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Current Trends in Management of Arteriovenous Malformations of the Maxillofacial Region: A Review Article

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Abstract

Arteriovenous malformations (AVMs) are congenital high- flow vascular malformations that lack the normal capillary beds shunting blood from the arterial system to the venous system. They are often misdiagnosed at birth as other vascular lesions because of the delay in presentation of the characteristic signs of the malformations. Puberty and trauma trigger the growth of the lesion and manifestation of its troublesome symptoms. They are infiltrative causing destruction of local tissue and often life-threatening secondary to massive bleeding. Extracranial AVMs are different from their intracranial counterpart and are found in several areas in the cervicofacial region. This article highlights the pathogensis, classification of arteriovenous malformations with an emphasis on the updates in diagnostic and treatment modalities.

Introduction

Vascular anomalies are a group of lesions derived from blood vessels and lymphatic with widely varying histology and clinical behavior. They constitute the most common congenital abnormalities in infants and children. James Wardrop, a London surgeon, first recognized the differences between true hemangiomas and the less common vascular malformations in 1818. Despite Dr. Wardrop's work, descriptive identifiers such as strawberry hemangioma and salmon patch continued to be used until the 1980s. This terminology, in fact, did not correlate with either the biological behavior or the histological patterns of these lesions. In 1982, Mulliken and Glowacki [1] greatly advanced the field by introducing a biological classification which differentiated vascular lesions into two distinct entities: hemangiomas and vascular malformations.Arterivenous malformations, either intracranial or extracranial, were referred to by Mulliken and Glowacki as a subdivision of the vascular malformations group.

Arteriovenous malformations are caused by an abnormal connection between an artery and a vein, in which, the first portion of the distal vein is known as the nidus [2]. Although, arteriovenous malformations are relatively rare, they represented a challenge to the surgeons not only in relation to early detection and proper diagnosis, but also in available management options as improper treatment may be accompanied by high morbidity and poor outcomes. Therefore, and due to their complexity, a multidisciplinary approach is frequently necessary in managing these lesions and includes a team of specialists [3,4]. Around half of all extracranialarteriovenous malformations affect the head and neck [5] and a slight female predominance (1:1.5) has been reported [6]. Thus, the current article reviews the updates on recent developments in the diagnosis, management, and pathogenesis of arteriovenous malformations affecting the maxillofacial region.

Classification of vascular anomalies

Vascular anomalies are congenital lesions of abnormal vascular development. Previously referred to as vascular birth- marks, vascular anomalies are now classified based on a system developed by Mulliken and Glowacki that considers histology, biological behavior, and clinical presentation of these entities [1]. A primary distinction is made between a vascular tumor, which grows by cellular hyperplasia, and a vascular malformation, which represents a localized defect in vascular morphogenesis. Due to the differences in biologic and radiographic behavior, malformations are further divided into slow-flow and fast-flow lesions [6] (Table 1).

Both vascular tumors and malformations may occur anywhere on the body. In brief, hemangiomas are vascular tumors that are rarely apparent at birth, grow rapidly during the first six months of life, involute with time and do not necessarily infiltrate but can sometimes be destructive. Vascular malformations are irregular vascular networks defined by their particular blood vessel type. In contrast to hemangiomas, they are present at birth, slow growing, infiltrative, and destructive. Almost all vascular malformations and nearly 40% of hemangiomaseventually require intervention [6,7].

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Vascular tumors	Vascular malformations
Infantile hemangioma	Slow-flow Capillary malformations
Congenital hemangioma	Venous malformations Lymphatic malformations
Tufted angioma	
Kaposiform	
Hemangioendothelioma	Fast-flow Arteriovenous malformations

Table 1: Classification of vascular anomalies [1]

