Arteriovenous Malformations: Extracranial

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Introduction

An arteriovenous malformation (AVM) is a fast-flow vascular anomaly characterized by the shunting of blood from the arterial to venous circulation. Shunting reduces capillary oxygen delivery to tissues, causing ischemia. AVMs can produce deformity, ulceration, bleeding, congestive heart failure, and/or destruction of vital structures (see Fig. 7.1a). Treatment consists of embolization and/or resection. Certain AVMs are part of inherited syndromes (see Fig. 7.1b, c): (1) capillary malformation-arteriovenous malformation (CM-AVM), (2) hereditary hemorrhagic telangiectasia (HHT), and (3) PTEN-associated vascular anomaly (PTEN-AVA).

Key Points

- The most common site of extracranial AVM is the head/neck, followed by the limbs, viscera, and trunk [1].
- AVM worsens over time, and can be classified according to the Schobinger staging system (see Table 7.1) [2, 3].
- Despite the high likelihood of recurrence, embolization, and/or resection can palliate an AVM by reducing its size and alleviating pain and bleeding.
- AVM should be treated in a vascular anomalies center by a multidisciplinary team.

Biology and Epidemiology

AVM results from abnormal vascular development during embryogenesis. Lack of a capillary bed causes shunting of blood directly from the arterial to venous circulation through a fistula (direct connection of an artery to a vein) or nidus (abnormal channels bridging the feeding artery to the draining veins) [4]. Although the presence of AVM may be problematic, expansion of the lesion is the main cause of morbidity [3].

Pathophysiology

- Increasing tissue mass requires neovascularization to support its expansion through angiogenesis (growth of new blood vessels from pre-existing vasculature) [5, 6] or vasculogenesis (de novo formation of new vasculature) [7–9]. Vasculogenesis, rather than angiogenesis, may contribute to the expansion of AVM [10].
- Although neovascularization may be a primary stimulus for AVM growth, it might be secondary to ischemia. Ischemia, a potent stimulator of neovascularization, causes enlargement of AVM after proximal arterial ligation or trauma [2, 11, 12]. Alternatively, increased blood flow from arteriovenous shunting may promote vascular endothelial growth factor (VEGF) production and endothelial proliferation [13, 14].
- Both males and females have a two-fold risk of progression in puberty; increased circulating hormones during this period may promote AVM expansion [3].

Molecular/Genetic Pathology

- CM-AVM is an autosomal dominant condition that results from a loss-of-function mutation in *RASA1*, which encodes p120RasGAP. This protein inhibits RAS p21 control of cellular proliferation, survival, and differentiation [15].
- HHT is due to an alteration in endoglin and activin receptor-like kinase 1 (ALK-1) which affect transforming growth factor-beta (TGF-β) signaling [16, 17].
- PTEN-AVA is an autosomal dominant disease caused by a mutation in *PTEN* (phosphatase and tensin homologue)

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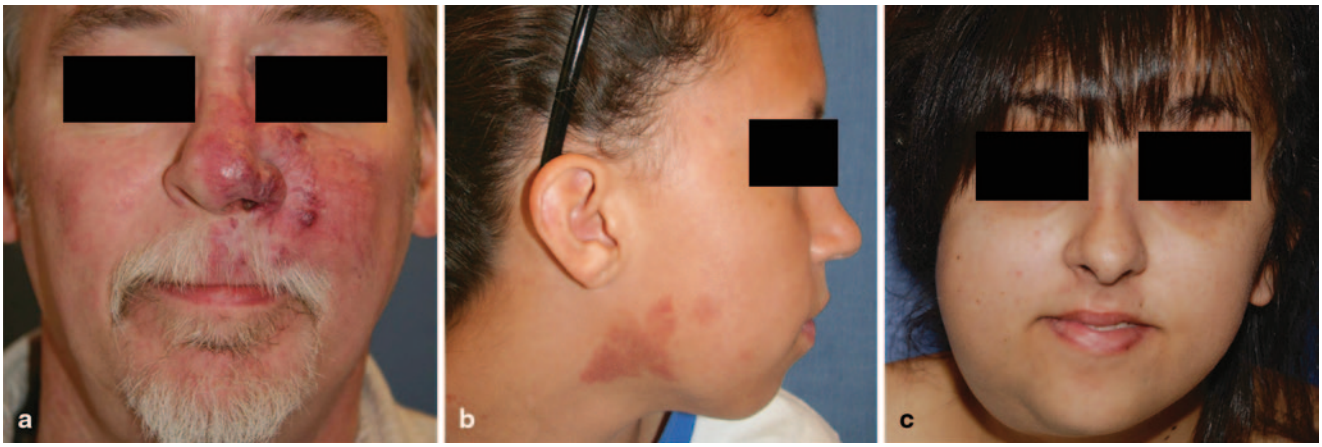

