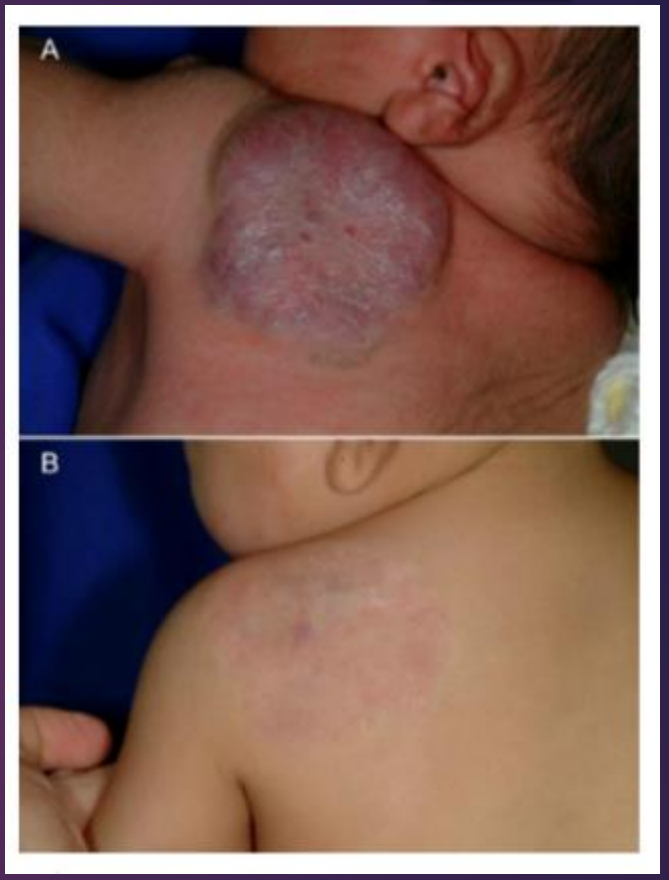

بسم الله الرحمن الرحیم

# همانژیومای شیرخواران
# Infantile Hemanigioma

دکتر مهدی شهریاری

آبان ۱۴۰۳



# Introduction

Infantile hemangiomas (IHs) are the most common tumors of childhood. Unlike other tumors, they have the unique ability to involute after proliferation, often leading primary care providers to assume they will resolve without intervention or consequence.

# Introduction

Unfortunately, a subset of IHs rapidly develop complications, resulting in pain, functional impairment, or permanent disfigurement. As a result, the primary clinician has the task of determining which lesions require early consultation with a specialist.

# Agenda

To update the pediatric community regarding
1:recent discoveries in IH pathogenesis,

2:treatment,

3: clinical associations

4:and to provide a basis for clinical decision-making in the management of IH.

هر گردی گردو نیست! هر آنومالی عروقی در شیرخواران دیدیم همانژیومای شیرخوارگی نیست!

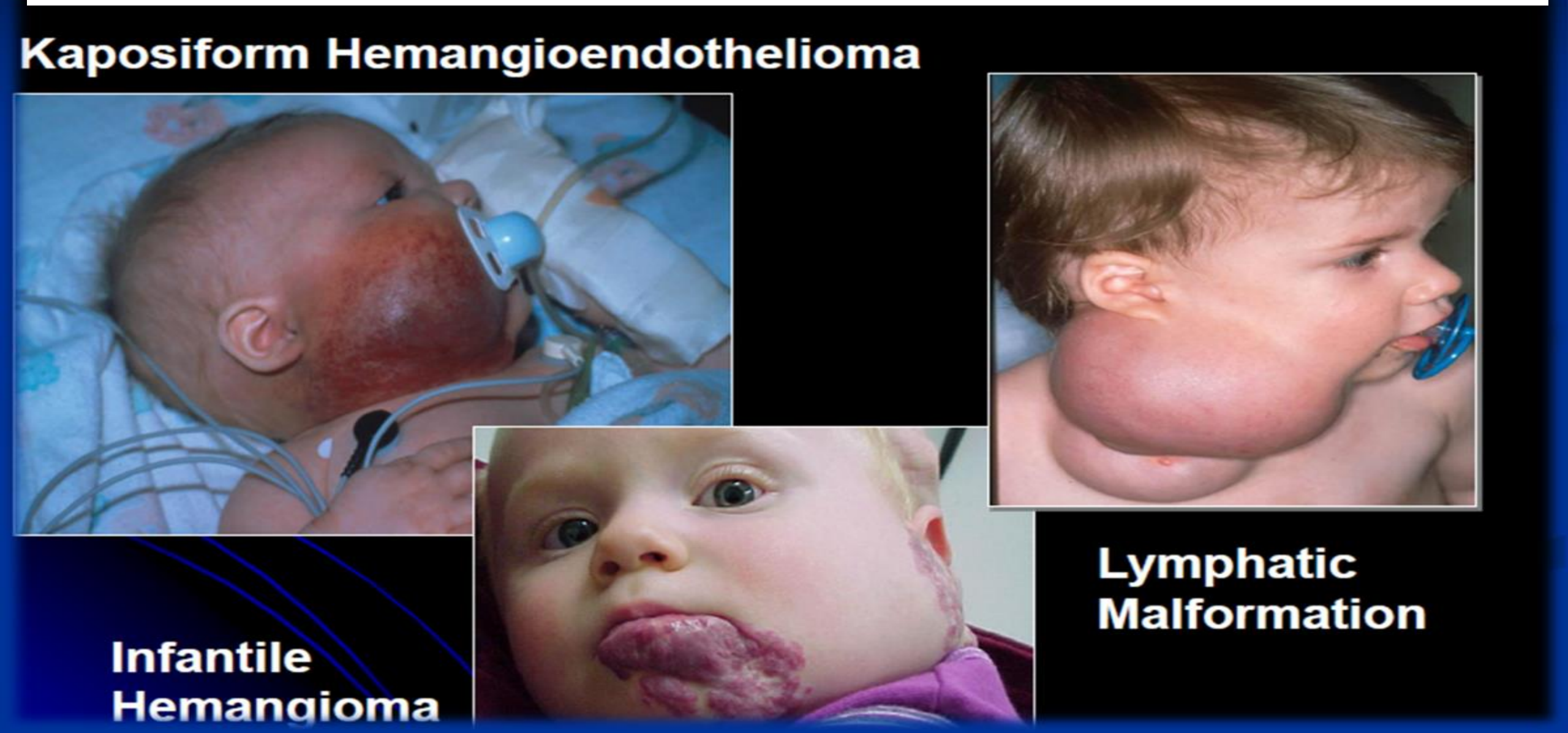


**TABLE 1** Classification of Cutaneous Vascular Anomalies, 2014

| |
|---|
| ***Vascular malformations*** |
| Venous malformations |
| Lymphatic malformations |
| Capillary malformations |
| Arteriovenous malformations and fistulae |
| Mixed (combined) malformations |
| ***Vascular tumors*** |
| *Benign* |
| Infantile hemangioma (IH) |
| Congenital hemangioma (rapidly involuting [RICH]; non-involuting [NICH]) |
| Lobulated capillary hemangiomas (LCH) (pyogenic granuloma)* |
| Tufted angioma (TA) |
| Others |
| *Locally aggressive* |
| Kaposiform hemangioendothelioma (KHE) |
| Kaposi sarcoma |
| Others |
| *Malignant* |
| Angiosarcoma |
| Others |