Arteriovenous Malformations

Pathogenesis

Despite the fact that the origin and pathogenesis of arterivenous malformations (AVMs) still blurred. A defect in vascular stabilization is thought to cause AVM, but it remains unclear whether these lesions are primarily congenital in origin. Most AVM, are present at birth, but there are several case reports of these lesions presenting after trauma in adults. Defects in TGF-beta signaling and a genetic two-hit hypothesis are the prevailing theories to the pathogenesis [8,9]. Progesterone receptors have been isolated in AVMs explaining their expansion during puberty [10]. Although arteriovenous malformations are congenital, they commonly remain dormant during childhood and increase in size during adolescence and adulthood [11]. About 80% are detected during childhood and all will ultimately progress [11,12]. Spontaneous regression is almost never seen [10]. The exact aetiological and pathological factors involved in their development remain uncertain, although they are thought to result from an error in vascular development during embryogenesis [11]. Hormonal changes during puberty and pregnancy, together with injury, have been suggested as potential triggers that stimulate expansion [6,11-13]. However, Liu et al. [14] did not find progression in pregnant mothers with quiescent lesions.

At the cellular level, lesions do not show the abnormal growth of endothelial cells seen in vascular tumors, and angiogenesis and vasculogenesis are thought to account for their expansion. Increased blood flow can cause collateralization, dilatation of existing vessels and thickening of adjacent vesselsand increased pressure is thought to stimulate cellular hypertrophy [6,11].Increased levels of matrix metalloproteinase (MMP) have also been found in the tissue and the urine of patients with active lesions and a similar possible role has been suggested [15,16]. However, despite ongoing recognition and understanding of the genetic mutations that result during the development and progression of lesions, the identification of precise therapeutic targets seems daunting. Research into cerebral lesions has shown that over 860 different genes are up-regulated or down-regulated in them [17].

Classification

Historically, lesions have been described as focal or diffuse. Focal lesions have a single artery and well-defined nidus. Diffuse lesions have multiple feeding vessels, they cross and usually destroy tissue boundaries and are more difficult to treat successfully without recurrence [18].

Several methods of clinical and radiological classification have been advocated, including a classification by Houdart et al, [19]which was introduced in 1993 based on the number of arterial and venous communications and niduses.This classification was further modified by Cho et al. [20] in 2006 with a highlighting on the potential outcome (Table 2).

The International Society for the Study of Vascular Anomalies (ISSVA) introduced an updated classification in 2018 to clarify the ambiguous nomenclature that frequently causes miscommunication and confusion among clinicians [21].

Anatomically, five types of extracranialarterivenous malformations were reported, mucous/cutaneous (type I), submucosal/subcutaneous (type II), glandular (type III), intraosseous (type IV) and deep visceral (type V). Subsequently, various treatment modalities were suggested based on the anatomical location of the lesion [22].

Clinical features

During childhood, often termed the quiescent or dormant phase, lesions can present as small vascular stains, and they become increasingly pulsatile and overgrown with soft tissue as they progress [14]. Many of the clinical features at this time are attributable to the chronic haemodynamic effects of hyper vascularity and venous hypertension. Typical manifestations include pain, tissue expansion and destruction, ulceration, disfigurement, and bleeding. They are also warm and often pulsatile. The presence of a thrill also supports clinical differentiation from other vascular malformations. The severity of these features varies, and often reflects the size and the level of activity within a lesion. They are staged using the Schobinger clinical staging system, which assesses progression and highlights the need for intervention [23] (Table 3).

The natural and most common course of arteriovenous malformation is early quiescence, late expansion, and ultimately infiltration and destruction of local soft tissue and bone. Common sites for occurence are the midface, oral cavity, and limbs. Oral lesions can present early due to gingival involvement, disruption of deciduous teeth, and profuse periodontal bleeding [6].

Arteriovenous malformations (AVMs) of the jaws are relatively rare, with fewer than 200 cases reported in the literature. Their real importance lies in their potential to result in exsanguination, which usually follows an unrelated treatment, such as tooth extraction, surgical intervention, puncture wound or blunt injury in involved areas, with the dentist unaware of the existence of the AVM [24].

