Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Infantile hemangioma and other vascular tumors of infancy

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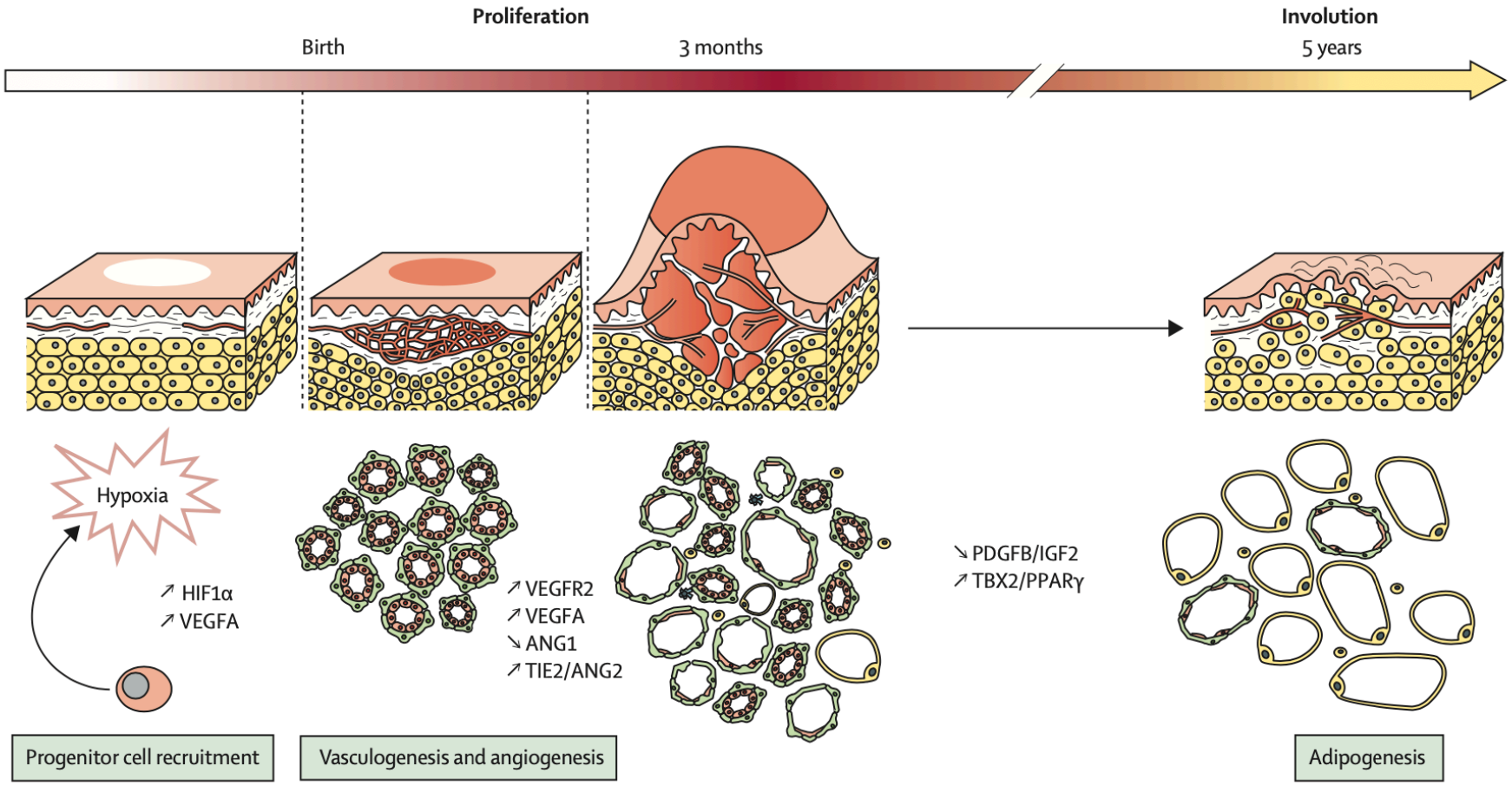
Training course in pediatric dermatology

20.01.2022

Infantile Hemangioma (IH)

- Benign vascular tumor of infancy
- Most common pediatric vascular tumor (affects 4% of infants)
- F>M (2.3-2.9x)
- Risk factors:
  - Prematurity
  - Low birth weight
  - White race
  - Multiple gestations
  - Familial history of hemangioma
  - Preeclampsia, placenta previa

Pathogenesis



C. Léauté-Labrèze. Lancet 2017.

Pathogenesis

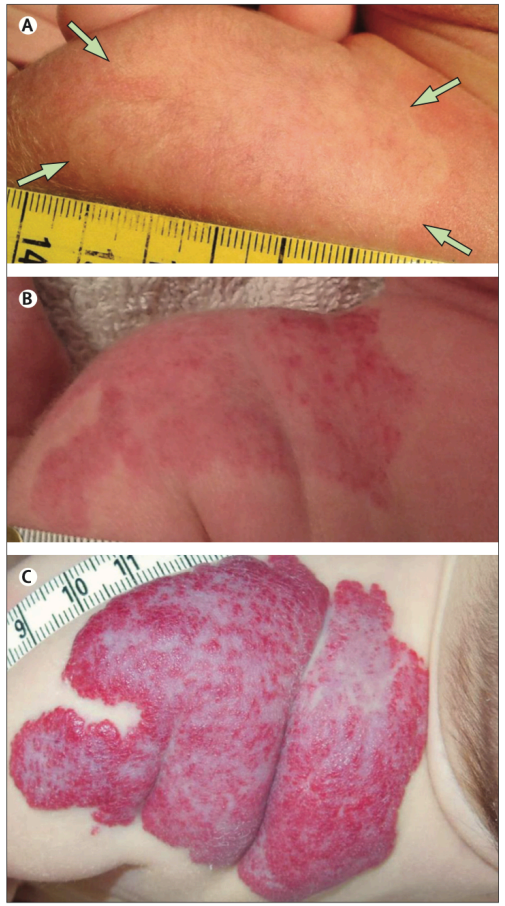
Role of renin-angiotensin system (RAS)

- Angiotensin 

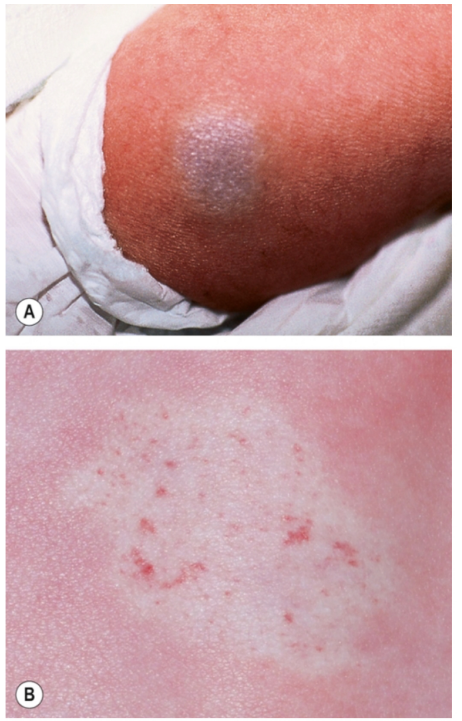
ATI ATII
- High levels of Renin is physiological during infancy
- ATII promotes the secretion of the vascular endothelial growth factor system and osteoprotegerin, a protumor survival factor, maintaining a favorable environment for vasculogenesis and antiapoptosis

Clinical Features

- Absent at birth and appears during the first weeks of life
- Precursor lesions:
  - Telangiectasia with vasoconstrictive halo
  - Pale area
  - Pink patch
  - Bluish tumefaction
  - DD: anemic naevus or capillary malformation
- Localization:
  - Anywhere on the skin and mucosal surface
  - 50% on trunk



C. Léauté-Labrèze. Lancet 2017

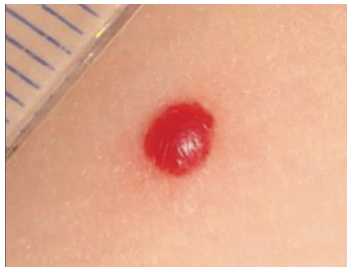


Bolognia texte book

3 Types of IH

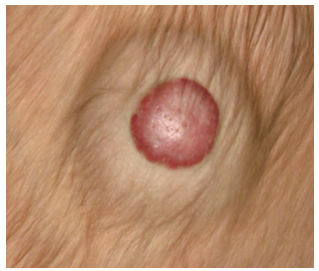
Superficial

- Superficial dermis
- Most common (50-60%)



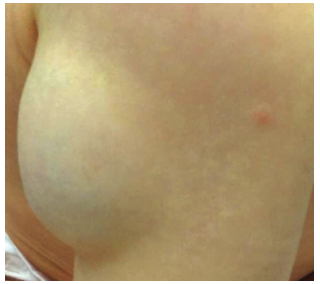
Mixed

- 25-35% of IH



Deep

- Deep dermis or/and subcutaneous tissue
- Skin colored or blue subcutaneous mass
- 15% of IH

