Diagnosis and natural history of hemangiomas.

Mulliken and Young's Vascular Anomalies: He Malformations

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Diagnosis and Natural History of Hemar

Chapter: Diagnosis and Natural History of Hemangiomas
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And the blots of Nature's hand

Shall not in their issue stand;

Never mole, hare-lip, nor scar,

Nor mark prodigious, such as are

Despised in nativity,

Shall upon their children be.

Oberon, King of the Fairies Shakespeare, *A Midsummer Nig*

(Act V, Sc. i., 406)

Incidence

Hemangioma is the most common tumor of infancy and childl et al., 1983); the incidence is reported to be 1.0–2.6% in Caucas hemangiomas appear during the first to fourth week of life; the are often not discovered until 2–3 months after birth. By age 1 hemangioma (Holmdahl, 1955; Jacobs, 1957; Hoornweg et al., et al., 1986). The incidence has been reported to be 1.4% in Afri much lower in our Vascular Anomalies Center.

Hemangiomas were initially reported to occur in an equal freq however, this study included few neonates of less than 1,500 g hemangioma was 23% in premature infants who weighed less (Amir et al., 1986). This was corroborated by an unpublished s appeared in 30% of premature infants weighing less than 1,000 regression showed that low birth weight (defined as less than was a positive family history (Drolet et al., 2008). This analysis risk of hemangioma increased by 40%. Earlier studies had sho g have the same frequency of hemangioma as full-term infants are also more frequent in preterm infants; however, female pre Hemangiomas arising in prematures occurs in the same locati regression as tumors in full-term infants. Gutiérrez and colleag weighing less than 1,500 g who developed postnatal hemangio hemangioma. In the hemangioma group, they found a high in hematoma, ischemic infarction, vasculitis, and chorioamnioni changes in placental circulation could be related to hemangio

A large prospective study from seven U.S pediatric dermatolog likely to be female, white, premature, and the product of multi found that maternal age was significantly higher and that the p eclampsia. The finding that hemangioma occured more comm weight in multiple gestations. There are other compounding fa multiple pregnancies, and prematurity is more likely following Judah Folkman hypothesized that the common pathway for th placenta previa, etc.) involves decreased endogeneous angiog surveillance.

The female-to-male ratio for hemangioma is 3:1 (Bowers et al.,

misapplication of material in this work. Except where otherwise stated, drug dosages and recommendations are for the non-pregnant adult who is not breastfeeding.

higher (90%) with problematic tumors (Enjolras et al., 1990; En
hemangioma is associated with structural anomalies (Gorlin e
prematures who develop hemangioma is closer to 1:1 (Amir et
preterm infants are more commonly male. There are reports th
women who have had transcervical chorionic-villus sampling
al., 1995; Bauland et al., 2010). A higher incidence of prematuri

Location

Infantile hemangioma (IH) most commonly arises in the head
(25%) and the extremities (15%) (Finn et al., 1983). This region
tendency for parents to bring a child with a facial hemangioma
that the distribution and morphologic forms of facial hemangi
growth: focal facial lesions (occurring along lines of embryoni
prominences), such as frontonasal, maxillary, and mandibular
(2006) led them to designate eight facial "segments" that they l
hypothesized that "segmental" hemangiomas are predetermin
have otherwise disappeared.

The term "segmental" is confusing when used in the clinical co
Embryologic texts describe craniofacial development in terms
segments. The word "segmentation" denotes very early patter
lower life forms, such as annelids and arthropods. In later cran
the complex interplay of germ layers and neural crest to form t
whether "segmental" speculation provides heuristic insights in
known of etiopathogenesis at a molecular level, this author pr
focal (solitary), *multifocal* (multiple), or *regional* (territorial). R
terms for facial anatomic regions, that is, frontal, temporal, nas

Familial Hemangiomas

Infantile hemangiomas are not considered inheritable. Nevert
more frequently in fair-skinned families and in those with a pr
evidence for Mendelian inheritance in a study of monozygotic
a family history of hemangioma was elicited in 10% of infants
that suggest familial transmission in an autosomal-dominant p
(Blei et al., 1998). These "familial" hemangiomas are indistingu
pedigrees there appears to be coexistence of hemangioma and
family, as well as in the same individual. A putative locus was i
al., 1999).

Precursor Lesions

Approximately one-third of infantile hemangiomas are presen
natal period. Signs of nascent hemangioma include: erythema
ecchymotic-like mark, and localized telangiectasia, surrounde

1972) (Figures **4-1**, **4-2**, **4-3**). Ulceration may also be a harbinge
hemangioma can be nearly fully grown at birth and thus confu
lesions exhibit some progression and slow regression, just as t

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Figure 4-1
Precursor lesions of hemangioma. A. Newborn male with pink
a superficial dome-shaped tumor with central ulceration. C. Ne
pallor. D. At 8 months, this deep/superficial hemangioma at ap

Click t
Downl

Figure 4-2

Nascent hemangioma. A. Newborn female with pale patch and
vascular lesion is a macular stain. C. At 1.5 months, raised supe

Click t
Downl

Figure 4-3
Premonitory hemangioma. A. Newborn with large pale patch a
the superficial tumor is more obvious and beginning to elevat

Multifocal Hemangiomas ("Hemangiomatosis")

Eighty percent of infantile hemangiomas are focal, whereas 20
Museles, 1965). The purported first description of multiple neo
remarkable case report of a 6-day-old neonate with 834 lesion
3–4 millimeters (mm), raised, and dome-like. There can also b
same infant (Figure **4-4A**). These tiny hemangiomas are often
short time, and often blister, blacken, and disappear. The mech
unknown. It is also curious that new, tiny lesions can appear w

Figure 4-4
Multifocal hemangiomas. A. Multiple dome-like lesions and la
lesions in female infant with multifocal intrahepatic tumors an
hemangioma (superior-medial segment) in 1-month-old boy

(Courtesy of Dr. Madina Holmuhamedova)

Multifocal cutaneous hemangiomas often occur with intracran
termed “miliary” or “disseminated hemangiomatosis” (Kunds
1984). Other authors have used the terms “benign” or “diffuse”
Alexander, 1970; Stern et al., 1981). The modifier “diffuse” is im
“Diffuse” derives from the Latin *diffusus*, past participle of *diffi*
about.” Thus, “diffuse” more accurately denotes an extensive h
side of the face or neck, a large area of an extremity, or the enti
inexact because it also has been used to designate intraosseou

Extracutaneous hemangiomas have been found at autopsy in v
pancreas, gallbladder, liver, thymus, thyroid, gastrointestinal t
(Kundstadter, 1933; Andries and Kaump, 1944; Cooper and Bol
Stern et al., 1981; Balaci et al., 1999). The most common extracu
intestine (Lopriore and Markhorst, 1999) (Figure **4-4B**). In our
rare. It is not known whether multifocal hemangiomas are the
from one hemangioma can emigrate to another site. Another p
the past called “angioblasts”) are present in multiple anatomic
tumors.

It is rare that an infant with visceral hemangiomas does not ha
is, some infants with multiple cutaneous lesions do not have h
Street Hospital, hepatic lesions were found in 45% of infants w

cutaneous lesions; and 12–14% with one large or three or more
small hepatic tumors do not develop congestive cardiac failure
hemangiomas is a suspect for having visceral tumors, particula
screened by ultrasonography (U/S) and/or magnetic resonanc
pharmacologic therapy, infants with multiple cutaneous and in
secondary to arteriovenous shunting in the liver. There are sev
hemangiomas of the iris, often involving the eyelid margins an
vascular lesion of the iris in one or both eyes (Haik et al., 1983)
include hyphema, vitreous hemorrhage, and subretinal hemor
confirmed the typical findings of infantile hemangioma in the
retina (Chang et al., 1998). Glaucoma is a potential complicatio
(Weiss and Ernest, 1976). Follow-up ocular examination shoul
and indirect ophthalmoscopy. As would be expected, iridal he
al., 1999) and respond to corticosteroid therapy (Ruttum et al.,

Neuraxial Hemangioma

Intracranial infantile hemangiomas can occur, particularly wh
large facial tumors (Billson and Gillam, 1984; Tortori-Donati e
Vascular Anomalies Center, 15/1,454 (approximately 1%) of in
central nervous system (CNS): intracranial, intraspinal, or both
to our center, the true frequency of neuraxial hemangioma is p
was traced from a cutaneous extracranial or extraspinal tumor.
orbital fissure, foramen rotundum, and hypoglossal canal. The
accompanying extra-CNS tumor.

