Hemangioma: Review of Literature

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ABSTRACT

Hemangiomas are tumors identified by rapid endothelial cell proliferation in early infancy, followed by involution over time. All other abnormalities are malformations resulting from anomalous development of vascular plexuses. The malformations have a normal endothelial cell growth cycle that affects the veins, the capillaries or the lymphatics and they do not involute. Hemangiomas are the most common tumors of infancy and are characterized by a proliferating and involuting phase. They are seen more commonly in whites than in blacks, more in females than in males in a ratio of 3:1.

Keywords: Hemangiomas, Tumor, Vascular malformations.


Source of support: Nil
Conflict of interest: None declared

INTRODUCTION

Hemangioma is the most common tumor in infants (10-12%) and the head and neck region is the most commonly involved site (60%). Most lesions are solitary (80%), and girls are more affected than boys (3:1). Most hemangiomas are found within the soft tissues (mucosa, skin and muscle) and only a small percentage of cases occur intraosseously.

Hemangiomas usually appear soon after birth (though up to 30% may be present at birth), typically proliferate during the first year of life and then involute during the childhood years (up to 12 years). The terms capillary and cavernous hemangioma are out of date and the lesions are more appropriately described according to the depth of the lesion as superficial, deep and compound hemangioma.

The natural history of hemangiomas should influence the timing and type of intervention. Benign neglect is often advocated but can be unacceptable given the natural history of these lesions. A useful approach to the management of hemangiomas can be based on the stage of the lesion (proliferative or involuting phase), type of lesion (superficial, deep, compound) and the management of residual deformity. The therapeutic modalities currently available surgery alone or in combination with endovascular embolization, intralesional injection of sclerosing agents, lasers, systemic steroids.

CLASSIFICATION OF HEMANGIOMAS

Classifying vascular neoplasms has always been a challenge. Until recently, most classification of these neoplasms was based on a mixture of clinical, radiological and pathological features, and there was little agreement on histopathologic classification. Some of the most accepted classifications are as:

I. Blood vessels and lymphatics by David I Abramson follows (1962)
   • Capillary hemangioma (strawberry mark)
   • Cavernous hemangioma
   • Mixed cavernous and capillary angioma
   • Hypertrophic or angioblastic hemangioma
   • Racemose hemangioma
   • Port-wine stain or nevus vinosus
   • Spider angioma (nevus araneus)
   • Nevus flammeus (DeMorgan’s spot)
   • Systemic hemangiomatosis or hemangioma unilateralis, infectious hemangioma, pyogenic granuloma
   • Special regional hemangiomas of the brain, tongue, gastrointestinal tract, liver, skeletal muscle and bone.
   • Congenital neurocutaneous syndromes associated with angiomatosis.
     i. Von Recklinghausen’s neurofibromatosis with angiomatosis
     ii. Bourneville’s syndrome with tuberous sclerosis
     iii. Sturge-Weber’s disease (encephalofacial angiomatosis)
     iv. Lindau-Von Hippels disease (hemangiomatosis of retina and cerebellum).

II. Classification by Shafer et al (1993):
   • Capillary hemangioma
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JcDP

The Journal of Contemporary Dental Practice, September-October 2013;14(5):1000-1007

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• Cavernous hemangioma
• Angioblastic or hypertrophic hemangioma
• Racemose hemangioma
• Diffuse systemic hemangioma
• Metastasizing hemangioma
• Nevus vinous or port-wine stain
• Hereditary hemorrhagic telangiectasia

III. WHO classification of soft tissue tumors by Ivan (1996)
• Benign
• Papillary endothelial hyperplasia
• Hemangioma
• Capillary hemangioma
• Cavernous hemangioma
• Venous hemangioma
• Epithelial hemangioma (angiolympoid hyperplasia, histiocytoid hemangioma)
• Pyogenic granuloma (granulation tissue type hemangioma)
• Acquired tufted hemangioma (angioblastoma)
• Lymphangioma
• Lymphangiomyoma, lymphangiomyomatosis, angiomatosis, lymphangiomatosis