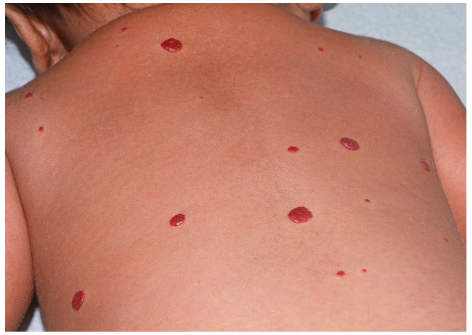


Pattern of involvement

Focal

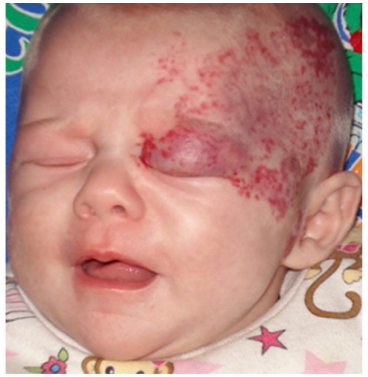
www.seattlechildrens.org

Multifocal



Bologna texte book

Segmental

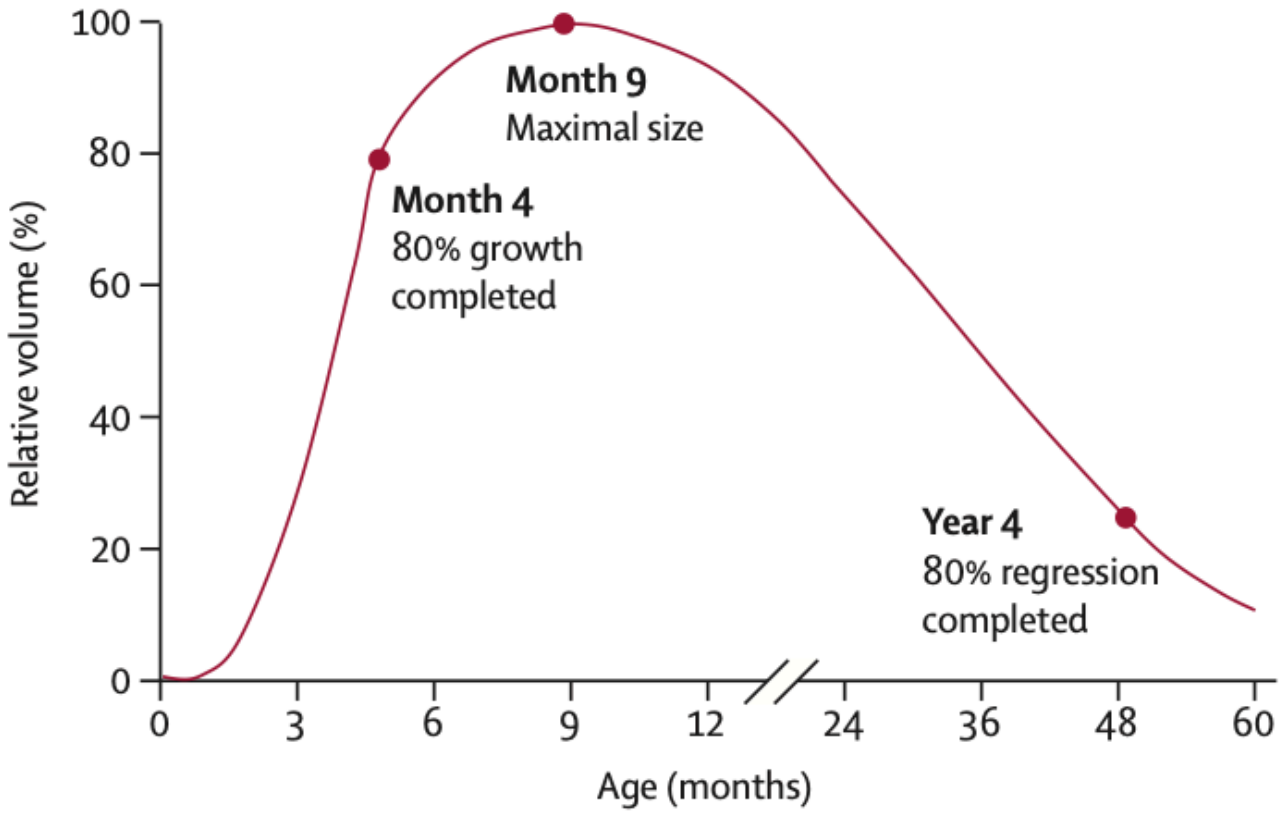


Garzon Mc et al. J pediatr 2016.

lindeterminate

ISSVA 2018

Natural history



C. Léauté-Labrèze et al. Infantile hemangioma. Lancet 2017

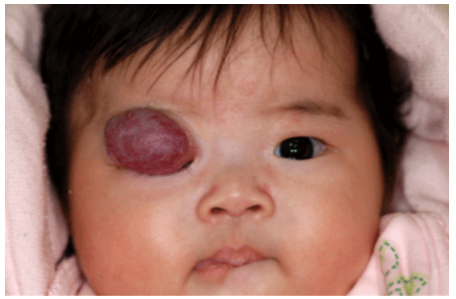
Exceptions:

- IH located on head and neck, deep IH and segmental morphology:
  - Late growth can occur in children after 3 years of age
- Deep IH: later regression (7-8 years)
- Mixed IH:
  - Overlap of growth and regression phase
  - Regression of superficial part and growth of the deep part

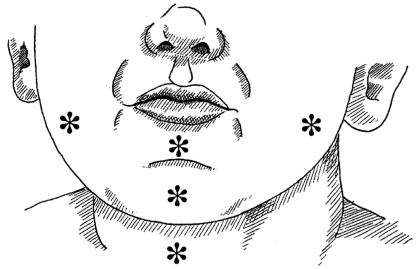
Locoregional complications

Obstruction and functional impairment

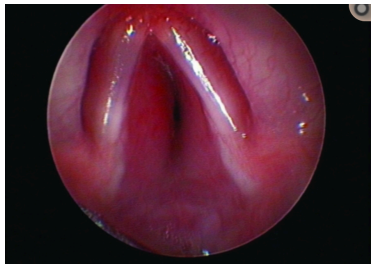
- Periocular IH => astigmatism (33%), visual axis obstruction, nasolacrimal duct obstruction, ptosis, amblyopia and strabismus
- Peri-oral IH => Feeding difficulties, delay in tooth eruption and enamel hypoplasia
- External acoustic meatus IH => conductive hear loss
- IH of “beard area” => may be associated with airway IH => obstruction



Omicsonline.org



Orlow SJ J Pediatr 1997



Spinks J. BMJ case report 2010.

Ulceration

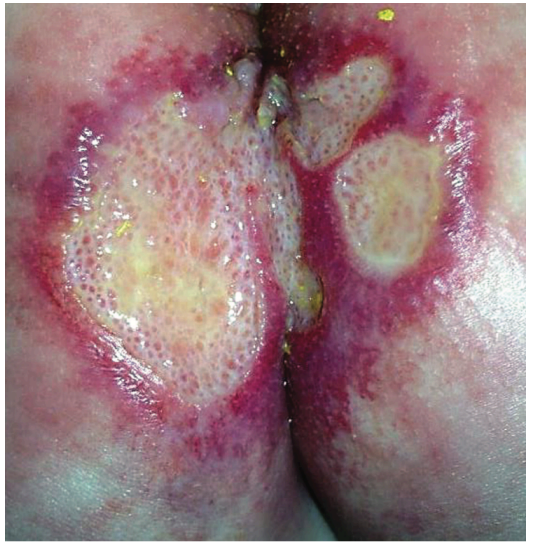
Most common complication (around 16% of patients with IH)

Observed mainly during 4th and 8th months of age (proliferative stage)

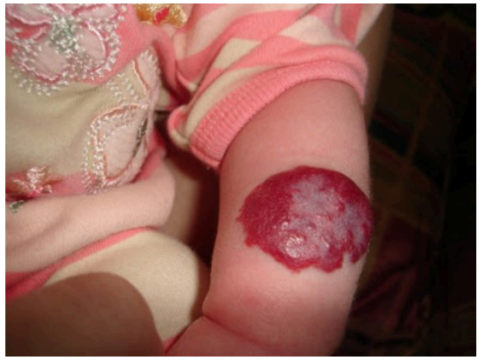
Pain, discomfort, bleeding, infection and leaves scars

Risk factors:

- Proliferative stage
- Large, segmental, thick superficial and mixed IH
- Localization: Lower lip, neck, anogenital region



C. Léauté-Labrèze. Lancet 2017

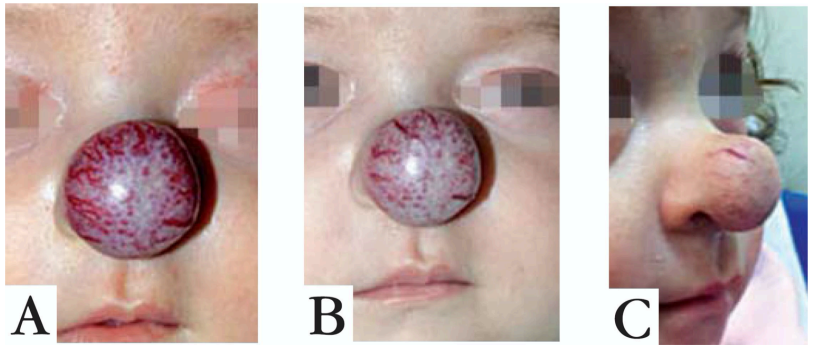


Sashasay.com

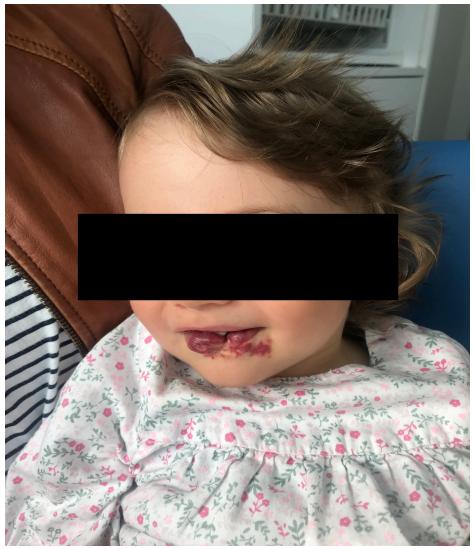
Disfigurement

IH located on the center of the face

- Nose
  - Cartilage destruction and nasal deformity
- Lips



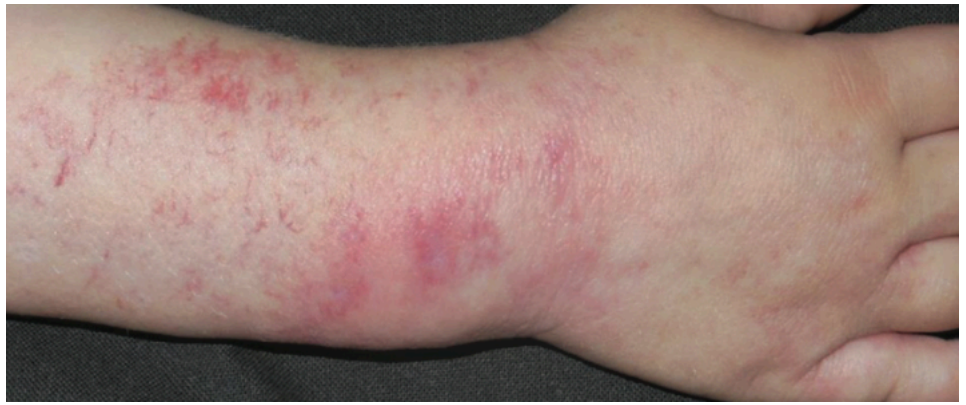
J Nakano De Melo. An Bras Dermatol 2013



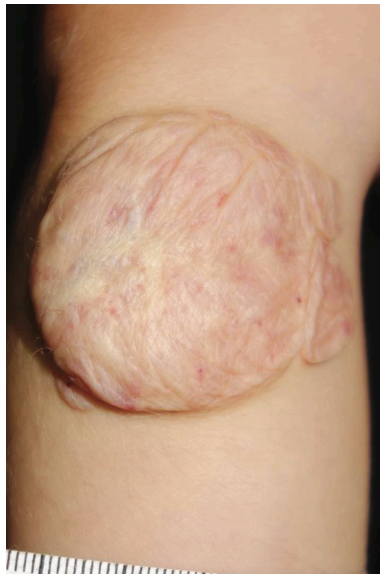
Cosmetic sequelae

~70% of untreated IH

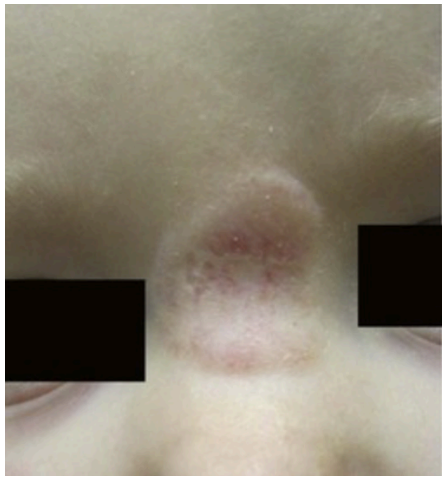
- Telangiectasia
- Fibrofatty tissue
- Anetoderma
- Redundant skin
- Scarring



