A Closer Look at the Diagnosis and Management of Peripheral Vascular Lesions of the Oral Cavity: Report of 4 Cases with Review of Literature

Bacem AE. Ottoman

Maxillofacial Surgery and Diagnosis, Cairo University, Egypt

Abstract

Since treatment options for vascular anomalies are widely variable and often debated, it is fundamentally significant to differentiate vascular tumors from vascular malformations. On the one hand, vascular malformations are usually congenital and potentially progressive without involution. They usually expand because of hormonal changes such as trauma, puberty, aging or pregnancy. On the other hand, vascular tumors are neoplastic. Hemangiomas are interchangeably used to depict all vascular lesions. Technically, a hemangioma is an early childhood tumor that may gradually grow over a period of time typically should undergo gradual involution and mostly or totally disappear. This paper reports four exemplary cases of peripheral vascular lesions of the oral cavity; two cases whose diagnosis were recurrent low flow vascular malformation of the lower lip, a case of low flow vascular lesion of the tongue and arteriovenous malformation of the chin with history of recurrence as well as cosmetic disfigurement from incomplete excision. It contrasts the used diagnostic tools and modalities of treatment to similar cases in literature with exploring the advantages and disadvantages of sclerotherapy. Eventually, this paper suggests that excising a peripheral vascular malformation of low-flow is quite easy using nerve block anesthesia.

Keywords: Peripheral Vascular Malformations, Low-Flow Vascularity, Labial Vascular Lesions, hemangiomas, Sclerotherapy

1. Introduction

Classically, incisional biopsies are combined with numerous prerequisites including medical history, clinical examinations, imaging and laboratory investigation to establish a suspected diagnosis. Incising a section from a vascular tumor, however, is mostly a timorous intervention secondary to reported cases that were associated with surgical comorbidities. Accordingly, Imaging modalities come abreast. By consulting the medical corpora, hemangiomas collocates, the most, with vascular lesions. Moreover, the keywords of vascular lesions prove to be high-flow and low-flow. This is not advocating the haphazard usage of incisional biopsies in all vascular lesions. It is, rather, considering the collateral damage and adverse effect on the average reader; that is to say, neither all vascular lesions nor their surgical interventions are fatal. Vascular lesions include true tumors and malformations. Even within the scope of vascular malformations, they develop a wide range of anomalies including high-flow malformations (e.g. Arteriovenous fistula and arteriovenous malformations) as approved by the international Society for the Study of Vascular Anomalies (ISSVA) at the 20th ISSVA Workshop in April 2014. This paper will try to fathom the nature of the peripheral vascular malformation of the oral cavity by revisiting the literature and reporting exemplary cases [1]. Surgery, Nd:YAG laser therapy, and sclerotherapy are available options for treating vascular malformations. The treatment of choice is determined according to the hemodynamics, size, site of the lesion and its correlation to other vital structures [2].

2. Materials and Methods

Besides reviewing the literature, 4 exemplary cases of peripheral vascular lesions were consented and studied clinically, histologically and radiologically. For the radiographic examination, sonographic study was the first choice. MRI was recruited in an extensive lesion. From the block of the represented case, serial sections from formalin-fixed, paraffin-embedded specimen block of 4 μm thickness were deparaffinized in xylene and rehydrated in decreasing concentrations of ethanol. Endogenous peroxidase activity was blocked by immersing the sections in 3% H₂O₂ with methanol for 30 min. For antigen retrieval, sections were boiled in 10 mmol/L citrate buffer (pH 6.0) for 15 minutes in a pressure cooker. After treatment with protein block serum at room temperature, sections were covered with primary antibodies; GLUT-1. Immunoreaction was performed using the labeled
streptavidin-biotin method and overnight incubation. For all antibodies, negativity or positivity was evaluated.