Intracranial hemangioma grows in the subarachnoid space an
other typical locations are the cavernous sinus and fourth vent
colleagues (2009), none of the neuraxial hemangiomas invade
effect. Other findings were hydrocephalus (n=3), thrombosis o
association (n=3). Two of the intraspinal hemangiomas had an
5C, D). Two of the seven patients with intraspinal hemangioma
intramedullary angiolipofibroma. There is a report of an intras
in a 2-month-old infant; this was ascribed to intratumoral hem

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Figure 4-5
Neuroaxial hemangioma. A. Large upper eyelid hemangioma c
traversing orbital foramen and extending into left cavernous si
and continuing along trigeminal nerve to abut ventral surface
Reticular hemangioma on posterior thorax is "tip of the iceber
indicate intraspinal, extradural tumor posterior to thecal sac; b
red arrows show tumor in prevertebral space.

PHACE(S)-Associated Malformative Anomalies

Geneticists often mistakenly include "hemangioma" on the lis
terminologic errors. These mislabeled vascular lesions are usu
(Burns et al., 1991; Hand and Frieden, 2002). Capillary malform
in the genetic literature. Because infantile hemangiomas are so
pathogenically associated, in a rare syndrome. Nevertheless, th
malformations (capillary, lymphatic, venous, and arterial) are
particular disorder.

An International Working Group of geneticists recommended
to be pathogenically related and occurring in non-contiguous
is defined as a nonrandom occurrence of several morphologic
identified as either a sequence or a syndrome (Cohen, 1997). A
related, although the etiology is unknown. Association alerts th
anomalies. As a working criterion, an abnormality must occur
designated as "associated" rather than an aleatory finding.

There are curious, and relatively uncommon, instances wherei
occurs in association with structural anomalies that are not alw
hemangioma in the presence of malformations of the hindbra

and colleagues (1975) described two patients with coarctation
hemangioma and smaller tumors on the lip and chin. Pascual-
anomalies (including cerebellar malformations) by angiograp
Schneeweiss and coworkers (1982) described four cases of faci
great vessels. Goh and Lo (1993) proposed the term "3C syndr
hemangioma, cerebellar hypoplasia, and coarctation of the ao
Some infants with large facial hemangioma and anomalies of t
syndrome (Billson and Gillam, 1984) or Wyburn-Mason syndr

The association between cerebellar, cerebrovascular, and aort
until Frieden and colleagues designated the catchy acronym P
face; *a*rterial abnormalities; *c*ardiac defects and coarctation; an
et al., 2001). Often these malformations are ipsilateral to the fa
70% of affected patients have only one extracutaneous anomal
Curiously, females are affected more than males, 9:1; this ratio
the prevalence of hemangioma in association with a structural
selected population of patients who were referred with proble
much lower. In a large, inter-institutional prospective cohort s
discovered in 2.3% of children (Metry et al., 2006). Ascertainme
infants with a large cervicofacial hemangioma. Comparison of
no major demographic or perinatal differences (Metry et al., 20

The "many faces of PHACE" are usually recognizable (Metry et
the major and minor diagnostic criteria is available (Metry et a
Figure **4-6**. PHACE association will receive syndromic status o

Figure 4-6
PHACES association: Clinical spectrum. A. Infant female with d
stenotic left intracranial internal carotid artery; persistent right
subclavian artery. B. 3-month-old female given corticosteroid
revealed hypoplastic cerebellar vermis and dysmorphic cereb

facial hemangioma and anisocoria (small right pupil), esotrop
internal carotid artery and persistent trigeminal artery; echoca
with deep right frontal hemangioma presented with seizures a
arterial stroke and moyamoya. Fundoscopic examination reve
pigmentation. E. Neonatal female with reticular hemangioma
and stenosis of left (contralateral) internal carotid artery. F. 15-
hemangioma (necessitating tracheostomy) and bilateral conge
raphe and split manubrium.

Posterior Fossa

Dandy-Walker malformation is the most common developme
hemangioma; others include: subependymal and arachnoidal
or vermis, corpus callosum, cerebrum, and septum pellucidum
malformation, only 10% had a facial hemangioma (Hirsch et a

Several cerebral (supratentorial) abnormalities are associated
migration anomalies. Encephalomalacia, microcephaly, and ca
caused by vascular insufficiency *in utero* (Pascual-Castroviejo
developmental anomalies cannot be ascribed to vascular sten
cortical heterotopias (Grosso et al., 2004).

There are several reports documenting intracranial hemangio
periorbital hemangioma (Poetke et al., 2002; Bhattacharya et a
cranial base and posterior fossa; they seem to have a predispo
and internal auditory meatus (Tortori-Donati et al., 1999; Judd
noted above, intracranial hemangiomas extend within the sub

Hemangioma

Facial hemangioma in PHACE manifests at birth as a regional
like, pebbly, or reticular. Although the reticular form is the mos
deep and superficial) type of hemangioma also can occur (Ros
PHACE association is with tumors in the frontal and temporal
the maxillary and mandibular areas. PHACE association may b
many as 20–30% with a large, regional facial hemangioma (Me
mandibular areas are involved ("beard distribution"), laryngea
hemangiomas are often ipsilateral to the intracranial and cervi

An epidemiologic study showed that these regional facial hem
gestational age with a higher birth weight, and that there is a hi

PHACE anomalies also can occur in the absence of a facial hem
hemangiomas (Honey et al., 1975; Billson and Gillam, 1984; Va
2002). Internal hemangiomas have also been found with PHAC
(Metry et al., 2004). PHACE vascular abnormalities have also b
the upper limb.

Arterial and Cardiac

Angiography and magnetic resonance angiography (MRA) hav
most common finding in PHACE association. There are two typ
difficult to differentiate (Heyer et al., 2008). The structural anor
arteries (such as, primitive trigeminal artery, hypoglossal arter
carotid-vertebrobasilar anastomoses, segmental agenesis, hyp
vessels (Pascual-Castroviejo, 1978; Pascual-Castroviejo et al.,
development of the vertebral arteries and posterior communic
than 1% of the population), but the prevalence is 17.4% in PHA
basilar segment (foramen lacerum) of the internal carotid and
Castroviejo et al., 1996; Aeby et al., 2003; Grosso et al., 2004). Pr
(Oza et al., 2008). These cerebrovascular abnormalities tend to
contralateral and bilateral. Serial imaging has documented pro
arterial anomalies, including evidence of worsening stenosis a
vessels, resembling moyamoya (Burrows et al. 1998; Baccin et
proliferative phase of the hemangioma. Neurologic sequelae i
stroke, and developmental delay. These ischemic events are us
Progressive cerebrovascular stenosis can cause neurologic dis
delay, seizures, stroke, and also late-onset migraine headaches
narrowing/non-visualization of at least one great cerebral vess
there are rare patients in whom hypoplasia of the aortic arch h
have regressed (Pascual-Castroviejo et al., 2003).

There are also examples of intracranial AVM/AVF with PHACE
hemangiomas of the posterior scalp and subglottis, typical intr
osteodural AVF, likely a separate arteriovenous shunt at T5, an
well-documented cases of pial-dural AVM/AVF and other exam
(2011). They also noted that the intracranial fast-flow anomalie

Extracranial vascular anomalies in PHACE association include
branches (Burrows et al., 1998); aberrant subclavian artery; coa
ductus arteriosus, septal defects, aortic valvular stenosis, pulm
1982; Vaillant et al., 1988); and dilatation of the carotid siphon.
the facial hemangioma and the side of the aortic arch anomaly
common vascular malformation (Metry et al., 2001). Coarctatio
and shoulder. Aortic aneurysms found in PHACE association o
innominate artery, both with and without predisposing aortic a
anomalies, particularly aortic aneurysm, can evolve.

