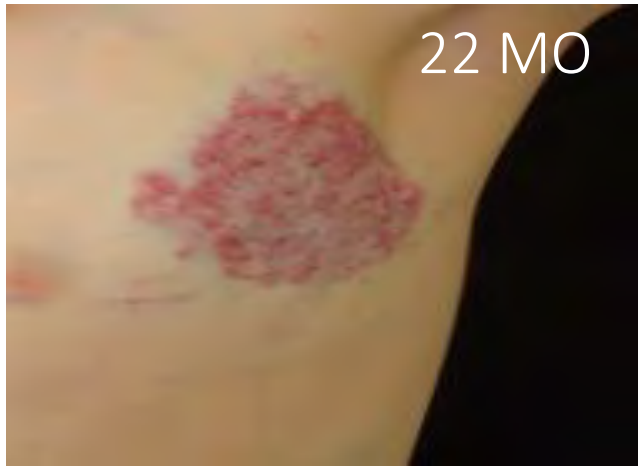
NICH





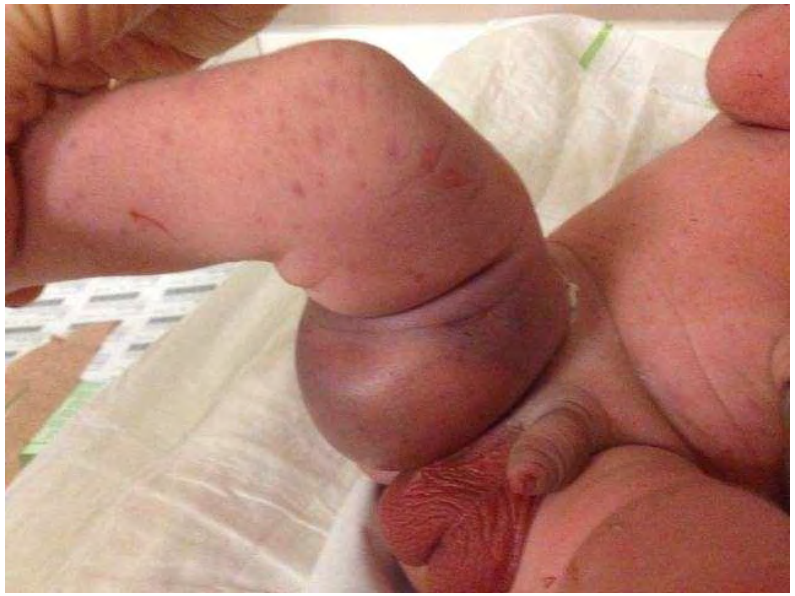
PICH

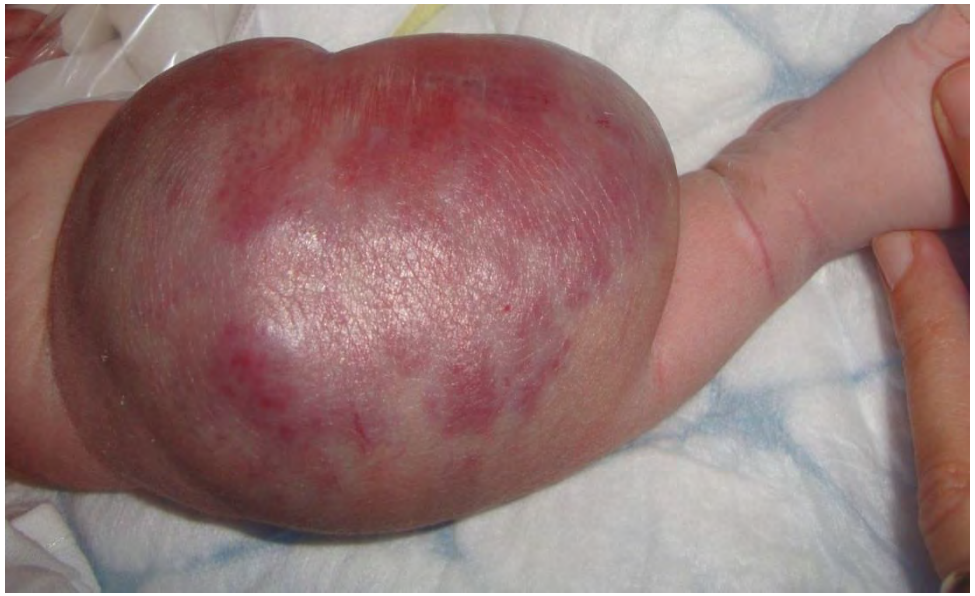




ISSVA

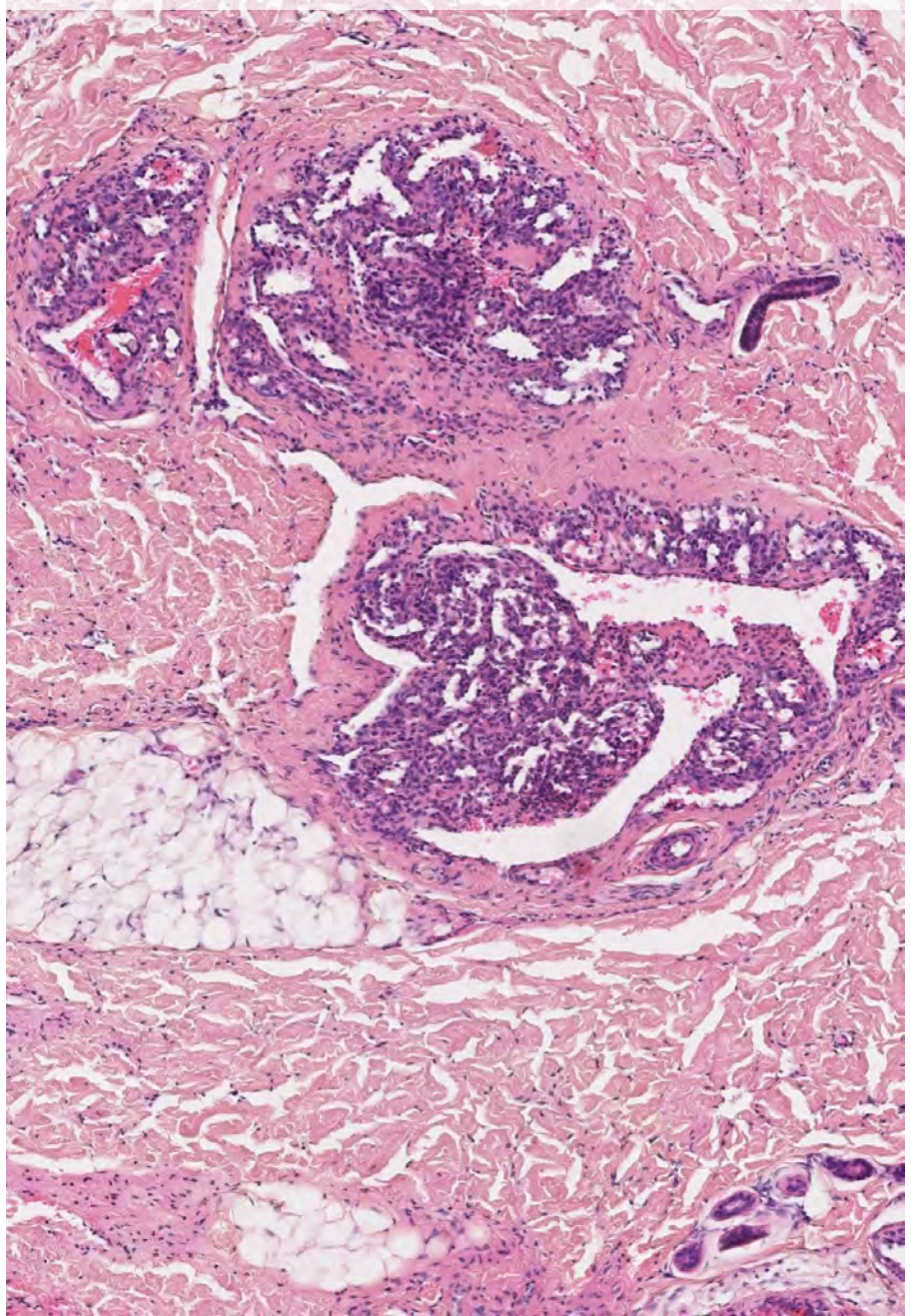
Rapidly involuting congenital hemangioma	Transient mild/moderate thrombocytopenia, +/- consumptive coagulopathy and elevated D-dimer

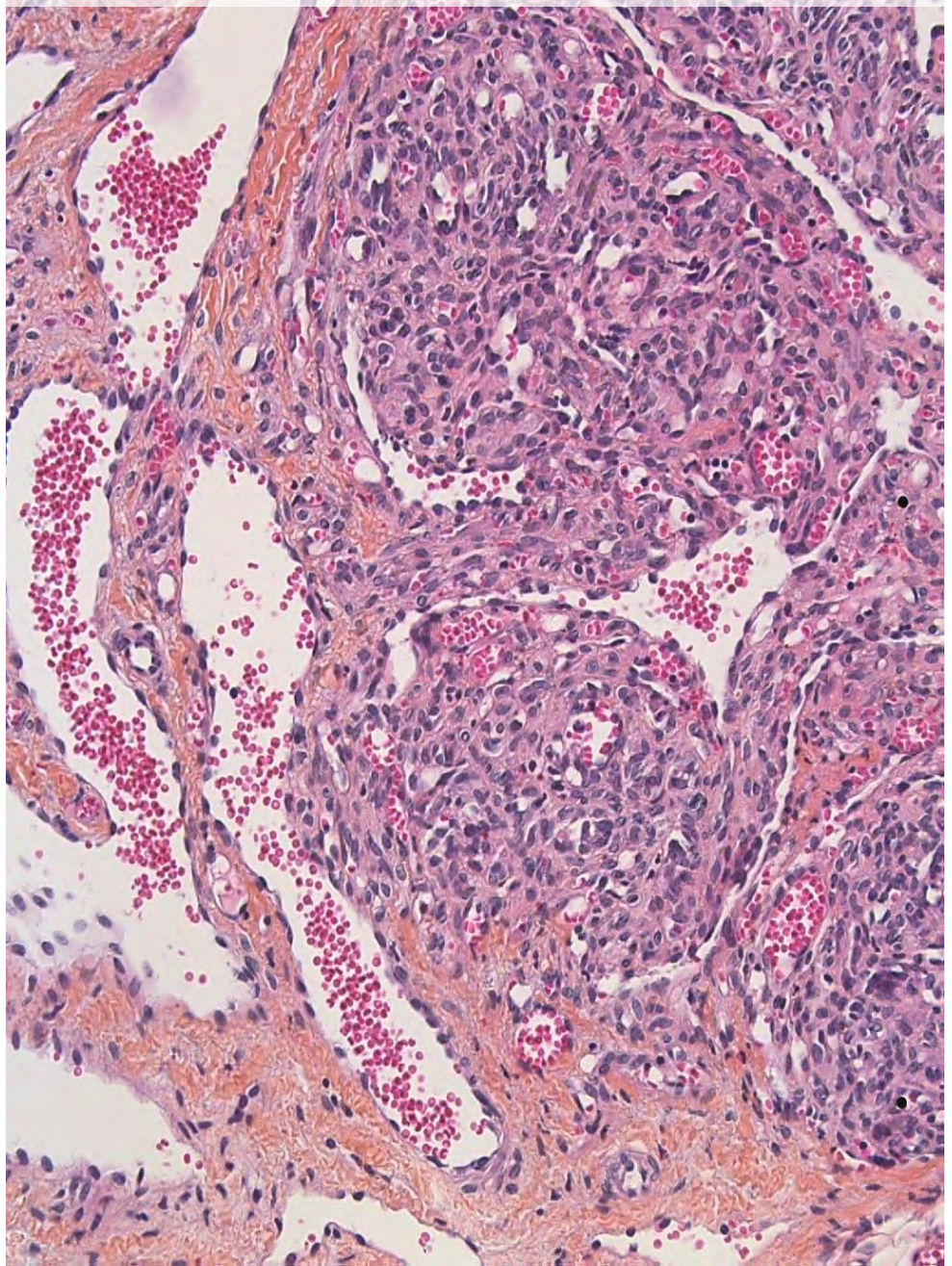




Treatment of choice: wait for spontaneous regression!