Adapted from the International Society for the Study of Vascular Anomalies, 2014, ref 1 (issva.org/classification).
*Reactive proliferating vascular lesion

# 2014 Classification of vascular anomalies

- 1: Vascular Malformations:

- **Venous Malformations**
- **Arterial Malformations**
- **Capillary Malformations**
- **Arteriovenous Malformations , and shunts**
- **Lymphatic Malformations**
- **Mixed Malformations**

# 2014 Classification of vascular anomalies

- **2- Benign Vascular tumors:**
  - **Infantile Hemangioma (IH)**
  - **Congenital Hemangiomas: Rapidly involuting(RICH), Non-involuting(NICH)**
  - **Pyogenic Granuloma: (lobulated Capillary Hemangioma)**
  - **Tufted Angioma (TA)**
- **3- Locally aggressive Kaposi Sarcoma, and Kaposiform Hemangioendothelioma**
- **4- Malignant: Angiosarcoma**

# Congenital Hemangioma

congenital hemangiomas are present and fully formed at birth;

they do not exhibit the postnatal proliferative phase.

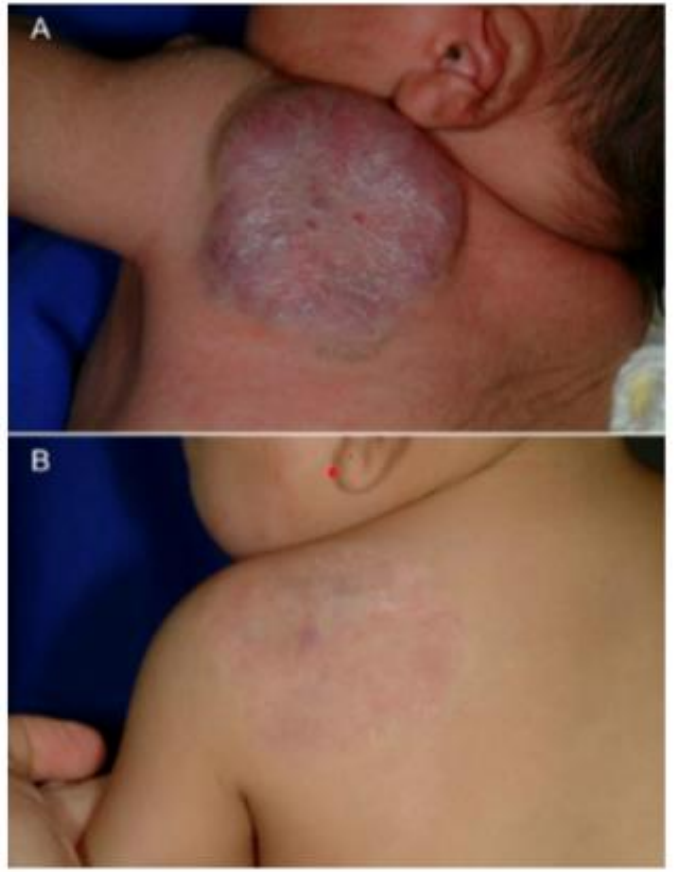
The 2 variants are **the non-involuting congenital hemangioma (NICH)**,

which remains stable without growth or involution,

and **the rapidly involuting congenital hemangioma (RICH),**

which undergoes a rapid involution phase beginning in the first year of life .

**Unlike IH, neither lesion expresses glucose transporter protein isoform 1 (GLUT1).**



# Pyogenic granuloma

- **Pyogenic granuloma, also known as lobular capillary hemangioma, is neither pyogenic nor granulomatous.**
- It is a reactive proliferating vascular lesion that is classified as a vascular neoplasm. This common acquired vascular lesion of the skin and mucous membranes primarily affects infants and children and is frequently misdiagnosed as IH; they are most **commonly located on the head and neck**, rapidly enlarge to a median size of 6.5 mm, **frequently develop a pedunculated base, and, with erosion, are prone to bleeding.**