Eye

Ocular abnormalities of PHACES include microphthalmia, irid
glaucoma, lens coloboma, persistent papillary membranes, co
nerve hypoplasia or atrophy, and excavated optic disc anomal
(Coats et al., 1999; Metry et al., 2001; Lasky et al., 2004) (Figure
anomaly of the optic disc; it is usually unilateral, or it can be bi
glial tuft, retinal vessels that exit in a radial fashion from an en
the globe), and variable peripapillary pigmentation. It is not pa
(idiopathic) or in association with other disorders, for example

anomalies (e.g., basal encephalocoele, pituitary dwarfism, and
al., 1998), moyamoya disease (Massaro et al., 1998; Lenhart et a
type) (Brodsky et al., 1999). Abnormal development of the intra
thread that ties morning glory fundus to these various conditio
also be part of the PHACE spectrum.

Figure 4-7
PHACE association: Ocular anomalies. A. 5-year-old girl with r
(eccentric location of the pupil) giving a coloboma-like appear
ectasia of the left internal carotid artery; dysmorphic cerebellu
ophthalmological findings reported by Lasky et al. (2004). B. 2-
occipital scalp. Normal MRI/MRA. Exotropia and nystagmus pr
"morning glory disc" O.S. (Left) Funnel-shaped excavation of p
dysplastic optic disc—notable for peripheral displacement of c
emanating from disc. Yellowish central glial tuft pulls tempora
O.D.

Sternum

The original acronymic designation PHACE did not include ex
craniofacial and cervical hemangioma can be associated with s
(Hersh et al., 1985; Igarashi et al., 1985; Gorlin et al. 1994). Som
most common sternal cleft involves the manubrium (Figure 4-
the letter S was added to make PHACES (Metry et al., 2001). S a
diastasis recti, other rare midline abdominal anomalies in the s
aortic arch anomalies and in the absence of a facial hemangio
Figure 4-8.

Figure 4-8
Extra-craniofacial PHACES. A. Infant girl with focal sternal defe
Sagittal MRI revealed fusiform aneurysm in ascending and tra

PHACES Diagnostic Evaluation and Management

An infant with an extensive temporal-frontal or lower facial he
for possible PHACE association. An echocardiogram should be
indicated for possible aortic arch abnormalities. Ultrasonogra
MRI/MRA of the brain, head, neck, and chest is needed to dem
diffuse periorbital hemangioma in order to rule-out retrobulb
anomalies, including intracranial hemangioma (Judd et al., 20
CT angiography is fast and can be done without sedation, but i
radiologic studies is debatable. In some centers, imaging is do
other units, general anesthetic is recommended prior to age 3
Ophthalmologic consultation is also indicated to rule out ocul
with cerebral/extracranial vascular anomalies or intracranial s
disorders is indicated if MRI reveals evidence of intracranial v
neurologic sequelae.

Children who have suffered an acute ischemic stroke have bee
2006). It is unclear whether an asymptomatic infant with anom
prophylactically anticoagulated (with low molecular weight he
there are cerebral vascular anomalies and until it is certain tha
changes on the initial examination in a child with obvious PHA

Neurologic symptoms of cerebrovascular involvement can pre
had an imperceptible involuted hemangioma of the forehead.

Figure 4-9
PHACES association: Late presentation. A. Female infant with c
obstruction; treated successfully with systemic corticosteroid. I
years. She presented with migraine headaches and a transient
artery and left moyamoya. “Pial synangiosis” done promptly; t
hemispheres, persistent tortuosity of intracranial vessels, and

PHACES Association-Plus

PHACES is a useful acronymic mnemonic. More initials might
be on the spectrum, such as lingual thyroid (Metry, 2001); ager
2006); and hypopituitarism due to partially empty sella turcica

There are also rare cases of hemangioma arising along the late
lip/palate (Lo et al., 1994; Williams et al., 1997; Sarifakiouglu et
median mandibular cleft (Morioka et al., 2003). It is appealing
lines of fusion; Virchow called these “fissural angiomas.” More
penetration of the ectodermal envelope (merging).

Figure 4-10
Cleft lip and hemangioma: Association or coincidence? A. Bilat
element. (Courtesy of Dr. Fernando Ortiz-Monasterio) B. Bilate
vermilion hemangioma on left incomplete side.

Associated Ventral-Caudal Anomalies

Focal hemangioma located over the cervical or thoracic spine
structural defects, and usually imaging is not necessary. In con
located in the thoracic, lumbosacral, or perineal regions, may
The concurrence of hemangioma and ventral-caudal structura
counterpart of PHACE association (Mulliken et al., 2007b). Also
common; however, solitary and raised tumors occur as well. A
the area of a lumbar hemangioma. Hemangioma is one of seve
spinal dysraphism, for example, lipoma and lipomeningocoel
"space" or "cleft" + *myelos,* "marrow" or "spinal cord"] (Goldbe
hemangioma can extend to involve an intraspinal lipoma or ex
paraparesis. Signs and symptoms of spinal dysraphism may n
paresis of the lower extremities, muscular atrophy, and inconti
prevent permanent neurologic sequelae. Ultrasonography (U/
months because of incomplete ossification of the posterior spi
lumbosacral MRI (and sedation) is necessary after that age. If t
for tethering, MRI is mandatory. MRI (with contrast), plus MRA
and other vascular anomalies.

Figure 4-11
Hemangioma and associated ventral-caudal anomalies. A. Ret
Pebbly lumbar tumor with acrochordon and meningocoele. C.
lower limb with imperforate anus, duplex left kidney, and tethe

(Courtesy of Dr. Steven J. Fishman)

Perineal hemangioma can also be associated with urogenital a
imperforate anus (often with fistula), renal anomalies, bladder

absence of the labia minora), and hypospadius (Goldberg et a
D). There may be a persistent sciatic artery, hypoplastic ileofer
(Mulliken et al., 2007b; Kircher et al., 2010); perhaps these corr
PHACE association. We also described an infant at the extreme
reticular hemangioma, dilatation of the common iliac artery w
limb, and cardiac overload (Mulliken et al., 2007b).

The acronyms PELVIS (Girard et al., 2006) and SACRAL (Stockn
the similarities between hemangioma with ventral-caudal ano
incorrectly labeled a "syndrome" and, as in many acronyms, i
necessary as a mnemonic aid, LUMBAR is the most inclusive: *l*
*m*yelopathy, *b*ony deformities, *a*norectal malformations and a
The *u* also denotes the likelihood of ulcerations in this setting.

This same combination of congenital abnormalities (in the ab
septum malformation sequence (Wheeler and Weaver, 2001). Th
weeks of development there is incomplete breakdown of the c
the caudal region of the embryo.

Pathogenesis of Hemangioma and Associated Stru

The concurrence of infantile hemangioma and malformative a
common pathogenesis. Perhaps these associations represent a
mesodermal development and angioblastic tissue (Hersh et al
and neural crest cells give rise to the cellular components of in
smooth muscle cells, as well as most connective tissues in the
of infantile hemangioma and associated structural anomalies
mesenchymal progenitor cell in one or more patterning genes
consequent alterations in morphogenetic instructions.