3. Clinical Presentation

Case 1

A 10-years-old male visited our department of maxillofacial surgery and diagnosis, Cairo, Egypt with a unilateral slowly growing blue swelling of lower lip and labial mucosa (figure 1). The exophytic lesion was lobulated. Aspiration produced scanty bluish blood. The sonographic study with Doppler interrogation revealed low-flow vascular lesion. The feeding vessel was piercing it centrally. The guardian mother reported a recurrence after injecting a sclerosing agent 3 years ago. Laboratory results showed normal CBC, ESR and bleeding profile. Transthoracic echocardiogram was also normal. After signing a written consent, the patient was scheduled for surgical excision under local anesthesia (inferior alveolar nerve block using 2% lidocaine ®). A horizontal incision was made in the vestibular mucosa where dissection was accessed. Feeding vessels were ligated before cutting off the vascular lesion to be submitted for microscopic examination.

The histological study revealed a large, dilated vascular space, vein, with a central thrombus (figure 2). The immunohistochemical test for GLUT1 was negative. The diagnosis of venous malformation was, then, established.

Figure 1. Clinical pictures showing the peripheral vascular malformation before (right) and after excision (left).

Figure 2. A photomicrograph of H&E stained histologic sections, Original magnification (x 10). It shows a large, dilated vascular space, vein, with a central thrombus.
Case 2

A 23-years-old female visited our department of maxillofacial surgery and diagnosis with a unilateral gradually growing swelling of lower lip and labial mucosa (figure 3). The exophytic lesion was blue and smooth with no lobulation. Aspiration produced scanty bluish blood. The patient was seeking a better cosmetic look and erotic gain. The sonographic study with Doppler interrogation revealed low-flow vascular lesion. The feeding vessel was piercing it centrally and peripherally along the commissure of the mouth. Laboratory results showed normal CBC, ESR and bleeding profile. Transthoracic echocardiogram showed some rheumatic affection of the mitral valve with no influence on the cardiac output. After signing a written consent, the patient was scheduled for surgical excision under local anesthesia (inferior alveolar nerve block using 2% lidocaine ®). A horizontal incision is made in the vestibular mucosa where dissection was accessed. Feeding vessels were ligated before cutting off the vascular lesion to be submitted for microscopic examination. The histological study demonstrated dilated vascular spaces and a main infiltrating thrombus. The section revealed neither endothelial proliferation nor encapsulation. The immunohistochemical expression of GLUT1 was negative. The diagnosis of venous malformation was, consequently, established.

Figure 3. Clinical pictures showing the peripheral vascular malformation before (right) and after excision (left).

Figure 4. A photomicrograph of H&E stained histologic sections. Original magnification (x 10) shows dilated vascular spaces and a main infiltrating thrombus. The section reveals neither endothelial proliferation nor encapsulation.
4. Results

All lesions stained negatively with GLUT-1. Sonographically, all cases were low-flow except for case 3. Table 1 summarizes the results of each case.

In the medical literature as well as these reported cases, excised lesions whose vascularity were sonographically low-flow reported no excessive hemorrhage in the surgical scene.

Case 3

A 17-years-old female visited our department of maxillofacial surgery and diagnosis with a gradually growing swelling embracing the lower anterior teeth and infiltrating the chin. The lesion bleeds easily and causes intermittent pain. The related teeth are slightly loose. Aspiration, from the labial vestibular mucosa, produced strawberry blood (figure 5).

The patient reported recurrence three times after injecting a sclerosing agent and two surgeries. The sonographic study with Doppler interrogation revealed high-flow vascular lesion with arteriovenous shunt. The MRI (with contrast) confirmed the sonographic results (figure 6). The patient refused any surgical interventions and postponed, all of the sudden, all treatment strategies. The immunohistochemical expression of GLUT1 was negative. The diagnosis of arteriovenous malformation was, therefore, established.