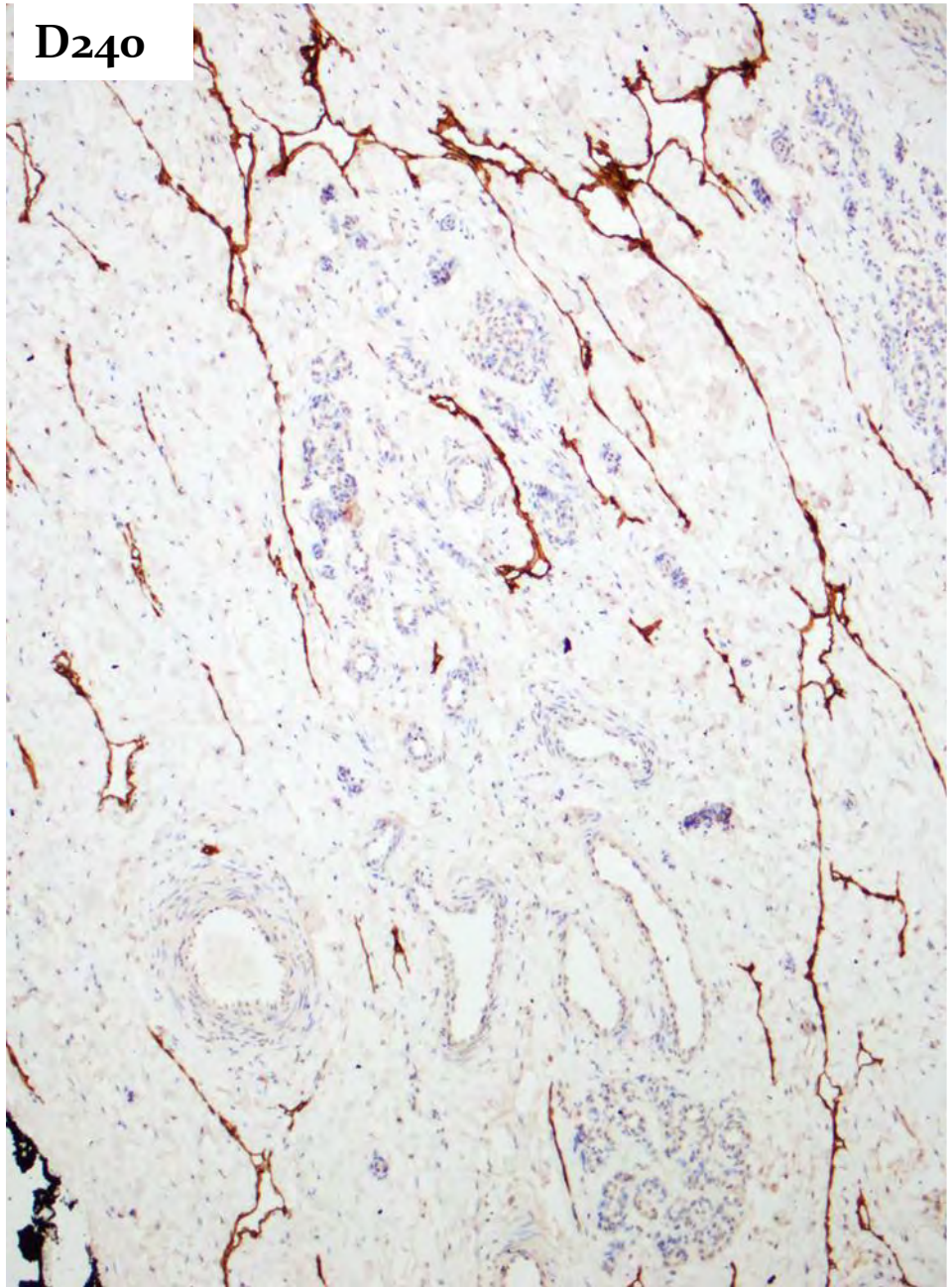
Congenital hemangioma ≠ Tufted angioma/KHE

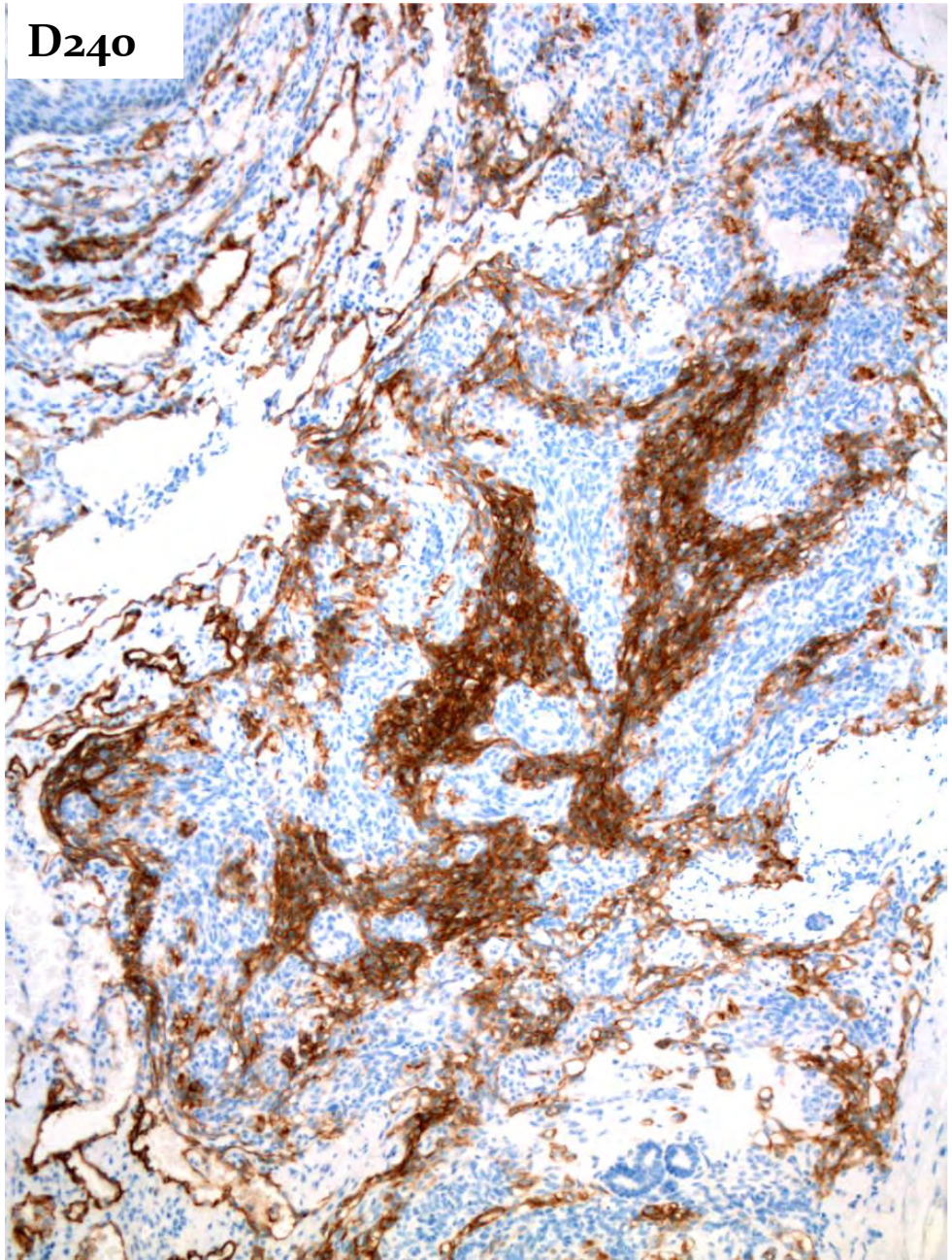




Congenital hemangioma ≠ Tufted angioma/KHE

Clue!