C. Léauté-Labrèze. Lancet 2017

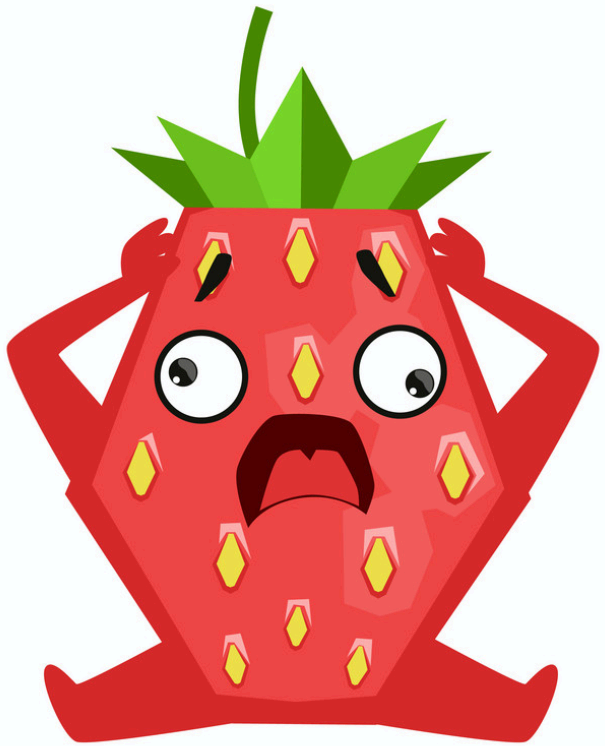


C. Léauté-Labrèze. Lancet 2017



plasticsurgerykey.com

Systemic complications and associated syndrome



- **Multifocal IH**

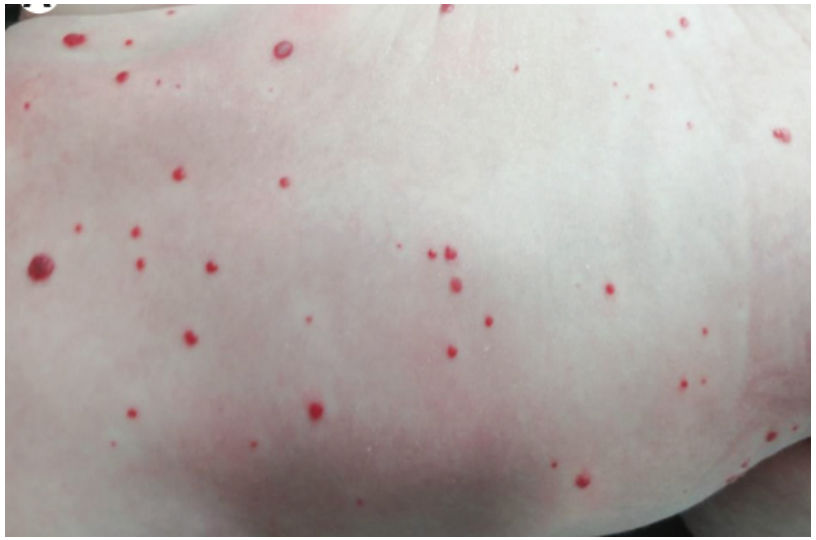
≥ 5 => risk of hepatic infantile hemangioma (HIH)

Hepatic hemangioma

Focal (27%)
- Congenital hemangioma
- Not associated with skin lesions

Multi Focal (57%)

Diffuse (16 %)



C. Léauté-Labrèze. Lancet 2017

<u>Complications of HIH:</u>

- Bleeding
- Abdominal compartment syndrome
- Congestive cardiac failure
- Hypothyroidism

Hypothyroidisme

Production 3 iodothyronine deiodinase by IH => deactivation of T3 and T4

May occur in patients with:

- Large cutaneous lH
- HIH

Segmental IH of the face or scalp
> 5 cm

PHACE syndrome

(31 to 58% of patients with large facial segmental IH)

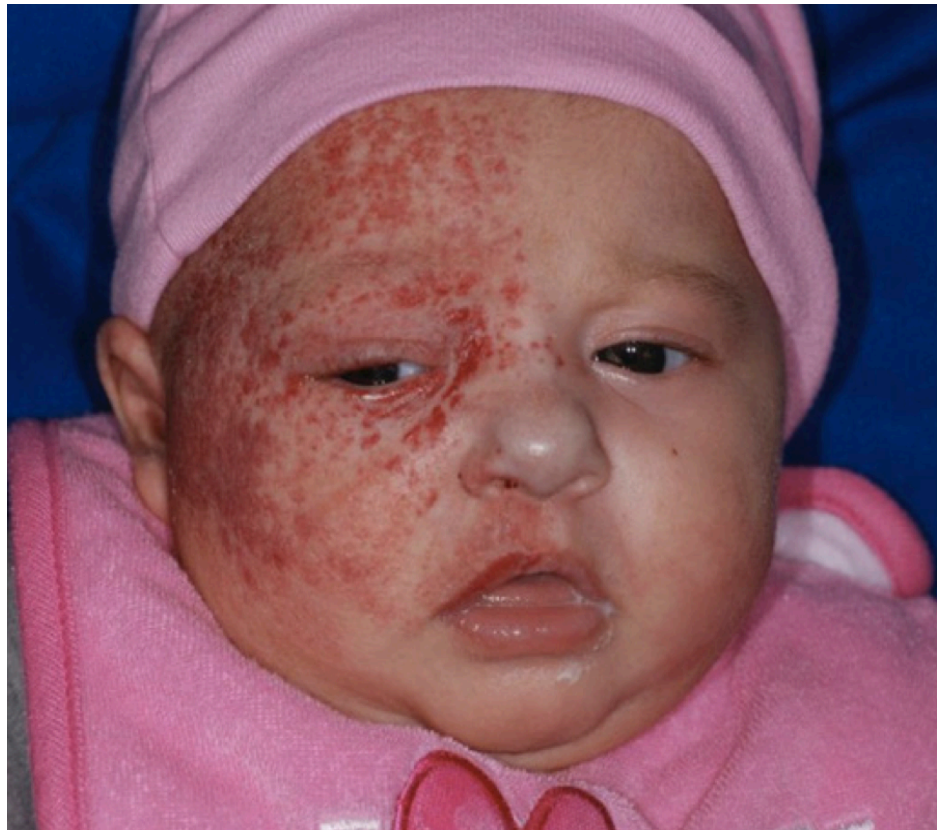
P: posterior fossa anomalies

H: hemangioma (Segmental IH, >5 cm)

A: arterial lesions

C: cardiac abnormalities/coarctation of the aorta

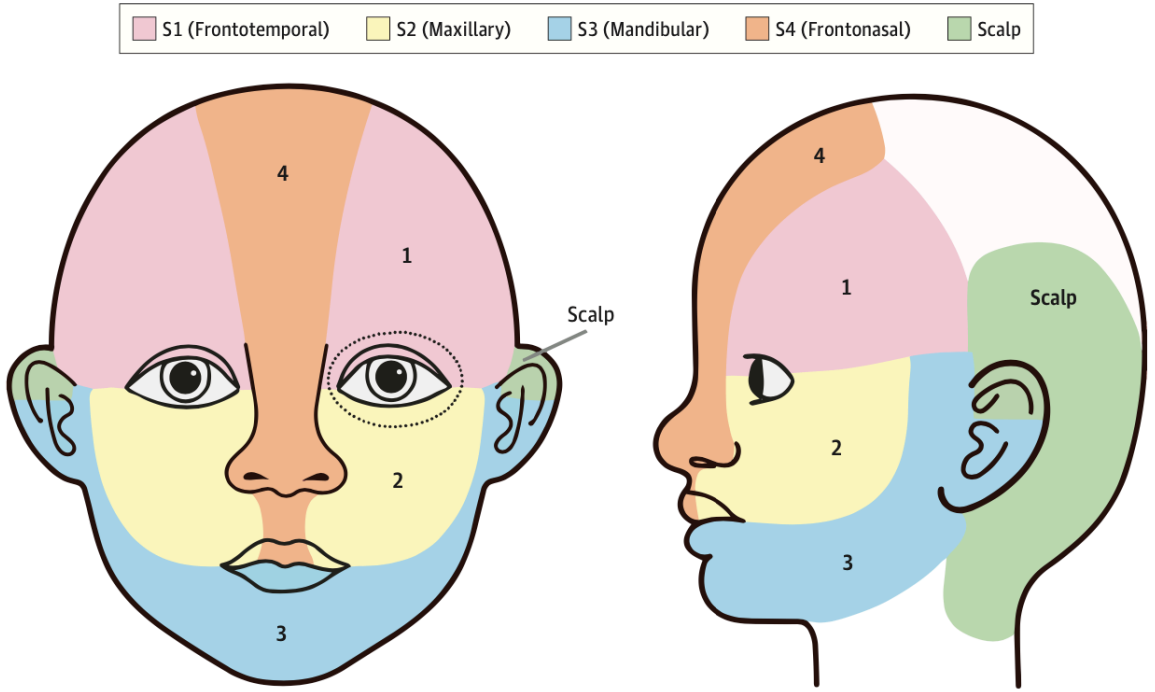
E: eye anomalies



H. Darrow. Pediatrics 2015

PHACE syndrome

- Increased risk with:
  - Size of IH
  - Involvement of the forehead
  - Numbers of segment involved
- Cerebrovascular anomalies represent the most common extracutaneous features => risk of stroke
- Associated with large IH involving extra facial locations:
  - Posterior scalp
  - Neck
  - Upper trunk
  - Upper arms
- May occur with:
  - Focal or small IH
  - Even in absence of IH



