

Hemangioma - A Review

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Citation

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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.

INTRODUCTION

Vascular lesions are among the most common congenital and neonatal abnormalities. In the past, sometimes confusing classifications were developed characterized by a colorful, inconsistent terminology. As a consequence, a clear understanding of the various biological characteristics of vascular tumors has been impeded. This has led to the misconception that most of these lesions spontaneously disappear within the first few years of life. As a consequence, congenital vascular malformations were often misdiagnosed and left untreated.

Hemangioma is a benign, localized tumor of the blood vessels. Most of the benign vascular lesions occurring in the head and neck region have a malformational, hamartomatous basis. In recent years, the classification of vascular tumors and tumor-like conditions has been extensively modified, with the addition of several newly described entities and the redefinition of several previously known lesions. Consequently, the number of benign angiomatous lesions placed in the updated classification scheme is expanding. Some of these have been characterized only in the recent years, and thus may produce diagnostic difficulties.¹

Hemangiomas occupy a gray zone between hamartomatous malformations and true neoplasms: they are frequently designated and regarded as tumors because of their usually localized nature and mass effect. The fact that they consistently lack chromosomal alterations, speaks against a true neoplastic nature.²

Although clearly benign, over half of these cases are in head

and neck region. They can also occur in the trunk or extremities. Most hemangiomas are solitary; when multiple (with or without associated lesions in internal organs) or affecting a large segment of the body, the condition is known as multifocal angiomatosis. This occurs more commonly in whites than in blacks.

They are the most common tumors of infancy and are characterized by a proliferating and involuting phase. Growth in early infancy, during the proliferative phase, is embodied by rapidly dividing endothelial cells forming syncytial masses; thickened, multilaminated basement membranes; and elevated mast cell concentrations. Proliferating-phase hemangiomas display a ten-fold increase in mast cell concentration.

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:-

I. BLOOD VESSELS AND LYMPHATICS, BY DAVID.I.ABRAMSON (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 unilateris, infectious hemangioma, pyogenic granuloma
- Special regional hemangiomas of the brain, tongue, gastro-intestinal tract, liver, skeletal muscle and bone.
- Congenital neurocutaneous syndromes associated with angiomatosis.

(i) Von Reckling Hausens neurofibromatosis with angiomatosis

(ii) Bourneville's syndrome with tuberous sclerosis

(iii) Sturge- Weber's disease (encephalo-facial angiomatosis)

(iv) Lindau-Von-Hippels disease (hemangiomatosis of retina and cerebellum).

II. CLASSIFICATION BY SHAFER ET AL (1993)

- Capillary hemangioma
- Cavernous hemangioma
- Angioblastic or hypertrophic hemangioma
- Racemose hemangioma
- Diffuse systemic hemangioma
- Metastasizing hemangioma
- Nevus vinosus or port-wine stain
- Hereditary hemorrhagic telangiectasis

III. WHO CLASSIFICATION OF SOFT TISSUE TUMORS BY IVAN (1996)

- Benign
- Papillary endothelial hyperplasia
- Hemangioma
- Capillary hemangioma

- Cavernous hemangioma
- Venous hemangioma
- Epithelial hemangioma (angiolymploid 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.D.M.FLETCHER (2003)

- Hemangioma:
- Capillary hemangioma
- Variants:
- Tufted angioma
- Verrucous hemangioma
- Cherry angioma
- Lobular hemangioma
- Cavernous hemangioma
- Variants:
- Sinusoidal hemangioma
- Arteriovenous hemangioma
- Variants:
- Superficial (cirroid aneurysm)
- Deep
- Microvenular hemangioma
- Targetoid hemosiderotic hemangioma ("hobnail" hemangioma)
- Epitheloid hemangioma (angiolymploid hyperplasia with eosinophilia)
- Venous hemangioma

- Spindle cell hemangioendothelioma
- Deep hemangiomas
- Variants: -
- Intramuscular, Synovial, Neural, Nodal
- Angiomatosis

HISTORICAL PERSPECTIVE

First case of hemangioma was documented by Liston (1843).⁷ Later in 1867 Virchow described the first case of vertebral hemangioma.⁷ Kasabach and Merrit (1940) reported a case of hemangioma involving the skin and deep soft tissues of the thigh that was associated with extensive purpura.⁷ The theory that hemangiomas are neoplasms was strongly supported by the study of Mulliken and Glowacki (1982).⁷ Derancy et al (1994) defined skeletal-extra skeletal angiomatosis as benign vascular proliferation involving the medullary cavity of bone and at least one other type of tissue.⁷ 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.⁸ 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.⁹ Recently in 2004, Danielle A Katz defined hemangioma as an abnormal proliferation of blood vessels that may occur in any vascularised tissue and that considerable debate exists as to whether these lesions are neoplasms, hamartomas or vascular malformations.⁷