IV. Classification of vascular tumors by Christopher DM Fletcher (2003)
• Hemangioma
• Capillary hemangioma
• Variants
• Tufted angioma
• Verrucous hemangioma
• Cherry angioma
• Lobular hemangioma
• Cavernous hemangioma
• Variants
• Sinusoidal hemangioma
• Arteriovenous hemangioma
• Variants
• Superficial (cirsoid aneurysm)
• Deep
• Microvenular hemangioma
• Targetoid hemosderotic hemangioma (hobnail hemangioma)
• Epitheloid hemangioma (angiolympoid hyperplasia with eosinophilia)
• Venous hemangioma
• Spindle cell hemangioendothelioma
• Deep hemangiomas
• Variants
• Intramuscular, synovial, neural, nodal
• Angiomatosis

REVIEW RESULTS

Historical Perspective

First case of hemangioma was documented by Liston (1843). Later in 1867, Virchow described the first case of vertebral hemangioma. In the 1940s, Kasabach and Merritt described a 2-month-old male infant who had thrombocytopenic purpura and a ‘giant capillary hemangioma’ on his left thigh. Thereafter, the double eponym ‘Kasabach-Merritt syndrome’ came to be used for hemangioma with platelet trapping.11 The theory that, hemangiomas are neoplasms, was strongly supported by the study of Mulliken and Glowacki (1982). In 1982, Mulliken and Glowacki proposed a binary classification system for vascular anomalies based on pathologic features.12

Later Douglas Marchuk (2001) in their study defined hemangioma as a benign tumor that exhibits an early and rapid proliferation phase during the first year of life, and is characterized by endothelial and pericytic hyperplasia, followed by a slower but steady involution phase that may last for years. Another definition came from Richard J Antaya (2002) who defined hemangiomas as benign vascular neoplasms that have a characteristic clinical course with early proliferation followed by spontaneous involution and were the most common tumors of infancy. Recently in 2004, Danielle A Katz defined hemangioma as an abnormal proliferation of blood vessels that may occur in any vascularized tissue and that considerable debate exists as to whether these lesions are neoplasms, hamartomas or vascular malformations.

DEMOGRAPHICS

Age

The first intradermal hemangioma was identified by Edgerton MT, Heibert JM (1978) and they stated that it is frequently present at birth.13 Walter, John Brahn (1979) reported that hemangiomas are usually present at birth or else appear soon afterward.14 In 1985, Marcus Connelly reported in his study that the average age of 46 patients with hemangiomas was 58 years and the range was from 17 to 78 years. There was no difference in the age between men and women.15 Wolf (1985) was of the opinion that intramuscular hemangiomas of the head and neck are most commonly present in the third decade of life. Thomas Fitzpatrick (1987) reported that capillary hemangiomas are first noted shortly after birth. He also stated that granuloma pyogenicum may occur at any age.16 Yih (1989) stated that the peak incidence of central hemangiomas of the jaws is in the second decade of life. Harry L Arnold Jr et al (1990)
were of the opinion that hemangiomas might be present at birth, which they observed in 38% of their cases. James L Rossiter (1991) reported that hemangiomas are the most common benign tumors of infancy. Bruckner and Anna L et al (2003) stated that hemangiomas of infancy can occur in 1.1% to 2.6% of term neonates and their frequency is estimated to be as high as 10 to 12% within the first year of life. Mark A Crowe et al (2003) reported that pyogenic granuloma is more common in the first 5 years of life. Rosai Ackerman (2004) was of the opinion that a high percentage of capillary hemangiomas were seen in children and many of them were present at birth. The peak incidence of central vascular malformations of the jaws is in the second decade of life. Intramuscular vascular malformation of the head and the neck most commonly present in the third decade of life.

Sex

Lister WA et al (1938) found that capillary hemangioma affected females slightly more than males. Barret (2000) observed that arteriovenous hemangiomas of the oral cavity have a predilection for males. Dan DeAngelis (2001) found that females outnumber male patients with hemangiomas in a ratio of 3:1. Andrew Carlson (2002) observed that targetoid hemosiderotic hemangioma is equally divided among both the sexes. Chiller KG (2002) was of the opinion that hemangiomas occur more commonly in girls. Mark A Crowe (2003) found that pyogenic granuloma is more common in females as it is pregnancy related. Daniel Katz (2004) was of the opinion that intramuscular hemangioma is equally found in males and females.