Fig. 7.1 Types of AVM. **a** Fifty-one-year-old male patient with a Stage II AVM of the left cheek, nose, and orbit, causing epistaxis. **b** Nine-year-old female patient with capillary CM-AVM (positive for RASA-1 mutation) and fast-flow stains of the right cheek and neck. **c** Twenty-one-year-old female patient with PTEN-AVA (positive for PTEN mutation) with an enlarging right cheek and submandibular lesion

Table 7.1 Schobinger staging of AVM

Stage	Clinical Findings
I (Quiescence)	Warm, pink-blue, shunting on Doppler
II (Expansion)	Enlargement, pulsation, thrill, bruit, tortuous veins
III (Destruction)	Dystrophic skin changes, ulceration, bleeding, pain
IV (Decompensation)	Cardiac failure

[18]. The gene encodes a tumor suppressor lipid phosphatase that mediates cell cycle arrest and apoptosis [19]. Patients with PTEN mutations have PTEN hamartoma tumor syndrome (PHTS) [18].

Incidence and Prevalence

- AVMs comprise 14.3 % of vascular malformations treated in a vascular anomalies center [20].
- The prevalence of CM-AVM is estimated to be 1 in 100,000 Caucasians [15].

Age Distribution

- Although present at birth, AVM may not become clinically evident until childhood or adolescence [3].
- Approximately three-fourths of patients with AVM require treatment in childhood or adolescence; the remaining individuals do not need intervention until adulthood [3].

Sex Predilection

- Males and females are affected equally.

Risk Factors

- The offspring of patients with CM-AVM or PTEN-AVA have a 50 % risk of inheriting the mutated gene; however, phenotypic heterogeneity is common within families [15, 18, 21].
- Progesterone-only oral contraceptives are recommended because estrogen has greater proangiogenic activity than progesterone [1, 22–25].
- Pregnant women with Stage I lesions do not have an increased rate of progression, compared to non-pregnant women [3]. However, pregnancy in women with Stage II-IV AVM has not been studied, and thus pregnancy may exacerbate the malformation.

Relationships to Other Disease States, Syndromes

- Parkes Weber syndrome (PWS) is a diffuse AVM of an extremity with an overlying capillary malformation (CM) [26]. The extremity is overgrown and the lower limb is most commonly affected [26]. Patients are at risk for leg length discrepancy and congestive heart failure [26].

Presentation

Arteriovenous Malformation

- Lesions appear pink-red, are warm, have a palpable thrill or bruit, and may be mistaken for a CM or hemangioma [1].
- Hand-held Doppler shows fast flow.

Capillary Malformation-Arteriovenous Malformation

- Although the CM is rarely problematic, 30% have associated AVMs that can cause major morbidity: PWS (12%), extracerebral AVM (11%), or intracerebral AVM (7%) [21].
- An individual may have as many as 53 CMs, ranging in size from 1 to 15 cm, although 6% of patients have a solitary lesion [21].
- An association between CM-AVM and spinal arteriovenous lesions exists [27].
- Five percent of patients have benign or malignant tumors, most commonly involving the nervous system (neurofibroma, optic glioma, vestibular schwannoma) [21].
- Patients with PWS should be followed by a cardiologist to monitor signs of congestive heart failure. Orthopedic evaluation is necessary to rule out a leg length discrepancy [21].

PTEN-Associated Vascular Anomaly

- Patients with PTEN mutations have PHTS. Approximately one-half (54%) of patients have a unique fast-flow vascular anomaly with arteriovenous shunting [18].
- Patients may have multiple PTEN-AVAs (57%), and 85% are intramuscular [18].
- Patients with PHTS are followed for the presence of tumors, particularly, endocrine and gastrointestinal malignancies [1, 18].

Symptoms

- Arteriovenous shunting causes ischemia, which can lead to pain, ulceration, bleeding, and congestive heart failure.
- AVM also may cause deformity, destruction of tissues, and obstruction of vital structures.
- High-pressure shunting of blood can cause venous hemorrhage and rupture of arteries in weakened areas, such as aneurysms.
- Arterial bleeding most commonly occurs at skin or mucosal surfaces from erosion into a superficial component of the lesion.