DEMOGRAPHICS

AGE

The first intradermal hemangioma was identified by Edgerton M T, Heibert J M (1978) and they stated that it is frequently present at birth.¹⁰ Walter, John Brahn (1979) reported that hemangiomas are usually present at birth or else appear soon afterwards.¹¹ In (1985) Marcus. Connelly reported in their study that the average age of 46 patients with hemangiomas was 58 years and the range was from 17-78 years. There was no difference in the age between men and women.¹² Wolf (1985) was of the opinion that intramuscular hemangiomas of the head and neck are most

commonly present in the third decade of life.¹³ Thomas. Fitzpatrick (1987) reported that capillary hemangiomas are first noted shortly after birth. He also stated that Granuloma pyogenicum may occur at any age.⁴ Yih (1989) stated that the peak incidence of central hemangiomas of the jaws is in the second decade of life.¹³ 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.¹⁴ James L Rossiter (1991) reported that hemangiomas are the most common benign tumors of infancy.¹⁵ C L Hebeda et al (1993) identified tufted angiomas, as rare hemangiomas, mostly seen in children in Japan.¹⁶ Jamal T Hamdi (1994) reported that cavernous hemangiomas usually present in late childhood or early adulthood.¹⁷ Enzinger Weiss (1995) stated that hemangiomas are the most common soft tissue tumors of infancy and childhood. According to them capillary hemangiomas comprise the single largest group of hemangiomas. They appear during the first few years of life. Cellular hemangiomas of infancy are an immature form of capillary hemangioma, which occur during infancy at a rate of about 1 in every 200 live births.¹⁸ Douglas. Gnepp (1997) stated that hemangiomas of the face and neck are the most common tumors of infancy and early childhood.¹⁹ Luis.Requena. M. D (1997) observed that acral arteriovenous hemangiomas occur in mid adult life.²⁰ Barret (2000) observed 35 oral hemangiomas (vascular malformations) over a 48-year in his institution. In his observations the mean age was 52.6 years with a range from 12-90 years.¹³ Dan DeAngelis (2001) was of the opinion that capillary hemangiomas are present in approximately 1-2% of all neonates. He also proposed that all patients that eventually develop hemangiomas develop the same by the age of 6 months.²¹ Douglas Marchuk (2001) reported that hemangiomas are the most common tumors of any kind seen in infancy.⁸ Andrew. Carlson et al (2002) observed that targetoid hemosiderotic hemangioma occurs in the age group from 5-72 years and in most patients presents between 20-30 years.²² Chiller K G et al (2002) stated that hemangiomas are usually seen in patients less than 18 months of age.²³ Richard. Antaya (2002) was of the opinion that 30% of hemangiomas are present at birth and 70% of them initially appear in the first several weeks of life.⁹ Bruckner, 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.²⁴ Mark A Crowe et al (2003) reported that pyogenic granuloma is more common in the first five years of life.²⁵ Randall Wilk (2003) observed that

the incidence of hemangiomas increases to 23% in premature infants with a birth weight of less than 1000 mg. He proposed that intra-osseous hemangiomas most commonly occur in the fourth decade of life but range from infancy to the eighth decade of life.²⁰ Christopher D M. Fletcher (2004) found that hemangiomas are the most common benign vascular tumors of infancy affecting as many as 1 in every 100 births. He stated that cherry angiomas increase in number with age and lobular capillary hemangiomas can occur at any age. According to him venous hemangiomas have been described as a distinctive entity in the mesentery, retro-peritoneum and skeletal muscle of the limbs in adults. He also stated that intramuscular hemangiomas may present at any age and that synovial hemangiomas present more commonly in children and young adults.²⁶ Daniel. Katz, Timothy Damron (2004) stated that intramuscular hemangiomas occur most often in young people, with 80-90% presenting in persons younger than 30 years. They also stated that osseous hemangiomas can occur in patients of any age.⁷ 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.²

SEX

Lister W A et al (1938) found that capillary hemangioma affected females slightly more than males²⁷