Site

Kasabach and Merrit (1940) found that hemangiomas are benign vascular tumors that may occur in any tissue of the body. They said that skin is the structure, which is most commonly affected. Scarcella JV and Dykes ER et al (1965) stated that parotid cavernous hemangiomas present as a solitary lump in the parotid region. Castro et al (1974) in their study found that epitheloid hemangioma typically presents as single or multiple cutaneous red nodules in the head and neck region of middle-aged adults. Jerome B Taxy et al (1979) found that hemangiomas of the soft tissues in infants and children are rapidly growing, particularly in the head and neck area. Fred Daniel, Gregory T Wolf (1984) stated that intramuscular hemangiomas are uncommon tumors in the head and neck region. Hemangiomas arising within the skeletal muscle account for less than 1% of all hemangiomas and occur most frequently in the larger musculature of the trunk and extremities. Intramuscular hemangiomas are uncommon tumors in the head and neck region, with the masseter muscle representing the most common site of involvement. In 1993, Rossiter et al stated that 14 to 22% of intramuscular hemangiomas occur in the head and neck region. Infantile hemangiomas occur anywhere on the skin, but the head and neck is the most commonly affected, followed by the trunk and limbs. Hemangiomas may involve mucous membranes of the oral and genital regions. Microvascular hemangioma affects the upper limbs, particularly the forearms, but lesions on the trunk, face and lower limbs have also been reported. Neville et al (2002) observed that hemangiomas occur more frequently in the head and neck region. In the study, Richard J Antaya (2002) was of the opinion that 60% of cutaneous hemangiomas occur in the head and neck, 25% on the trunk and 15% on the extremities. Hemangiomas can also occur in extracutaneous sites, including the liver, gastrointestinal tract, central nervous system, pancreas, gall bladder, thymus, spleen, lymph nodes, lung, urinary bladder and adrenal glands. Recently Rosai, Ackerman (2004) stated that hemangiomas can occur in any organ, but its most common location is the skin.

CLINICAL FEATURES

Patients with intramuscular hemangioma present with a history of recent development of a facial or neck mass that is slowly enlarging. The tumors are frequently painful. Patients with intramuscular hemangioma present with a history of recent development of a facial or neck mass that is slowly enlarging. The tumors are frequently painful. Cope DA, Blanchard CL (1965) on palpation found that parotid cavernous hemangioma is usually soft but could be firm or sponge-like. Pain may or may not be present. Dempsey EF and Hurley RS (1970) noticed that cavernous hemangioma of the parotid becomes more prominent when the head is bent forward or patient lies horizontally (turkey wattle sign). Allen PW and Enzinger FM (1972) observed the clinical course and stated that intramuscular hemangioma presents with no enlargement of the tumor or valsalva (head dependency-turkey wattle sign). Conley JJ, Clairmont AA (1977) observed that palpation of intramuscular hemangioma mass is often misleading, because they are often located deep within a muscle and can vary in consistency from a diffuse, soft comprehensible mass to one that is very firm. Discoloration of the overlying skin is rare and presence of pulsations, thrills or bruit is unusual. Edgerton Heibert (1978) stated that intradermal hemangiomas present at birth are pink to purple in color. The salmon patch variety, which is faintly
IMAGING FEATURES

Workup of oral hemangiomas requires some form of imaging to determine their extent and flow characteristics. The following modalities may be helpful:

- **Angiography** is considered the most definitive of the studies, although the angiographic appearance of intraosseous lesions is less well defined than that of soft tissue lesions.
- **Ultrasoundography** can be used to determine that a lesion is angiomatous in nature, i.e. hemangioma, lymphangioma), but it cannot be used to differentiate a hemangioma from a lymphangioma.
- **Contrast-enhanced MRI** can be used to differentiate a hemangioma from a lymphangioma in the oral cavity. MRI appears to be highly reliable for lesions of either soft tissue or bone.
- **On plain films or panoramic radiographs, a central vascular malformation of the bone usually has a honeycomb appearance or cystic radiolucencies.** Intraosseous vascular malformations show a nonspecific reticulated or honeycomb pattern that is well demarcated from normal bone. A sunburst effect, created by spicules radiating from the center, is often present.
- **CT scans** often show an expansile process with a high-density amorphous mass that may be suggestive of fibrous dysplasia.