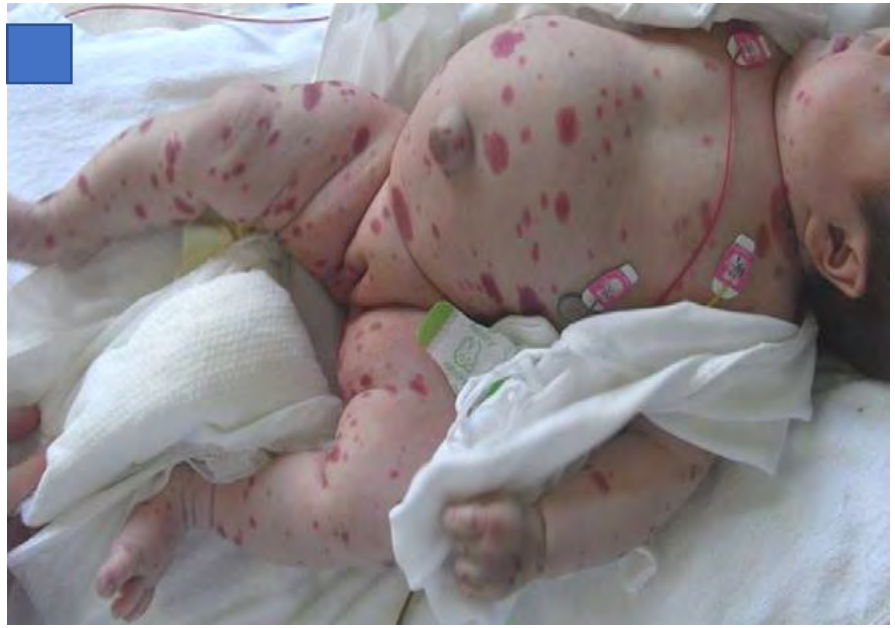




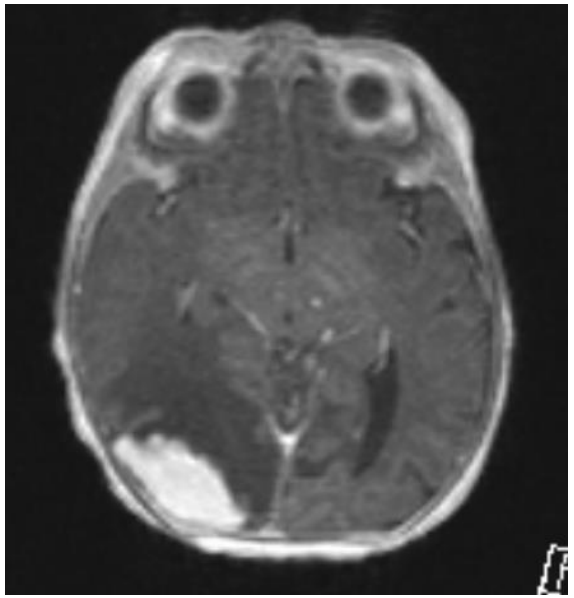
Clinical history

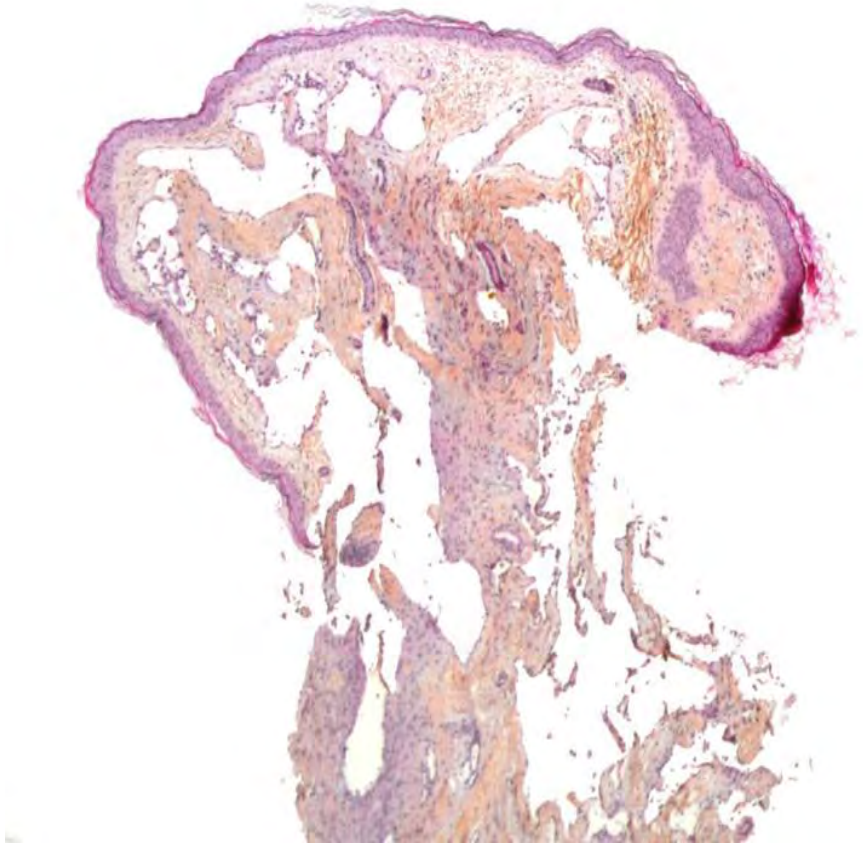
Quiz

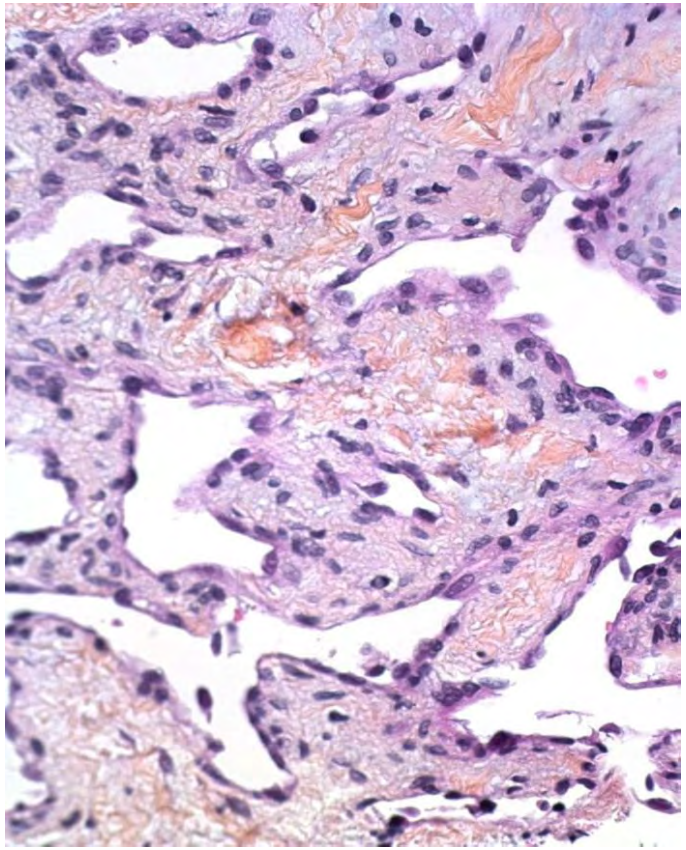
- Full-term newborn
- Numerous 3 mm to 1 cm, **violaceous plaques**, all over the body
- Present at birth
- Good general condition



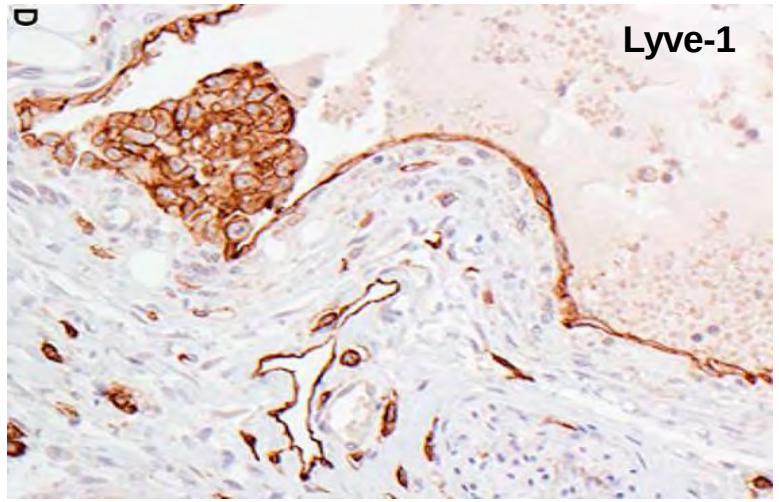
- At 4 days of age: **GI bleeding** (melena)
- **Thrombocytopenia** ($82x10^3$/ml) + **anemia,** no disseminated intravascular coagulation (D-dimer and serum fibrinogen level normal)
- Work up:
  - Endoscopy: 2 *mucosal gastric lesions*
  - US: *liver, spleen and kidney involvement*
  - XR: *osteolytic bone lesions*
  - Cranial MRI: *extraparenchymal lesion* with mass effect