Case 4

A 56-years-old female visited our department of maxillofacial surgery and diagnosis with a recurrent gradually growing swelling of the anterior tongue that first appeared in 2008. A sclerosing agent was injected in 2011 and recurred after 11 months. The lesion bleeds easily but causes no pain. Aspiration produced scanty blood. The sonographic study with Doppler interrogation displayed low-flow vascular lesion with no arteriovenous communication. The patient refused any surgical interventions because she has a surgery phobia. The follow-up of the patient showed inconspicuous growth in 37 months.
The lesion may be completely asymptomatic. Some are considerably more common in females than detected most often in patients between 10 and 20 years of age. They are present from birth, they may not become noticeable until later in childhood or adulthood. In the jaws, intrabony vascular malformations are result from persistent direct arterial and venous communication. Although they are connected vasculature. These lesions do not regress and continue to expand with time infiltrating neighboring tissues, spurring therapeutic interventions.

Controversially, vascular lesions have posed a great tergiversation for years, especially on the levels of pathophysiology, classification, diagnostics and treatment options. Toward resolving the nosologic confusion, Mulliken and Glowacki have proposed a classification in 1982 based on endothelial characteristics; thence, vascular malformations were categorized, according to their vascular channel components, into capillary, venous, lymphatic, arterial, and combined.

Genetically, these anomalies are caused by germline or somatic mutations in the TIE2 gene, which is involved in signaling between the endothelial and the mesenchymal cells during vasculogenesis and angiogenesis. Vascular malformations represent a heterogenous cluster of blood vessel disorders that are characterized by inappropriately connected vasculature. These lesions do not regress and continue to expand with time infiltrating neighboring tissues, thereby requiring prompt treatment.

Venous malformations (VM) are present clinically at birth and tend to grow steadily in proportion to the somatic growth. They may expand secondary to sepsis, trauma, or hormonal changes with no response to corticosteroids or antiangiogenic agents. VMs may occur anywhere in the body; however, they retain normal endothelial cell turnover. Vascular malformations of the head and neck can cause cosmetic and functional disturbances requiring prompt treatment. As the patient gets older, the lesion often darkens and becomes nodular because of vascular ectasia. Low-flow venous malformations encompass a wide spectrum of lesions from small isolated ectasias to complex growths that involve multiple tissues and organs. Phlebolith formation can occur.

Table 1. Findings and results of the four reported cases.

| Case  | Age | Gender | Site              | Duration | US findings | Treatment                     |
|-------|-----|--------|-------------------|----------|-------------|-------------------------------|
| Case 1| 10  | Male   | Left Mouth angle  | 3-5 years| Low-flow    | sclerosing agent/excision     |
| Case 2| 23  | Female | Left Mouth angle  | 7-10 years| Low-flow    | excision                      |
| Case 3| 17  | Female | Labial mucosa     | 3-5 years| High-flow   | sclerosing agent/ incomplete excisions |
| Case 4| 56  | Female | Tongue            | 3-5 years| Low-flow    | sclerosing agent/ Nil         |

Vascular malformations appear, in 80% of cases, as hypoechoic or heterogeneous and compressible lesions. However, even on ultrasound, differentiation between venous and lymphatic malformations can be difficult. MRI is the mainstay for radiographic evaluation of deep vascular lesions of the head and neck and can aid in the differentiation of vascular tumor from vascular malformation. “Ultrasound and Doppler interrogation” scanning is the first choice for noninvasive evaluation of patients with vascular malformations, doppler mode to assess flow characteristics. Minimally invasive tests such as MRI and MRV are useful to confirm the extent and type of venous malformations, delineates feeding and draining vessels, distinguishes between different soft tissues (muscle, fat) and the vascular structures.

Arteriovenous malformations are high-flow lesions that result from persistent direct arterial and venous communication. Although they are present from birth, they may not become noticeable until later in childhood or adulthood. In the jaws, intrabony vascular malformations are detected most often in patients between 10 and 20 years of age. They are considerably more common in females than males and occur twice as often in the mandible as the maxilla. The lesion may be completely asymptomatic. Some examples are, however, associated with pain and swelling. Mobility of teeth or bleeding from the gingival sulcus may occur.

Histologically, venous malformations may be ectatic or microvenular. The degree of ectasia increases with advancing age at a variable rate. Calcification and formation of phleboliths occur through dystrophic calcification of organizing thrombi, as a result of stasis in these low-flow lesions. Arteriovenous malformations are characterized by enlarged venous channels lined by a single flattened layer of endothelial cells surrounded by sparse, irregularly distributed smooth muscle cells.