Bowers (1960) observed that patient's sex does not influence the speed or the completeness of involution of hemangiomas.¹³ Hidano (1972) reported that hemangiomas are more common in females than in males.¹³ Hayward (1981) observed that intra-osseous hemangiomas are about three times more common in females than in males.¹³ According to Yih (1989) intra-osseous hemangiomas are about three times more common in females than in males.¹³ In (1997) Luis. Requena reported that sinusoidal hemangioma occurs more frequently in females.²⁰ Barret (2000) observed that arterio-venous hemangiomas of the oral cavity have a predilection for males.¹³ Dan. DeAngelis (2001) found that females outnumber male patients with hemangiomas in a ratio of 3:1.²¹ Andrew. Carlson (2002) observed that targetoid hemosiderotic hemangioma is equally divided among both the sexes.²² Chiller. K. G (2002) was of the opinion that hemangiomas occur more commonly in girls.²³ Jeffrey. Zapalac (2003) observed that hemangiomas occur more in females than males in a ratio of 3:1.²⁸ Mark. A. Crowe (2003) found that pyogenic granuloma is more common in females as it is pregnancy

related²⁵ Daniel Katz (2004) was of the opinion that intramuscular hemangioma is equally found in males and females.⁷ Fletcher. D. M (2004) stated that tufted angioma presents in small children with no sex predilection. According to him sinusoidal hemangioma shows a female predominance and targetoid hemosiderotic hemangioma shows male predominance. He also stated that while epitheloid hemangioma shows slight predominance for males, intramuscular hemangioma shows no sex predilection. Synovial hemangiomas present in young adults and children especially males.²⁶

SITE

Kasabach, 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.²⁹ Scarella JV Dykes ER et al (1965) stated that parotid cavernous hemangiomas present as a solitary lump in the parotid region.³⁰ Imperial R, Helmig et al (1967) observed that verrucous hemangioma presents usually as a warty blue-black lesion in the lower extremities of children.³¹ 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.³² JohnsonWC (1976) stated that cherry angiomas are very common and present as red papules on the trunk and upper limbs of middle aged and elderly adults.³³ 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.³⁴ Fred Daniel, Gregory T Wolf (1984) stated that intramuscular hemangiomas are uncommon tumors in the head and neck region.³⁵ Anderson. WAD (1985) stated that capillary angioma corresponds clinically to the familiar portwine stain on the face and neck.³⁶ In (1987) Strutton G, Weedon D observed that arterio-venous tumor typically presents itself in the skin of head and neck (especially the lips) of middle aged or elderly adults.³⁷ Suster S (1987) found that epitheloid hemangioma can occur in the lymph nodes.³⁸ Thomas. Fitzpatrick (1987) identified pyogenic granuloma to be the most common lesion on the extremities and the face, and also in any part of the body³⁹ Ezinger F M, Weiss S W (1988) stated that venous hemangioma is a distinctive entity in the mesentery, retro-peritoneum and skeletal muscle of limbs in adults.⁴⁰ in the head and neck region, but may also occur in the trunk and extremities. capillary hemangioma Madison. J. F, Cooper. p. W (1989) found that epitheloid hemangioma can occur in an ovarian teratoma.⁴¹

In (1990) Banks E R, Mills S E reported that epitheloid hemangiomas can occur in the testes.⁴² Stale. Sund, I, Gisle. Bing (1990) stated that intramuscular hemangiomas are found more in the head and neck region.⁴³ Rasquin. S, Mayayo et al (1991) reported a case of epitheloid hemangioma in the tongue.⁴⁴ Miyamoto. T (1992) stated that tufted angiomas presents as an acquired lesion usually on the neck or trunk of small children.⁴⁵ James.. Rossiter, Robert (1993) in their study reported that hemangiomas are the most common benign tumors of infancy, occurring most often on the cutaneous and mucosal surface. 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.¹⁵ O'Connell X L, Kidtapuran (1993) were of the opinion that epitheloid hemangioma can occur in the bone.⁴⁶ In (1993) Rossiter et al stated that 14-22% of intramuscular hemangiomas occur in the head and neck region.¹⁵ M. Shah, T P Kingston (1994) reported that pyogenic granuloma occurs more on the skin or mucous membranes.⁴⁰ In (1996) Bastug. D F, Ness D T et al observed that pyogenic granuloma is a benign vascular lesion that occurs most commonly on the acral skin of children.⁴⁷ Luis.Requena et al (1997) were of the opinion that pyogenic granuloma usually develops at the site of pre-existing injury. Sites of predilection include the gingiva, lips, mucosa of the nose, face and fingers. 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. Micro-venular hemangioma affects the upper limbs, particularly the forearms, but lesions on the trunk, face and lower limbs have also been reported.²⁰ Neville et al (2002) observed that hemangiomas occur more frequently in the head and neck region.⁴⁸ 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 extra-cutaneous sites, including the liver, gastro-intestinal tract, central nervous system, pancreas, gall bladder, thymus, spleen, lymph nodes, lung, urinary bladder and adrenal glands.⁹ Recently Rosai, Ackerman (2004) stated that hemangiomas can occur in any organ, but its most common location is the skin.²