**HISTOPATHOLOGY**

Girard DC et al (1974) identified histologically venous hemangiomas as showing densely aggregated, thick-walled and thin-walled vessels lined by a single layer of endothelial cells. The walls of the thick-walled vessels consist mainly of fibrous tissue, but in most instances contain also some smooth muscles.42

Kumakiri M, Muramoto F et al (1983) reported that the cardinal feature of tufted angioma is the presence of scattered round or ovoid lobules of closely packed capillaries in the dermis and superficial subcutis in a typically discohesive, ‘cannon ball’ distribution. Individual lobules are very similar to those seen in the early stages of strawberry nevus and consist of varying proportions of poorly canalized bloodless capillaries surrounded by pericytes. The endothelial cells are bland and mitotic figures are rare. Focally, cytoplasmic inclusions can be seen in the endothelial cells, the nature of which is unknown. A distinctive feature is the presence of dilated crescent shaped lymphatic-like vascular channels at the periphery of the tumor lobules.43 Marcus G Connelly MD (1985) observed that acral arteriovenous tumor, microscopically, is a well-circumscribed mass of large thick-walled vessels located in the superficial to middle
dermis. There is no capsule and no extension into the subcutaneous tissue.15

In early proliferation, hemangiomas are characterized by nonencapsulated masses and dense cords of mitotically active, plump endothelial cells in close association with pericytes. Few small caliber lumina are present. Special stains reveal well-developed basement membranes around primitive vessels. Mast cells are present in varying numbers in all stages. As the hemangioma proliferates, the vascular lumina enlarge. An increase of apoptotic endothelial cells and a decrease in plump, mitotically active endothelial cells herald the involution phase. As involution progresses, the endothelial cells continue to mature and assume a flatter appearance. The vascular lumina continue to enlarge until a few mature ectatic vessels remain. Much of the proliferating endothelial cell mass is replaced with fibrofatty tissue.

Salient histopathologic findings of vasoformative tumors that distinguish them are as follows:

- Hemangiomas (proliferative phase):
  - Endothelial cell hyperplasia forming syncytial masses
  - Thickened (multilaminated) endothelial basement membrane
  - Ready incorporation of tritiated thymidine in endothelial cells
  - Presence of large numbers of mast cells

- Hemangiomas (involuting phase):
  - Less mitotic activity
  - Little or no uptake of tritiated thymidine in endothelial cells
  - Foci of fibrofatty infiltration
  - Normal mast cell counts.

IMMUNOHISTOCHEMISTRY AND Markers

Factor VIII-associated protein in the well-canalized areas of the hemangioma, with inapparent staining in the immature cellular zones74 was demonstrated by Enzinger FM, Weiss (1988). Eduardo Colonje (1991) observed that factor VIII-related antigen, CD34 and lectin ulex europeaus stained the endothelial cells lining the vascular spaces.44 Enzinger, Franz M (1995) noticed that factor VIII associated protein can be identified within cellular hemangiomias of infancy and becomes significant in the well-canalized portions of the tumor. Factor XIII-positive interstitial cells are a consistent feature of these tumors.45 John B Mulliken (1999) reported that immunohistochemical studies showed angiogenic factors, specifically basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), which are prominent during the proliferating phase (0-12 months). During the same period, interferon (an inhibitor of endothelial migration) is diminished in the epidermis overlying the tumor.46 Johann et al showed that histological diagnosis alone is not sufficient to correct diagnoses of oral hemangiomia. Moreover, immunohistochemistry to GLUT1 is a useful and easy diagnostic method that may be used to avoid such misdiagnosis.47

MANAGEMENT

Kane et al49 developed a management algorithm that covers most of the current thinking regarding these tumors.

At initial presentation, a history and physical examination are performed, and an MRI is obtained to determine the extent of the lesion because extensive spread may not be evident on examination. Presence of bruits, pulsatility or deep extent would also make angiography a useful adjunct. If it is a hemangioma, then whether the lesion is proliferating needs to be ascertained. For proliferating lesions, either observation or steroids are options. In lesions that are not proliferating, whether the lesion is involuting needs to be determined. Involuting lesions can be managed by observation.