The structural anomalies that occur in PHACES and ventral-ca
preponderance of females (over 90%) suggests an X-linked do
Some males would survive, depending on the mutation in thei
genome. Males with PHACE association do not have more sev
hypothesis was provided by Levin and Kaler (2007), who analy
determined that an unaffected mother had skewed X-inactivati
mutation), whereas her daughter with PHACES showed a rand
the mutated X chromosome). Nevertheless, molecular and ge
pathogenesis of sporadic infantile hemangioma. Solving the m
investigation of mechanisms that cause the rare associated ma

The Proliferating Phase

Infantile hemangioma's hallmark is rapid neonatal growth. Th
observations and studies of cellular turnover (Mulliken and G
immunohistochemical analysis of tissue specimens (Takahash
hemangioma is variable; diverse forms are also seen in multif

appearance (Figure **4-12A**). If the tumor arises in the superficia
elevated surface and a vivid crimson color. Many superficial h
centimeters (cm) in diameter (Figure **4-12B**). In general, the ar
transformation" (Mulliken, 1991). Once the territory of a super
causes the tumor to protrude and present with a red, often circ
hallmark of the combined (deep and superficial), as well as the
from the tumor.

Figure 4-12
Fallacy of old term "capillary-cavernous" hemangioma. A. "Str
configuration. Same histopathologic pattern whether tumor in
hemangioma D. Combined superficial-deep hemangioma.

Entirely superficial lesions are diffuse, slightly raised, with a p
can be continued growth at the periphery, while the central are
form of reticular hemangioma remains flat (macular); however
within the involved area. Parents often comment that their chil
in the early morning. This observation is ascribed to increased

Deep hemangioma proliferates in the lower dermis, subcutis, o
normal or slightly bluish in color (Figure **4-12C**). The covering
telangiectatic vessels. Deep hemangioma often grows unnotice
proliferation in both the superficial and deep dermis, as well a
cavernous" hemangioma (Figure **4-12D**). Histologic examinati
hemangiomas shows that the proliferative endothelial pattern
particular tumor (Mulliken and Glowacki, 1982). Thus, the time
hemangioma), "cavernous" (denoting deep hemangioma), and
be discarded (Mulliken and Glowacki, 1982).

There are few indicators that predict the eventual volume of an
outcome of involution. The apogee of growth is around 6–7 m
months. A large prospective cohort study showed that most he
(Chang et al., 2008). Therefore, a young infant with emerging h

tumor's growth, anticipate complications, and consider treatm
stabilize earlier. It has been written that deep hemangiomas ha
furthermore, deep lesions seem to regress more slowly (Nakay
the difficulty in monitoring the life cycle of a deep hemangiom
more easily appreciated than diminishing volume.

There is a small subset of errant hemangiomas that continue t
(Figure **4-13 A–C**). It is traditionally believed that an involuted
tissue and a few residual vessels. A rare example of recrudesce
Figure **4-13D**.

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Figure 4-13
Atypic life cycle of infantile hemangioma. A. 6-year-old girl wit
partially resected. Histopathologic diagnosis: "hemangioma."
particles and Gelfoam; resected again at age 11 years. Histopat
age 4 years with evidence of fast-flow. GLUT1 positive; MIB-1 l
negative. D. 12-year-old (premenstrual) girl with involuted rig
telangiectatic residuum began growing again. Histopathology:
multilaminated basement membranes, and GLUT1 positive.

Differential Diagnosis

Clinical history is foremost in differentiating infantile hemang
premonitory cutaneous sign at birth or the tumor appears pos
that of the infant. In contrast, a vascular malformation, whethe
the child. The color of a vascular birthmark also helps in estab
scarlet color that gradually deepens during the first year. Vascu
whether there are arterial, venous, capillary, or lymphatic com

While palpating a vascular anomaly, it is helpful to imagine wh
hemangioma feels firm or rubbery; it is a dense cellular tumor
completely emptied of blood with compression, unlike a flat c
In contrast, a venous malformation is soft, easily compressible
and sparse parenchyma. Palpation of thrombi or phleboliths c
malformations, arteriovenous anomalies, and infantile heman
venous malformations.

In most instances, hemangiomas can be differentiated from va
diagnostic techniques (Finn et al., 1983; Mulliken, 1984). An ac
photographs, and physical examination should permit proper
handheld (continuous wave) Doppler unit demonstrates the ty
rechargeable instrument is very useful, particularly in the diag
of a radiologic assessment. If the diagnosis remains unclear, fo
next step, followed, if necessary, by magnetic resonance imagi
although it appears to be a harmless lesion, the physician can
2–3 weeks. Usually parents accept an explanation of the most l
necessary. Clearly, this kind of consultative plan requires an u
an accurate diagnosis is forthcoming.

There are two axioms that help to distinguish infantile hemang

Not All Hemangiomas Look Like Strawberries

The diagnosis of hemangioma is usually possible based on a h
palpation. Nevertheless, hemangiomas appear in a wide variet
raised tumor with a variable deep component. Less common is
can be variable, from pinpoint tumors to large nodules. Deep l
easily diagnosed by pattern recognition. Some of hemangioma

Figure 4-14
Axiom I: Not all hemangiomas look like strawberries. A. 4-mon
on left cheek with indistinct border. Lesion stopped growing b
"Arrested" infantile hemangioma. B. Raised hemangioma left c
mucosa limits elevation of tumor. C. 2-year-old girl with vascu
remained unchanged thereafter. Fast-flow suggested AVM. Sin
Histolopathology: tightly packed capillary-like vessels, plump
hemangioma.

Deep Hemangioma

The skin can be normal overlying a deep hemangioma in subc
and a few telangiectasia. A fibrofatty feel on palpation and the
hemangioma can be confused with other vascular lesions in th
malformation (Figure **4-15**). Hemangioma is the most commo
(50%), followed in frequency by pleomorphic adenoma (29%)
(Welch, 1986). Malignant epithelial tumors of the parotid are u
adolescence (Lack and Upton, 1988).

Figure 4-15
Deep hemangiomas. A. 2-year-old girl with spheroidal tumor r
diagnosed as angular dermoid cyst; fast-flow noted by Dopple
right lower neck manifested at 2 months, simulating macrocys
confirmed Dx: Infantile hemangioma. C. 5-month-old female i
hemangioma. Telangiectasia or tiny circular red spot usually c
duplex ultrasonography needed.

Lymphatic anomalies are not always obvious at birth; they can
Lymphatic lesions are either cystic and soft or tense; they can b
Lymphatic anomalies may have an overlying capillary stain; ti

A handheld (continuous wave) Doppler unit usually confirms
ultrasonography or MRI (with gadolinium) will precisely defin
ambiguity, consider fine needle biopsy, under fluoroscopic gu

Arrested Hemangioma

Hidano and Nakajima (1972) described two infants who prese

hemangioma; however, only “telangiectases” developed, and
called “port-wine like” and “telangiectatic” (Martínez-Pérez et
these lesions. An inchoate hemangioma presents as a flat, tela
predilection for the lower body and lower limbs; there may be
elsewhere (Figure 4-16). Often the central area of an arrested h
periphery and coalese. These stunted hemangiomas tend to in
infantile hemangioma that appear postnatally and exhibit a pr
preponderance as the more typical infantile hemangioma.

Figure 4-16
Arrested hemangiomas. A. Infant born with pale patch and cen
evolve and began fading before 1 year. B. Neonate with “telang
that never progressed. C. 2-month-old girl born with pink patc
failed to evolve further and slowly regressed. She also had 3 ot
old infant with stunted hemangioma on calf and multiple intra

Most arrested hemangiomas look reticular but not all reticular

Reticular Hemangioma

Infantile hemangioma can infiltrate the dermis, staining and sl
(“port-wine stain”) (Martínez-Pérez et al., 1995). This variant ty
few signs of rapid growth, further adding to possible confusion
hemangiomatous stain is inhomogeneous and network-like (u
variegated color, and irregular margins; often there are large d

These lesions have also been called “telangiectatic” (hemangi
histopathologically a telangiectasia. The adjective “reticular” r
(Mulliken et al., 2007b) The term originates from the Latin *retic*
Dictionary (27th edition) defines reticular as “a fine network fo

Reticular hemangioma is a variation of infantile hemangioma;
protein-1) positive. Reticular hemangioma phenotype present
localized macular lesion, usually in a limb, that fails to grow ar
not all reticular hemangiomas are “arrested.” At the opposite e
occurs in PHACE association (Figure 4-17A) or in the lower tru
(Figure 4-17B). Reticular hemangioma in an extremity can be a
pattern (Figure 4-17C). Extensive (regional) reticular hemangi

become raised. The plantar or palmar surfaces remain macula
proximally, the tumor exhibits the characteristic network-like a
capillary malformation, cutis marmorata telangiectatica conge
the limb can also be accompanied by the more typical forms o
PHACE association), gastrointestinal hemangiomas, and tiny r
been reported with reticular hemangioma in the upper extrem

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Figure 4-17
Reticular hemangiomas. A. Female infant with left facial reticul
PHACE association. B. 2-month-old female with reticular hema
with tethered spinal cord, imperforate anus, omphalocoele an
capillary malformation. C. 10-month-old girl with reticular her
postnatally and darkened over ensuing months. D. Diffuse reti
flow resulted in cardiac overload with a minor contribution by
demonstrates enlarged right common iliac artery with multipl
distal extremity.