CLINICAL FEATURES

In (1938) Lister observed that the appearance of capillary hemangioma and described it as a red-purple macule that slowly becomes raised and then regresses.²⁷ Shallow TA, Eger SA et al (1944) stated that 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.⁴⁸ Cope D A, Blanchard C L (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.⁵⁰ Scarcella JV. Dykes E R et al (1965) stated that parotid cavernous hemangiomas presents as a solitary lump in the parotid region.³⁰ Dempsey E F, Hurley R S (1970) noticed that cavernous hemangioma of the parotid becomes more prominent when the head is bent forward or patient lies horizontally (turkey wattle sign).⁵¹ Allen PW, Enzinger F M (1972) observed, the clinical course and stated that intramuscular hemangioma presents with no enlargement of the tumor or Valsalva (head dependency -turkey wattle sign).⁵² Castro C, Winkelmann R K (1974) observed that epitheloid hemangioma clinically presents as single or multiple cutaneous red nodules around the ear.⁵³ Johnson W C (1976) noticed that cherry angiomas present as red papules on the trunk. and upper limbs of middle aged and elderly adults.³³ Conley J J, Clairmont A A (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.⁵⁴ Edgerton. Heibert (1978) stated that intradermal hemangiomas present at birth are pink to purple in color The salmon patch variety, which is faintly pink to rust in color and flat on the skin surface, shows no spontaneous regression.⁵⁵ Faber R G, Ibrahim S Z (1978) observed on clinical examination that hemangiomas of the parotid become more visible and more easily palpable by tensing of the masseter muscle when the patient clenches his teeth.⁵⁶ Giraldo G, Beth. E et al (1980) observed that cherry angioma is a ruby red papule that measures a few millimeters in diameter and has a pale halo zone.⁵⁷ In (1981) Hayward from his study diagnosed that central jaw hemangioma shows hypermobility of teeth and distortion of arch form. Root resorption occurs in 30% of the cases of central hemangioma of the jaws, but all the associated teeth were vital.¹³ Sadowsky D Rosenberg (1981) examined the patients with hemangiomas of the jaws and observed that they present with pain, spontaneous hemorrhage, asymmetry

of the face, mobility of teeth, pulsations, blanching of tissue, parasthesia, early exfoliation of primary teeth, delayed eruption, missing teeth and root resorption. Some central hemangiomas may be entirely asymptomatic.⁵⁸ In another study W A D Anderson (1985) found that granuloma pyogenicum is characteristically polypoid and is generally present for no longer than 1-3 months and bleeds easily and repeatedly. Cavernous hemangiomas appear on the skin surface as purple, single, globular or multilobular tumors or as flat or slightly elevated strawberry nevus of infants. Sclerosing hemangioma is seen as a single, firm and slightly elevated subcutaneous nodule, averaging several millimeters to a centimeter in diameter.³⁶ Intramuscular hemangiomas cause distortion of the involved area and have a spongy texture on palpation,⁵⁹ this was observed by Wolf G F et al (1985). Thomas. Fitzpatrick(1987) observed the clinical appearance of capillary hemangiomas. He stated that they vary greatly in size and extend into the subcutaneous tissue. The surface is smooth or irregular and bosselated. Lesions that are superficially located are bright red, but those with deep components tend to be darker, with purple or blue hue. They grow rapidly after birth and occasionally reach a large size. Ulceration may occur and may be complicated by infection. Senile hemangiomas are usually multiple and are most often located on the upper portions of the trunk. The individual lesions are usually bright to dark red, raised and range in size from one to several millimeters. They are not easily compressed. Tiny petechiae-like lesions also may be seen, especially on the arms and chest.³⁹ Yih (1989) observed severe hemorrhage following dental extraction and reported that it is not an uncommon presentation of central hemangioma of the maxilla and the mandible. Central hemangiomas of the jaws clinically, present with gingival bleeding, swelling, pain, mobility of the teeth and bony expansion.¹³ In (1990) Lever identified venous hemangiomas as solitary dark red papules or nodules on the face or less commonly on the extremities. Most lesions measure less than 1cm in diameter.⁶⁰ Beral V, Bull D et al (1992) observed that intramuscular hemangiomas present simply as enlarging soft tissue masses with few signs or symptoms to believe their vascular nature.⁶¹ Miyamoto T, Mihara M et al (1992) observed the tufted angiomas clinically which present as an acquired lesion, usually on the neck or trunk of small children. Tufted angiomas present as ill-defined red or brown tender macules and papules.⁴⁵ James L Rossiter (1993) reported that intramuscular hemangiomas are deeply seated and are not suspected only on clinical grounds.¹⁵ Jayashree. Mantravadi et al (1993) observed that

hemangiomas of the parotid gland present clinically as a gradually enlarging, diffuse~ symptomless, soft tissue mass in the parotid region.⁶² Laurence. Boon M D et al (1996) were of the opinion that majority of the congenital hemangiomas manifest as three morphologic variations