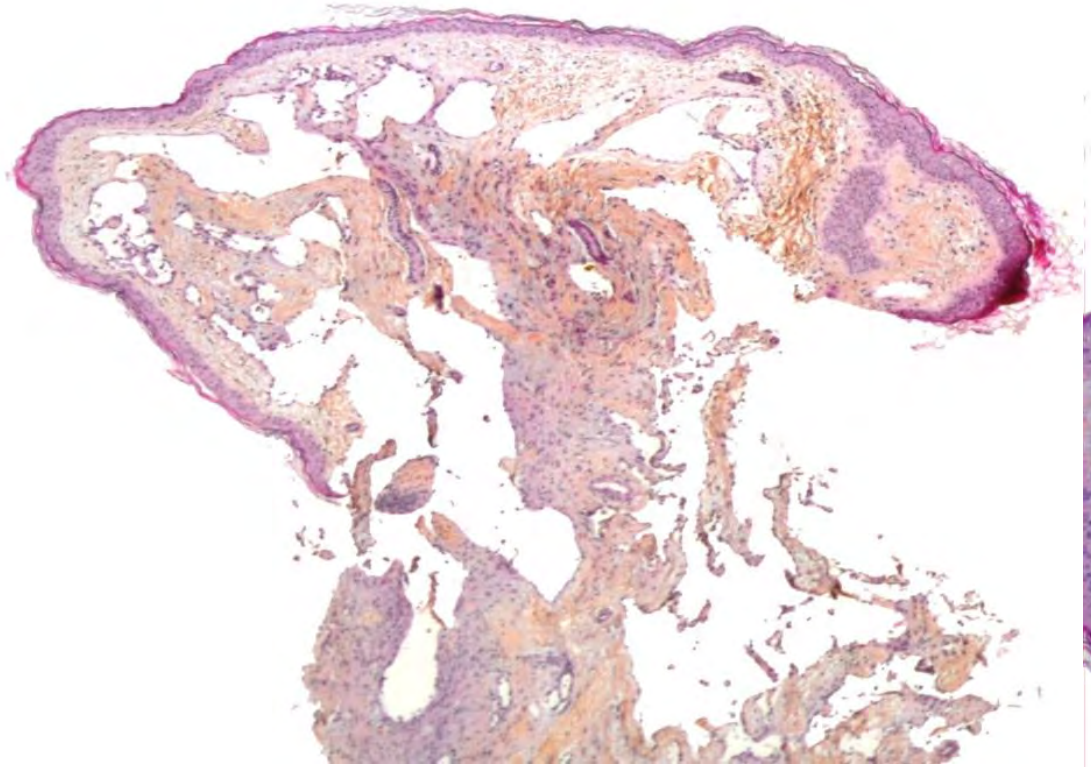


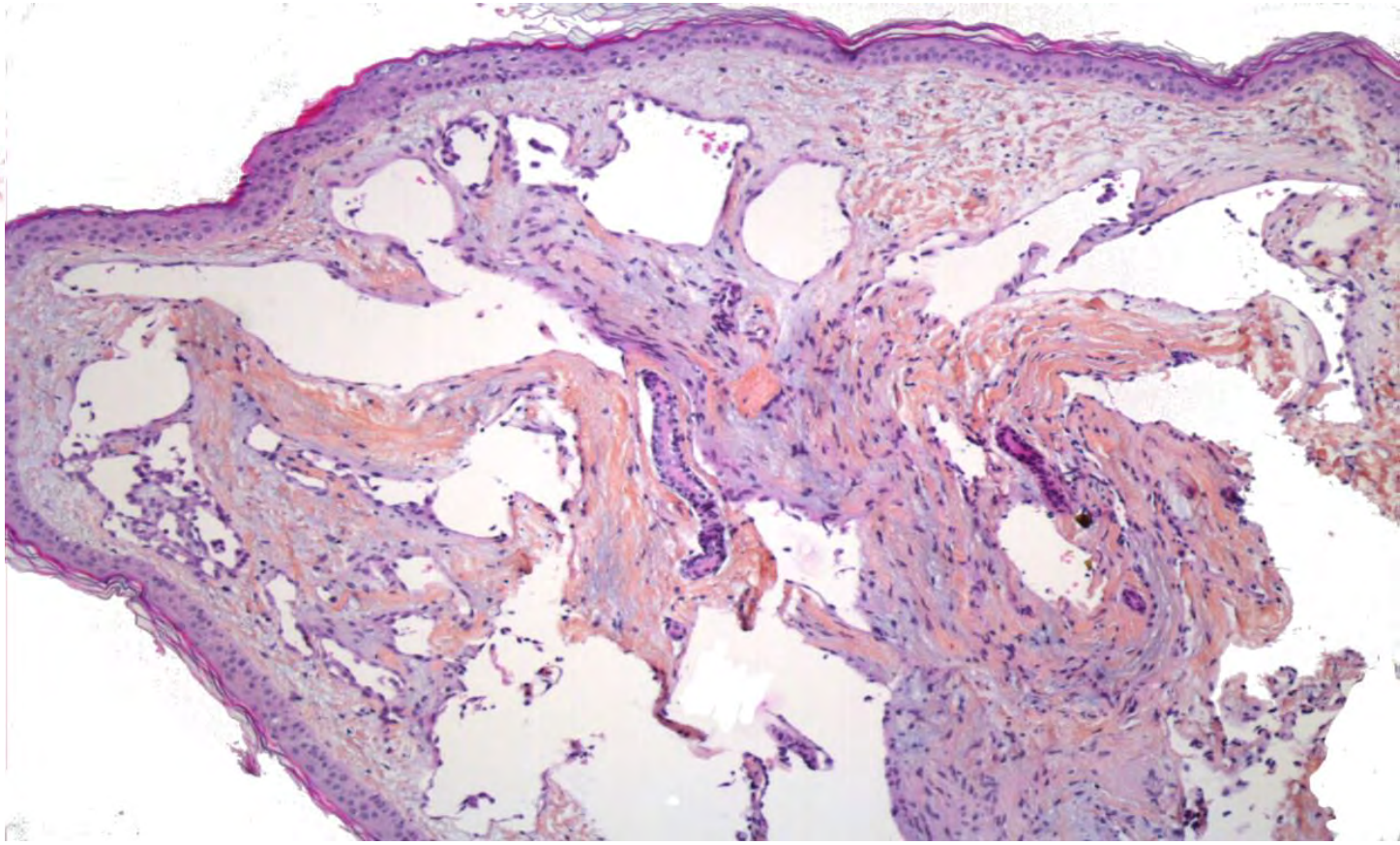




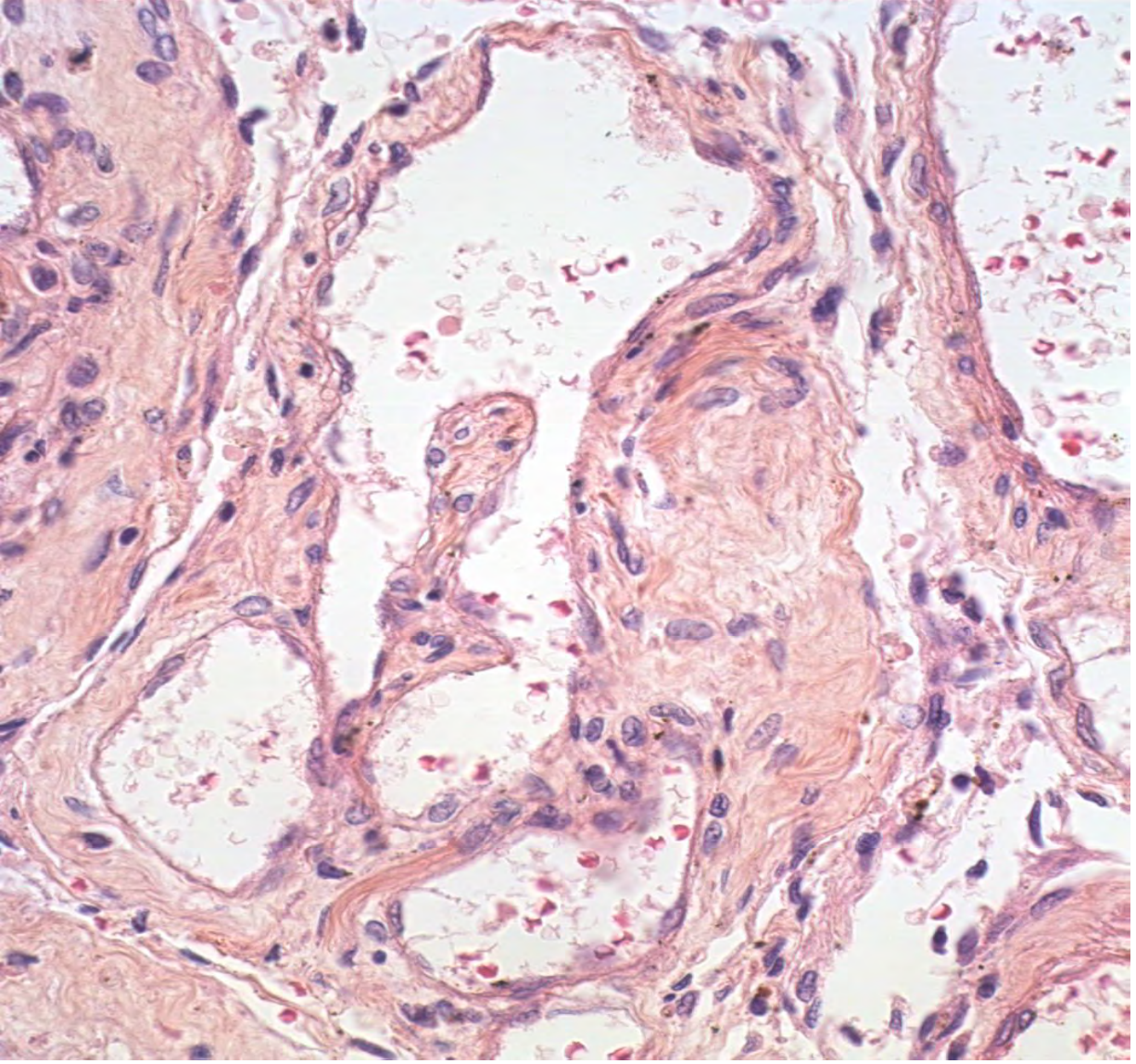
- Thin-walled well differentiated vessels in the dermis and subcutis
- Lined by hobnailed endothelial cells
- Intraluminal papillary projections
- **Glut1**-, D2-40-, **Lyve-1**+