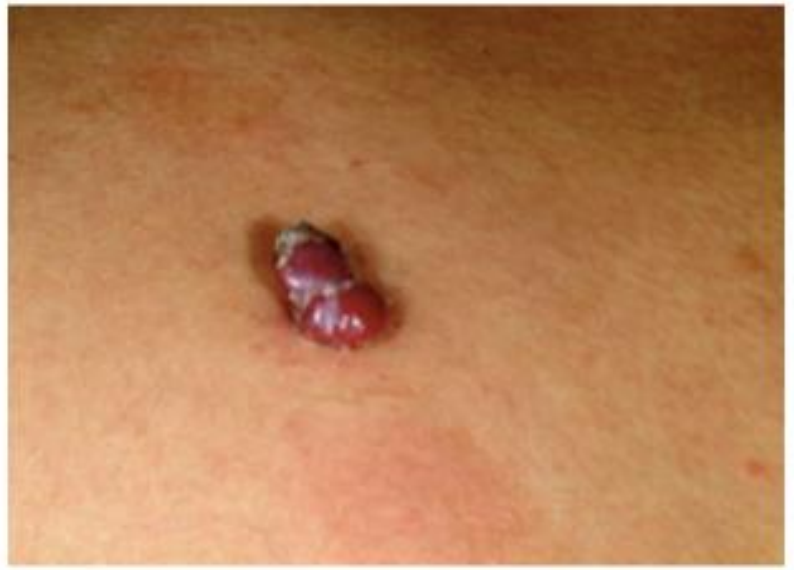


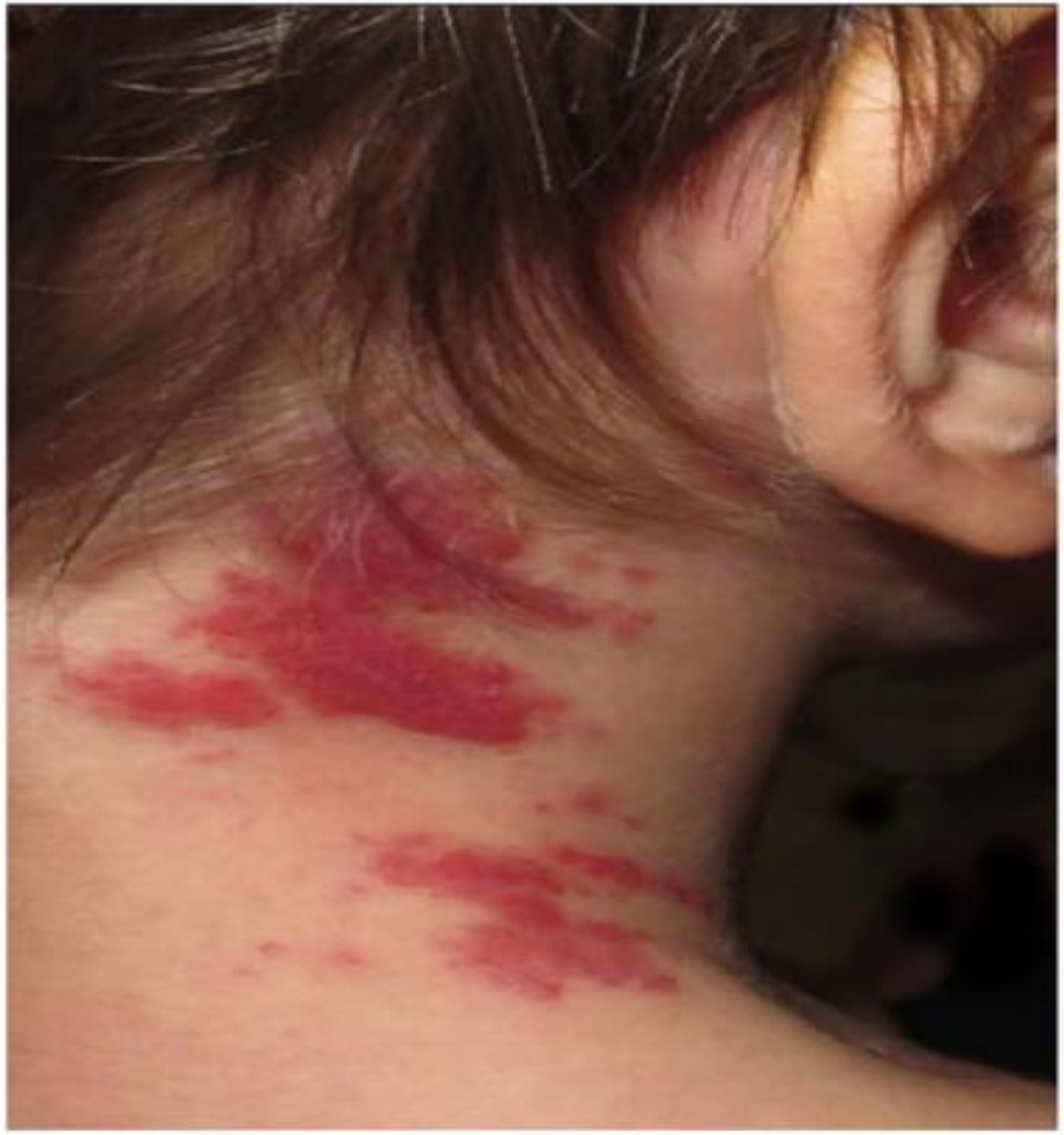
**FIGURE 2**
Pyogenic granulomas have some clinical and histologic features similar to IHs, but they are generally smaller, pedunculated, and more likely to bleed.

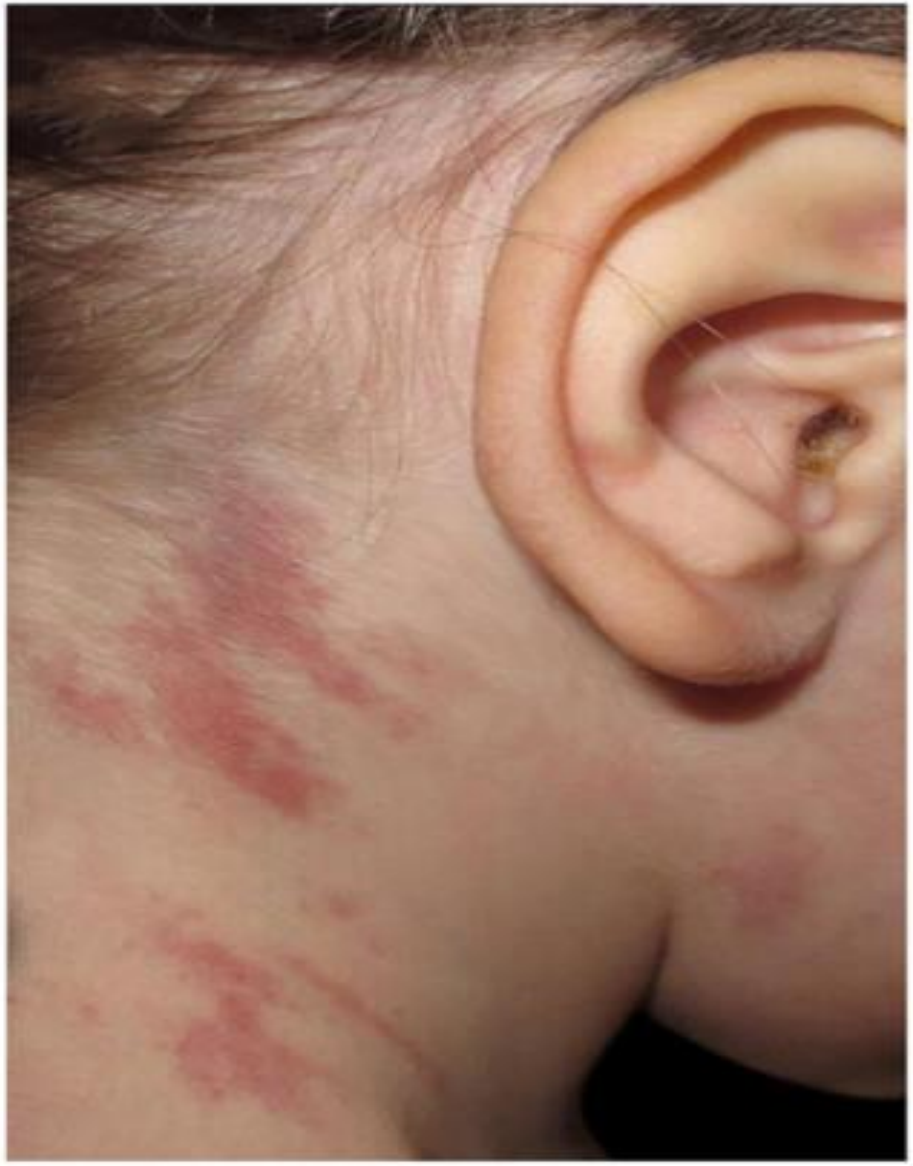
# kaposiform hemangioendothelioma (KHE)

- **Kaposiform hemangioendothelioma (KHE)** and tufted angioma (TA), have been confused with IH.
- **KHE** presents primarily in infancy but with a far wider age range than IH, which is usually apparent in the first month of life. KHE is considered a locally aggressive neoplasm that typically **appears as a deep, soft tissue mass.** This lesion has been associated with Kasabach-Merritt Phenomena (KMP), a potentially life-threatening consumptive coagulopathy characterized by severe platelet trapping.
- Histopathologically, KHE shows infiltrating sheets of slender, **GLUT1negative endothelial cells lining** slitlike capillaries.

# Tufted Angioma (TA)

- TAs are benign vascular tumors that occur in infants, children, or young adults and are usually located on the **neck or the upper part of the thorax**.
- Their clinical appearance is variable and includes erythematous to violaceous patches, plaques, and nodules.
- Histopathologically, TA shows well-defined tufts of capillaries in the dermis that lack cellular atypia or GLUT1 positivity and, **like KHE**, is associated with increased lymphatic vessels and a **predisposition to Kasabach-Merritt Phenomena (KMP)**.





Clinical images of tufted angioma (TA) lesions. (A) Violaceous macules and plaques on the right lateral aspect of the neck at the age of two; first presentation of TA when discontinuation of aspirin and ticlopidine. (B) Partial clearance after reintroduction of aspirin in monotherapy.