Reticular hemangiomas often progress to acral, proximal, and
anomalies); these tend to be deep and recalcitrant to the usual
and sometimes skin grafting may be necessary. Fast-flow throu
cardiac overload. In one such infant, embolization was necess
limb was eventually necessary because of extensive necrosis (
microscopy showed infiltrative growth of deep tissues, includi
2007b).

Reticular hemangioma sometimes regresses rapidly, but usual
localized form of the tumor. Axial overgrowth of the limb is po
following involution.

Reticular hemangioma over the thoracic spine is another, albe
both intra- and extrathecal. The tumor may cause compressio
D).

Not All Strawberries Are Hemangiomas

Tumors

Other vascular tumors of infancy can masquerade as common
tufted angioma, and various types of hemangioendothelioma
nasal glioma, juvenile xanthogranuloma, infantile myofibroma
al., 1995), cutaneous lymphoid hyperplasia, solitary ("self-hea
angiofibroma, giant cell angioblastoma, and pilomatrixoma (H
been misdiagnosed and mistreated as infantile hemangioma (
(ready to burst), purple-red with radial vessels, and firm to pal
infantile hemangioma include rhabdomyosarcoma, extraosseo
metastatic neuroblastoma (Hassanein et al., 2010) (Figure **4-20**
cutis") can be mistaken for hemangioma (Burnett et al., 2007) (
lipoblastoma of the forehead that was initially misdiagnosed a
mandatory if there is any inconsistency in the findings or any s
examination, or radiologic imaging.

Figure 4-18
Axiom II: Not all strawberries are hemangiomas. Multiple vasc
trunk and extremities. Curiously, only one tiny lesion grew on
(unspecified type, GLUT1 negative).

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Figure 4-19
Benign lesions. A. Congenital ovoid mass at nasal root. Dx: nas
old boy born with dark purple lesion right cheek. Histopatholo
MIB1 30%. C. 10-month-old girl with firm, yellow-pink, dome-
Histopathologic Dx: juvenile xanthogranuloma. D. 7-month-ol
purple raised lesion on buttock that arose at 4 months. Histopa
old boy with lobulated vascular lesion right cheek, unchanged
5-year-old boy born with depressed, purple lumbar stain; pare
ultrasonography. Histopathologic Dx: giant cell angioblastoma
months and slowly enlarged. Clinical diagnosis confounded b
with infantile hemangioma." Histopathologic Dx: pilomatricon

(Courtesy of Dr. Arin K. Greene)

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Figure 4-20
Malignant tumors. A. Frontal tumor appeared at 2 months of a
(Courtesy of Dr. Chantal van der Horst) B. 3-week-old male wi
intravascular coagulopathy. Histopatholoigc Dx: infantile fibro
hemangiomas of buttock and two subcutaneous lumbar masse
abnormally firm by palpation. Biopsy Dx: metastatic neuroblas

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Figure 4-21
Cutaneous leukemia. A. Glabellar mass appeared at 6 months, leukemic infiltrate in muscle. B. 6-month-old child with swellin skin; lesion slightly firm. Biopsy Dx: precursor B-cell acute lym

(Courtesy of Dr. Trevor J. McGill)

Pyogenic Granuloma

This common fruit-like cutaneous vascular tumor can be confu age group. Unfortunately, pathologists have muddied the term hemangioma." A better term would be "lobular capillary (or er infants and children, at a mean age 6.7 years; 12% occur in the which are more common in females, pyogenic granulomas in (Patrice et al., 1991). Usually there is no history of trauma or a arise *sui generis*; however, they often appear in a preexisting ca eyelids, or extremities. Less frequently, pyogenic granuloma oc et al., 1980). Typically they appear suddenly and grow rapidly. or pedicle. The typical pyogenic granuloma is small (average d epithelium sloughs, followed by crusting and by sloughing of episodes initiate visits to the local emergency room or the phy pressure or cauterization. Frequently the child arrives with an presentation prompted Thomson to call this entity "Band-Aid examination. Ultrasonography demonstrates a characteristic v

Figure 4-22
Pyogenic granuloma. A. Pedunculated lesion. B. Dome-like les
continued to appear until age 6 months. Several lesions excise
GLUT1 immunonegative capillaries in edematous stroma with
no recurrence at age 19 years. D. 10-year-old girl born with cap
like lesions appeared at age 1.5 years. Doppler and MRI reveal

Not all pyogenic granulomas ulcerate; some remain sessile, ci
22B). This papular form can be mistaken for a small infantile h
There are rare cases of multiple congenital pyogenic granulom
Multiple congenital pyogenic lesions vary in size; often they ar
excision. Nevertheless, they have a limited life span and gradu
childhood. Multiple pyogenic granuloma-like lesions can also
pyogenic granulomas are GLUT1 negative, whereas multiple, t
Multiple pyogenic lesions ("satellites") can also appear in the

The cause of pyogenic granuloma is unknown. Although they
induced by infection, nor are they granulomatous by histologi
vascular lesions in bacillary angiomatosis and in verruga peru
Nevertheless, immunohistochemical and molecular profiling
the protein or DNA sequences of *B. quintana* or *B. henselae* (Le

Vascular Malformations

Capillary, venous, and arterial malformations can be confused
at birth and commensurate growth, plus the findings by obser
hemangioma and AVM are warm on palpation. Hemangioma e
may not. AVM in an infant typically presents as telangiectasia
expanding during the first year, forming a tumor-like mass, so
proceed to ultrasonic study and MRI. In some cases, imaging n
lesions, such as Stage I AVM, AVM-like anomalies in Bannayan
Biopsy may be necessary.

Figure 4-23
Vascular malformations. A. Vascular birthmark on philtrum; no
capillary malformation. B. Purple vascular lesion of lower eyel
misinterpreted as “hemangioma.” Dx: venous malformation. C
exhibited postnatal nodular expansion. MRI and angiography
embolization. D. 5-month-old girl born with purple, enlarged r
angiography, interpreted as “hemangioma” because lesions di
negative and interpreted to be AVM.

Proliferating Phase Complications

Ulceration

Superficial hemangiomas, those proliferating just beneath the
epidermal crusting and dark discoloration are the immediate h
and colleagues (2010) have shown that an earlier whitish disco
younger) is a sign of impending ulceration, rather than an aug

The frequency of ulceration was 16% in a large multicenter pro
occurs around 4–6 months, at the height of the proliferative ph
specialist. For example, ulceration was documented in 59% of
commonly occurs in lower labial and anogenital hemangioma
and post-auricular sulcus. If the tumor grows in the form of hil
observations suggest that localized trauma, friction, and macer
any tense superficial tumor (Figure **4-24A, B, C**). Congenital ul
6-15).

Figure 4-24
Proliferative phase complication: Ulceration. A. Ulcerated deep right lower limb with perianal ulceration. C. Superficial ulcerat hemangioma with ulcerative necrosis of auricle and lower lip.