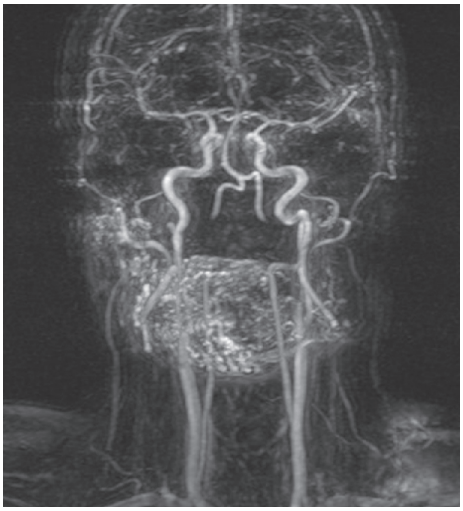

Figure 1: Magnetic resonance angiogram of an arteriovenous malformation of the lower lip and chin showing extensive vascular supply [31]

Imaging and diagnosis

Diagnosis is often made after clinical examination and recognition of the hallmark features of erythema, warmth, pulsatility, and thrill. Imaging is essential in identifying the extent of arteriovenous malformation (AVM). Magnetic Resonance imaging (MRI) may be useful, but Magnetic Resonance Angiography (MRA) and Computed Tomography Angiography (CTA) can give a superior outline of these lesions [25]. Numerous arterial flow voids are the hallmark of AVM by MRA (Figure 1). On the other hand, Computed tomography angiography (CTA) allows evaluation of surrounding tissues and

Figure 2: Three-dimensional computed tomographic angiography showing an AVM of the right lip and cheek [32]

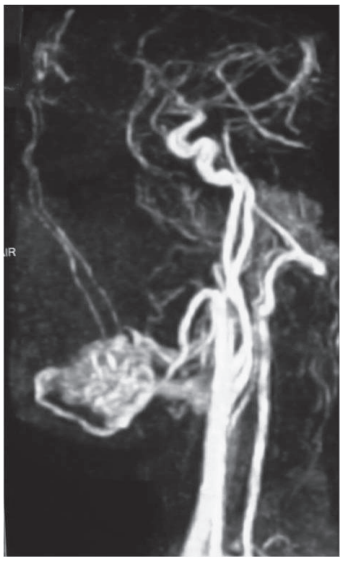

Figure 3: Digital subtraction angiography of submandibular hi-flow AVM [22]

bones (Figure 2). Individual arterial feeders can be visualized with this imaging as well [26].

Ultrasound, magnetic resonance imaging (MRI), and angiography are used to investigate the morphology and to plan treatment. Lesions have multiple vascular channels on ultrasonography, and Doppler studies show high flow and loss of normal venous damping [27].Their size, shape, and association with neighboring tissue show well on MRI and MRA. Angiography, usually digital subtraction angiography (DSA) is always required to identify the detailed vascular anatomy (Figure 3). Angiography typically shows dilated and tortuous feeding arteries, arteriovenous shunts, and greatly dilated draining veins with a good definition of central nidus of affected vessels which provide access for intravascular treatment when necessary [28].

The angioarchitectural features of an arteriovenous malformation provide key information regarding natural history and treatment planning. Because of rapid filling and vascular overlap, two-dimensional (2D) and three-dimensional (3D) digital subtraction angiography (DSA) are often suboptimal for evaluation of these features. A feasibility study by Sandoval-Garcia et al., [29] in 2016 developed an algorithm that derives a series of fully time-resolved four-dimensional volumes (4DDSA) at up to 30 frames/s from a conventional 3D DSA. They assumed that the temporal/spatial

Type	Description
I	No more than 3 arterioles shunting to the initial part of venous component
II	Multiple arterioles shunt to the initial part of venous component, with arterioles showing a plexiformappearance
IIIa	Multiple shunts between arterioles and multiple non-dilated venules
IIIb	Multiple shunts between arterioles and multiple dilated venules

Table 2: Cho et al. modification of the Houdart et al. [19] classification of arteriovenous malformations [20]

Stage	Description
1	Quiescent (stable)
2	Increasing in size
3	Symptomatic: pain, bleeding, disfigurement, disruption of function
4	Decompensating: high-output cardiac failure

Table 3: Schobinger clinical staging of high-flow arteriovenous malformations [23]

resolution of 4D reconstructions is significantly higher than that provided by current MR angiography and CT angiography techniques. 4D reconstruction allows viewing of an AVM from any angle at any time during itsopacification (Figure 4). Because of the limited number of cases included in this study (six cases), further experience is required to determine the ultimate utility of this technique.