# Infantile Hemangioma

**A female to-male ratios ranging from 3:1 to 5:1**,

The gender discrepancy appears to be increased among children with **PHACE syndrome** (**P**osterior fossa defects, **H**emangiomas, **c**erebrovascular **A**rterial anomalies, **C**ardiovascular anomalies including Coarctation of the Aorta, and **E**ye anomalies), in which studies have found a **9:1** female-to-male ratio.

# PHACE SYNDROME


**FIGURE 12**

A, Frontotemporal segmental IH typical of PHACE syndrome. B, Sternal clefting characteristic of PHACE syndrome (scar is congenital, not surgical).

# IH incidence and birth weight

The incidence of IH is increased among preterm infants, affecting **22% to 30% of infants weighing less than 1 kg**.

Multivariate analysis has revealed that low birth weight (LBW) is the major contributor to this risk; there is a **25% increase in risk of developing an IH with every 500-g reduction in birth weight.**

Other possible prenatal factors include **older maternal age, multiple gestation pregnancy, placenta previa, and preeclampsia**.

**Trans-cervical Chorionic Villous Sampling**, and **Placental anomalies**, such as retroplacental hematoma, infarction, and dilated vascular communications, have also been associated with IH development.

# Pathophysiology

There is migration of placental cells to embryo during neural differentiation.

It has been hypothesized **that hypoxia triggers a vascular response in infants**. LBW is a significant risk factor for IH, and in utero hypoxia is a common cause of LBW. Not surprisingly, **GLUT1**, a facilitative glucose transporter used as a marker for IH, **is an important sensor of hypoxia**. GLUT1 has been shown to be upregulated in hypoxic zones.

**The use of erythropoietin in preterm infants** increases the risk of developing an IH. Thus, **tissue ischemia** resulting in **neovascularization** from **circulating Endothelial progenitor cells (EPCs) or placental angioblasts** has been proposed as the stimulus leading to the development of IH.

# CLINICAL PRESENTATION, COMPLICATIONS, AND ASSOCIATIONS

IHs exhibit a characteristic life cycle, namely, **proliferation and involution.** Proliferation occurs during early infancy; most IH growth appears to occur between 1 and 2 months of age.

About 80% of IH size is generally reached by 3 months, and most growth is completed by around 5 months of age.

Gradual spontaneous involution or regression starts by 1 year of age , As IHs involute, most lesions flatten and shrink from the center outward.

An intermediate period between proliferation and involution during mid-to-late infancy, often referred to as the "plateau" phase.

# Three CLINICAL PRESENTATIONS:

**A:SUPERFICIAL IHs or STRAWBERRY TYPE** are those in which the surface of the tumor appears red and there is little to no discernible subcutaneous component;
**B:Deep IHs** are those in which the tumor resides deep to the skin surface, and their subcutaneous location results in a bluish surface hue or no evident surface changes; historically, or **"cavernous,"** an imprecise term that is no longer used.
**C:Combined, mixed, or compound IHs** (C) are those in which both superficial and deep components coexist.

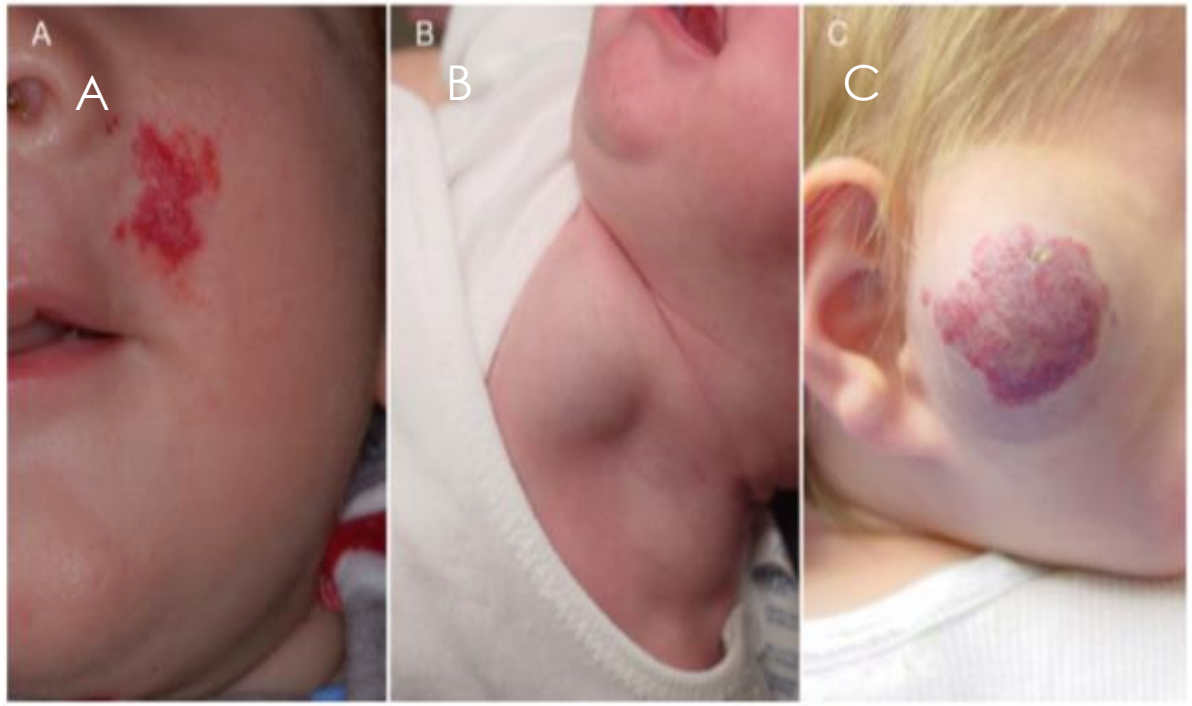



**FIGURE 6**
Cutaneous IHs may be classified on the basis of their depth. A, Superficial IHs are visible only at the skin surface and may be focal (as shown) or segmental. B, Deep IHs have no surface involvement. C, Mixed, or compound, IHs have both superficial and deep components.

# Telangiectatic IH

A specific subtype of superficial IH has been variably

referred to as an abortive, non-proliferative,

Arrested-growth, minimal-growth, reticular, or telangiectatic IH.

This type of IH presents as a macular, telangiectatic

patch that may be accompanied by blanching of

the involved skin .

Many of these telangiectatic IHs also involute more rapidly, sometimes before 1 year of age.

Complications such as ulceration may occur.