Endicott A et al. JAMA Dermatology November 2021

PHACE syndrome

Table II. Diagnostic criteria-revised

Organ systems	Major criteria	Minor criteria
Arterial anomalies	Anomaly of major cerebral or cervical arteries* Dysplasia† of the large cerebral arteries Arterial stenosis or occlusion with or without moyamoya collaterals Absence or moderate-severe hypoplasia of the large cerebral and cervical arteries Aberrant origin or course of the large cerebral or cervical arteries except common arch variants such as bovine arch. Persistent carotid-vertebrobasilar anastomosis (proatlantal segmental, hypoglossal, otic, and/or trigeminal arteries)	Aneurysm of any of the cerebral arteries
Structural brain	Posterior fossa brain anomalies Dandy-Walker complex Other hypoplasia/dysplasia of the mid and/or hind brain	Midline brain anomalies Malformation of cortical development
Cardiovascular	Aortic arch anomalies Coarctation of the aorta Dysplasia* Aneurysm Aberrant origin of the subclavian artery with or without a vascular ring	Ventricular septal defect Right aortic arch/double aortic arch Systemic venous anomalies
Ocular	Posterior segment abnormalities Persistent hyperplastic primary vitreous Persistent fetal vasculature Retinal vascular anomalies Morning glory disc anomaly Optic nerve hypoplasia Peripapillary staphyloma	Anterior segment abnormalities Microphthalmia Sclerocornea Coloboma Cataracts
Ventral/midline	Anomaly of the midline chest and abdomen - Sternal defect - Sternal pit - Sternal cleft - Supraumbilical raphe	Ectopic thyroid hypopituitarism Midline sternal papule/hamartoma

Definite PHACE	
Hemangioma >5 cm in diameter of the head including scalp PLUS 1 major criteria or 2 minor criteria	Hemangioma of the neck, upper trunk or trunk and proximal upper extremity PLUS 2 major criteria

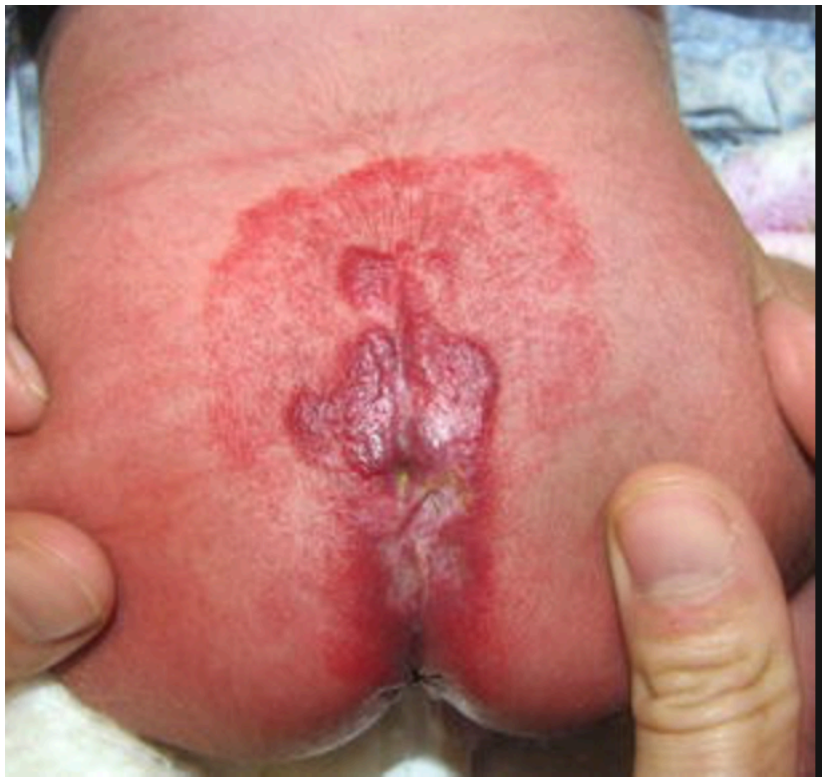
Possible PHACE		
Hemangioma > 5 cm in diameter of the head including scalp PLUS 1 minor criteria	Hemangioma of the neck, upper trunk or trunk and proximal upper extremity PLUS 1 major or 2 minor	No hemangioma PLUS 2 major criteria

Garzon *Mc et al. PHACE Syndrome: Consensus-Derived Diagnosis and Care Recommendations. J pediatr 2016;178:24-33.*

Large lumbosacral IH (2-5 cm)

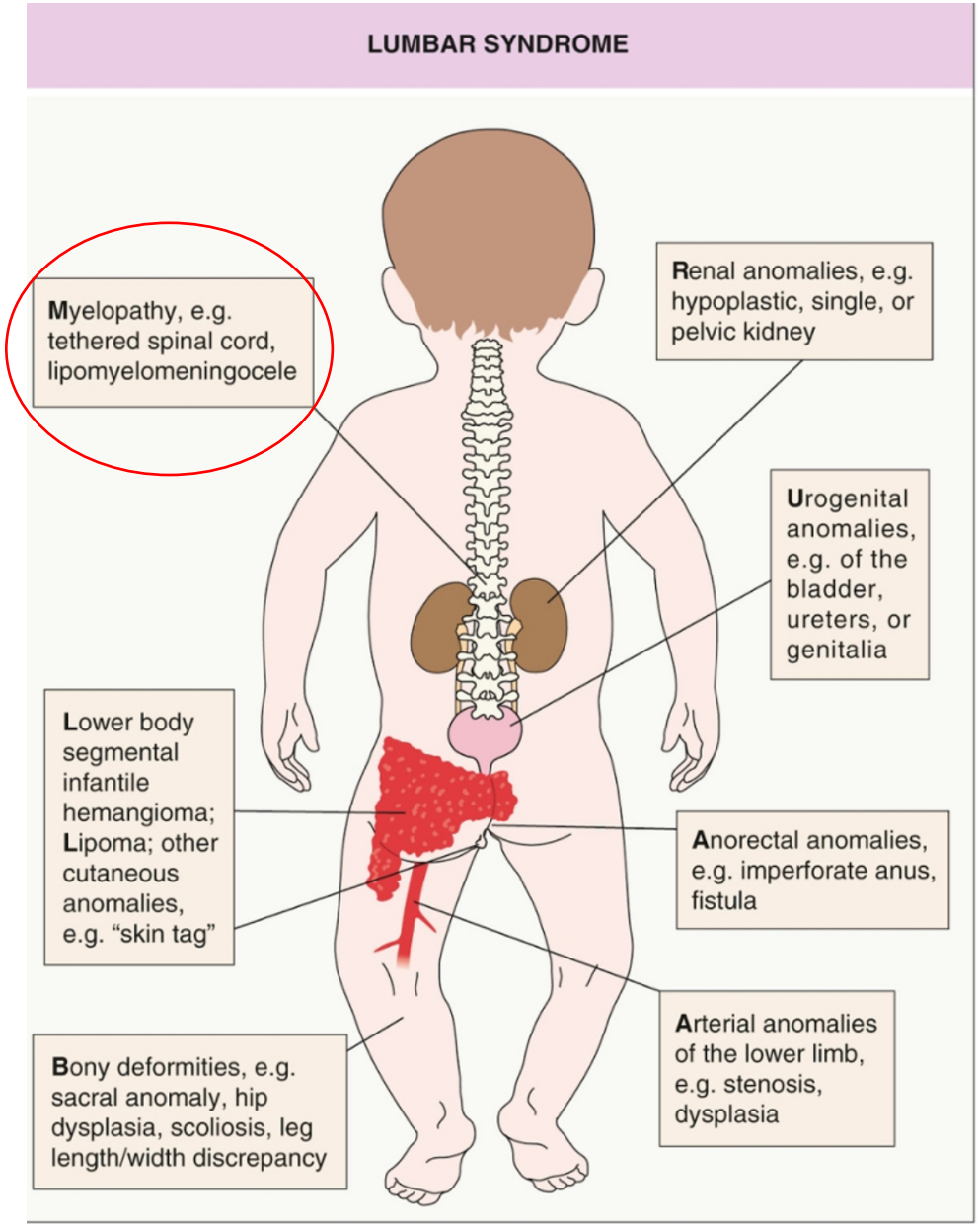
LUMBAR syndrome

- **L:** lower body IH (segmental IH of lumbosacral and anogenital region)
- **U:** Uro-genital anomalies
- **M:** Myelopathy
- **B:** Bony deformities
- **A:** Anorectal malformations
- **R:** Renal anomalies



Schumacher W. Pediatr radiol 2012

70-80% of patients

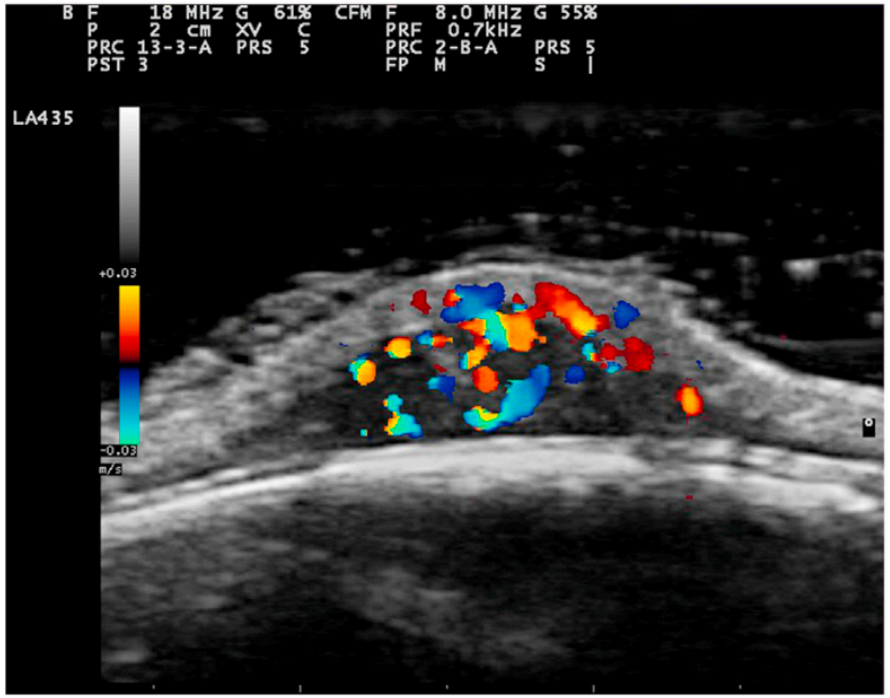


Bolognia texte book

Investigations

Diagnosis

- Is clinical in the majority of cases
- If doubt, particularly for deep IH => Doppler ultrasound



Rodriguez Bandera et al. JAAD 2021

Histology

- Proliferative stage

Dermal proliferation of lobules and sheets of tightly packed, capillary-sized vessels lined with plump endothelial cells.