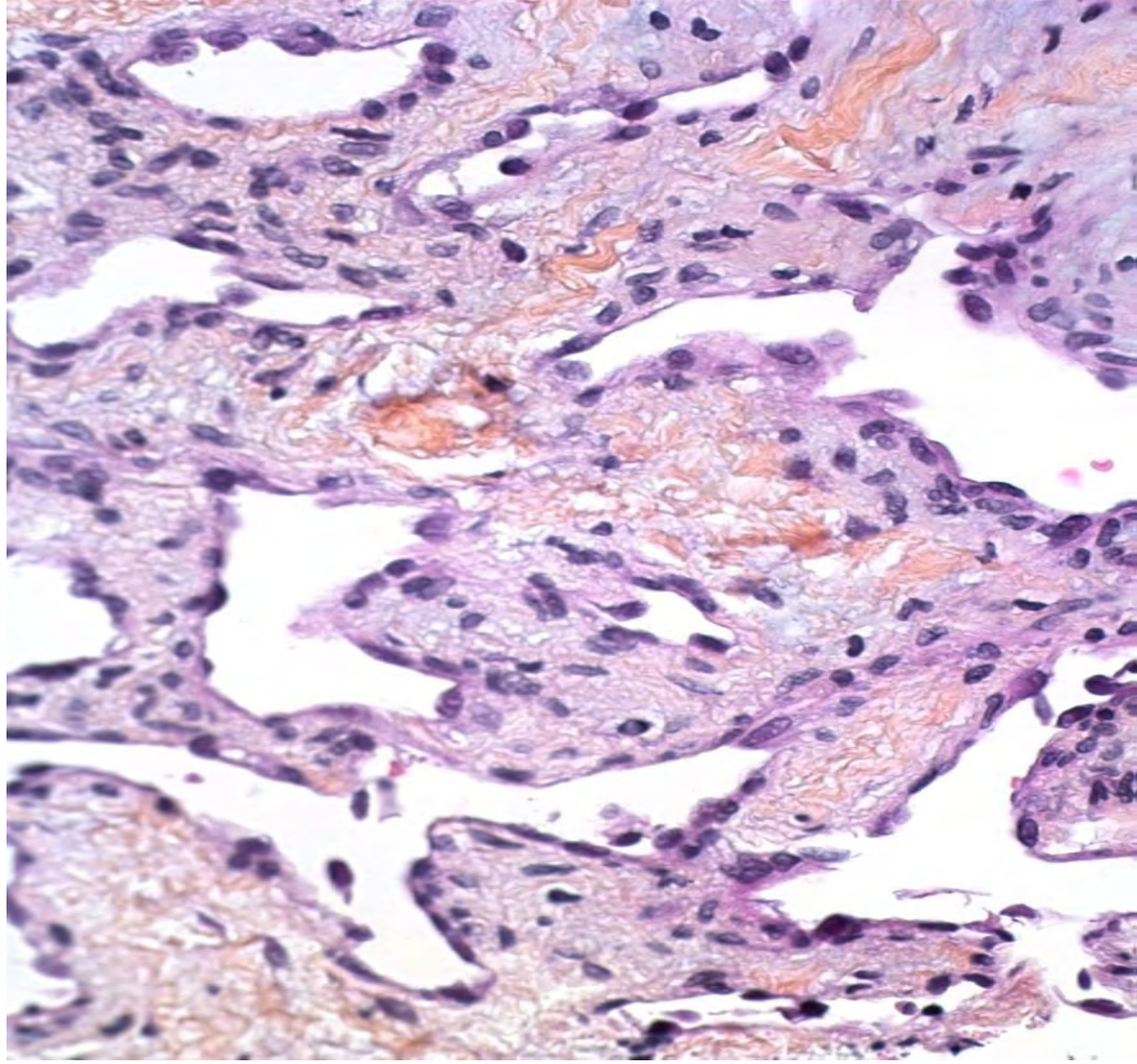




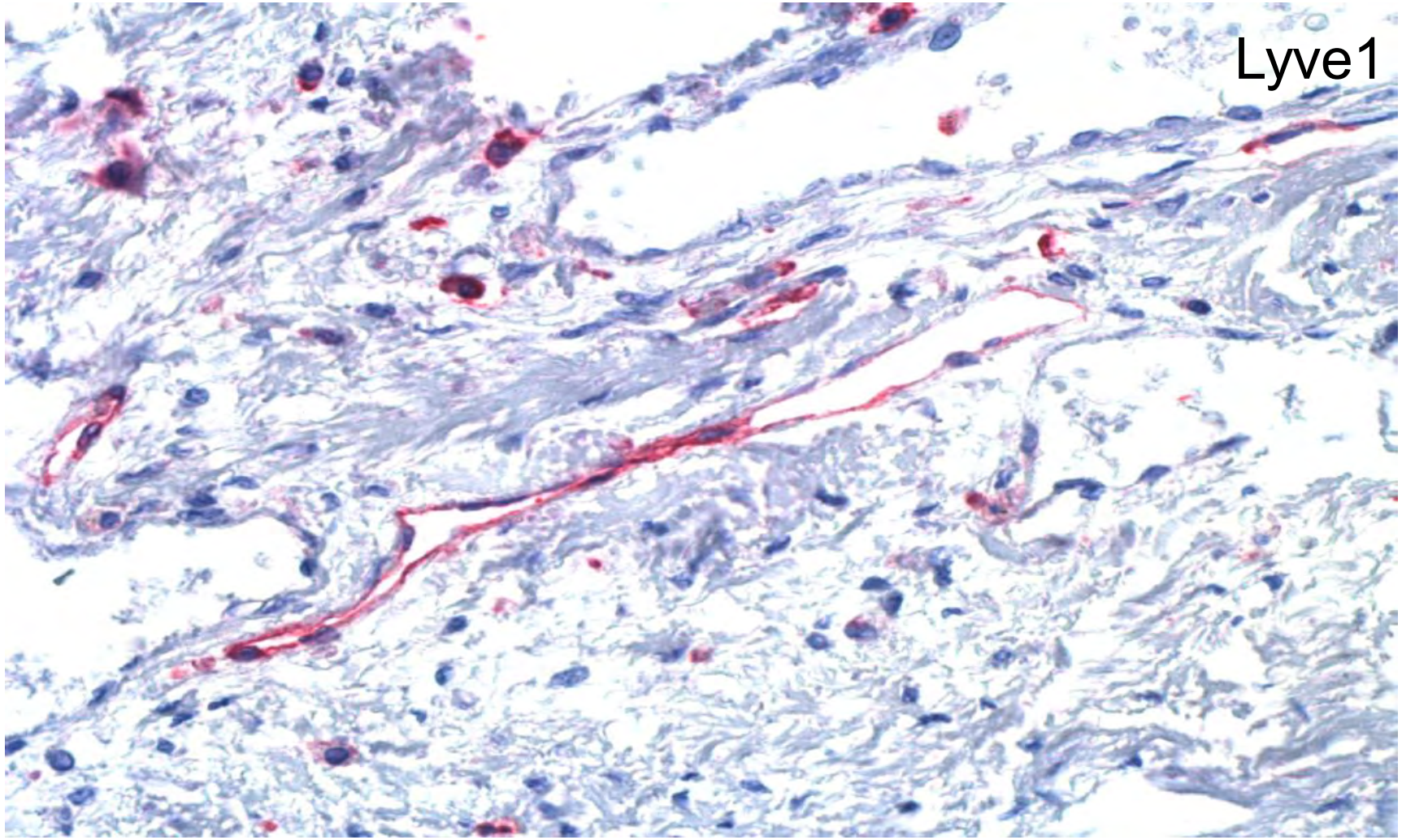


Thin-walled well differentiated dilated vessels in the dermis and subcutis





•Lined by hobnailed endothelial cells
•Intraluminal papillary projections



- Lyve1+
- D2-40 +/-
- Glut1 -

Multifocal lymphangioendotheliomatosis with thrombocytopenia

(cutaneovisceral angiomatosis with thrombocytopenia)

Multifocal lymphangioendotheliomatosis with thrombocytopenia

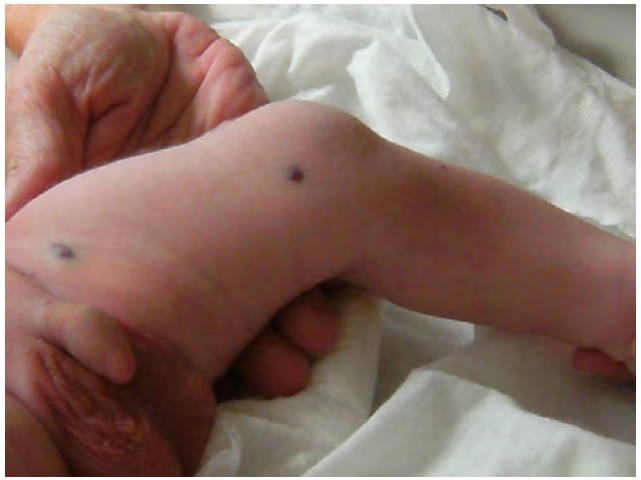
- Multifocal congenital vascular anomalies:

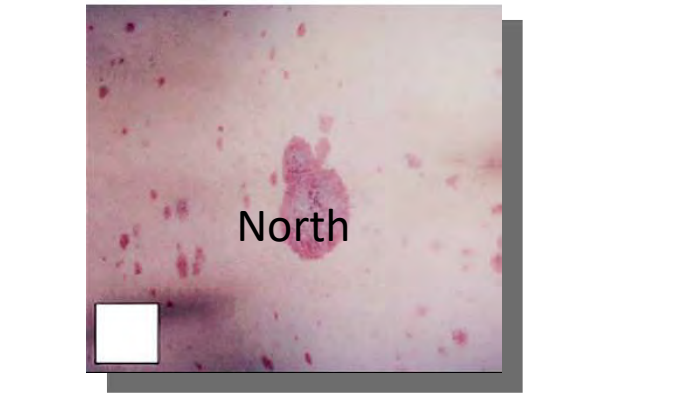
  flat or indurated , reddish-brown to burgundy, oval to round papules or plaques

- Appear at birth or within the first weeks of life
- Similar lesions throughout the GI tract

  ➡ life-threatening bleeding from lesions in the CNS or GI tract

- Most of them associated with a **severe thrombocytopenia**





Multifocal Lymphangioendotheliomatosis With Thrombocytopenia

A Newly Recognized Clinicopathological Entity

Paula E. North, MD, PhD; Teri Kahn, MD; Maria R. Cordisco, MD; Soheil S. Dadras, MD, PhD; Michael Detmar, MD; Ilona J. Frieden, MD

Background: Severe thrombocytopenic coagulopathy may complicate platelet-trapping vascular tumors such as kaposiform hemangioendothelioma and tufted angioma. Low-grade, chronic consumptive coagulopathy may occur with extensive venous and lymphatic malformations. We have also observed patients with rare multifocal, congenital skin and gastrointestinal (GI) tract vascular anomalies of distinctive and remarkably similar appearance, all associated with coagulopathy. We studied the clinical and histopathologic features of 3 patients demonstrating this previously uninvestigated phenomenon.

Observations: All 3 patients presented with hundreds of congenital red-brown skin plaques as large as a few centimeters, with similar lesions throughout the GI tract and severe GI tract bleeding. One patient had synovial involvement. All had significant thrombocytopenia, with prothrombin and partial thromboplastin times and fibrinogen levels near the reference range. Corticosteroids and/or interferon alfa treatment resulted in equivocal or no improvement. Skin lesions from all 3 patients were histologically distinctive and similar, including dilated, thin-walled vessels in the dermis and subcutis lined by hobnailed, proliferative endothelial cells (10%-15% immunoreactive for Ki-67), most displaying intraluminal papillary projections. Immunoreaction for the lymphatic marker LYVE-1 was uniformly present.

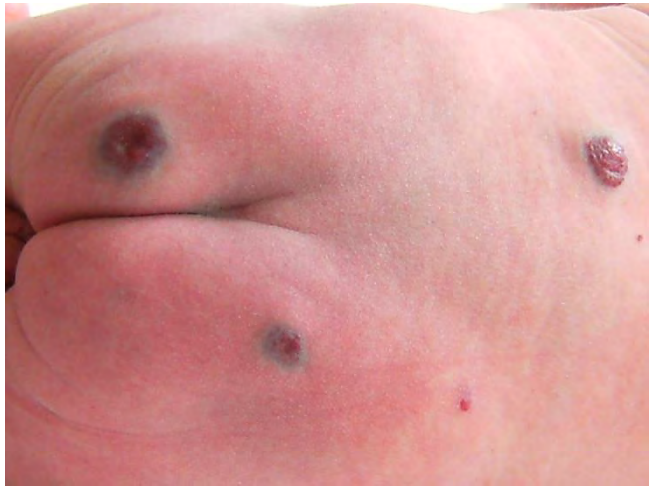
Conclusions: We propose the term *multifocal lymphangioendotheliomatosis with thrombocytopenia* to distinguish this newly recognized clinicopathological entity. These congenital lesions, like tufted angioma and kaposiform hemangioendothelioma, show lymphatic differentiation, strengthening the association between abnormal lymphatic endothelium and coagulopathy.

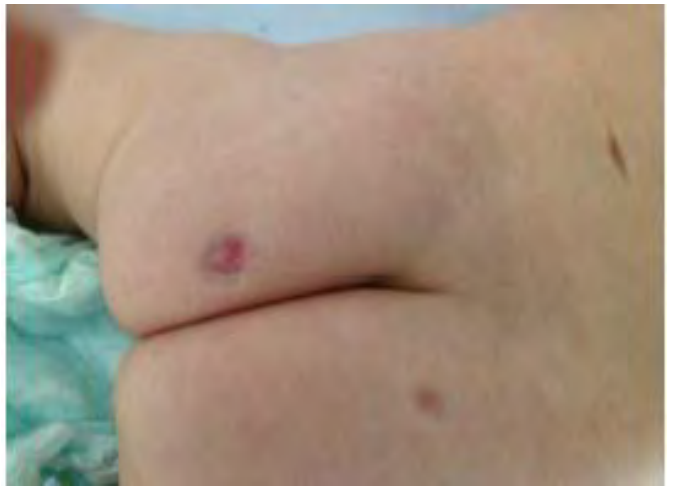
Arch Dermatol. 2004;140:599-606

Manor J et al. Clinical variability in multifocal lymphangioendotheliomatosis with thrombocytopenia: a review of the literature. Pediatr Hematol Oncol. 2021 May;38(4):367-377.