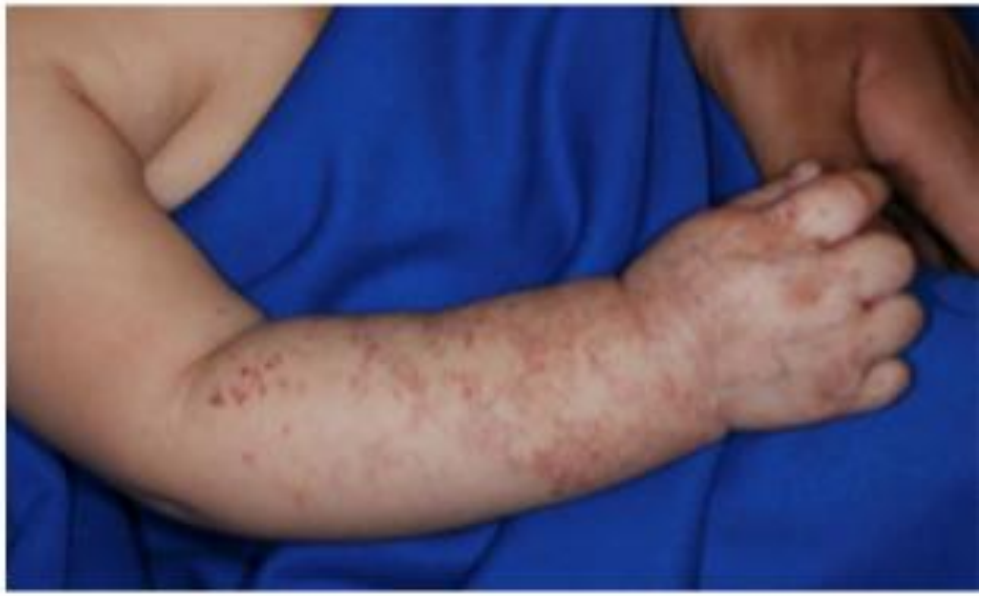


**FIGURE 7**
Abortive IHs are macular, telangiectatic patches that have failed to fully proliferate.

# Liver Hemangioma

The presence of a large or segmental (5 cm٢) cutaneous IH might prove a useful marker for hepatic IH. However, the number of cutaneous IHs rather than their size that is the more predictive factor.

When 5 or more IHs are present on cutaneous examination, ultrasonography may be helpful in assessing potential hepatic involvement.

Hepatomegaly, Hypothyroidism, and congestive heart failure also suggest the presence of liver IH.

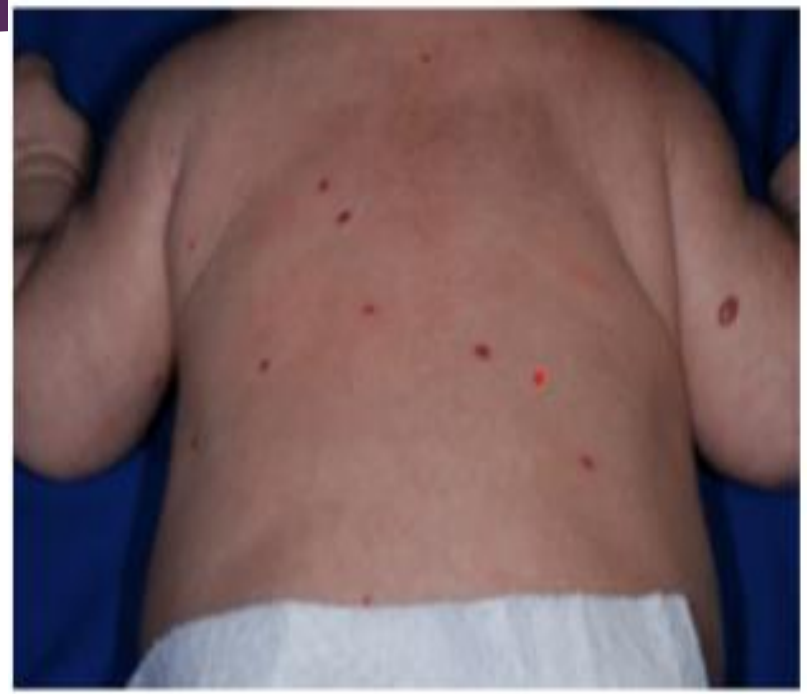
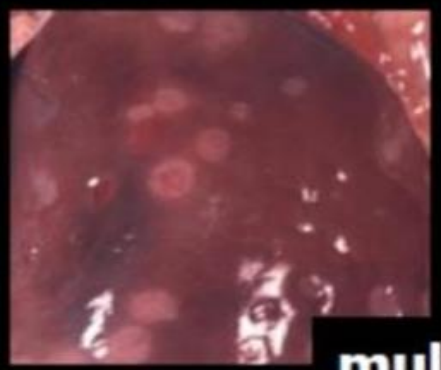
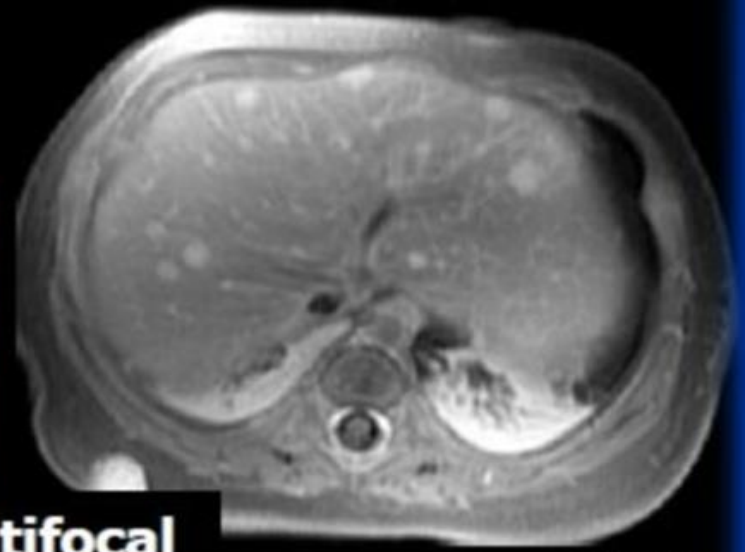


FIGURE 9
Multifocal cutaneous IHs in a child with IH of the liver.

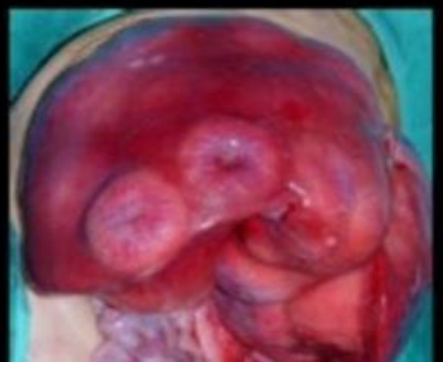
# Hepatic Hemangiomas

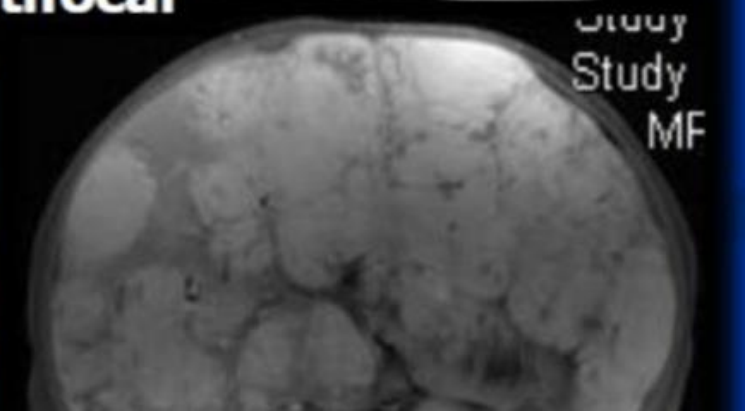
- Focal - May have arterio-venous or porto-venous shunts
- Multiple skin lesions common - often asymptomatic
- Diffuse lesions
  - High output CHF
  - Abdominal compartment syndrome
  - Profound hypothyroidism
  - Treatment:
    - Propranolol
    - Corticosteroids
    - Vincristine, Cytoxan
    - Thyroid replacement
  - Transplantation
  - Only 60% survive





multifocal





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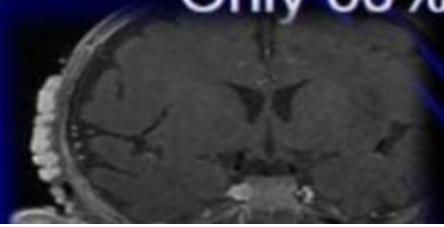