Once it was believed that ulceration was secondary to infection bacterial colonization of an ulcerated wound. A retrospective s polymicrobial cultures, either aerobic or anaerobic or mixed o uncommon; the usual offenders are *Pseudomonas* and *Staph. a* hemangioma progresses to extensive necrosis and destruction ear (Figure **24-D**). Thomson (1979) called these aggressive lesi large recalcitrant ulcerations characterize reticular hemangiom Ulcerated hemangiomas often bleed, but this is usually minor

Ulcerated hemangioma is notoriously slow to heal, despite all infant is irritable and unable to feed and to sleep. Nor do the p shown to be increased in the proliferative phase (Jang et al., 20 the ulcerated area is exposed to air or physical contact.

Mechanism

The cause of ulceration is not precisely known. The old specul breakdown and ulceration—either as the result of microvascul supply." Another possible explanation is that the loss of norma changes in the overlying epidermis (Beilenberg et al., 1999) pr

Bleeding

In 1940, Kasabach and Merritt described thrombocytopenic pu

with a rapidly enlarging “giant capillary hemangioma” of the l
years, the double-eponym “Kasabach-Merritt syndrome” was
variety of vascular anomalies. By the end of the last century, it
cause coagulopathy. Primary platelet-trapping is almost exclus
tumors, kaposiform hemangioendothelioma (KHE) and tufted
Sarkar et al., 1997). These vascular tumors that cause the Kasab

Spontaneous bleeding from a punctate area in florid superficia
episodic bleeding can frighten the parents and can be an anno
hemangioma also bleeds, but usually more slowly.

Obstruction

Visual

Amblyopia is defined as poor vision in an eye in which there is
in failure of normal development of binocular cortical cells. An
the incidence is reported to be 43–60% (Haik et al., 1979). Ther
and strabismic. The best-known is deprivational amblyopia (c
vision (Robb, 1977; Stigmar et al., 1978; Thomson et al., 1979; H
weeks, will diminish input to the immature developing occipit
periods of obstruction are even more injurious (Figure **4-25**). I
anisometropia (asymmetrical refractive error), secondary to pr
difference in refraction of 2 diopters or more is significant enou
astigmatic and sometimes myopic (Robb, 1977; Haik et al., 197
cornea. Hemangioma exerts pressure on the globe in a directio
the tumor predicts the axis of greatest corneal curvature (Robb
astigmatism, probably because lesions in this location often ha
by pressure on the equator of the globe (due to blepharoptosis
Strabismus (misalignment of the eyes) is an uncommon ophth
Strabismus is usually secondary to ambylopia, but paralysis (s
be a primary cause of amblyopia (Stigmar et al., 1978).

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Figure 4-25
Proliferative phase complication: Ocular obstruction. A. Newb
supraorbital area and upper eyelid. C. By day 14, stain darker v
orbital hemangioma obscures visual field.

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Figure 4-26
Proliferative phase complication: Corneal deformation. 3-mon
hemangioma causing astigmatism (2.5 diopters); she is at risk

Retrobulbar hemangioma usually does not cause astigmatism globe (usually proptosis or dystopia), ocular muscular imbala Epiphora and recurrent conjunctivitis is another relatively freq hemangiomatous obstruction of the nasolacrimal drainage sys

Ultrasonography is useful in determining the anatomic extent extraconal, or intraconal (Bowman et al., 2004). It can be accom MRI is indicated if there is concern about possible intraorbital include attention to the brain, looking for possible PHACE cere intracranially.

Every child with a periocular hemangioma should be refracted the upper eyelid or supraorbital area, frequent periodic refract cheek should also be followed closely, although lesions in this this is because the lower eyelid lies slightly below the cornea, globe to rotate upward during sleep—babies' usual mode. Nev evaluated by an ophthalmologist. Rarely, a large hemangioma vision. One possible mechanism is that the tumor elevates wit supine positioning of the baby. Even when infants are propped raise the head to look over a malar tumor.

Absence of an asymmetrical refractive error is a favorable prog hemangioma (Robb, 1977). Late residual complications of peri blepharoptosis, and even optic atrophy (Stigmar et al., 1978).

Airway

Proliferative phase hemangioma could possibly block the nas breather. In clinical practice, this is an extremely rare occurren adapts and learns to breathe through the oral passage. It has a hemangioma can destroy the lower lateral cartilages. This is ap distorted, when exposed during resection of the tumor.

More insidious and life-threatening is hemangiomatous prolif asymptomatic at birth, but within 6–8 weeks they slowly devel noticeable during feeding, crying, or upper respiratory tract inf months; the mean age is 3.6 months (Shikhani et al., 1986). Oft misdiagnose the problem as protracted laryngotracheitis or re Approximately one-half of infants with subglottic hemangioma area (Ferguson and Flake, 1961). Thus, the absence of cutaneo appearance of the cutaneous lesion indicate the presence of, o early involution in the cutaneous lesion (e.g., softening and a c hemangioma is slowly narrowing the airway. The term "beard hemangioma can be associated with subglottic hemangioma (inappropriate since most hemangiomas occur in little girls.

Any infant who is suspected of having subglottic hemangioma infant does not permit full visualization of the subglottis. Gene bronchoscopy. The typical finding is a localized, smooth, comp there are a few telangiectatic vessels in the submucosa. Subglo

stain subglottis and trachea in the absence of mucosal elevatio
epiglottic folds, and piriform fossae. Extension into the hypopl
hemangioma can also be circumferential and can encroach on
airway also may be compromised due to extrinsic compressio
indicated whenever there is circumferential narrowing.

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Figure 4-27
Proliferative phase complication: Airway obstruction. A. Locali
Unilateral tumor more commonly seen on left side. (Courtesy
subglottic hemangioma with 95% narrowed airway.

(Courtesy of Dr. Reza Rahbar)

Hemangioma in the postcricoid region of the hypopharynx is r
or obstructive symptoms can be subtle and appear late; these i
(Awwad and Mortelliti, 2006). If the infant is straining, flexible
postcricoid region. Postcricoid lesions are less easily visualize
anesthestic (Awwad and Mortelliti, 2006).

Auditory

Obstruction of the external auditory canal, unilateral or bilater
parotid gland (Figure **4-28A**). Narrowing of the canal can resul
is relieved with regression of the hemangioma. This should no
year, when auditory conduction is necessary for normal develo

Figure 4-28
Proliferative phase complication: Skeletal distortion. A. Deep p
narrowing of external auditory canal. B. Prominent ear second
hemangioma causing orbital elevation (maxillary overgrowth)

It is curious that facial nerve palsy is almost never seen, given
hemangiomas have a predilection to invade nerves. In our uni
with a parotid hemangioma. This was likely caused by a separ
nerve in the temporal bone, that is, in the internal auditory can
Judd and coworkers (2007).

Skeletal Distortion

Infantile hemangioma rarely affects nearby bone. A minor defo
include deviation of the nasal pyramid caused by a tumor of th
large scalp lesion (Boyd et al., 1984). Extensive intra- and extra
cavity (Williams, 1979; Boyd et al., 1984), just as in experimenta
typically overgrows in the presence of a large parotid hemangi
causes the ear to protrude (Figure **4-28B**). Malar enlargement c
also cause elevation of the ipsilateral orbit (Figure **4-28C**). Bon
hypervascularity. Localized hemangioma in a limb does not ca
Nevertheless, a minor limb length discrepancy can occur with
2007a).

Cardiac Overload

An extensive infantile hemangioma can divert enough blood th
cardiac failure. This scenario most commonly occurs with mul
multiple cutaneous tumors. The infant typically presents in the
cardiac overload (Boon et al., 1996). The cutaneous lesions are
they can also have the other typical morphologic features of so
intrahepatic hemangiomas are discussed in Chapter 5; diagnos

In rare instances, a large infantile hemangioma, whatever the l
cardiac output. Perhaps the most common site is the parotid gl
of 100 parotid hemangiomas (Greene et al., 2004). Cardiac dec
infantile hemangioma involving an extremity; the large tortuo
AVM (Mulliken et al., 2007b).

Fetal (congenital) hemangiomas, either cutaneous or solitary i
cardiac failure at birth (*vide infra*).