Treatment

Treatment is challenging, and an interdisciplinary approach and extensive clinical experience are recommended.It aims to control shunting and to palliate the clinical manifestations. When available, endovascular approaches are currently considered the first line of treatment, and are often combined with resection of focal lesions or those with a well localized nidus. Unfortunately, diffuse lesions are less easy to treat, and multiple staged procedures are often done to prevent excessive damage to local tissue and to contain recurrent disease early. In many cases, treatment is not curative, and it aims to palliate by down-grading the lesion and decreasing the risk of potentially life-threatening complications and further disfigurement. Given the side effects and potential problems of treatment, intervention is often reserved for progressive lesions of Schobinger stage 2 and above. Taking into consideration that the fundamental principle in the treatment of all arteriovenous malformations is complete removal [13].

Although the effective surgical management of high flow lesions without preoperative embolisation has been described, for instant, Nair et al., [22] reported the use of external carotid control combined with surgical resection in a series of 115 patients with arteriovenous malformations despite their accepted success rate the technique did not gain popularity among the clinicians. Instead,resection after embolisation has become the most accepted treatment. Preoperative embolisation can help delineate the extent of a lesion and dramatically reduce intraoperative bleeding, and multiple embolisations before operation have been found to lessen the risk of recurrence [30].

Embolisation

Traditionally, this treatment modality has aimed to obstruct all arterial feeders but it results in early revascularisation, and inevitably in a more complex vascular supply. When resection is impossible, this approach can make subsequent embolisation more challenging because more niduses form, and the vascular structure becomes more complex. It is now known that the lesion is better controlled when the nidus is obliterated, and efforts are now being directed at

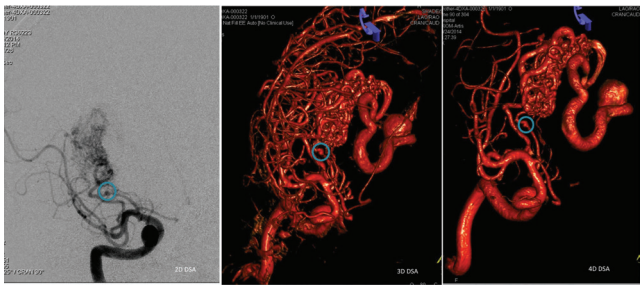

Figure 4: Figure 1 Flow-related feeding artery aneurysm

The left panel shows a two-dimensional digital subtraction angiography (2D DSA) image, the middle panel shows a three-dimensional DSA image, and the right panel shows an early time frame of a four-dimensional (4D DSA) image. A very small aneurysm is clearly visible inside the blue circle, which is more clearly visualized in the 4D DSA image with elimination of vascular overlap [29]

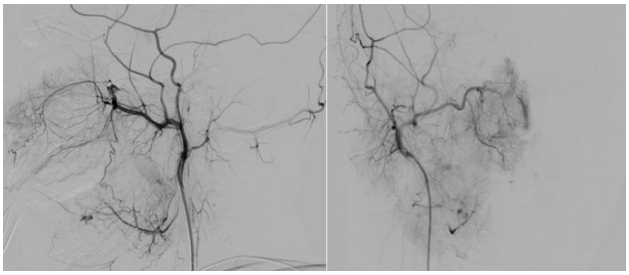

Figure 5: Post embolization angiogram showing marked decrease flow of a mandibular arteriovenous malformation and increased venous stagnation [33]

embolic materials that can safely obstruct it [31].