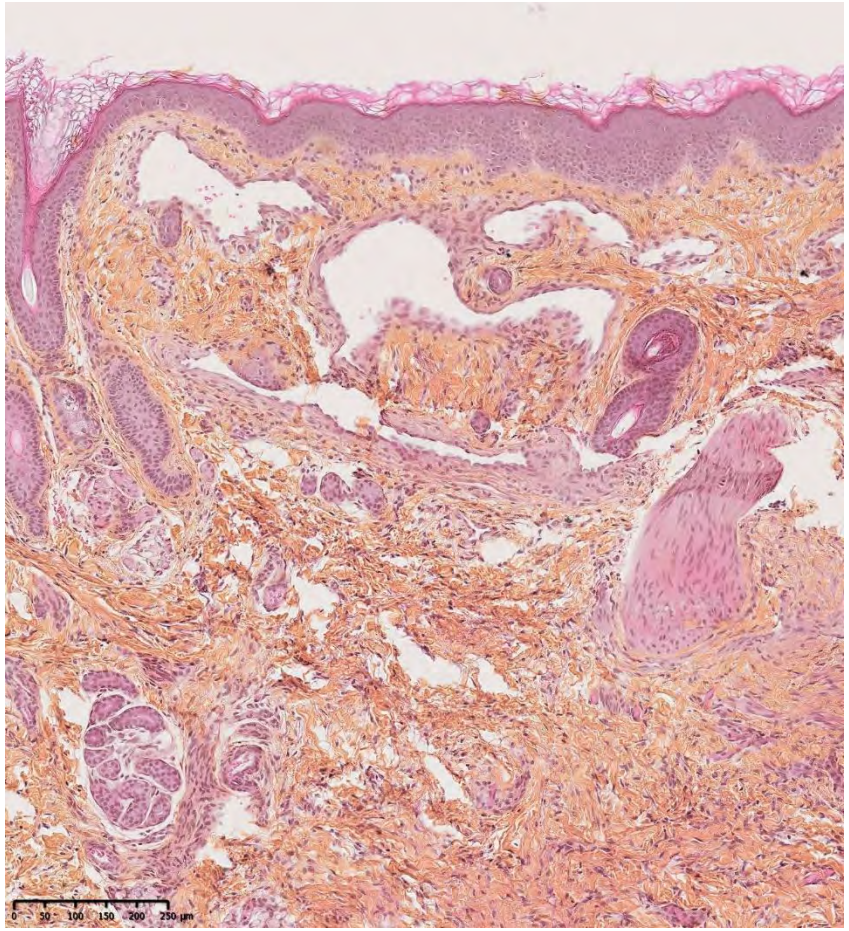
Outcome

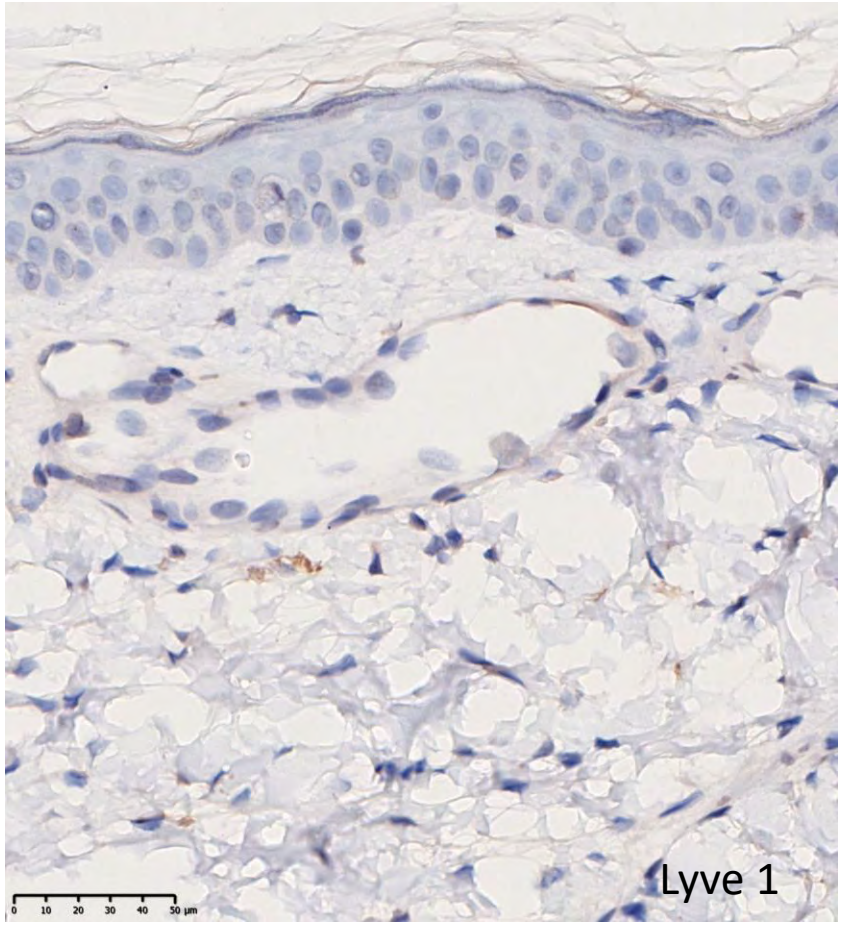
- From 4 to 30 days: **daily bleeding** that required erythrocyte transfusion once a week
- At the age of 2 months: Sirolimus (0,1 mg/kg/day)
  - **complete resolution of cutaneous lesions after 3 months**
  - healing of bone fractures
  - decrease in size of the kidney, liver, spleen and brain lesions





Droitcourt C, Boccara O, Fraitag S, Favrais G, Dupuy A, Maruani A. Multifocal Lymphangioendotheliomatosis With Thrombocytopenia: Clinical Features and Response to Sirolimus. Pediatrics. 2015 Aug;136(2):e517-22



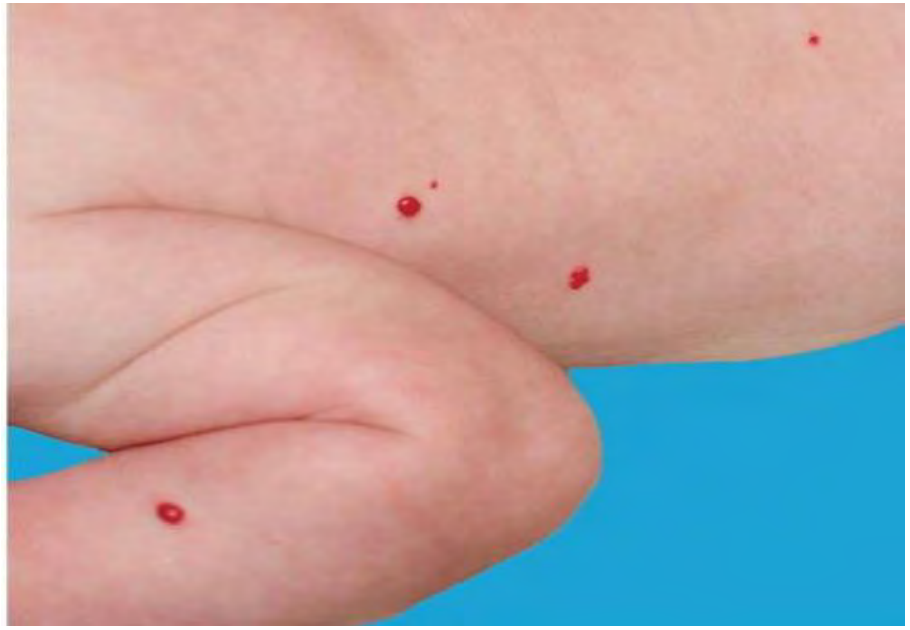


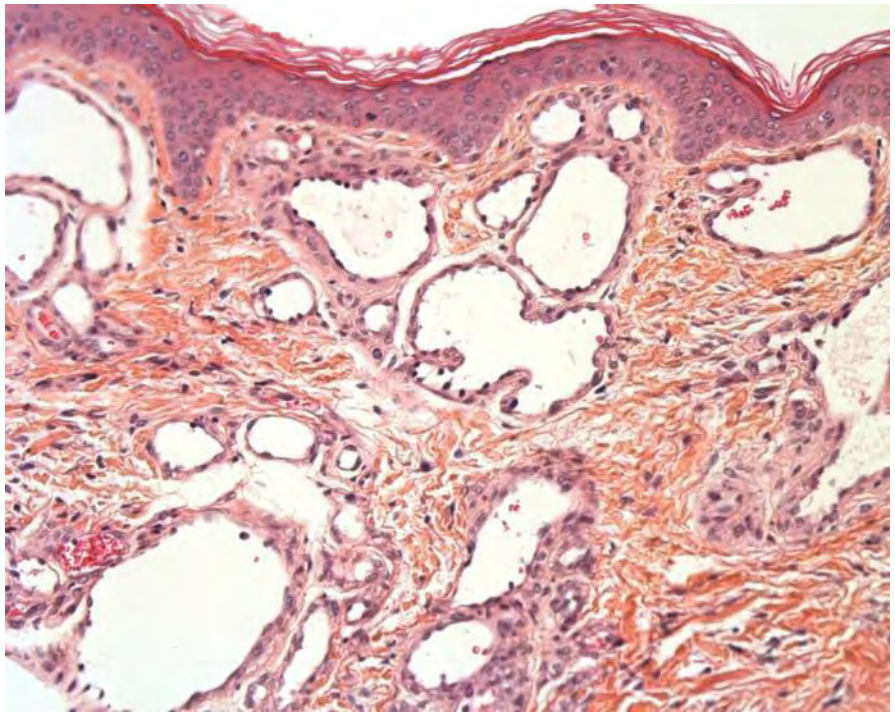
Biopsy is crucial: ≠ other multiple vascular lesions

May be cured by **Sirolimus**

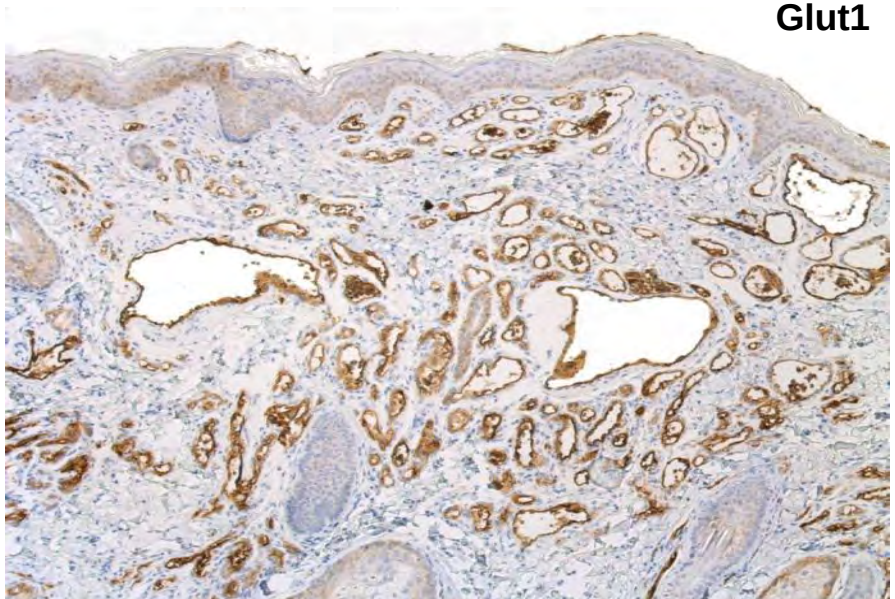
Be careful, D2-40 may be negative: Prox 1 or Lyve 1