# Complications Up to 24% of the referred patients

**Ulceration** accounts for the majority of IH complications;

others include **bleeding, visual impairment, auditory impairment, congestive heart failure, and airway obstruction.**

**Gastrointestinal bleeding** has been reported as a complication of segmental intestinal hemangiomatosis, in which the IH is typically situated in the distribution of the mesenteric arterial system.

# Focal IHs

Focal His have the potential to cause complications primarily by virtue of their location on or near vital structures, such as the eye (amblyopia, astigmatism), nose (anatomic distortion and cartilaginous destruction), ears (anatomic distortion and cartilaginous destruction), lips (anatomic distortion and ulceration), airway (obstruction), or anogenital region (ulceration).

# Ulceration of IH in the anogenital area

**Ulceration** can lead to significant pain, bleeding, and secondary infection. Ulceration occur **more frequently in infants younger than 4 months**.

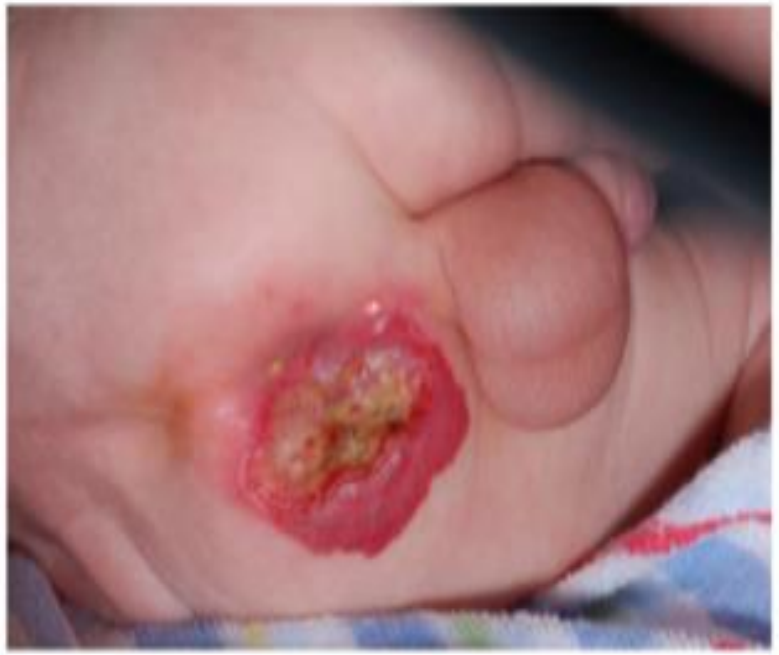

FIGURE 10
Ulcerated segmental IH of the perineal/perianal region.

# Congestive Heart Failure and Hypothyroidism

Although rare, high-output congestive heart failure can occur in infants with large IHs as a result of **arteriovenous shunting** of a large blood volume through the lesion.

This complication has been reported in infants with **large cutaneous IHs and RICHs** and in those with diffuse or multifocal **hepatic IHs.**

Symptomatic infants may present with difficulty feeding, poor growth, heart murmur, or hepatomegaly.

**Diffuse lesions of the liver** may also be associated with severe **consumptive hypothyroidism** caused by excess production of type 3 iodothyronine deiodinase.

# DIAGNOSIS: CLINICAL AND RADIOLOGIC

**Ultrasonography** is a reasonable initial imaging modality for diagnosing IH, because it is inexpensive and does not require sedation.

The sonogram generally reveals a well-defined

**high-flow parenchymal mass** with possible shunting.

**During the involution phase**, areas of increased echogenicity (fat replacement) can be seen within the lesions.

**Ultrasonography** is also a good first-line modality to screen patients with multifocal IHs **for liver or visceral involvement**, although **MRI** is preferable to assess complicated or extensive visceral lesions.

# Management:

The first consideration in the management of IH is whether intervention is necessary. The indications for intervention include the following:

(1) **emergency treatment of potentially life-threatening complications**;

(2) **urgent treatment of existing or imminent functional impairment**, **pain, or bleeding**;

(3) evaluation to identify structural anomalies potentially associated with IH;

(4) elective treatment to reduce the likelihood of long-term or permanent disfigurement.

**Life-threatening lesions include** obstructing IHs of the airway as well as liver IHs associated with high-output congestive heart failure and severe hypothyroidism.

# Treatment consideration

Relevant factors include age and medical condition of the patient; growth phase, location, and size of the lesion or lesions; degree of skin involvement; severity of complication and urgency of intervention; potential for adverse psychosocial consequences; parental preference; and clinician experience.

# Treatment Modality

Lesion-related factors, such as location, size, and degree of skin involvement or ulceration, often dictate the feasibility of a given treatment modality.

For example, a pedunculated eyelid lesion causing ptosis or ectropion or a small, ulcerated lesion that is certain to scar may lend itself better to early surgical excision rather than medical therapy. Conversely, an extensively ulcerated segmental IH or a lesion of the genitalia is more appropriately addressed with medical therapy.

# MANAGEMENT OF ULCERATED IHS

The management of ulcerated IHs includes attention to wound care, pain, and IH growth.

16% of ulcerated IHs were considered to be infected on clinical grounds, and cultures revealed pathogens in half of these cases.

Re-epithelialization may be facilitated by debriding crusts with the use of warm compresses. The ulcer is then covered with a barrier to prevent excessive drying, control pain, reduce the risk of trauma and potential bleeding, and reduce the risk of bacterial colonization or infection.

# MANAGEMENT OF ULCERATED IHS

Several case series have reported successful treatment of IH ulceration with propranolol therapy. **Topical timolol** has been reported to be successful for ulceration, but its absorption is unpredictable in this setting. **Systemic steroids** may also be a reasonable alternative.

In refractory cases, **pulsed-dye laser** (PDL) therapy may also be effective in managing ulcerated His. however, it has been recommended that laser therapy be used with caution in patients with proliferating Ihs (<6mo) because of the risks of atrophic scarring and/or ulceration.

**Surgical excision** may also be a consideration for small ulcerations that are poorly responsive to medical therapy.

# MEDICAL THERAPY FOR IH

- Topical agents may be a consideration for smaller, more superficial IHs or those for which systemic therapy is contraindicated.
- Systemic therapy is usually initiated for large IHs, those with a high risk of functional impairment or disfigurement, and those refractory to other initial therapies.
- Beginning in the 1960s, **systemic and intralesional steroids** were the cornerstone of medical therapy for IH.