Treatment of vasoformative tumors represents a challenge because the morbidity can range from minor bleeding and swelling to life-threatening hemorrhage and airway embarrassment. Because of the propensity of hemangiomas to regress spontaneously, approaches to management depend on the size, their location, their behavior and the age of the patient. Hemangiomas are usually managed conservatively.

Most true hemangiomas require no intervention, but 10 to 20% require treatment because of their size, their location or their behavior.50 Individualized therapy depends on the age of the patient, the size and the exact location of the lesion, the stage of growth or regression and the functional compromise. In general, the treatment of small hemangiomas that do not compromise function is observation. Conservative management consists of periodic visits, parental support and photodocumentation. The ultimate result of involution for capillary hemangiomas is far superior to primary excisional therapy. Excision can be justified under certain conditions, especially when function is compromised. The two primary medical treatments are steroids and beta-blocker therapy.51-53

Steroids have become a mainstay in the treatment of proliferating hemangiomas in infants and children. High doses of systemic or intralesional steroids are the first-line treatment, and a dramatic response is observed in 30% of patients.50 Fost and Esterly54 first reported the use of systemic steroids in the treatment of hemangiomas. Prednisone at a dose of 20 to 30 mg/d was given for 2 weeks to 4 months. Both of the patients with capillary hemangiomas had a definite response, and three of the four patients with mixed hemangiomas had a definite response. Fost proposed that therapy be discontinued if no response
occurred after 2 weeks because of the multiple adverse effects of systemic steroids in infants. Edgerton also proposed the use of systemic steroids in the treatment of hemangiomas. He followed seven patients receiving 20 to 40 mg/d of prednisone for 30 to 90 days, with a definite response occurring in all of the patients.

Although the effectiveness of interferon alfa in the treatment of hemangiomas has been documented in many reports, the risk of spastic diplegia generally favors an alternative agent. Blei et al reported the use of interferon alfa-2a in parotid hemangiomas (13 females, 1 male) in which the response was poor. Greinwald et al described a prospective randomized trial of interferon alfa-2a involving 24 patients with massive or life-threatening hemangiomas of the head and the neck.

Surgical or invasive treatment of oral hemangiomas has evolved. Complete surgical excision of these lesions offers the best chance of cure but, often, because of the extent of these benign lesions, significant sacrifice of tissue is necessary. For example, lesions of the tongue may require near-total glossectomy, which is followed by severe functional impairment to vital functions, such as swallowing, speech and airway maintenance. As a result, multiple adjunctive procedures have been introduced to eradicate the disease, leaving less of a functional impairment. These adjunctive procedures have also been used to reduce both the blood loss and the morbidity of surgical procedures. Embolotherapy is one of the more commonly used adjunctive procedures in the treatment of vascular tumors. Embolization literally means the occlusion of a vessel by the introduction of a foreign body. In a broader definition, it also means any other occlusion that is obtained with a proliferating reaction of the vessel wall. As technical expertise with interventional radiology advances, the options for treatment of vascular malformations and hemangiomas become broader. The principle of vascular embolization for head and neck tumors is not new. In 1904, Dawbain, Lussenhop and Spence described the preoperative injection of melted paraffin-petrolatum into the external carotid arteries of patients with head and neck tumors. In 1930, Brooks introduced particulate embolization when he described the occlusion of a traumatic carotid-cavernous fistula by injecting a fragment of muscle attached to a silver clip into the internal carotid artery.

Use of laser therapy for the treatment of hemangiomas has gained popularity. Lasers have evolved to where more selective photothermolysis can be attained rather than nonselective tissue destruction. The yellow light lasers (578-585 nm) are selectively absorbed by hemoglobin. The only other competing chromophore with these lasers is melanin. Oral mucosa may be amenable to these lasers because little melanin is present in the mucosa. Little to no damage to the mucosa or the epithelium has been reported. In the macular stage of development, a 585 nm pulsed dye laser has been used to treat a capillary hemangioma. Apfelberg reported using a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser to treat massive hemangiomas and vascular malformations in the head and the neck via intralesional laser photocoagulation.