- (i) Raised violaceous tumor with large radial veins.
- (ii) Hemispheric tumor covered with multiple tiny cutaneous telengectasis surrounded by a pale rim and pink to violaceous tumor firm to palpation.
- (iii) Tumors of third variety located in the lower extremity.⁶³

Douglas. Gnepp (1997) observed that intramuscular hemangiomas are a distinct type that present in the skeletal muscle. On palpation oral mucosal hemangiomas are typically soft, moderately well circumscribed, painless masses that are red or blue in color.¹⁹ Luis. Requena et al (1997) were of the opinion that pyogenic granuloma presents typically as a papule or polyp with a glistening surface, which bleeds easily. Targetoid hemosiderotic hemangioma is clinically characterized by a brown or violaceous central papule, surrounded by a thin pale area and a peripheral ecchymotic ring. Microvenular hemangioma presents clinically as an acquired, slowly growing asymptomatic lesion with an angiomatous appearance. It is usually solitary varying from 0.5- 2 cm in diameter. Acquired tufted angioma presents clinically with some variability. Some of them are characterized by enlarging erythematous or brown macules or plaques with angiomatous appearance, but other lesions resemble granulomas or connective tissue abnormality. Some lesions are tender and others may show hyperhidrosis on the surface. Raised papules resembling pyogenic granulomas are sometimes seen within the area of the lesion.²⁰ John B Mulliken (1999) observed the clinical course and stated that hemangiomas appear about 2 weeks after birth. However about one-third or more of the hemangiomas manifest in the new born nursery, as a premonitory vascular "birthmark" - either as a tiny red papule, telangiectasia, pale nodule or pseudoecchymosis.⁶⁴ Enzinger, Weiss (2001) were of the opinion that capillary hemangioma during the early stage resembles a common birth mark and is seen as a flat red lesion that intensifies in color when the infant cries or strains. Acquired tufted angioma is characterized by slowly growing erythematous macules or plaques involving the dermis of the upper portions of the body. Hobnail hemangioma (targetoid hemosiderotic hemangioma) usually develops on the skin of extremities as an angiomatous or pigmented or exophytic

mass and has a distinctive biphasic appearance. Verrucous hemangioma may undergo reactive hyperkeratosis of the overlying skin and consequently confused with a wart or keratosis. Epiheloid hemangioma can be detected early as small, dull red, pruritic plaques. Crusting, excoriation, bleeding and coalescence of lesions are common secondary features.¹⁸ In (2002) Neville reported that fully developed hemangiomas are rarely present at birth, although a pale macule with thread-like telangiectasis may be noted on the skin.⁴⁸ Requena L., Kutzner H (2002) noticed that acquired elastotic hemangioma presents clinically as a solitary erythematous plaque with variable morphology and in some cases with a clearly angiomatous appearance.²⁰ Andrew. Carlson (2003) observed the targetoid hemosiderotic hemangioma and described them as solitary pigmented lesions consisting of a central small (2-3 mm), violaceous papule (bull's eyes) surrounded by an erythematous-to-ecchymotic ring or halo. Overall dimensions can vary from 1-2 cm.²² Jeffrey S Zapalac (2003) reported that hemangiomas tend to be rubbery, firm, well-circumscribed lesions. When they develop in the superficial dermis, the proliferation of cells causes the skin to become raised and bright red. In contrast, lesions in the deeper dermis or subcutaneous tissues may be less demarcated and may have a bluish hue.²⁸ Mark A Crowe (2003) observed that pyogenic granulomas are smooth firm nodules, with or without crusts and may have a bright or dusky red color. They are usually solitary, well-circumscribed, dome-shaped, 1-to mm in diameter and sessile or pedunculated. In pregnant women, pyogenic granulomas are often found on the gingival mucosa, but they have been known to appear in non-oral areas such as the fingers and inguinal crease.²⁵ Randall Wilk (2003) observed that cavernous hemangiomas present as typically soft, poorly defined tumor and readily blanch with compression, giving a characteristic "bag of worms" feel.¹³ Recently in (2004) Danielle. A. Katz stated that intramuscular hemangioma clinically presents with increased temperature in the area, discoloration of overlying skin and pain. Intramuscular hemangiomas typically are compressible and decrease in size on elevation of extremity. Larger hemangiomas may be associated with a bruit or thrill. Large intramuscular hemangiomas occasionally may be associated with significant shunting of blood flow. This is uncommon, but in rare cases may lead to murmurs and/or congestive heart failure. Synovial hemangiomas typically present as a painless mass. In synovium of a joint, they may present with recurrent effusions, pain and even mechanical symptoms, suggesting intra-articular derangement. A

