Current Management of Complicated Hemangiomas

Family Medicine Review
November 3rd, 2010

Sherry Bayliff, MD, MPH
Department of Pediatrics
Division of Pediatric Hematology/Oncology
Objectives

- Review the nomenclature, presentation, and character of pediatric vascular lesions—what identifies a complex hemangioma that may require intervention.
- Review updated medical management options, their efficacy and potential adverse effects.
- Review the use of pulsed-dye laser in the management of complex hemangiomas—its benefits, optimal timing, and limitations.
Definitions

- 2 major categories of vascular lesions:
  - tumors (primarily hemangiomas)
  - malformations

- an accurate diagnosis is *essential*
  - history and physical examination
  - +/- radiologic examination
  - +/- biopsy
Vascular lesions

- Vascular tumors
  - Hemangiomas
    - Infantile hemangiomas
    - Common hemangiomas
    - Hemangiomas of Infancy
    - Strawberry hemangiomas
    - Capillary hemangiomas
  - Pyogenic granuloma
  - Kaposiform hemangioendothelioma
  - Tufted angioma
  - (RICH and NICH)

- Vascular Malformations
  - Capillary malformations
  - Venous malformations
  - Lymphatic malformations
  - Arterial venous malformations
  - Complex combined vascular malformations
  - (RICH and NICH)
VMF and associated Disorders

- Macular Stains
- Hereditary Hemorrhagic Telangiectasias
- Cutis Marmorata Telangiectatica Congenita
- Phakomatosis Pigmentovascularis
- Blue Rubber Bleb Nevus Syndrome
- Klippel-Trenaunay Syndrome
- Sturge Weber Syndrome
Figure 2 - Endoscopic view. Notice the purse string suture in the lower left slide.
Diagnosis: Getting it Right
## Hemangiomas vs. Vascular Malformations

<table>
<thead>
<tr>
<th>Hemangiomas</th>
<th>Vascular Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>exhibit cellular proliferation</td>
<td>dysplastic vessels</td>
</tr>
<tr>
<td>grow during infancy</td>
<td>no endothelial proliferation</td>
</tr>
<tr>
<td>involute in childhood</td>
<td>growth proportional to patient’s growth</td>
</tr>
<tr>
<td>never appear in adolescent or adult</td>
<td>never regress</td>
</tr>
</tbody>
</table>
Hemangiomas

- Most common tumors of infancy
- Incidence:
  - 4 to 5% of Caucasian children by 1 year of age
  - more common in white non-Hispanic infants vs other racial groups
  - as high as 30% incidence in LBW premature infants
  - female to male ratio ranges 2-3:1
  - 10% with elicited family history
- Multiple hemangiomas in 20%
- Prenatal associations: older maternal age, placenta previa, pre-eclampsia
- Predilection for Head and Neck
Pathogenesis

- superficial proliferating angioblastic endothelial cells with few capillary lumina
  - clonal proliferations of endothelial cells resulting in from vasculogenesis

- Imbalance between positive and negative vasculogenic factors expressed
  - Increased expression: CD34, CD31, CD133, LYVE-1, IGF, integrins
  - Overexpression: bFGF, FGF2, VEGF, etc.
  - Suppressed: VEGFR1 expression, VEGFR2 signaling
A) Normal endothelial cells (ECs)

- VEGF bound to VEGFR1
- VEGF bound to VEGFR2

B) Hemangioma ECs

- VEGF bound to VEGFR2
- VEGF bound to VEGFR1

- TEM8
- VEGFR2
- Integrin
- Mutated multiprotein complexes

EC proliferation

NFAT

Hemangioma
Life-Cycle of Hemangiomas

- Appearance—within days to months
- Proliferation
  - 80% size reached by mean age 3 mos.
  - 3% documented growth after 9 mos.
- Quiescence/Plateau
- Involution
- Sequelae

Categorizing Hemangiomas

- Visualization
  - Superficial
    - “strawberry” or “capillary” hemangiomas
  - Deep
    - “subcutaneous” or “cavernous” hemangiomas
  - Combined

- Spatial Character
  - Localized
  - Segmental
Complications:

- ulceration
- infection
- localized hemorrhage
- high output cardiac failure
- disfigurement
- compression of vital structures
- (Kassabach-Merritt Phenomenon)
Approach to Management