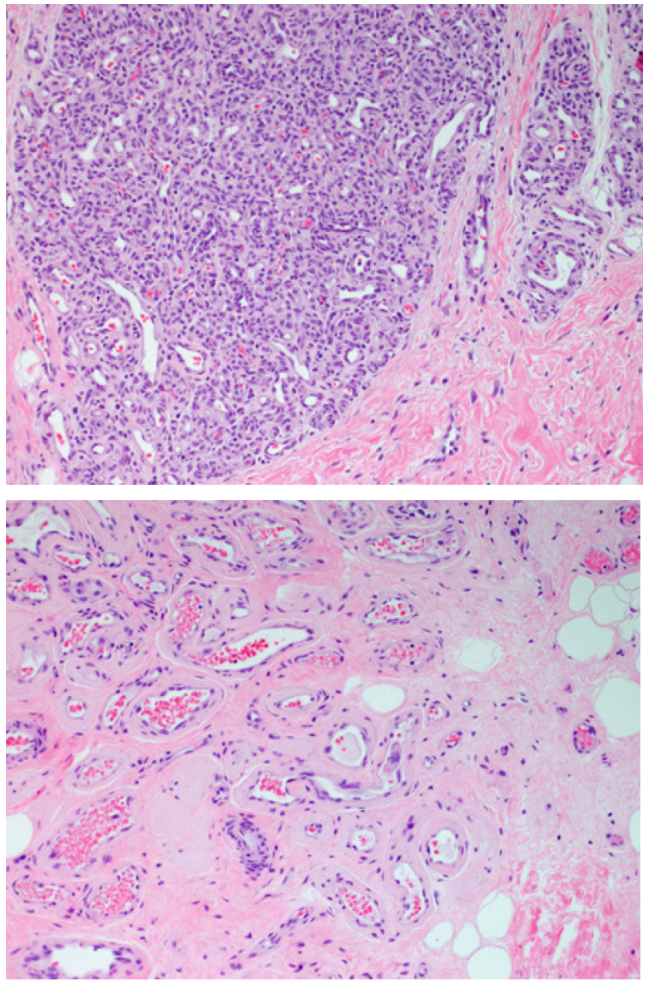
Moderate mitotic figures are present.

- Involution stage

Decreased density of capillaries surrounded by fibro-fatty tissue.

Reduced numbers of mitotic figures.

Immunohistochemestry: GLUT-1 +



X100, coloration hematoxylin and eosin

Investigations in specific situations

If multifocal infantile hemangioma ≥ 5 => liver ultrasound for HIH

If HIH or large cutaneous IH => TSH

If segmental IH (face and neck or lumbar) => investigations to search extracutaneous complications

- Head and neck MRI (including aortic arch)
- Echocardiography
- Refer to ophthalmologist
- Spinal MRI
- Pelvic and abdominal US

Periocular IH => referral to ophthalmologist

Peri oral IH => Referral to dentist

Beard region => Referral to ORL

Management

Is active medical treatment is indicated?

1. Ulceration or locations likely to ulcerate; eg, neck, perineum, other flexures
2. Anatomic location likely to cause functional impairment
   - periorbital – astigmatism, amblyopia, etc
   - nasal – airway obstruction
   - "beard" distribution – subglottic hemangioma causing airway outlet obstruction
   - perioral – feeding difficulties
   - ear – external acoustic meatus obstruction
3. Infantile hepatic hemangioma
4. Syndromic
   - PHACES
   - LUMBAR
5. Disfigurement
   - Face, breast (in females), genitalia etc.

Sebaratnam et al. Infantile hemangioma. Part 2: Management. J Am Acad Dermatol 2021;85:1395-404

History of medical treatments

- 1960s
  - Systemic and intralesional corticosteroids
  - Side effects …
- 1980s and beginning of 1990s
  - Interferon-alpha: used against Kaposi sarcoma in HIV patients
  - Used in IH resistant to CS
  - Side effect: neurotoxicity
- 2008
  - Léauté-Labrèze et al: IH undergo involution in 2 infants treated with propranolol for cardiac reasons
- 2009
  - Léauté-Labrèze et al: report their experience with 32 patients with IH successfully treated with propranolol 2 to 3 mg/kg/day.

Propranolol

- Lipophilic nonselective β-adrenergic receptor-blocking agent
- Completely absorbed after oral administration
- After first hepatic pass => 25% reaches the systemic circulation
- Maximum plasma concentration is reached after 1 to 4 hours of administration
- The metabolism is mainly hepatic and metabolites are excreted in urine
- The half life of plasmatic elimination is 3 to 6 hours

What is the mechanism of action of propranolol ?

Not yet elucidated but several hypothesis:

- Inhibition of angiogenesis
- Induction of apoptosis
- Diminution of renin-angiotensin axis
- Inhibition of nitric oxide production
- Vasoconstriction

Propranolol

Initial dosage: 1 mg/kg/d divided in 2 doses

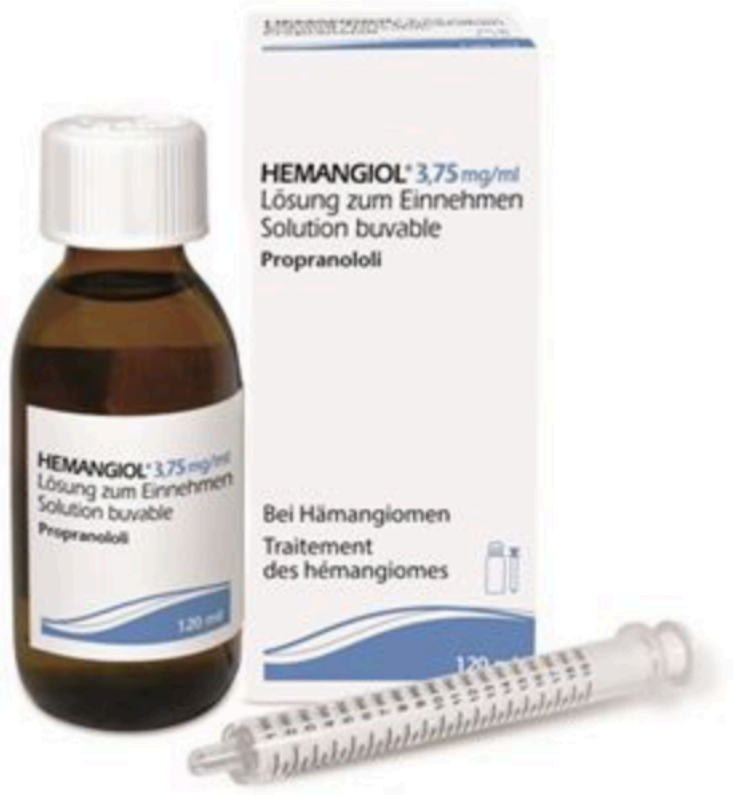
1 week

Increase to 2 mg/kg/d

1 week
In special cases

Increase to 3 mg/kg/d

First dose and each increase of dosage is done under clinical observation at hospital.



Monitoring

Blood pressure and pulsations

- Before introduction of propranolol
- 30 min after
- 60 min after
- 2 h after

Blood pressure > 70 mmHg
Pulsations:
> 100/min
If baby is sleeping >70/min

Age	0-3 mois	3-6 mois	6-12 mois
Fréquence cardiaque (battements/min)	100	90	80

Age	0-3 mois	3-6 mois	6-12 mois
Pression artérielle (mm Hg)	65/45	70/50	80/55

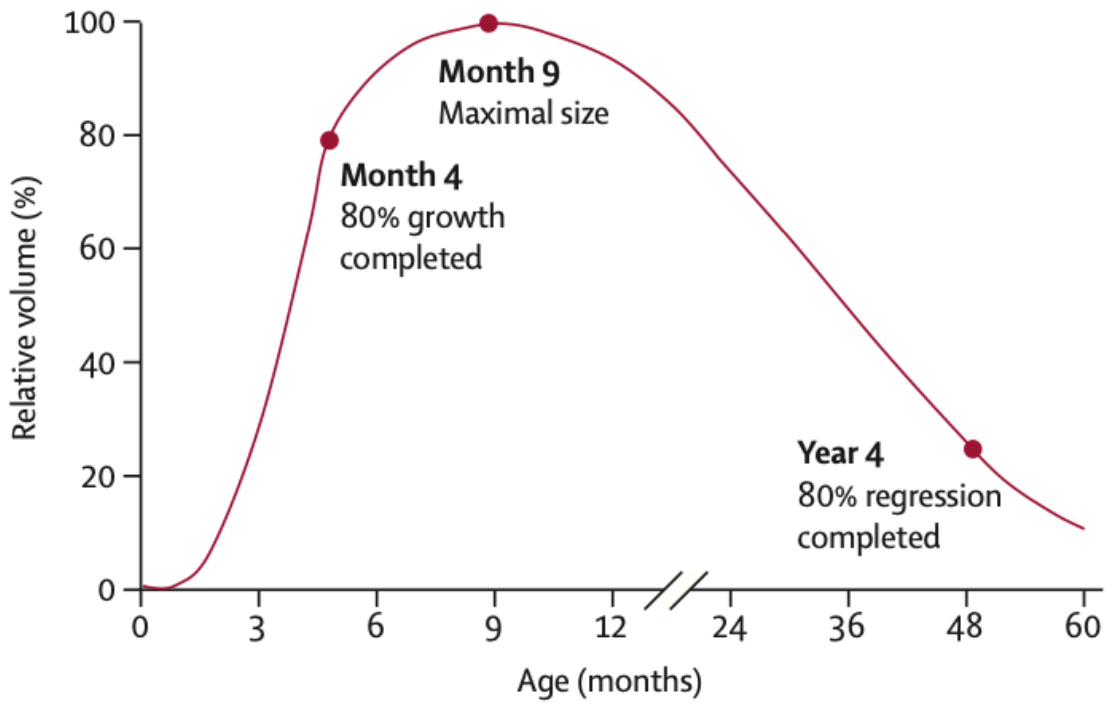
Compendium suisse des médicaments

Propranolol

Complications	Contraindication
❖ Sinusal bradycardia ❖ Hypotension ❖ Bronchospasm ❖ Cold extremities ❖ Hypoglycemia ❖ Sleep disturbance, nightmares ❖ Diarrhea	❖ Sinusal bradycardia ❖ Hypotension ❖ A-V block of second and third degree ❖ Cardiogenic shock/ uncontrolled cardiac insufficiency ❖ Hyper sensibility to propranolol or one of the excipients ❖ Infants prone to hypoglycemia

When to start and stop the treatment?