palpable, spongy compressible mass may be present and it may decrease in size with elevation of extremity.⁷ Fletcher C D M (2004) observed that glomeruloid hemangioma presents with numerous angiomas. Microvenular hemangioma presents as red or bluish papules on the trunk and upper limbs of middle-aged and elderly adults. Synovial hemangiomas present as slowly growing asymptomatic or painful masses, affecting especially the knee and elbow and rarely the finger.²⁶ J. Phillip. Sapp et al (2004) stated that portwine stains are purple, diffuse macules with irregular borders that are sharply demarcated from the normal skin.⁶⁵ Marx, Stem (2004) noticed that cherry hemangioma or Campbell de Morgan spots are small superficial red papules that appear on the skin of the chest, back and extremities. Cavernous hemangiomas are large in size, diffuse and located deeper. Capillary hemangioma appears as a red-blue multinodular mass with a thin overlying skin⁶⁶

IMAGING FEATURES

BraunIF, HoffmonJC (1984) noticed that CT scans are useful in the investigations of hemangioma.⁶⁷

In (1986) Levine et al were of the opinion that MRI (magnetic resonance imaging) is superior to CT scan in the investigation of cavernous hemangioma.⁶⁸ Yih (1989) considered angiography the most definitive of the studies, although the angiograph of the intraosseous lesions is better defined than that of soft tissue lesions. On plain films or panoramic radiographs, a central hemangioma of bone usually presents as honeycomb appearance or cystic radiolucency.¹³ PaltielHJ et al (1992) found that ultrasonography with color doppler, magnetic resonance imaging or both demonstrate fast blood flow in case of hemangioma.⁶⁹

JamesLRossiter (1993) observed that computed tomography of intramuscular hemangioma shows an enhancing, well-circumscribed intramuscular mass.¹⁵ Luis . Requena (1997) suggested that computed tomography with dye injection could be used to help differentiate hemangioma from vascular malformation. A proliferating hemangioma demonstrates a well-circumscribed homogenous density, whereas a vascular malformation shows a heterogenous density, occasionally with calcifications and multilocular cystic spaces.²⁰ Yonetsu (1999) reported that contrast enhanced MRI can be used to differentiate a hemangioma from a lymphangioma of the oral cavity.¹³ Dan DeAngelis (2001) observed that ultrasonography shows a lesion with irregular contour and low to medium internal reflectivity.

Computed tomography scan reveals a poorly circumscribed mass with no bony erosion. The lesion usually enhances with intravenous contrast.²¹

HISTOPATHOLOGY

Girard D C 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.⁷⁰

Johnson W C (1976) in the histological section of cherry angiomas observed dilated and congested capillaries with lobular architecture situated in the papillary dermis.³³ In (1979) Walter, John. Brian stated that microscopically hemangiomas consist of poorly demarcated, non-encapsulated masses and vascular channels, most of which contain blood.¹¹ 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.⁷¹ 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.¹² Harry L Arnold, Jr et al (1990) observed the strawberry hemangiomas histologically and reported that these are composed of primitive endothelial cells similar to those that are found prior to the embryonic development of true venous channels. Cavernous hemangiomas histologically, present with large irregular spaces filled with blood and may be present in the lower dermis and subcutaneous tissue. These spaces are lined by a single layer of endothelial cells and fibrous wall of varying thickness.¹⁴

Lever, Walter F (1990) observed that venous hemangiomas show 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.⁶⁰ Eduardo. Calonje (1991) observed the sinusoidal hemangiomas microscopically and found that they contain dilated blood vessels filled with red blood cells; however, the striking feature is the presence of intercommunicating thin-walled blood vessels, producing a characteristic sinusoidal appearance. As a result of the dilated nature of the vascular lamina, there are frequent elongated, pseudopapillary structures covered by endothelial cells with a paucicellular or hyaline fibrous core.⁷² C L Hebeda (1993) reported that tufted angioma of late onset presents with sharply demarcated lobular proliferations of capillary vessels throughout the dermis consisting of closely packed mesenchymal cells with ovoid, monotonous nuclei. Mitotic figures are rare.¹⁶ Jayashree. Mantravadi et al (1993) reported that hemangiomas involving the parotid are composed of proliferating endothelial cells that replace the glandular parenchyma and surround involuted acini and ducts. The lobular architecture of the gland is preserved. The endothelial cells are arranged in solid zones that blend imperceptibly with vascular channels of varying sizes. Nuclear pleomorphism and atypia are absent.⁶² Enzinger, Franz. (1995) observed the capillary hemangioma histologically and found that early lesions are characterized by plump endothelial cells that line vascular spaces with small inconspicuous lumina.¹⁸ C Pesce et al (1996) noticed that intravascular lobular capillary hemangioma of the lips is microscopically composed of capillary buds and spaces arranged in a lobular fashion. The nuclei of the endothelial cells occasionally prominent with sparse mitosis. The loose connective tissue supporting the capillaries shows plump fibroblasts and sparse lymphocytes.⁷³ In the study by Luis. Requena (1997) reported that fully developed pyogenic granuloma is a polypoid lesion that shows a lobular pattern, because fibrous septa intersect the lesion. Each lobule is composed of aggregations of capillaries and venules with plump endothelial cells. Histopathologic findings in infantile hemangioma vary with the age of the lesion. Early hemangiomas are highly cellular and characterized by plump endothelial cells that line vascular spaces with small inconspicuous lumina. Cherry angiomas microscopically consist of dilated capillary blood vessels with variable thickened walls located in the papillary dermis. In fully developed lesions, there is loss of rete ridges of the epidermis, with the formation of a collarette of adrenal epithelium at the periphery. Targetoid hemosiderotic hemangioma, histopathologically presents with variations depending on the age of the lesions. In early stages, the