Multifocal infantile hemangiomatosis



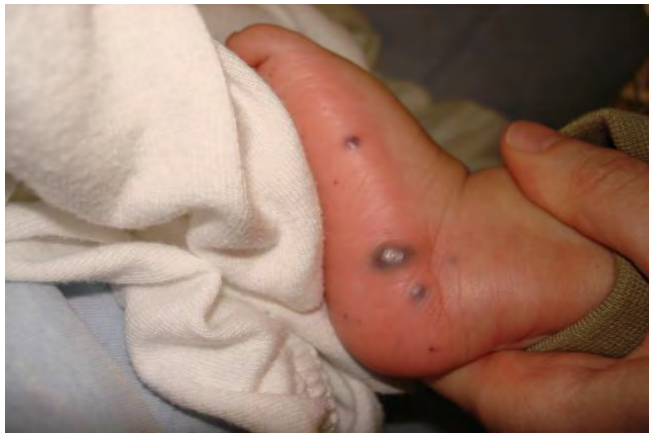


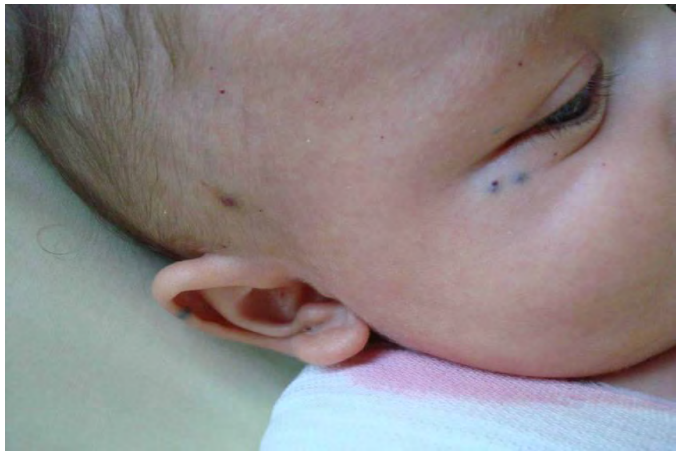
Glut1



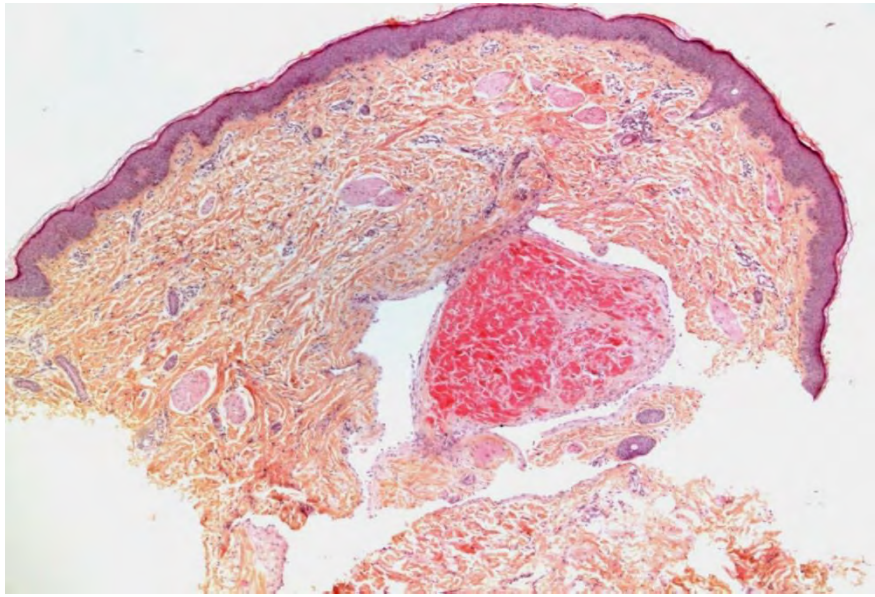
- Typically present in the first few weeks of life
- Skin lesions *can be associated with* ***organ involvement*** (**liver**)
- Involute by 2-5 years of age
- Can be treated by **propranolol**

Bean syndrome (blue rubber bleb naevus)



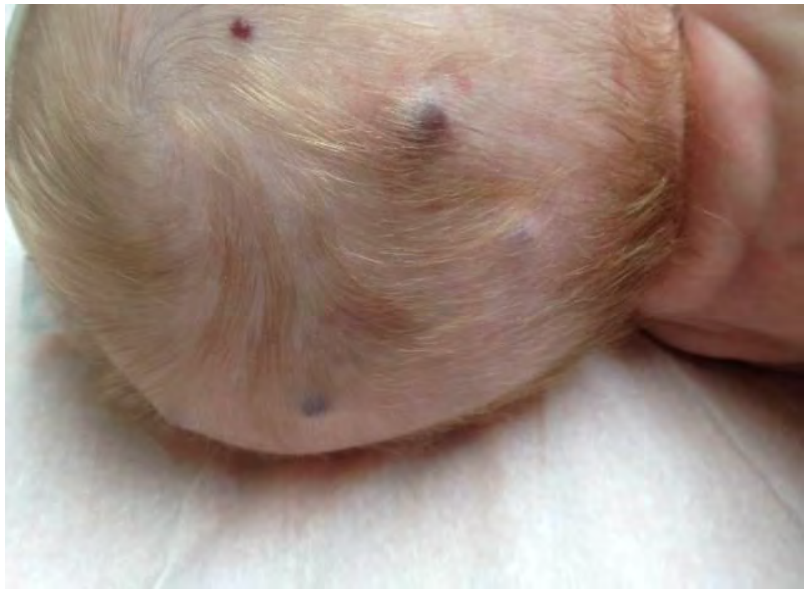


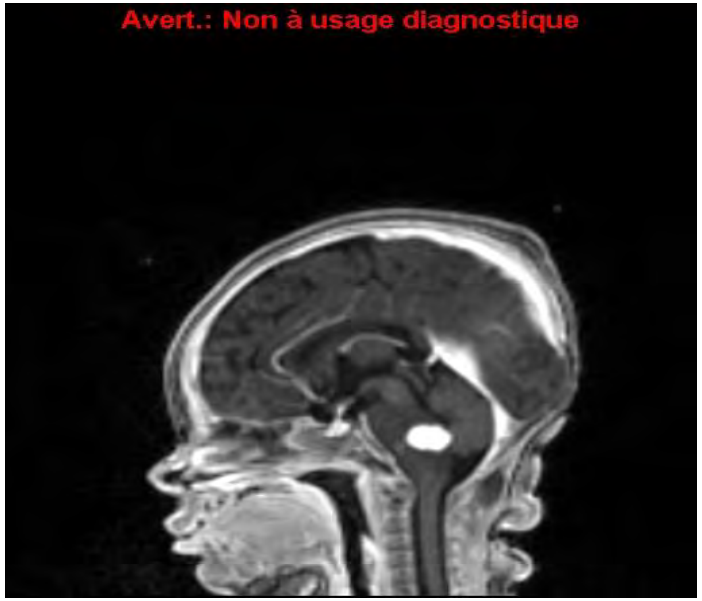
- Rare disorder
- **Multiples soft blue nodules**: skin, mucous membranes, solid organs
- Due to somatic activating mutations in the gene coding for TEK/Tie2
- **The GI tract, muscles, joints, CNS, eyes….may be affected**
- Often associated with a large « dominant » venous malformation
- Acute, life-threatening hemorrage and localized IV coagulation
- **Sirolimus**

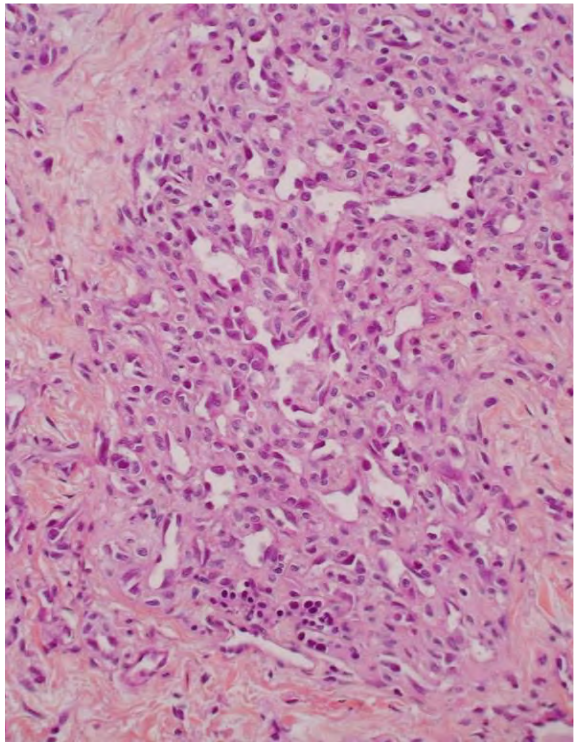


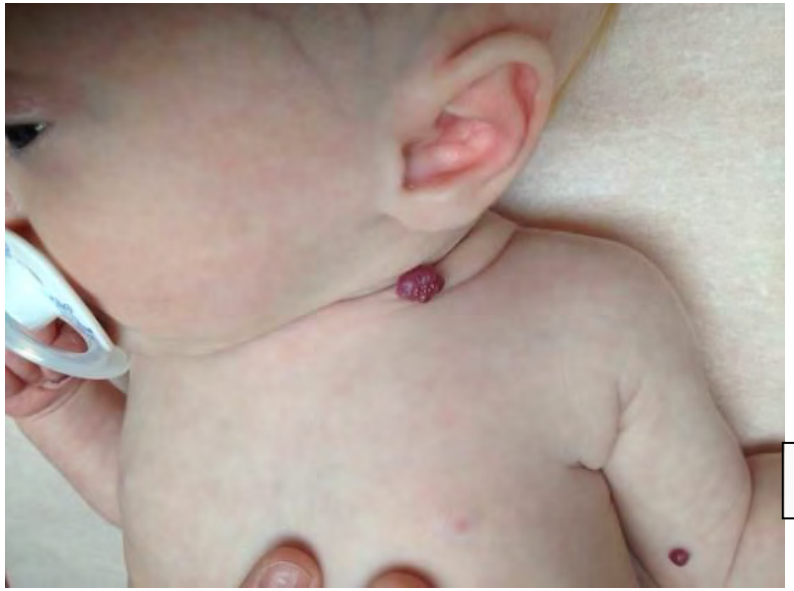
Weiss D et al. Long-term sirolimus in the blue rubber bleb nevus syndrome. Case report and review of the littérature. Pediatric Dermatol 2021, 38, 464-468