- Initiation during proliferative phase
- Can still lead to improvement when started at 9-12 months
- Stop: 12 to 18 months of age
- Predictive factors for rebound growth after cessation of treatment:
  - Female sex
  - Localization head and neck, segmental and deep IH
  - Discontinuation of treatment before 6 months of age



C. Léauté-Labrèze et al. Infantile hemangioma. Lancet 2017.

Other systemic beta blockers

- Atenolol

Large, hydrophilic, selective β1-adrenergic receptor blocking agent

Atenolol compared to propranolol had similar efficacy and fewer adverse events in the treatment of infants with problematic IHs

Ji Y et al. JAMA Otolaryngol Head Neck Surg. 2021;147:599-607

- Nadolol

Non selective beta blocker

Advantage: do not cross blood brain barrier => obviating sleep disturbances

Risk: not metabolized => excreted unchanged via feces => risk of reabsorbtion and accumulation in case of constipation

1 reported case of death in a new born

McGillis E et al. Pediatrics. 2020;145:e20191035

Topical Timolol

- Timolol maleate 0.5%, a nonselective β-blocker
- Effective for treatment of thin, superficial IH
- Poor efficacy in thick or deep IH
  - Systemic absorption is documented
- Topical timolol is well tolerated in the treatment of early proliferative IH but provides limited benefit in the resolution of lesions when given during the early proliferative stage.

Munoz-Garza et al. Efficacy and safety of topical Timolol for the treatment of IH in the early proliferative stage. JAMA Dermato. 2021;157:583-587.

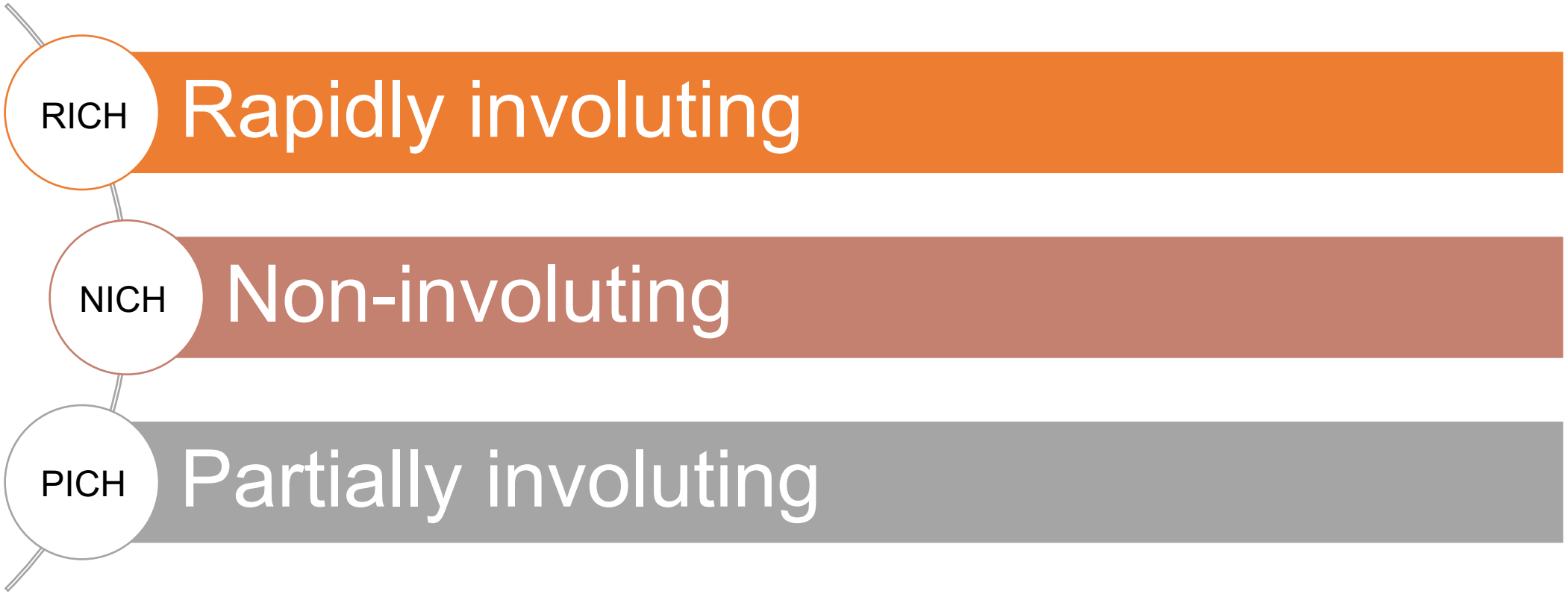
- Dosage: 1 drop/kg but some authors suggest not to exceed 2 drops per day

Treatment of complications

- Telangiectasia => vascular laser such as PDL
- Structural deformity => surgery
- Scars => ablative fractionated laser

Congenital hemangioma

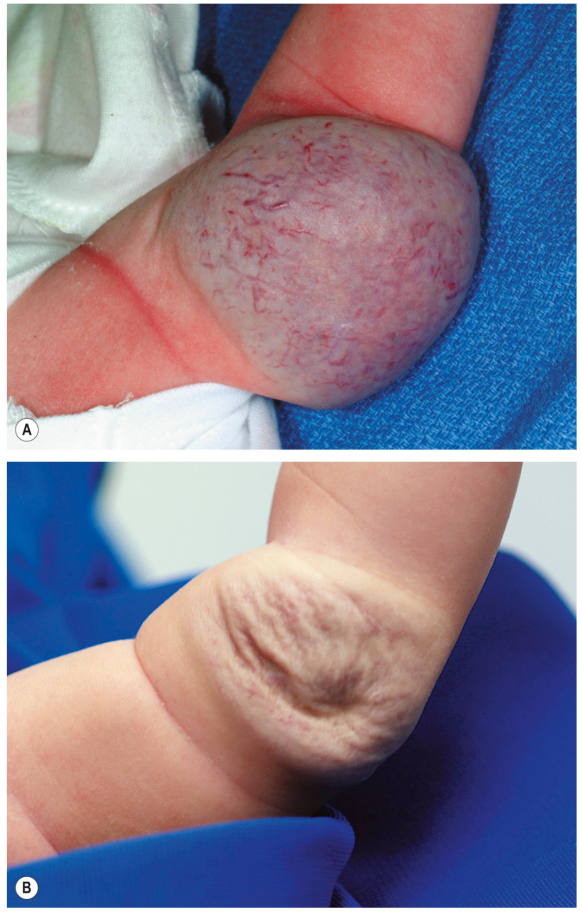
Congenital hemangioma



ISSVA 2018

RICH

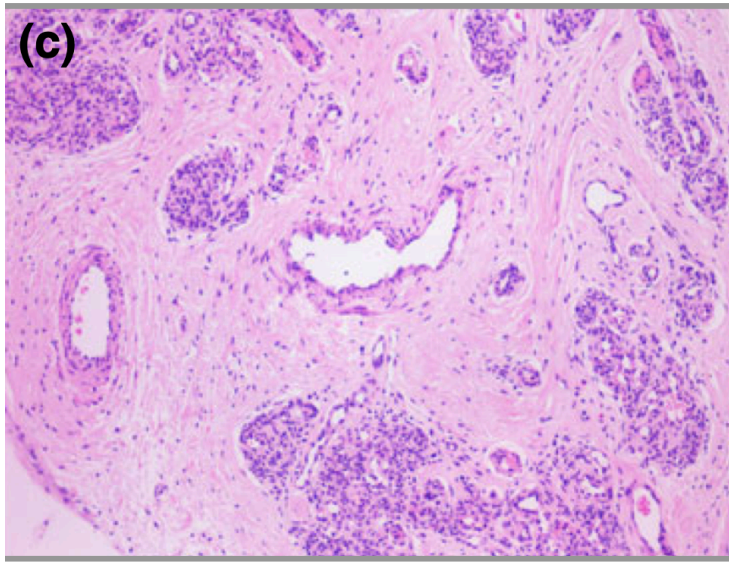
- Present at birth
- F=M
- Spontaneous involution during the first year of life
- Asymptomatic
- Violaceous mass with telangiectasia at surface
- Localization: mainly on lower limbs
- Complications:
  - Transitory thrombocytopenia
  - Necrosis
  - Ulceration
  - Hemorrhage

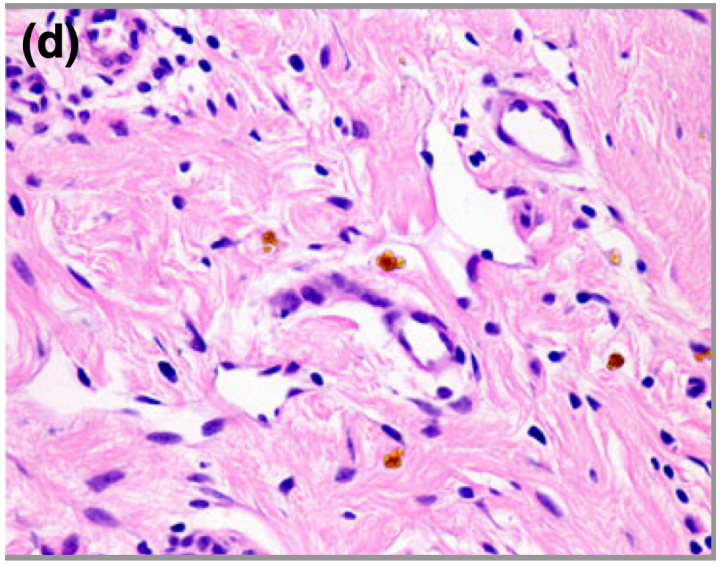


Bologna text book

RICH (histology)

- Small lobules of capillaries embedded in a fibrous stroma
- Immunohistochemestry: GLUT-1 negative