center of the lesion is composed of dilated, irregular, thin-walled, ecstatic, vascular spaces positioned in the papillary dermis. These vascular spaces sometimes exhibit intraluminal papillary projections and fibrin thrombi in different stages of organization. Papillations are lined by prominent plump endothelial cells. Deeper and peripheral areas of the lesion are different because they show irregular, angulated, thin-walled, slit-shaped, vascular channels that dissect between collagen bundles of the dermis. In these cases, hemosiderin deposits, extravasated erythrocytes and a mild mononuclear inflammatory infiltrate are frequent findings. Later, lesions show collapsed vascular lumina, fibrosis and presence of abundant hemosiderin. Acral arteriovenous hemangioma histopathologically, presents as a well-circumscribed proliferation of thick-walled muscle containing blood vessels, lined by a single layer of endothelial cells involving the upper and mid-reticular dermis. Intermingled with thick walled blood vessels, there are also thin-walled dilated blood vessels. The thick-walled blood vessels resemble arteries, but a well-formed elastic internal membrane is absent. Micro-venular hemangioma histologically appears as a poorly circumscribed proliferation of irregularly branched, round to oval, thin-walled blood vessels lined by a single layer of endothelial cells. They involve the entire reticular dermis and a variable degree of dermal sclerosis is present in the stroma. The lumina of the neoplastic blood vessels are inconspicuous and often collapsed with only a few erythrocytes within them. Tufted angioma, histologically, presents as multiple separated cellular lobules within the dermis and subcutaneous fat. The aggregations are most prominent in the middle and lower part of the dermis. Each lobule is composed of aggregates of endothelial cells that are concentrically whorled along a pre-existing vascular plexus. Some lobules bulge the walls of the dilated thin-walled vascular structures, giving the vessels a slit-like or semilunar appearance. This appearance in addition to the angiocentricity prompted the name "tufted angioma."²⁰ Dan. DeAngelis (2001) reported that capillary hemangiomas histologically include proliferation of a single layer of endothelial cells and pericytes. Endothelial cells of the basement membrane, characteristically have large amounts of endoplasmic reticulum.²¹ Andrew. Carlson (2001) observed that targetoid hemosiderotic hemangioma shows a biphasic vascular pattern with a wedge shaped profile. Depending on the age and size, well-formed dilated vascular spaces with protuberant endothelium are present in the superficial dermis and compressed (pseudo-

angiosarcomatous) vascular spaces are present within the deeper reticular dermis. Protruding or hobnailed endothelial cells line superficial vessels. Not uncommonly, a feeder vessel is located at the apex. The feeder vessel is a muscular vessel found in association with dilated lymphatic vascular spaces. Variable amounts of hemosiderin and extravasated red blood cells may be present between the dermal vascular channels.⁷⁴ Richard J Antaya (2002) studied the histopathology of hemangioma and reported that it varies according to the stage of hemangioma. In early proliferation, hemangiomas are characterized by non-encapsulated 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 ecstatic vessels remain. Much of the proliferating endothelial cell mass is replaced with fibrofatty tissue.⁹ Bruckner et al (2003) reported that on routine histology, proliferating hemangioma of infancy are composed of masses of plump, rapidly dividing endothelial cells with and without lumens. Multilamination of the basement membrane is also seen. As involution progresses, the vascular lumens dilate, endothelial cells flatten and fibrous tissue is deposited, giving the hemangioma a lobular architecture. Fully involuted hemangioma of infancy contains few capillary like feeding vessels and draining veins with flattened endothelium in a stroma of fibrofatty tissue, collagen and reticulin fibers. In addition to endothelial cells, hemangioma of infancy contains pericytes, fibroblasts, interstitial cells and mast cells.²⁴ Jeffrey. Zapalac (2003) stated that the proliferative phase is embodied by rapidly dividing endothelial cells forming syncytial masses, thickened, multilaminated basement membranes and elevated mast cell concentrations. Proliferating phase hemangiomas display a ten-fold increase in mast cell concentration over involuting lesions and normal tissue. These mast cells are thought to mediate cell-to-cell communication and angiogenesis. During the involuting phase, endothelial cell activity decreases, and cellular parenchyma is replaced by fibrofatty tissue.²⁸ Mark Crowe A (2003) reported that pyogenic granuloma presents with proliferation of capillaries, with prominent endothelial