The technique for selective intra-arterial embolization have been described by Zhao et al., [32] they used the Seldingercatheterisation technique for digital selective angiography through the femoral artery. The catheter was passed into the common carotid artery, and angiographs of the external and internal carotid arteries were taken to show the arteriovenous malformations (AVMs) in thirteen cases within the maxillofacial region. The origin of each feeding artery (facial, superior temporal, and lingual arteries) was embolised individually. The angiogram after embolisation showed obviously reduced blood flow, (Figure 5) and the colour of the skin over the AVM was clinically normal. The soft tissue pulsation decreased. The catheter was removed after embolisation, and the puncture site compressed with a bandage. Typically, surgical excision was performed 24-48 hours following the embolization [31,32].

Embolisation material: The ideal anabolic agent, which should be safe and allow controlled deployment, would fully penetrate the nidus and draining veins and give a permanent occlusion. Historically, coils, plugs, and liquids were used, but newer semi-liquid, chemical, embolic agents are now available. Modern agents consist of non-adherent copolymers dissolved in a solvent that gives greater flow. Additions such as tantalum (Onyx®, ev3 Endovascular Inc, Covidien, Plymouth, USA) and iodine (PHIL™, MicroVention Europe SARL, Saint- Germainen-Laye, France) giveradiopacity, which allows real time, controlled delivery of fluoroscopic images [31,33].

Onyx® is a liquid embolic agent that is dissolved in dimethyl sulphoxide (DMSO) and opacified by tantalum powder. It became popular as a neurovascular embolic agent, and has recently been used in peripheral lesions. On contact with blood, the DMSO diffuses out of the mixture and leaves the ethyl vinyl alcohol to polymerise. Polymerisation first occurs peripherally within the mixture, and over a few minutes gradually hardens towards the center of the plug.This extends the working time and allows more time for the injection. Once hardened, Onyx® leaves a rigid cast that plugs the nidus permanently, and gives a characteristic appearance on future imaging. However, its use is not without complications. DMSO is an irritant that can cause serious local and perivascular inflammation that can potentially damage otherwise healthy tissue, and the black tantalum powder can stain the adjacent skin. Coloration can help to define the extent of embolization at resection of a lesion obliterated with Onyx®, and characteristic sparking occurs upon contact with diathermy. As with any embolic agent, misplacement can lead to hypoxia, and can damage otherwise normal structures, and result in blindness or stroke [33].

PHIL™ (precipitating hydrophobic injectable liquid) is a new embolic agent that is being used in the endovascular management of cerebral neurovascular diseases. Three concentrations are available, with various viscosities and different flow characteristics that lead to deeper penetration of the nidus. As the material looks white on clinical inspection, the risk of staining is minimalized. The benefits of PHIL™ are now being recognized in the management of extracranial arteriovenous malformations, with successful endovascular embolisation and subsequent resection. Like Onyx®, PHIL™ also uses the solvent DMSO, and therefore has the same risk of perivascular inflammation and tissue damage, but it also has the less dangerous side-effect of a garlic-like odour from the breath and skin of patients. Patients may also report a garlic-like taste [31,32].

Sclerotherapy

Combined selective embolization and percutaneous sclerotherapy was also suggested as a line of treatment for arteriovenous malformation of the cervicofacial area [32]. It includes an injection of fibrin glue (Guangzhou Bioseal Co., Ltd., Guangzhou, China) combined with OK- 432 (streptococcal pyrogenic exotoxin A; Shandong Lukuang Pharmaceutical Group, Luya Co., Ltd., Jinan, China) and bleomycin (Nipponkayaku Co., Ltd., Tokyo, Japan). Patients were given an injection of the percutaneous sclerosant using the fibrin glue 20 ml combined with OK- 432, 5 mg and bleomycin 30 mg in a single procedure. The injections, which were given every 5-6 weeks, were repeated three to five times and given under general anaesthesia in hospital. Within a follow up period of 27 months, none of the patients developed a recurrence, or presented with haematological toxic effects or signs of pulmonary involvement such as pulmonary fibrosis or pulmonary embolism. Based on analysis of blood chemistry, all patients had normal liver and kidney function [32].