Cryosurgery for cutaneous lesions has been associated with scarring, but it may have a role in the treatment of oral mucosal lesions. Several authors have used cryosurgery for treating oral vascular tumors, although this technique has fallen into disfavor in recent years. Hartmann reported minimal scar contracture, good hemostasis and little discomfort with the use of cryosurgery to remove a large oral hemangioma.

Some of the most commonly used sclerosing agents are sodium tetradecyl sulfate, sodium morrhuate, sodium psylliate. Successful treatment of facial hemangiomas using STDS has been reported in the literature. Local reactions consisting of pain, urticaria or ulceration may occur at the site of injection. Sloughing and necrosis of tissue may occur following extravasation of the drug. Allergic reactions, such as hives, asthma, hay fever and anaphylactic shock, have been reported. Mild systemic reactions that have been reported include headache, nausea and vomiting. In our case, no such adverse effects were seen.

Our literature search to the best of our knowledge shows total of 1695 articles related to oral hemangiomas treated with different modalities. Very few cases have been reported managed using the local sclerosant injections. Local sclerosing therapy is beneficial in cases of small hemangiomas at sites, where surgical excision could result in significant functional compromise.

Various sclerosants used include 3% sodium tetradecyl sulfate, 5% ethanolamine oleate, pingyangmycin, polidocanol, sodium morrhuate. Zonghua et al compared the clinical therapeutic effects between pingyangmycin and sodium morrhuate injections in venous malformations of maxillofacial regions and concluded that pingyangmycin is more effective than sodium morrhuate. Kuo HW et al have reported the effectiveness of polidocanol in treating venous lake of lip. In a larger series of 83 cases, Hogue S, Das BK have reported the safety and effectiveness of ethanolamine oleate in treating venous malformations. Sclerotherapy followed by surgery have been reported for two cases by Mariano FV et al. Currently, sclerotherapy is employed largely because of its efficiency and ability to conserve the surrounding tissues. Surgery can be used exclusively or associated with sclerotherapy in lesions that do not show complete resolution. Sunita Agarwal et al conducted a study on 20 cases of clinically diagnosed hemangiomas treated...
using 3% sodium tetradecyl sulfate. They concluded that, when used in appropriate doses, sclerosing agent, 3% sodium tetradecyl sulfate (STD), is very effective for treatment of oral hemangioma.

More extensive studies and a larger series of cases are required to effectively assess the dosage, efficacy and side effects of various sclerosants.

**SUMMARY AND CONCLUSION**

Hemangiomas are tumors identified by rapid endothelial cell proliferation in early infancy, followed by involution over time. All other abnormalities are malformations resulting from anomalous development of vascular plexuses. The malformations have a normal endothelial cell growth cycle from anomalous development of vascular plexuses. The time. All other abnormalities are malformations resulting from anomalous development of vascular plexuses. The malformations have a normal endothelial cell growth cycle from anomalous development of vascular plexuses. The time.

Hemangiomas are the most common tumors of infancy and are characterized by a proliferating and involuting phase. They are seen more commonly in whites than in blacks, more in females than in males in a ratio of 3:1.

A number of growth factors including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor-beta (TGF-beta) and interleukin 6 (IL6) have been demonstrated as regulators of angiogenesis. A number of cellular markers have been outlined, such as TIMP-1, bFGF, proliferating cell nuclear antigen, type IV collagenase and urokinase.

Hemangiomas of the oral cavity are not common pathologic entities, but, among hemangiomas, the head and neck are common sites. Most hemangiomas involute with time, but a certain small percentage do not, which may present with complications that require treatment.

To conclude, hemangiomas pose perplexing questions that will only be answered as the events that initiate hemangiogenesis are elucidated. In addition, the anatomical predilection for the head and neck of juvenile hemangiomas must be explained, perhaps most intriguing from a therapeutic standpoint is the spontaneous involution of the lesion. This distinguishing characteristic has been shown to be due in part to apoptosis of the endothelial cells, but the trigger for this process remains unknown. Can this apoptotic program be switched on earlier and be accelerated? These are some of the questions that have to be addressed in the future.

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