cells and edematous gelatinous stroma in a characteristic lobular configuration. A dense infiltrate and granulation tissue with polymorphonuclear leukocytes may be seen. Hyperproliferation of the epidermis is usually present at the margins of the vascular growth in a collarette of epidermis.²⁵ Randall, Wilke (2003) observed that hemangiomas in proliferative phase show endothelial cell hypertrophy forming syncytial masses, thickened endothelial basement membrane, ready incorporation of tritiated thymidine in endothelial cells and Presence of large numbers of mast cells. Hemangiomas in involuting phase show less mitotic activity, little/no uptake of tritiated thymidine in endothelial cells, foci of fibrofatty infiltration and normal mast cell count.¹³ Daniel Katz (2004) observed that hemangiomas can be divided histologically into capillary (small vessels), cavernous (large vessels) and mixed types. Capillary hemangiomas have abundant vessels approximately 10-100 microns in diameter with walls 1-3 cells thick. Cavernous hemangiomas have a much higher number of cells present. Distinct lumina are still identifiable.⁷ Rosai, Ackerman (2004) reported that capillary hemangiomas microscopically present with a vaguely lobular configuration on low power examination. Masses of closely packed spindle cells are seen with neofomed spaces that contain little blood, components of pericytes and fibroblasts. Mitotic figures are usually present. Perineural involvement has also been reported²

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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 europaeus stained the endothelial cells lining the vascular spaces.⁷² Enzinger, Franz M (1995) noticed that factor VIII associated protein can be identified within cellular hemangiomas of infancy and becomes significant in the well-canalized portions of the tumor. Factor XIII-positive interstitial cells are a consistent feature of these tumors¹⁸ Luis. Requena (1997) reported that immunohistochemical studies in hemangioma demonstrate the cells that line the lumina and these cells express endothelial markers such as factor VIII-related antigen and CD34. Some of the interstitial cells show positivity for CD34 and alpha-smooth muscle actin. The cells lining the lumina are negative for these markers, whereas they stain strongly for factor VIIIa. The cells lining the of microvenular hemangioma show positivity for factor-VIII-related antigen and lectin ulex europaeus.⁴⁸ 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.⁶⁴ Dan De Angelis (2001) reported that immunohistochemical staining is positive for factor VII in hemangioma.²¹ Duff B, Weigel J A (2002) observed that the endothelium of hepatic cavernous hemangiomas demonstrates vascular but not sinusoidal differentiation based on the absence of hyaluronan receptor for endocytosis and presence of CD31 and factor VIII.⁷⁵ Dadrass SS, North. P.E (2004) noticed that infantile hemangiomas are positive for the expression of lymphatic endothelial hyaluronan receptor 1 (LYVE-7), Prox-1, CD31 and CD34.⁷⁶ In (2004) Franke FE, Steger K came to conclusion that, their study suggested a lymphatic origin for hobnail hemangiomas as CD34 showed negativity for endothelial cells and lack of actin-labelled pericytes, both characteristics of lymphatic vessels.⁷⁷ Fumi Ide, Kumi Obara (2004) reported that in spindle cell hemangiomas, spindle cell areas are focally positive for factor VIII-related antigen, CD34 and CD31 and diffusely positive for Vimentin (V9, 1:200;Dako). Lesional cells are immuno-positive for alpha-smooth muscle actin (IA4, 1: 1 000; Dako).⁷⁸

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 that affects the veins, the capillaries, or the lymphatics and they do not involute.⁷⁹

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: 1.⁷

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, b FGF, proliferating cell nuclear antigen, type IV collagenase and urokinase.¹³

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. For example, the strong gender predilection of hemangioma towards female over male infants [3: 1 or more] suggests hormonal effects in hemangiogenesis. In addition, the anatomical predilection for the head and neck of juvenile hemangiomas must be explained, perhaps most intriguing from a therapeutic standpoint in 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? ⁷ These are some of the questions that have to be addressed in the future.

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