Laser photocoagulation

Laser therapy was also advocated for management of areteriovenous malformations of the extremities, but its application was limited to superficial lesions with stage I in Schobinger classification. A Multiplex laser system was mainly used because a more superficial laser, such as a pulsed dye laser, and insufficient doses would not treat the deepest part of the lesion and might, in fact, trigger progression of the malformation [34]. Nd: YAG laser alone can be effective, as Bekhorand Ditchfield [35] have shown, but high flounces are required for optimal results and these may increase the risk of complications.

Pharmacological agents

Recently pharmacological approaches and antiangiogenic drugs have been targeted as potential treatments. Marimastat is an antiangiogenicmatrix metalloproteinase (MMP) inhibitor, initially developed for the treatment of metastatic breast cancer,but trials were abandoned because of poor outcomes [36]. However, it has been used successfully in the management of a progressive lesion in the limb of a child [37].To my knowledge, no other clinical use has been described.

The treatment of hereditary haemorrhagic telangiectasia is progressing [38]. Patients with this autosomal dominant condition develop multiple telangiectases and arteriovenous malformations of the solid organs through disregulated angiogenesis. Bevacizumab, a humanized anti-Vascular Endothelial Growth Factor (anti-VEGF) antibody, has shown promising results in early clinical trials to control nosebleedsand arteriovenous malformations of the liver [39]. Side effects include hypertension, severe proteinuria, decreased wound healing, and gastrointestinal bleeding [40], and its effect on cutaneous and cerebral lesions is as yet unknown. Thalidomide, together with its second generation successor lenalidomide, has antiangiogenic properties as well as immunomodulatory effects. Both have been shown anecdotally to control bleeding from gastrointestinal lesions,although their role in cutaneous lesions has not been reported [41,42].

Radiosurgery

Radiosurgery refers to single high dose localised irradiation, given using either a gamma unit (gamma knife, multiheaded cobalt unit) or a linear accelerator (linac radiosurgery, X-knife radiosurgery). It aims to destroy blood vessels of the AVM nidus, while avoiding injury to normal brain and this is achieved by focusing radiation onto the lesion. The effectiveness of radiosurgery is generally measured in terms of disappearance of abnormal blood vessels on angiography [43]. Kurita *et al. [44]* in 2000 advocated radiosurgery as a "viable" treatment modality for brainstem AVMs which is "safe and effective" for small lesions.

Radiosurgery is used with increasing frequency, not only for the treatment of cerebral arteriovenous malformations (AVMs), but also for the treatment of other well-defined lesions including acoustic neuromas, meningiomas, pituitary adenomas as well as solitary metastases [45]. Although investigators have addressed dosimetric aspects of stereotactic radiosurgery in terms of target volume, little if any attention has been focused on the absorbed doses received at extracranial sites. Therefore, the treatment of extracranial arteriovenous malformations using radiosurgery did not gain popularity among clinicians and its use was limited for management of other vascular anomalies such as haemagiomas [46].

Recurrence

The risk of re-expansion and recurrence after intervention is thought to be similar to factors that result in the progressive expansion of a lesion, and it is well known that embolic and surgical treatments can stimulate recurrence through the creation of a proangiogenic environment [31].

Embolisation leads to local hypoxia and increased levels of vascular endothelial growth factor (VEGF), Meanwhile, Operation and healing also induce local hypoxia and inflammation, which are known stimulants of angiogenesis through VEGF, basic fibroblast growth factor, and matrix metalloproteinase (MMP) [47]. To reduce hypoxia and recurrence after resection, several authors have proposed reconstruction with free-tissue transfer [48]. However, these studies were short term, and those that reported a longer period of follow up have not shown significantly lower recurrence after free tissue reconstruction [49].

In conclusion, no accepted single method for treatment of arteriovenous malformations has been identified. Simple focal lesions are usually managed properly by embolization followed by surgical excision of the lesions. Meanwhile, more diffuse lesions are more difficult to treat and usually require a multidisciplinary approach. Taking into consideration that guaranteed curative intervention must include resection if technically possible. Given the difficulty in establishing surgical margins and the need for wide resection, it is important to remember to avoid a treatment that is even worse than the disease.

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