The commonly affected sites include the cheek, neck, eyelids, lips, tongue, soft palate, parapharyngeal space, and floor of the mouth. Diascopy, blanching of the lesion on compression, can be used to separate these lesions from hemorrhagic lesions in soft tissue where the blood is extravascular and cannot be displaced by pressure. Venous malformations also have the rare condition termed blue rubber bleb nevus syndrome (Bean’s syndrome), in which multiple small and large cavernous hemangiomas are present on the skin and throughout the gastrointestinal tract, including the mouth.

According to the imaging features of the draining veins, venous malformation is divided into four types. Type I, isolated malformation without venous drainage; Type II, malformation with drainage into normal veins; Type III, malformation with drainage into dilated veins; and Type IV, dysplastic venous ectasia. This proposed classification scheme is helpful for selection of sclerosing agents in sclerotherapy.

Ultrasound of vascular malformations depends upon the type of lesion. Some exhibit small cystic spaces with minimal or no flow (microcystic lymphatic malformations). Others exhibit high flow through enlarged, ectatic vascular channels (arteriovenous malformations). Venous malformations appear, in 80% of cases, as hypoechoic or heterogeneous and compressible lesions. However, even on experienced radiological hands, differentiation between venous and lymphatic malformations can be difficult. MRI is the mainstay for radiographic evaluation of deep vascular lesions of the head and neck and can aid in the differentiation of vascular tumor from vascular malformation. “Ultrasound and Doppler interrogation” scanning is the first choice for noninvasive evaluation of patients with vascular malformations, doppler mode to assess flow characteristics. Minimally invasive tests such as MRI and MRV are useful to confirm the extent and type of venous malformations, delineates feeding and draining vessels, distinguishes between different soft tissues (muscle, fat) and the vascular structures.
Immunohistochemically, a family of glucose transporter isoforms (GLUT), which is currently composed of 13 members, facilitates the entry of glucose into cells. GLUT-1, a member of this family, is a basic high-affinity glucose transporter normally expressed in erythrocytes, endothelial cells, the perineurium of peripheral nerves, germinal centers of reactive lymph nodes, renal tubules, and placenta. An increased GLUT-1 expression has also proved to be associated with endothelial tumors especially infantile hemangioma. Vascular immunostains such as D2-40, PROX1, and vascular endothelial growth factor receptor 3, which distinguish lymphatics from arteries and veins, have been of immense help in daily practice.

Sclerotherapy has been used extensively for treatment of VM. The sclerosants most commonly used include ethanol and sotradecol. Complications of sclerotherapy include skin and mucosal injury, swelling leading to airway compromise, infection, and nerve injury. In addition, each sclerosant has its own risk profile.

Sclerotherapy, the mainstay of treatment is the injection of an agent to induce inflammation and obliteration of affected veins. For small cutaneous or mucosal lesions, local injection may be effective. Intralesional sclerotherapy, using liquid sclerosing agents, produces good outcomes in smaller lesions. Sclerosants may be detergents, osmotic agents, or chemical irritants with minor complications. Such complications typically include the presence of small skin ulcers and superficial skin breakdown which responded well to the application of silver sulfadiazine. Intralesional sclerotherapy has promoted a considerable success when the sclerosing agent was selected and injected cautiously. Adjuncts include selective arterial embolization and sclerosant therapy. Laser therapy is another accepted form of primary treatment of selected vascular lesions. Because the margins of these lesions are often ill-defined, total elimination may not be reachable.

Venous malformations are associated with spontaneous thrombosis and thrombolysis as well as elevated D-dimer levels (> 0.5μg/ml) in 42% of patients—a novel diagnostic tool that might help confirm the diagnosis early.

6. Conclusions
The management of peripheral vascular lesions is not surgically contraindicated. Surgical excision of small vascular lesion of low-flow is POSSIBLE under local anesthesia. The sonographic examination with Doppler interrogation is, however, very mandatory.