- size
- location
- presence of complications
- age of the patient
- rate of growth at the time of evaluation
- evaluation for associated conditions
Associated Anomalies or Conditions

- hemangiomas in a “beard distribution”
- periorbital hemangiomas
- lumbosacral hemangiomas
- multiple, cutaneous hemangiomas
- PHACE syndrome
- hypothyroidism
| P  | Posterior fossa brain malformations  
Most commonly the Dandy-Walker variant |
| H  | Hemangiomas, particularly large, segmental facial lesions |
| A  | Arterial anomalies |
| C  | Cardiac anomalies and coarctation of the aorta |
| E  | Eye abnormalities and endocrine abnormalities |
| S  | Sternal cleft, supraumbilical raphe, or both |
Indications for Immediate Treatment

- interference with vital structures
- possibility of permanent scarring
- potential for disfigurement
- ulcerated hemangiomas
Treatment of Hemangiomas:

- Corticosteroids
- Propranalol
- Interferon
- Anti-fibrinolytic therapy
- Chemotherapy
- Wound care
- Pain management
- Pulsed-dye laser
- Embolization
- Surgery
- Radiation
Corticosteroids

- **first line** of therapy
  - first used in 1958 for these lesions
- oral, topical or injected
- response rate ~ 70%
  - usually w/in first few weeks
- exact mechanisms of action unclear
  - anti-vasculogenic effect
  - decreased endothelial cell proliferation
  - endothelial cell apoptosis
Dosing of Steroids

- initial dose of 2-3 mg/kg/day
- given QD in the am
- most common preparations
  - Prelone 15 mg/5cc
  - Pediapred 1mg/1cc

(“always” give with Ranitidine)
Expected Side Effects of Steroids

– Cushingoid facies
– personality changes
– gastric irritation
– weight gain
– diminished gain of height
– immunosuppression
– non-systemic fungal infections

(all complications usually resolve with discontinuation of therapy)
Potential Side Effects of Steroids

- hypertension
- suppression of hypothalamic-pituitary adrenal function
- hyperglycemia
- myositis
- osteoporosis
- hypertrophic cardiomyopathy
- cataracts
Management on Steroids

- close monitoring of height, weight, and HC
- BP checks
- urine checks
- physical exam every 1-2 weeks until on a stable dose
- NO live immunizations
- MD visit if temp > 38.5
- caution if varicella exposure (Call MD immediately)
Interferon

- first described for use in hemangiomas in 1989
- potent inhibitor of angiogenesis (down regulates bFGF)
- response in about 60% of patients
- alpha-2a or alpha-2b
- subcutaneous injection
Interferon Drawbacks

- neurotoxicity in about 30% of patients
  - spastic diplegia (may be permanent)
  - other developmental motor delays
- other side effects: flu-like syndrome, anemia, neutropenia, alterations in liver enzymes, irritability
Management of Interferon

- baseline neurologic evaluation
- neurological exam weekly
  - if neurological changes occur—consider discontinuing drug
- baseline CBC and LFTs, then every other week
- thyroid function
- physician experience
Vincristine

- chemotherapy agent
  - used in the treatment of many malignant and non-malignant disorders

- mechanisms of action:
  - induces apoptosis in endothelial cells
  - interferes with mitotic spindle microtubules

- central access
Side Effects of Vincristine

- Early:
  - peripheral neuropathy
  - constipation
  - jaw pain
  - rare hematological toxicity

*very limited long term effects
(usually tolerated well)
Propranalol

- non-selective beta-blocker
- many potential mechanisms
  - vasoconstriction
  - decreased expression of VEGF and bFGF
  - +/- apoptosis
- rapid improvement
Side Effects of Propranolol

- Hypotension
- Bradycardia
- Bronchospasm
- Hypoglycemia
- Contraindicated in PHACE syndrome
Wound Care

- Cleanliness
- Barrier creams
- Non-stick dressings
- Metronidazole, Silvadene, Mupirocin
- Oral antibiotics
- Pain management
**Pulsed-dye laser**

- lightens or resolves PWS in 50-75%  
  - greatest decrease in smallest lesions and youngest children  
  - may redarken