# Interferon a

- In the late 1980s and early 1990s, interferon-a showed some promise in the treatment of steroid-resistant IHs. This drug is a cytokine produced by leukocytes that play a role in the innate immune response against viruses.
- However, it is now clear that significant neurologic toxicities, including impairment of higher cortical and motor function, can occur and generally preclude its use as a first-line therapy.

# Beta Blockers

β-Adrenergic Blockers For most clinicians treating complicated IHs, **propranolol** has become the first-line medical therapy; however, optimal dosing, treatment timing and duration, and risk of complications have not yet been established in randomized trials, and recommendations for monitoring are still evolving. An oral formulation free of alcohol, sugar, and paraben developed for use in children. Atenolol has same efficacy with the same dose.

Like systemic corticosteroids, propranolol appears to stabilize IHs in their growth phase; however, it may also be effective after proliferation has ended.

# Pretreatment Assessment, Contraindications, and Risks of Therapy

A **complete history and physical examination**, with special attention to the cardiac and pulmonary systems, aid in assessing a child's candidacy for propranolol initiation.

**ECG** is often ordered as well, particularly in younger infants, those with a low heart rate, and those with an examination or family history consistent with congenital heart disease.

**Relative contraindications** to the use of propranolol for IH include: cardiogenic shock, sinus bradycardia, hypotension, heart block greater than the first degree, heart failure, bronchial asthma, and known hypersensitivity to the drug

# Dosing of propranolol

Initiating therapy at a dose of 1 mg/kg per day, with escalation to a target dose of 1 to 3 mg/kg per day, ( the FDA approval of Hemangeol, maximally 3.4 mg/kg per day). Treatment should be continued **at least 3-12 months**.

The drug has been dosed twice daily and showed both safety and efficacy as three times/day. Because the peak effect of oral propranolol on heart rate and blood pressure is 1 to 3 hours after administration, measurements be taken at baseline, 1 and 2 hours after the first dose, and 1 and 2 hours after each dosage increase of 0.5 mg/kg per day. Heart rates or blood pressure measurements lower than 2 SDs from the mean suggest the need for cardiologic evaluation.

**The risk of hypoglycemia** may be reduced by administering propranolol and feeding children at intervals not to exceed 6 hours in younger infants.

# Steroid therapy

- **Corticosteroid therapy** has several effects on IH, involving both vasculogenesis and adipogenesis. Steroids inhibit neovessel growth.
- Corticosteroids also **inhibit the expression of proangiogenic proteins**, including VEGF-A, urokinase plasminogen activator receptor, monocyte chemoattractant protein-1, IL-6, and MMP-1, from human IH stem cells in a murine model.
- And **promote adipogenesis** by increasing the expression of peroxisome proliferator activated receptor. This activity is thought to explain the development of the fibrofatty residuum during involution of the vascular components of IH.

# Prednisolone vs Propranolol

- In a prospective, randomized, investigator-blinded trial comparing prednisolone and propranolol dosed at 2.0 mg/kg per day, the drugs showed similar efficacy for reducing the area of symptomatic IH; however, although prednisolone showed a somewhat faster response rate, propranolol was better tolerated with significantly fewer severe adverse effects.
- Rebound growth occurs in 14% to 37% during dose tapering, occasionally requiring the resumption of steroid therapy.

# dosing

- Optimal dosing of systemic corticosteroids  appears to be 2 to 3 mg/kg per day. The duration of therapy depends on response rate as well as the age of the patient and phase of IH growth but generally ranges from 4 to 12 weeks at full dose, followed by tapering over several months and completion of treatment by 9 to 12 months of age.

# intralesional vs Systemic

- The effectiveness of intralesional corticosteroid therapy for problematic IHs was first described in 1967 to be as effective as systemic steroids.
- In general, corticosteroid injection is reserved for small, well localized IH lesions.
- Large or diffuse IHs are more difficult to manage with intralesional corticosteroids because of the following:

(1) a large volume of injectable steroid is more likely to cause systemic adverse effects

(2) it is difficult to evenly distribute the corticosteroid throughout a large tumor.

(3) In lesions that are relatively flat or superficial, intralesional steroid injection carries an increased risk of localized complications involving the overlying skin or underlying tissues.

# Intralesional steroid injection

- In most studies, patients were injected with either triamcinolone alone or a mixture of triamcinolone and betamethasone, at total equivalent doses of triamcinolone doses of 3 mg/kg, by using a 27- or 30-gauge needle.
- The interval between injections varied from 1 to 6 weeks.
- Accelerated regression in 77% to 100% of patients will be seen.
- The effects of the steroid last approximately 3 to 4 weeks, and thus patients may require additional treatments during the proliferating phase for rebound growth.
- Local complications of intralesional corticosteroids include fat and/or dermal atrophy and/or hypopigmentation (0%–3%)

# Topical Corticosteroids

The use of high-potency topical corticosteroids in IH is usually limited to thin, superficial lesions.

Topical Clobetasol for periorbital IH has 68% good to excellent efficacy.

A more recent comparison of topical mometasone versus intralesional triamcinolone in superficial IHs less than 5 cm in diameter showed that 86.5% (50% excellent, 36.5% good) of patients in the topical group and 95.7% (63.8% excellent, 31.9% good) in the intralesional group responded to the therapy.

# Other Medical Therapies

- Before the discovery of the therapeutic efficacy of propranolol for IH, several other agents were used: vincristine, interferon-a, and imiquimod.
- **1- Vincristine** appears to be particularly useful in patients with corticosteroid-resistant KMP, but it is not a first-line therapy for IH.
- **٢-Imiquimod** (Imidazoquinoline 5%) This topical immune-response modifier stimulates the innate immune system by augmenting the production of cytokines, including interferons (a, b, and g); IL-10, IL-12, and IL-18; and tumor necrosis factor. Only for superficial lesions.

# Other Medical Therapies

- **٣-Interferon-α 2a and 2b** have both been used successfully for IH in children. Interferon-α is given subcutaneously with an initial dose of **1 million IU/m2, increasing to 3 million U daily** over the first month of therapy while monitoring neurologic status, white blood cell count, and liver function status. Most patients have required between 2 and 12 months of therapy. Adverse effects are significant and include flu - like reactions, rash, gastrointestinal symptoms, transaminitis.
- Up to 20% of children treated with interferon-α appear to develop spastic diplegia

# Sirolimus (Rapamycin)

- Rapamycin is a macrolide known to have both immunosuppressant and antiangiogenic actions, and therefore the risk-benefit ratio of this agent will need to be clearly established before it can be considered a safe alternative to the agents currently available for the treatment of IH.
- At present, it should be used as a salvage treatment.

# LASER THERAPY FOR IH

- Before the discovery of the efficacy of propranolol in the treatment of IH, PDL therapy was frequently a component of the treatment strategy for His.
- However, given their limited depth of penetration of less than 2 mm, these lasers proved useful primarily for superficial lesions and for deep and compound lesions in which salvage of the superficial skin was desired.
- laser therapy still have a role in IH management, particularly when used as a part of multimodal therapy or in ulcerating lesions refractory to other therapies.