Hypothyroidism

Type 3 iodothyronine deiodinase (D3) is normally present in t
triiodothryonine to biologically inactive metabolites. Placenta
hormones. The finding of severe hypothyroidism in an infant v
the tumor (Huang et al., 2000). Elevated D3 has also been foun
and also in a 21-year-old female with hepatic hemangioendotl
hemangioma degrade the thyroid hormones at rates that excee

TSH levels should be checked in an infant with a large hemang
therapy. This "consumptive hypothyroidism" should be prom
points are lost for each month in which an infant with hypothy

Newborn serum TSH screening is useful in the differential diag
infant with hemangioma could also indicate coincidental, cong
such an infant, the TSH level promptly falls to normal level foll

The Involuting Phase

Hemangioma's growth stabilizes by the end of the first year of
as the child, followed thereafter by slow regression. Neverthele
cycle. Some hemangiomas to continue to grow beyond age 1 y
proliferating and involuting phases (Brandling-Bennett et al., 2
life cycle of a hemangioma. Gradually, apoptosis begins to pre
phase. The central region of a superficial hemangioma can app
periphery of the lesion. Histologically, proliferation and involu
thymidine uptake into endothelial DNA (Mulliken and Glowac
1998) have demonstrated diminishing cellular turnover until a
(Razon et al., 1998).

One of the first signs of regression is fading of the shiny crimso
assumes a mottled, grayish mantle, and on close examination,
involved skin becomes slightly wrinkled. Bleeding and ulcerat
often begin centrally and spread, in a centrifugal fashion, towa

Whereas a young, tense hemangioma is often tender to the tou
the hemangioma seems less painful and that their child is not
and strains, the hemangioma does not swell up the way it once
handheld Doppler probe, as initially described by Bingham (1
disappearance of fast-flow Doppler signal in involuting phase
years in some children; it persists longer in many children. The

The involuting phase extends from 1 year until 5 to 7 years of a
Two examples of regression are shown in Figure **4-29**. Clinical
occurs in over 50% of children by age 5 years and in over 70% l
remaining children until age 10–12 (Lister, 1938; Pratt, 1953; Sir

298 hemangiomas, 80% of lesions that had not completely inv
deformity, as opposed to 38% “imperfect” results for lesions th
neither sex, race, site, size, nascent presence at birth, duration
involution (Bowers et al., 1960; Finn et al., 1983). There is a ling
regress than smaller tumors. Our experience (Finn et al., 1983)
coworkers (1960), that the rate and completeness of resolution
correlation between the final result of regression and the age a

Figure 4-29
Involuting-involuted phases. A. 4-month-old girl with superfic
Accelerated regression underway at age 1.5 years. C. Minor cut
cheek relatively unchanged at age 2 years. E. Some regression
complete at age 14 years. Nasal deviation barely noticeable wi

The clock of regression begins ticking as hemangioma’s growt
on a similar time schedule for both deep and superficial tumo
in low-birth-weight prematures follows the same time course
duration of proliferation in a premature infant is determined a
cutaneous lesions of multiple hemangiomatosis usually involu
age 2 years.

It is also commonly observed that involution proceeds more s
(Bowers et al., 1960). At the cellular level, all infantile hemangi
involution are often seen in the same microscopic field; howev
findings by anatomic region. A likely explanation is that hema
deposits more fibrofatty tissue during regression. This variable
and persistent “tumor.”

Although uncommon, an infantile hemangioma can have a pro
some cases, pharmacologic therapy may have to be continued
signs of regression, the tumor should be excised. Histopatholo

reveal features characteristic of a much earlier stage in hemang

The Involuted Phase

Nearly normal skin is restored in approximately 50% of childre atrophy, telangiectatic vessels, and slightly pale skin. A crepe-l matrix and the destruction of elastic fibers (*anetoderma*). This t sharply demarcated, superficial, bossed tumor. Extra skin after expander. Involuted tumors often have residual purplish drain phase, this area will become a pale or discolored patch of scar involution without intervening ulceration. Another curious obs adolescent acne in skin of an involuted hemangioma.

Protuberant hemangioma of any size is more likely to result in (subcutaneous) hemangiomas may well regress totally, leavin fibers are relatively undisturbed.

In general, it is difficult to accurately foretell the outcome in te residual fat (Figure **4-30**). Hemangioma in certain anatomic lo regression. Tumor in the scalp can expand or destroy hair folli is common with a supraorbital hemangioma. Periorbital hema imbalance of the extraocular muscles. Nasal hemangioma spla producing spherical enlargement of the tip. Labial hemangiom vermilion-cutaneous junction, and pale discoloration of the ve behind dark blue veins, fine telangiectasias, and sometimes a rare instances of recurring, deep, well-localized ulcerations ye extremity.

Figure 4-30
Involuting-involuted phases. A. Regressing deep parotid hema expanded skin. See proliferative phase, Figure **4-28A. B**. Involu

minor crepey skin. See proliferative phase Figure **4-12B. C**. Inv
telangiectasias remain; prominent ear secondary to retroauricu
intracranial vascular anomalies. See proliferative phase Figure
11 years. Note pigmented, atrophic skin, nasal deviation, and e
E. Multiple thoracic hemangiomas regressed at age 5 years, lea
F. Involuted reticular hemangioma, age 13 years. Foot/toes sli
veins. See proliferative phase Figure **4-17C**.

Fetal (Congenital) Hemangiomas

There are neonatal vascular tumors that do not follow the expe
hemangioma. These tumors are distinguished as fully grown a
(Boon et al., 1996). Congenital hemangioma can also be called
defining feature of congenital tumors is that they do not exhibi
within the first year of life, whereas others do not regress at all
are designated by acronyms: RICH, *rapidly involuting congenit*
hemangioma. Both forms of congenital hemangiomas have a d
postnatally. RICH's clock runs fast and stops, whereas NICH's
(fetal) hemangioma occur in a 1:1 sex ratio, just as the commor

Rapidly Involuting Congenital Hemangioma (RICH)

Accelerated regression of a large "strawberry nevus" was proba
seminal paper on the natural history of hemangioma. Two oth
but the significance of this unusual behavior was underapprec
highlighted five tumors, all located in the extremities, as curiou
al., 1995). The following year, the vascular anomalies teams in
term "congenital hemangioma" to designate the type that exhi

Increasing use of prenatal ultrasonography has generated seve
Treadwell et al., 1993; Maynor et al., 1995). Often the tumor is d
12-week fetus (Boon et al., 1996). Doppler study demonstrates
Shunting in a large fetal vascular tumor can cause hydrops feta
case described by Daniel and Cassady (1968) was retroperiton
ultrasonic literature describe a large single tumor in the scalp/
Khoury, 1994). These lesions have often been confused with o
occipital "hemangioma" was detected in a 14-week fetus and c
intrahepatic fetal hemangioma can also cause hydrops fetalis (
vascular tumors either regressed rapidly during early infancy (
et al., 1995; Viora et al., 2000), were excised in early infancy (To
al., 1995; Boulot et al., 1996; Carlotti et al., 2000), or, less comm
al., 1998; Shiraishi et al., 2000). Based on careful examination o
called "hemangioma" or "hemangioendothelioma," are examp

RICH reaches its greatest size during the final weeks of the thir
prior to delivery. At birth, RICH presents as a solitary tumor wi
raised grey or violaceous mass with ectatic, radial veins, centra

31 and 4-32). There may be central ulceration, scar, or nodular
brown, corrugated patch. Initially there is fast-flow, but the typ
variant is likely the result of rapid regression toward the end o
lesions are also uncommon (Figure 4-33 C, D). There are rare
34). RICH has a predilection for the craniofacial region and lov
diagnosis for a solitary hepatic lesion (see Chapter 5). Being in
rare instances, infantile hemangioma can be protrusive in a ne

Figure 4-31
Rapidly involuting congenital hemangioma (RICH). A. Newbor
causing cardiac overload. Note pale halo. B. Age 6 weeks, after
regression by age 6 months. D. Newborn boy with vascular tur
Residual cutaneous laxity at age 1.5 years.