- superficial hemangiomas only  
  - penetration to 1.2 mm

- ulceration, postinvolution erythema, and telangiectasias
Vascular Lesions

• Port Wine Stains
• Hemangioma
Hemangioma

Vascular Lesions

**Evaluation** – airway, vital structures, MRI

**Treatment**
Medical: Oral steroid, oral Beta-Blocker, interferon.


*Claire Sanger, DO*
Port Wine Stains

Claire Sanger, DO
Port Wine Stains
Side Effects of Laser

- transient hyperpigmentation
- potential hypopigmentation
- textural changes
- promotion of ulceration
- scarring
Summary

- making the correct diagnosis is essential
- early referral for complex hemangiomas is optimal
- management is multidisciplinary
- education for the patient and family is an absolute and ongoing necessity
Multidisciplinary VMF Clinics

- Hematology/Oncology
- Radiology
- Interventional Radiology
- Plastic Surgery
- Dermatology
- Otolaryngology
- Pediatric Surgery
- Basic scientists
- Patient/family support staff
Thanks to . . .

- Dr. Claire Sanger
- Elizabeth Lewis, RN, CPON
- Dr. Denise Adams
- The PHO Clinic Staff
Case

- 2 month old white female presented to the ER with rapidly growing hemangioma on arm; mother also noted petechiae and dark stools
- Laboratory evaluation: platelet count 5,000; Hgb 7.6; fibrinogen 78.3; D-dimer > 1.25 and normal PT/PTT
- Treatment: high dose steroids for 6 weeks, interferon for 4 months
- Response: 3 - 4 months
Kasabach-Merritt Phenomenon

- 1940-Kasabach and Merritt

- cardinal features:
  - enlarging vascular lesion
  - profound thrombocytopenia
  - microangiopathic hemolytic anemia
  - consumptive coagulopathy
Kaposiform Hemangioendothelioma

- uncommon, aggressive vascular tumor
- high mortality rate if left untreated
- most common in children < 2 yrs. of age
- M:F ratio is equal
- usually unifocal
  - retroperitoneum, deep neck, mediastinum, pelvis, upper back and limbs
- angiogenic growth factors not consistently elevated
KHE-Clinical Presentation

- early appearance similar to a hemangioma
- mature lesions: violaceous color, infiltrative, nodular growth pattern, warm, firm, telangiectasias, ecchymoses
- can be associated with lymphangiomatosis
KHE-MRI Imaging

- ill-defined tumor margins
- involvement of multiple tissue layers
- small number of feeding or draining vessels
- signal voids without flow-related enhancement (hemosiderin, blood products, fibrosis)
KHE-Pathology

- lobules or sheets of tightly packed spindled or rounded endothelial cells and pericytes
- atypia, nuclear hyperchromasia, and mitoses absent or rare
- cellular areas infiltrate dermis, subcutaneous fat and muscle
- areas of hemorrhage and fibrosis common
- cell markers for endothelial cells (CD34, CD31, von Willebrand factor antigen) are often positive
Kassabach–Merritt Phenomenon

- Heparin may worsen the clinical course
- Transfusions may worsen the clinical course
- Residual lesions are common
  - Type I: pseudo port-wine stain, fibrotic feel
  - Type II: red telangiectatic streaks and swelling
  - Type III: firm, irregular, nodular, subcutaneous lesion
- Relapse of KMP may occur
Treatment of KMP

■ corticosteroids - variable results
■ interferon (alfa-2a, alfa-2b) - significant neurologic toxicity
■ antifibrinolytic agents (tranexamic acid, aminocaprioc acid)
■ antiplatelet agents (aspirin, dipyridamole)
■ chemotherapy (vincristine, cyclophosphamide)
■ surgery
■ embolization
■ radiation
Kasabach-Merritt Phenomenon: A Retrospective Study of Treatment with Vincristine

- 10 males (71%) and 4 females (29%)
- age 2 weeks to 28 months
  - Mean: 7 months; median: 5.5 months
- location of lesions
  - Extremities: 4 (25%); Trunk: 5 (36%); Head/Neck: 5 (36%)
- ↑ in platelet count: 14/14 (100%)
- ↑ in fibrinogen: 12/12 (100%)
- ↓ in size: 12/14 (86%)
- length of treatment: mean 22 wks (5-44 wks)
- length of follow-up: mean 12.6 mos (1-30 mos)
- relapse: 3 of 14 (21%)
- minimal side effects (3 patients, 7%)