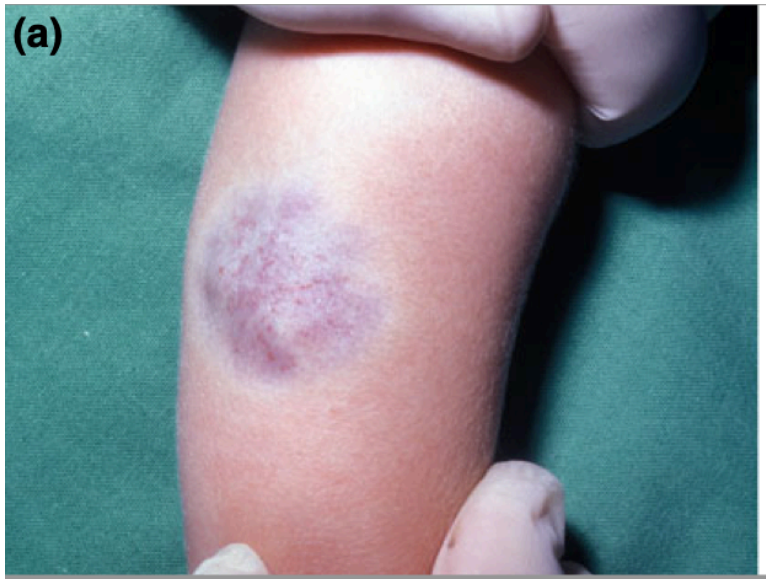




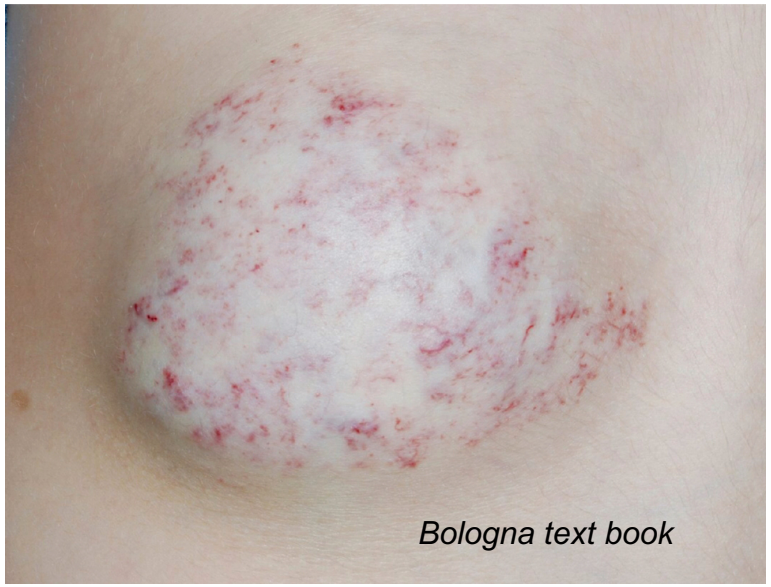
P.H. Hoeger
BJD 2014

NICH

- Present at birth
- 2 subtypes:
  - Nodular
  - Patch
- Well demarcated pink to blue patch/nodule with overlying telangiectasia and a pale or bluish rime
- Location predilection: extremities and postauricular
- Sometimes painful
- Thermic gradient

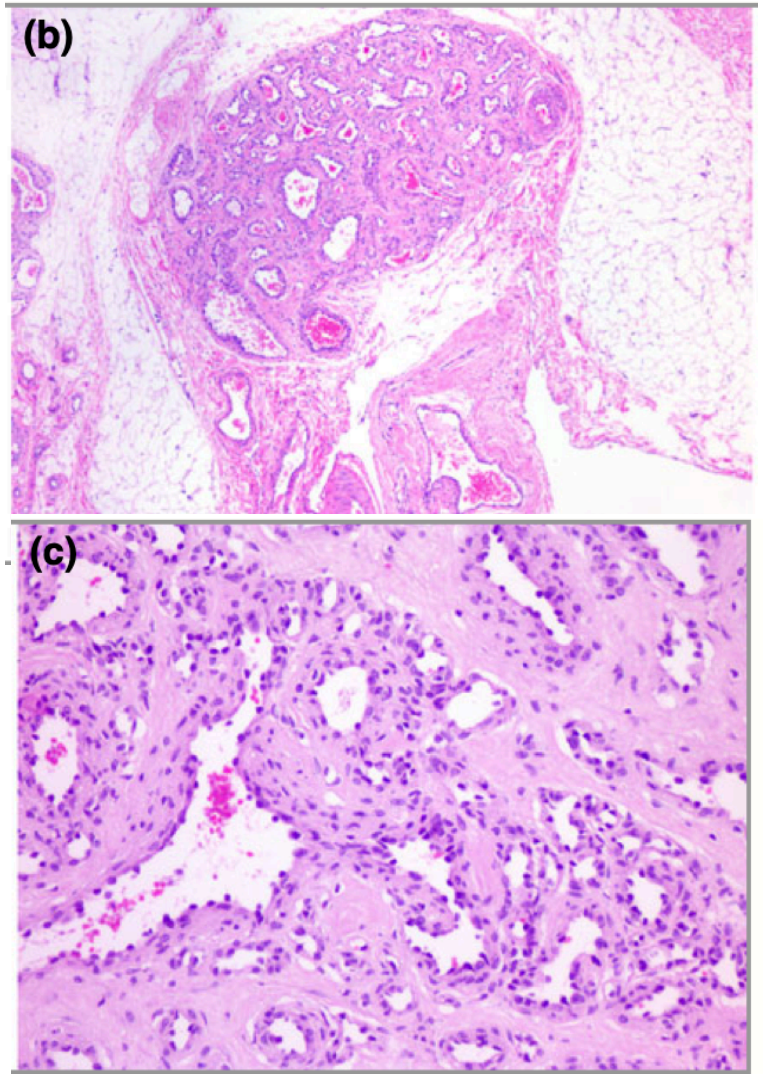


P.H. Hoeger
BJD 2014



NICH (histology)

- Large fibrotic lobules of dilated vascular channels
- Nonatypical hobnail endothelial cells lining the vascular channels
- Immunohistochemestry: GLUT-1 negative



P.H. Hoeger
BJD 2014

Partially involuting congenital hemangiomas: A report of 8 cases and review of the literature

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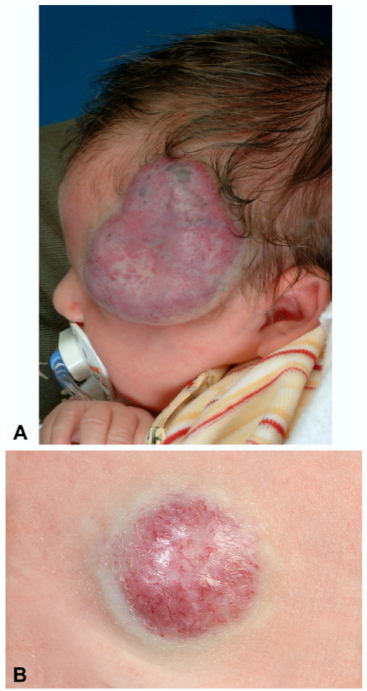


Fig 1. Partially involuting congenital hemangioma. Vascular lesions on left temple (**A**) and right arm (**B**) at 1 month of age with red-purple color, telangiectasia, and surrounding pallor.

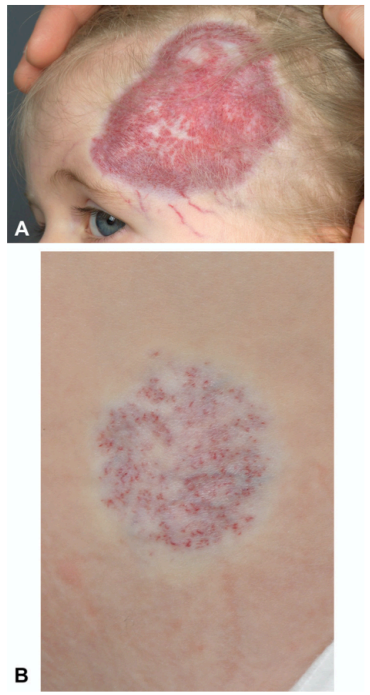


Fig 2. Partially involuting congenital hemangioma. Residual vascular lesions on left temple (**A**) and right arm (**B**) at 3 years of age showing red-purple color, telangiectasia, and surrounding pallor.

Treatment

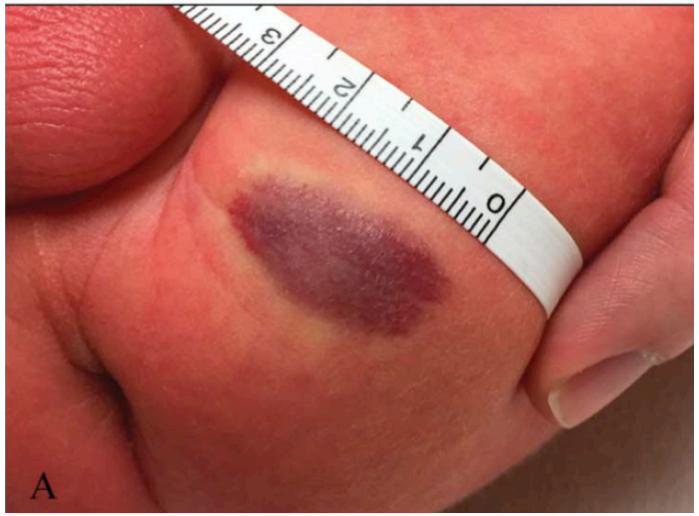
RICH	NICH
No treatment needed Watchful waiting	In cosmetically sensitive area: Nd-YAG lasertherapy Surgery

Tufted angioma (TA) and Kaposiform hemangioendothelioma (KHE)

- Many experts believe that KHE and TA are part of a spectrum.
- They both have a podoplanin-positive lymphatic endothelial immunophenotype.
- Podoplanin is a natural ligand for CLEC-2 (C type lectine receptor) expressed on platelets that has a powerful platelet activation upon binding to podoplanin.
- Both tumors have potential to induce Kasabach–Merritt phenomenon (KMP) which is a profound thrombopenia due to platelet trapping in the tumor.
- GNA 14 mutations are detected in both tumors

Tufted angioma

- 15% are present at birth and majority appear before age of 5 years
- F = M
- They either stay stable, regress or progress
- Complete regression is rare
- Mottled Pink-red/Red-brown plaque or patch with super imposed angiomatous plaque
- Localization: Upper trunk, neck/ shoulders
- May be painful
- 38% develop KMP



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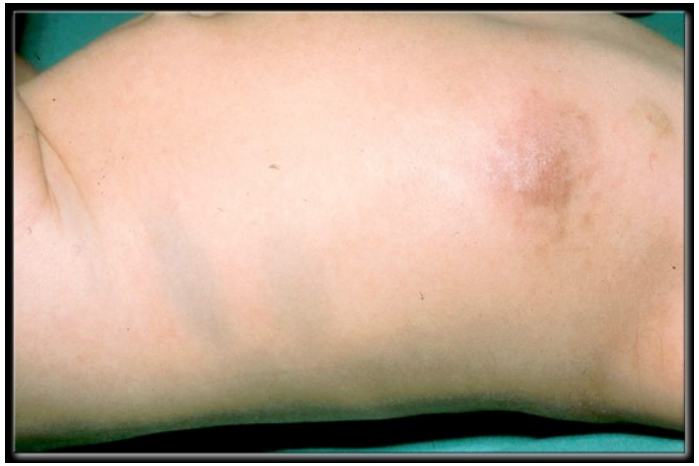
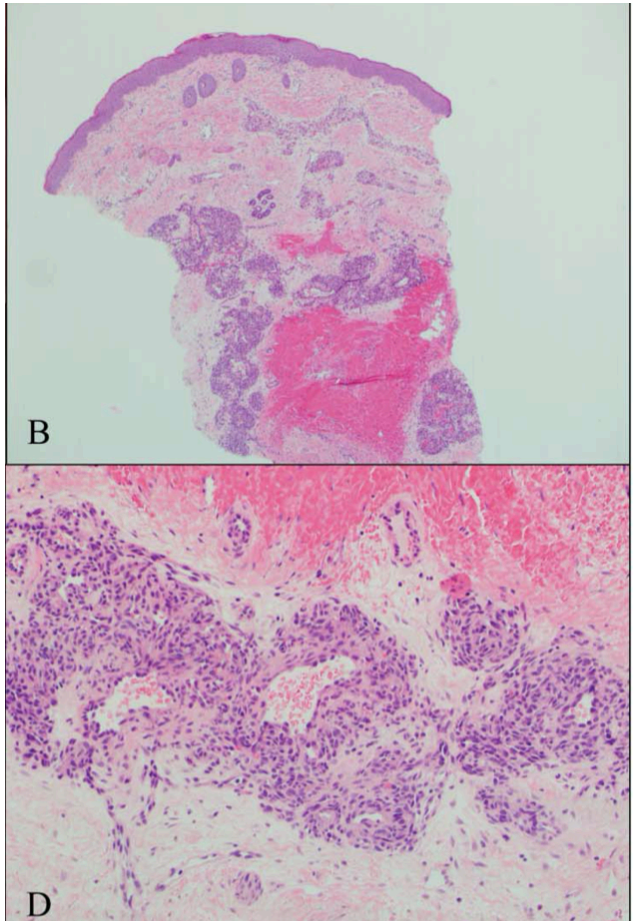