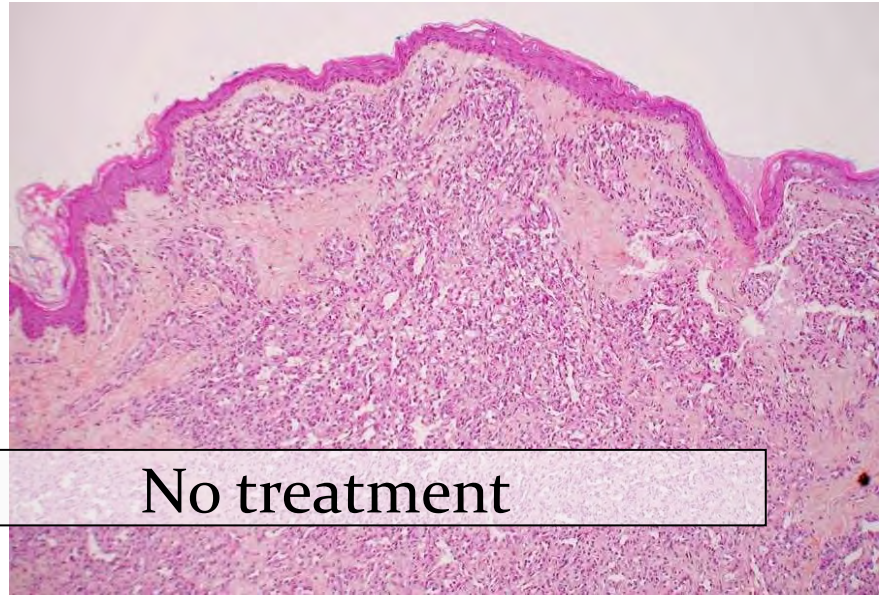
Multiple neonatal pyogenic granulomas



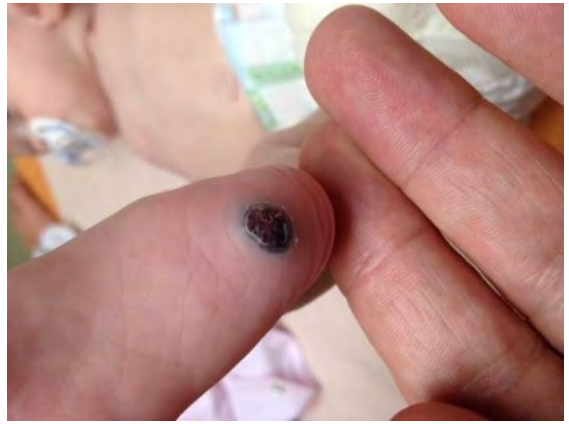






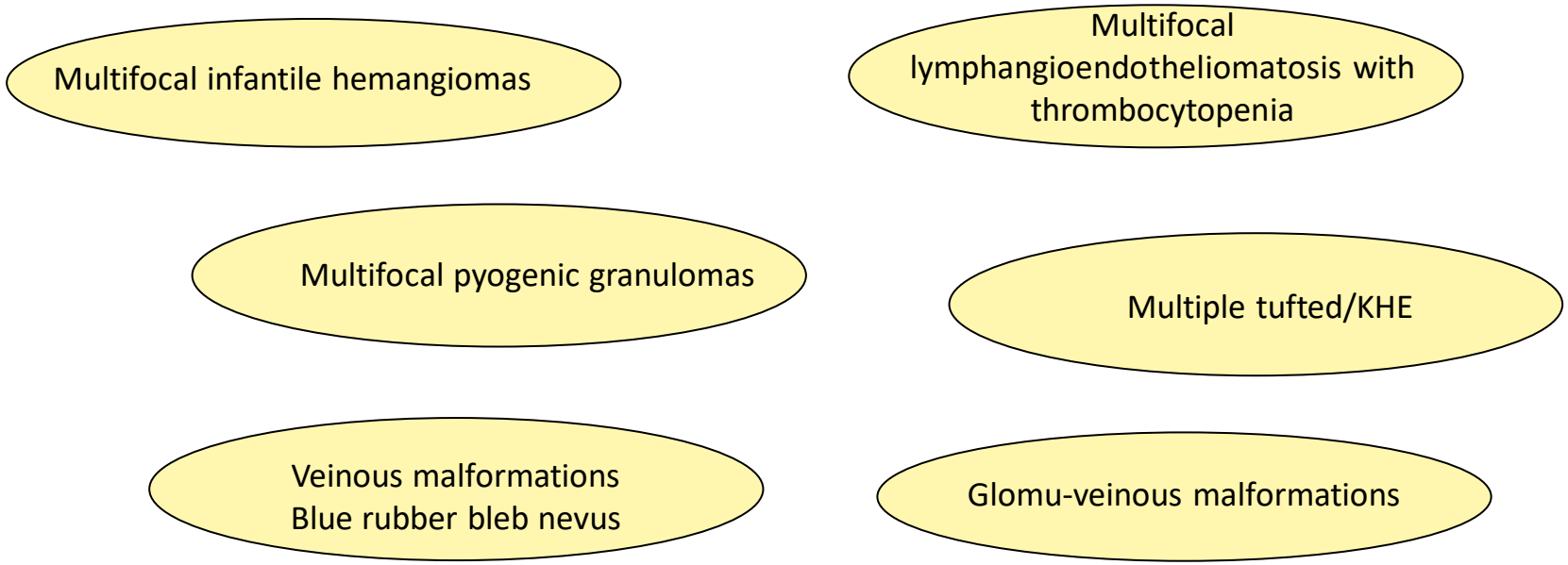


No treatment



Congenital and disseminated pyogenic granuloma-like vascular lesions
S Mallet, C Rebelle, I Ligi, D Scavarda, C Bouvier P, S Fraitag, M Wassef Acta Derm Venereol. 2015 Oct 5;95(7):860-861

« Diffuse neonatal hemangiomatosis »: multiple disorders



It is crucial to biopsy these multiple neonatal vascular lesions

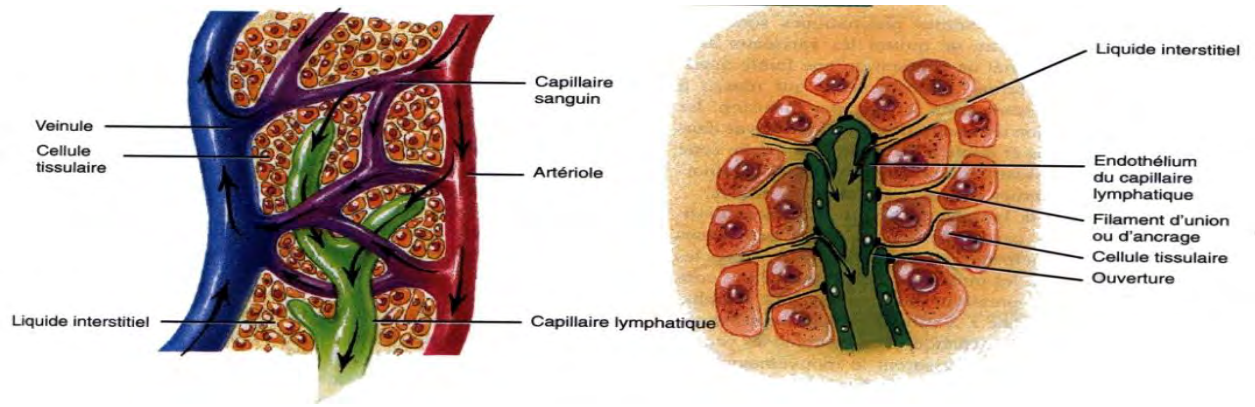
↓

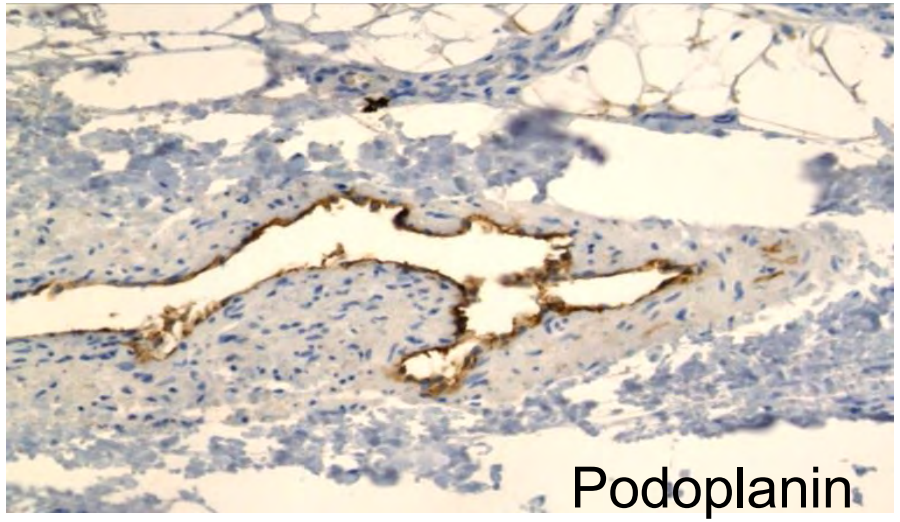
Adequate therapy

Fraitag S, Boccara O. What to Look Out for in a Newborn with Multiple Papulonodular Skin Lesions at Birth. Dermatopathology (Basel). 2021 Aug 17;8(3):390-417.

What do these entities have in common?

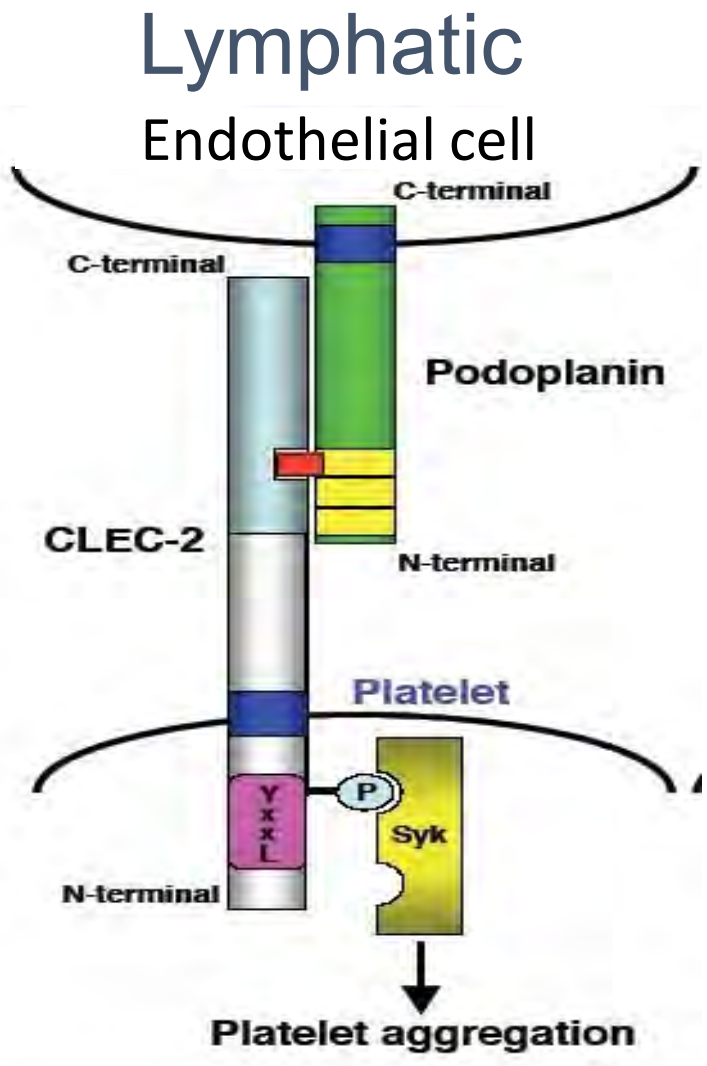
- TA/KHE
- RICH
- Multifocal lymphangioendotheliomatosis with thrombocytopenia





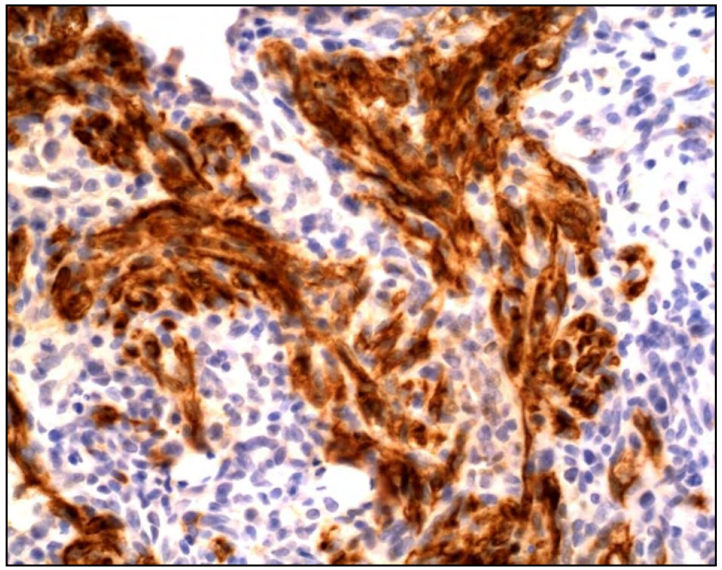
Lymphatic vessels and thrombocytopenia!

- **Podoplanin** is found in endothelial cells of lymphatic vessels
- Podoplanin: ligand of CLEC-2, highly expressed on platelets and reponsible for platelet activation
- Binding of podoplanin to CLEC-2 : predominant **initiator of blood clotting** observed in tumors with a podoplanin + lymphatic phenotype



Navarro-Nünez L et al. Thromb haemost. 2013; 109(6): 991-998
Baselga E et al. Br J Dermatol 2008;158: 1363-1370

Vascular anomalies



The lymphatic phenotype era!

Can be of considerable help in the classification of a vascular tumor in children!

Hôpital Necker-Enfants Malades