REFERENCES
[1] Dasgupta, R, and Fishman S. "ISSVA classification." In Seminars in pediatric surgery, 2014; 23(4),158-61. WB Saunders. DOI: 10.1053/j.sempedsurg.2014.06.016
[2] Glade R, Richter G, James C, Suen J, Buckmiller L. Diagnosis and management of pediatric cervicofacial venous malformations: retrospective review from a vascular anomalies center. Laryngoscope. 2010;120(2):229–35.
[3] Mulliken J B, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg. 1982;69(3):412–422.
[4] Vikkula M, Boon L M, Mulliken J B. Molecular genetics of vascular malformations. Matrix Biol. 2001;20(5–6):327–335.
[5] Boon L, Mulliken J, Enjolras O, Vikkula M. Glomuvenous malformation (glomangioma) and venous malformation: distinct clinicopathologic and genetic entities. Arch Dermatol. 2004 Aug;140(8):971–6.
[6] Richter T, Gresham A. Hemangiomas and Vascular Malformations: Current Theory and Management. Int J Pediatr. 2012; 2012: 645678. doi: 10.1155/2012/645678
[7] Chava V, Shankar A, et al. Multiple Venous Malformations with Phleboliths: Radiological-Pathological Correlation J Clin Imaging Sci. 2013; 3(1): 13. doi: 10.4103/2156-7514.
[8] Neville B, Damm D, Allen C, Bouquot J. Oral and maxillofacial pathology. St. Louis: Saunders/Elsevier; 3rd edition 2009. : 540–44.
[9] Dompmartin A, Vikkula M, Boon L. Venous Malformation: update on etiopathogenesis, diagnosis & management Phlebology. 2010; 25(5): 224–235., doi: 10.1258/phleb.2009.009041
[10] Regezi J, Scibbba J, Jordan R. Oral Pathology. Clinical Pathologic Correlations, Saunders, Philadelphia, Pa, USA, 5th edition, 2007: 114-7.
[11] Puig S, Casati B, Staunenherz A, Paya K. Vascular low-flow malformations in children: current concepts for classification, diagnosis and therapy. Eur J Radiol 2005; 53: 35-45.
[12] Trop I, Dubois J, Guibaud L, et al. Soft-tissue venous malformations in pediatric and young adult patients: diagnosis with Doppler US. Radiology. 1999;212(3):841–845.
[13] Macheda M, Rogers S, Best J. Molecular and cellular regulation of glucose transporter (GLUT) proteins in cancer. J Cell Physiol. 2005;202(3):654–62.
[14] Cornford E, Hyman S, Swartz B. The human brain GLUT1 glucose transporter: ultrastructural localization to the blood-brain barrier endothelia. J Cereb Blood Flow Metab. 1994;14(1):106–12.
[15] Kayano T, Burant CF, Fumamoto H, et al. Human facilitative glucose transporters. Isolation, functional characterization, and gene localization of cDNAs encoding an isofrom (GLUT5) expressed in small intestine, kidney, muscle, and adipose tissue and an unusual glucose transporter pseudogene-like sequence (GLUT6) J Biol Chem. 1990;265(22):13276–82.
[16] North P, Waner M, Mizeracki A, Mihm J. GLUT1: A newly discovered immunohistochemical marker for juvenile hemangiomas Human Patholo, 2000; 31(1):11-22.
[17] Gupta A, Kozakewich H. Histopathology of vascular anomalies. Clin Plast Surg. 2011 Jan;38(1):31-44. doi: 10.1016/j.cps.2010.08.007.
[18] Berenguer B, Burrows PE, Zurakowski D, Mulliken JB. Sclerotherapy of craniofacial venous malformations: complications and results. Plastic and Reconstructive Surgery. 1999;104(1):1–11.

[19] Wang YA, Zheng JW, Zhu HG, Ye WM, He Y, Zhang ZY. Sclerotherapy of voluminous venous malformation in head and neck with absolute ethanol under digital subtraction angiography guidance. Phlebology. 2010;25(3):138–44.