Histology

- “cannonball” distribution of lobules of capillaries lined with bland endothelial cells and surrounded by pericytes. Involving the dermis and superficial subcutis.
- Immunohistochemestry:
  - Glut-1 -
  - CD 31 et CD 34 +
  - D2-40 (podoplanin/lymphatic endothelioma) et LYVE-1 focally +



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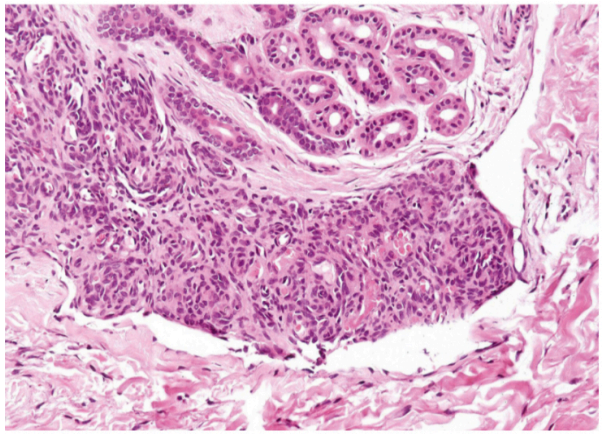
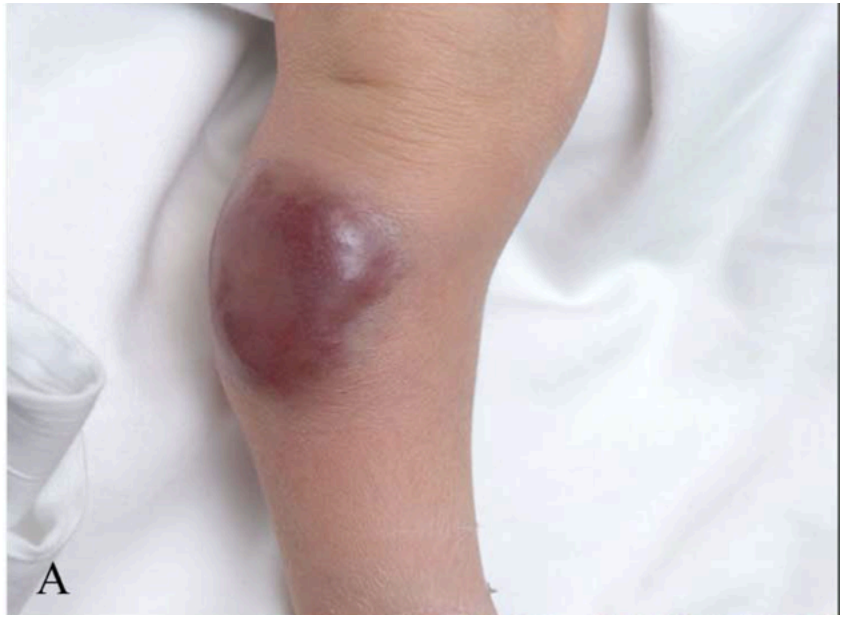


Mckee dermatopathology texte book

Kaposiform hemangioendothelioma (KHE)

- Rare 0.91/100000 enfant
- F = M
- 60% present at or within 1 month of birth
- Superficial, locally infiltrative maculopapule or plaque or indurated mass.
- Localization: Extremities, trunk, head and neck
- Locally aggressive tumor
- 71% develop KMP



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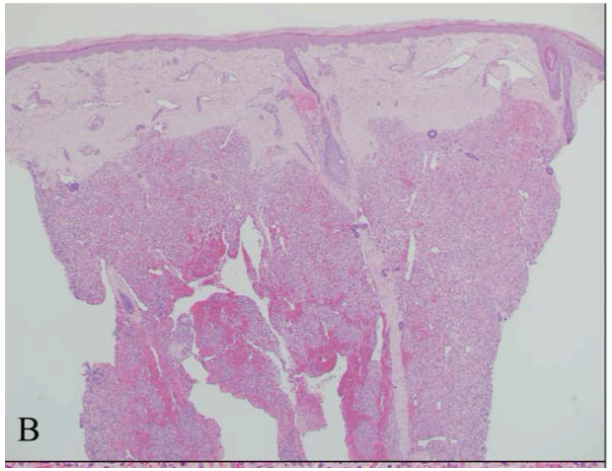
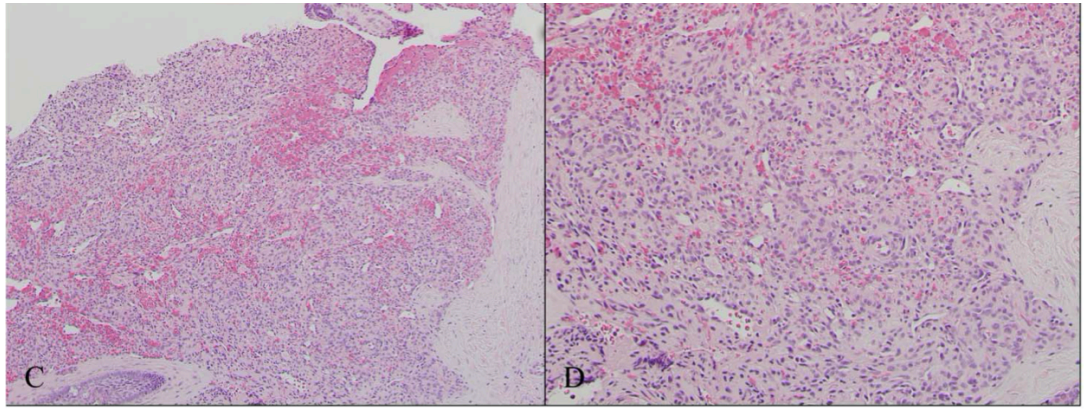
Histology

Coalescing lobules of infiltrative spindled endothelial cell fascicles.
Spindle cells are surrounded by nests of more epithelioid endothelial cells.

Immunohistochimie:

Glut-1 -
CD 31 +
CD 34 focally +
D2-40 +
LYVE-1 focally +
Prox 1 +





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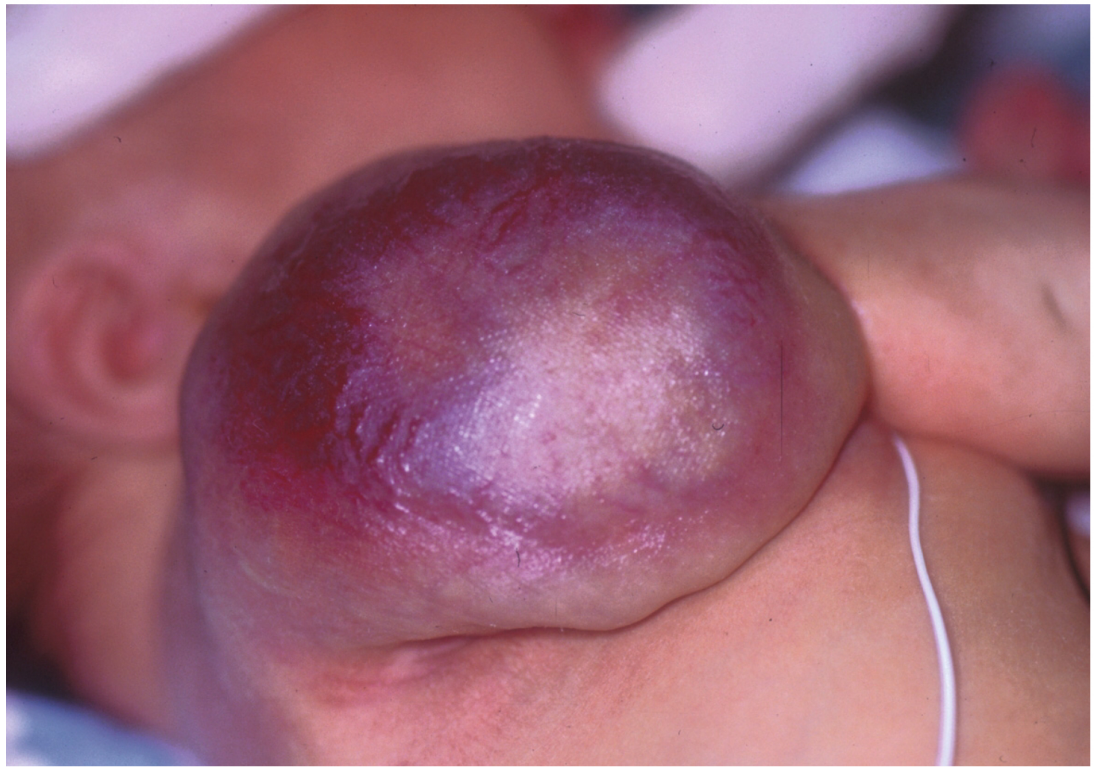
Kasabach-Merritt phenomenon (KMP)

- Rapidly growing tumor
- Associated with pain and purpuric aspect
- Lab tests:
  - Hb drop
  - Thrombocytopenia
  - Decrease of fibrinogen
  - Elevation of D-dimer
  - PT et aPTT: Normal or slightly increased



Bologna text book

Treatment

TA	KHE	If KMP
Clinical follow-up Small lesions: surgical excision	If localized or superficial: surgical excision Sirolimus alone in association with prednisone	Hemodynamic stabilization Sirolimus (rapamicine: mTor inhibitor): -alone -in association with prednisone Vincristine (efficient in 60-70% of cases)

Thanks for your attention

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