# LASER THERAPY FOR IH

- Although small IHs may be treated without sedation, children with larger lesions often require general anesthesia. Recent data suggest that early exposure to general anesthesia may have a negative effect on learning and behavior.
- Proposed uses for PDL in IH management include the following:
- **(1) early superficial facial IHs,**
- **(2) treatment of compound IHs in which sacrifice of the overlying skin is undesirable,**
- **(3) refractory ulceration,**
- **(4) significant residual telangiectasia or flat IH persisting after involution.**

# SURGICAL THERAPY FOR IH

- Elective resection of an IH during the proliferative phase is usually not necessary and occasionally ill advised.
- Given their young age and the vascularity of the tumor, affected patients are at greater risk of anesthetic morbidity, blood loss, and iatrogenic injury.
- **(1) contraindication to pharmacotherapy,**
- **(2) failure of pharmacotherapy to ameliorate the problem,**
- **(3) focal involvement in an anatomically favorable area,**
- **(4) a high likelihood that resection will be necessary in the future (due to bulk or ulceration) and the scar will be the same.**

# IHS WITH SPECIAL ANATOMIC CONCERNS

- **Eye and Orbit** : refractive errors, strabismus, and amblyopia.>> local and systemic Rx.
- **Airway:** biphasic stridor and barky cough. 50% have oral and facial IH.>> Systemic steroid + propranolol.
- **Perineum:** prone to ulceration

# IHS WITH SPECIAL ANATOMIC CONCERNS: Liver

- The liver is the most common location for visceral IH. Patients at risk of hepatic and other extracutaneous IHs are those with multiple or multifocal cutaneous IHs. Infants with >5 need screening for hepatic lesions with abdominal ultrasonography. Hepatic IHs have been characterized as occurring in **3 patterns: focal, multifocal, and diffuse.**

Focal singular lesions are usually detected on antenatal imaging or as an abdominal mass in the newborn infant. They spontaneously involute 90% volumetrically by 13 months of age.

**If shunts are present** and causing high-output failure, selective embolization can ameliorate cardiac failure, and the lesion can be allowed to involute.

# Hepatic IH

- Hepatic IHs have been characterized as occurring in 3 patterns: focal, multifocal, and diffuse.
- Focal singular lesions are usually detected on antenatal imaging or as an abdominal mass in the newborn infant. They spontaneously involute 90% volumetrically by 13 months of age, If shunts are present and causing high-output failure, selective embolization can ameliorate cardiac failure, and the lesion can be allowed to involute.
- Virtually all diffuse hepatic IHs cause acquired hypothyroidism attributable to the inactivation of thyroid hormones by type 3 iodothyronine deiodinase constituent in the lesions.
- An infant who presents with massive hepatomegaly and abdominal compartment syndrome occasionally has multifocal disease that cannot wait for drug-induced involution; in rare cases, such a child may be a candidate for hepatic transplantation.

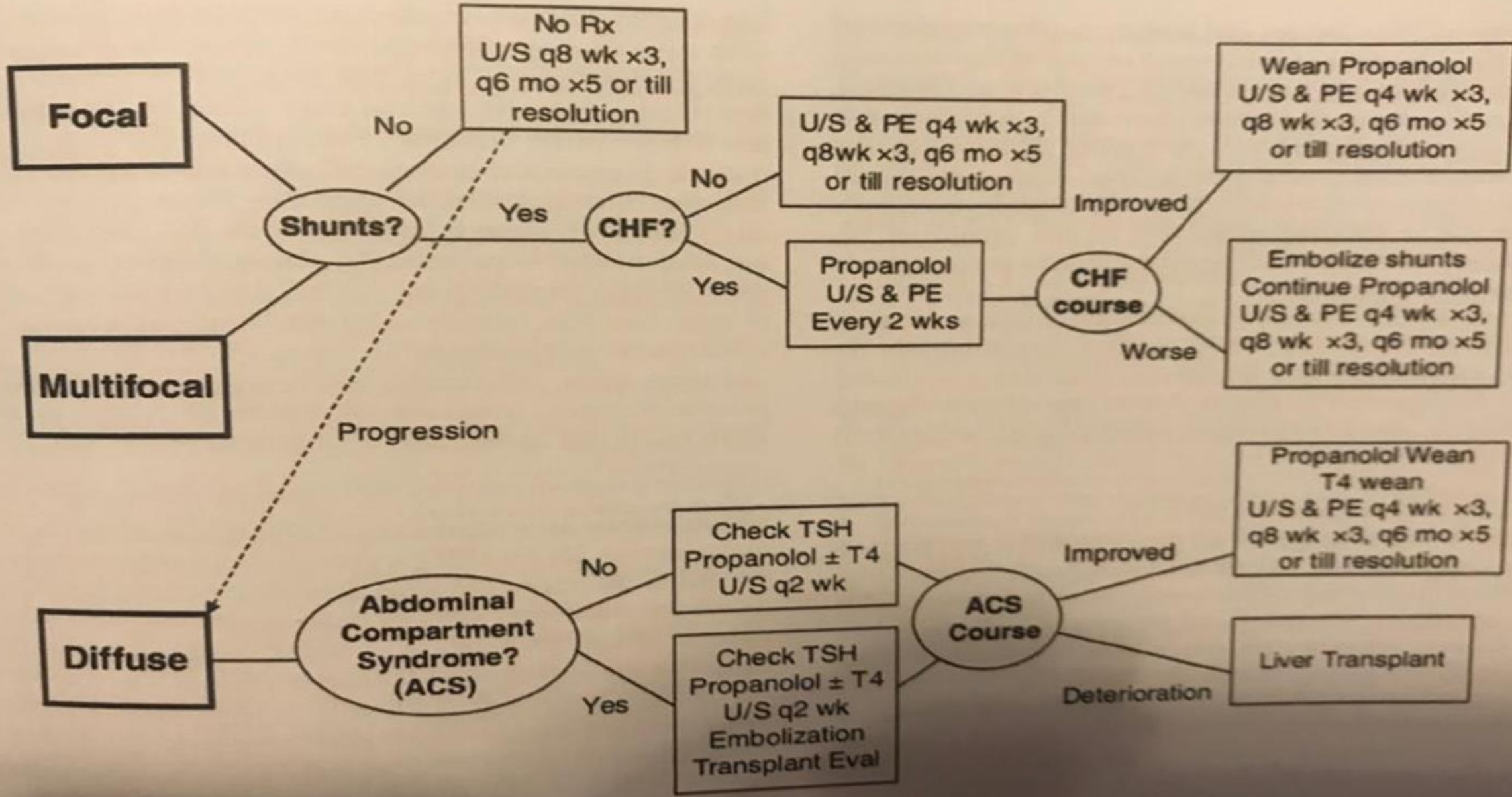


Figure 28.20 Treatment algorithm of infantile hepatic hemangioma.

# Conclusion:

- The management of IHs has evolved considerably in the past decade.
- Timolol, a topical b-blocker, ( in different strengths include 0.1, 0.25 or 0.5% cream) has shown promise as a potential therapy for superficial lesions.
- A greater understanding of the indications and limitations of laser therapy also has emerged.
- It is important for pediatricians to be aware of advances in IH management, because the types of intervention and the threshold for their use are likely to evolve.
- When complications are likely or the threshold for intervention is uncertain, referral to an experienced specialist or a multidisciplinary vascular anomalies center may be advantageous.


Thank you for Attention
Any comments, or
questions?