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Figure 4-32
Plaque-like RICH. A. 2-month-old with a slightly raised, violac
birth. B. Accelerated regression at 6 months of age. C. Atrophy a
age 4 years; residual ectatic veins.

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Figure 4-33
RICH variations. A. Purple-brown plaque with central veins. B.
Deep posterior cervical congenital tumor. D. Rapid regression

Figure 4-34
Multiple RICH. A. Newborn with congenital vascular tumors of
diagnosis. B. Accelerated regression at one year. Note more co

Figure 4-35
Congenital or infantile hemangioma? A. Newborn with raised,
in temple. No subsequent rapid growth. B. Ulceration at 7 mon
resected at age 2 years. Histopathology: GLUT1 negative.

There are two complications with RICH, although both are unc
(Figure **4-36**). Fast-flow can cause sufficient shunting in a cutar
congestive heart failure. There are documented examples of re
sometimes the excised tumor is mistaken for an AVM (Price et
50,000 platelets/μL (sometimes lower) can be caused by a larg
thrombocytopenia also can occur in an infant in response to a
thrombocytopenic coagulopathy was considered to be a comp
labeled “Kasabach-Merritt phenomenon” (KMP). There are ol
radiation therapy and resection (Inglefield et al., 1961; Hill and
described to “liberate” platelets from “hemangioma,” and the
1961). In our original description of RICH (Boon et al., 1996), w

to describe minor thrombocytopenia in two patients. The hem
coagulopathy, that is, low platelets, low fibrinogen and elevate
has not been observed with thrombocytopenic RICH. Platelets
2008) (Figure **4-36**).

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Figure 4-36
Complications of RICH. A. Neonate with vascular tumor right r
and high output congestive cardiac failure. Dx: RICH confirmed
by 2 months, normal platelet count and cardiac function. C. Tu

Ultrasonography with color Doppler, MRI/MRA, and angiograp
common infantile hemangioma that evolves postnatally (Roge
in that RICH does not exhibit the same homogenous enhancer
angiography may demonstrate calcifications, focal aneurysms,
cardiac overload. Thrombi with focal calcifications can also be
thrombo-embolus originating in a RICH in the lower extremity

A large RICH, particularly one with thrombocytopenia, can be
hemangioendothelioma, tufted angioma, infantile myofibrom
any question about the diagnosis by history, physical examina

The defining clinical feature is accelerated regression. This beh
obvious within a few weeks after birth. Rapid involution is usu
skin, dermal and subcutaneous atrophy, prominent veins, and
Doppler examination for several years. In an adolescent, prom
residuum of a RICH in the lower limb. Curiously, very little sub
regressing infantile hemangioma that often changes to fat duri

Rapidly Involuting Fetal Hemangioma (RIFH)

In rare instances, the typical cutaneous findings of end-stage R
coloration, are seen at birth. The logical deduction is that this i
Indeed, prenatal monitoring can show regression prior to deli
that was discovered at 20 weeks gestation and disappeared by
halo (Ozcan, 2010). These tumors cannot be called RICH becau

accurate term is *rapidly involuting fetal hemangioma* (RIFH) (F

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Figure 4-37
Rapidly involuting fetal hemangioma (RIFH). 1. 5-year-old girl
Color gradually faded; however, atrophic skin remains unchan
unsuccessful.

Non-Involuting Congenital Hemangioma (NICH)

The second subgroup of congenital vascular tumor has many c
RICH, is a solitary tumor. The anatomic distribution is similar
NICH has a predisposition for the suboccipital neck, mandibul
2001). Just as in RICH, there is no female preponderance. NICH
had been mistaken for common infantile hemangioma or was
a well-circumscribed lesion, averaging 5–6 cm in diameter, the
typical NICH is slightly bossed or plaque-like, with a pink, blu
coarse telangiectasia, pale rim, and areas of intermingled pallo
reflect microscopic dermal arteriovenous shunting (steal phen
noted. By history, the lesion grows proportionately to the child
shoulder. Expansion in adolescent years can occur in this locat
excrescences (Figure 4-39). Fast-flow flow in NICH is easily do
imaging and angiographic features of NICH, like RICH, are alm
hemangioma. NICH often is mistaken for a small AVM. By angi
arterial feeders, and dilated veins, but without the early venou

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Figure 4-38
Non-involuting congenital hemangioma (NICH). A. 10-year-ol
telangiectasia and pale halo. B. 6-year-old female with congen
tumor with central telangiectasias. D. Abdominal tumor with c

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Figure 4-39
RICH transformation to NICH with late expansion. A. 16-year-
began to expand during early teen years. Arteriographic study
and especially occipital arteries with shunting to large venous
lesion that regressed by age 1 year leaving a minor stain. Expa
polypoid lesions. MRI and partial excision confirmed Dx: NICH

Missing Links

The growth curves for the fetal, two forms of congenital heman
Figure **4-40**. RIFH runs its course during the second and third t
curve has the same configuration as that of IH, but accelerated
to the left. The NICH curve remains flat after birth and into chil

stage, unable to undergo regression.

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Figure 4-40
Growth curves for fetal, congenital, and infantile hemangioma

RICH and NICH are similar in appearance, location, size, equa
features with infantile hemangioma. Neither type of congenita
Berenguer et al. 2003), a standard marker for infantile hemang
these congenital vascular lesions are variations on a spectrum
Nothwithstanding GLUT1 immunonegativity in fetal hemangio
possible that these three clinically disparate tumors have a co

Speculation that fetal and infantile hemangiomas share a com
links. One such missing link is the coexistence of RICH or NICH
child (Mulliken and Enjolras, 2004) (Figure **4-41A**). Neverthele
because infantile hemangioma is so common, whereas RICH a
clinical examples of RICH that initially regress, then stop regre
transformed into its counterpart NICH (Mulliken and Enjolras,
stage of RICH. Further evidence for this hypothesis includes th
flow by ultrasonography, and characteristic histologic features
Mulliken and Enjolras, 2004). The histologic features and path
hemangioma are presented in Chapter 3.

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Figure 4-41
Links between congenital hemangioma and infantile hemangi
hemangioma and NICH on chest. B. RICH on ankle at birth reg
Figure 4-41C). C. NICH-like appearance at age 3 years: pale ma
flow by Doppler examination.

(Courtesy of Dr. Odile Enjolras)

Some clinical investigators are "lumpers," whereas others are
fetal and infantile (postnatal) vascular tumors, for the time bei
doing, accurate prognosis and appropriate therapy can be give
hemangioma), whatever their possible pathogenic relationshi

Possible Linkage to Chorangioma

We described a boy born with multifocal RICH in which one of
umbilical cord. The case suggested a possible biological conne
involving the terminal placental villi (Mulliken et al., 2007a). W
counterpart of fetal hemangioma, that is, cutaneous and solita
discovery, imaging characteristics, natural history, and histopa
tumors are single, some are diffuse. The male-to female ratio i
ultrasonography has shown that chorangioma appears early in
decrease in size near term. This is the same prenatal pattern of
imaging of chorangioma sometimes shows calcifications; initia
term (Zalel et al., 2002). These same rheologic features and fin

Chorangioma shares many histopathologic features with cutan
surprisingly, chorangiomas are GLUT1 immunopositive (Drut
visceral hemangomas occuring in association with 10% of cho
Shturman-Ellstein et al., 1978). These are either solitary cutane
tumors; most are infantile hemangiomas, but some are clearly
multiple hepatic hemangiomas, possible intrahepatic RICH, m
(Meirowitz et al., 2000). Analysis of 12 reported cases of combi
equal sex ratio with solitary cutaneous/hepatic lesions (RICH)
multiple cutaneous/hepatic lesions (infantile hemangiomas) (

Similarities between chorangioma, RICH/NICH, and infantile h
the pathogenesis of infantile vascular tumors. Nevertheless, w

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