Differential Diagnosis

Capillary malformation (CM)
Congenital hemangioma (CH)
Infantile hemangioma (IH)
Kaposiform hemangioendothelioma (KHE)
Lymphatic malformation (LM)
Pyogenic granuloma (PG)
Venous malformation (VM)

Diagnosis and Evaluation

Physical Examination

Arteriovenous Malformation

Ninety percent of AVMs are diagnosed by history and physical examination [28, 29].

Findings

- Lesions are usually warm, pink-red, and have a palpable thrill or bruit.
- Unlike IH, AVM expands after infancy.
- Hand-held Doppler examination showing fast flow excludes slow-flow vascular anomalies (e.g., CM, LM, VM).

Capillary Malformation-Arteriovenous Malformation

Diagnosis is made by history and physical examination. A patient presenting with multiple CMs, especially with a family history of similar lesions, should be evaluated for possible AVMs. Patients are counseled about the autosomal dominant inheritance pattern.

Findings

- Atypical CMs that are small, multifocal, round, pinkish-red, and surrounded by a pale halo (50%) [15, 21].
- Unlike sporadic CM, Doppler examination in CM-AVM often shows fast flow.
- An overgrown extremity with a CM suggests PWS [26].

PTEN-Associated Vascular Anomaly

Suspicion of a PTEN-AVA usually is initiated after reviewing the magnetic resonance imaging (MRI) or angiographic study of a patient thought to have an AVM. Vascular anomalies with fast-flow lesions consistent with a PTEN-AVA are evaluated for possible PHTS. PTEN-AVA is an autosomal dominant condition; patients are counseled about the risk of transmitting the gene to their offspring.

Findings

- Unlike typical AVM, PTEN-AVA can be multifocal, associated with ectopic fat tissue, and have disproportionate, segmental dilation of the draining veins [4, 18].
- Patients with PHTS have macrocephaly (>97th percentile), and all males have penile freckling [18].
- PHTS is associated with mental retardation/autism (19%), thyroid lesions (31%), or gastrointestinal polyps (30%) [18].

Laboratory Data

- *RASA1* gene testing confirms the diagnosis of CM-AVM. However, not all patients with CM-AVM clinically will have a *RASA1* mutation, suggesting that unknown mutations in *RASA1* or other genes may result in the same phenotype [21].
- *PTEN* gene testing is confirmative; however, a germline mutation is not found in 9% of families clinically diagnosed with PHTS [30].

Imaging Evaluation

Arteriovenous Malformation

Ultrasonography (US)	Exhibits a hypervascular lesion with arteriovenous shunting and no significant parenchymal mass. Color Doppler shows feeding arteries and large draining veins.
Computed Tomography (CT)	May be indicated if the lesion involves the bone.
Magnetic Resonance Imaging (MRI)	Demonstrates dilated feeding arteries and draining veins, enhancement, and flow voids [4]. MRI is usually indicated to: (1) confirm the diagnosis, (2) determine the extent of the lesion, and (3) plan treatment. MRI with contrast and fat suppression, as well as T2-weighted sequences, is necessary to adequately asses the anomaly [1, 4].
Angiography	Displays tortuous, dilated, arteries with arteriovenous shunting and enlarged draining veins [4]. The nidus manifests as dysplastic, tortuous, small vessels, with ill-defined larger contiguous vascular spaces. Angiography is indicated when: (1) the diagnosis is unclear after US and MRI, (2) embolization or resection is planned.

Capillary Malformation-Arteriovenous Malformation

Imaging features for CM-AVM are similar to non-syndromic AVMs. Patients with CM-AVM are at risk for intracranial and spinal fast-flow lesions; MRI of the brain and/or spine should be considered [31]. Because extracranial AVM has not been found to involve the viscera, exploratory imaging of other anatomical areas is not necessary [21].

PTEN-Associated Vascular Anomaly

Unlike typical AVM, PTEN-AVA can be multifocal, associated with ectopic adipose tissue, and have disproportionate, segmental dilation of the draining veins [4, 18]. Intramuscular lesions replace the architecture with disorganized fat, in contrast to non-syndromic muscular AVMs [18].

Pathology

Arteriovenous Malformation

AVM generally shows large, tortuous arteries, as well as dilated, thick-walled veins [32]. In the early stage, veins have a hypertrophic muscular layer. As the lesion progresses, smooth muscle is replaced by collagen, and the vessel becomes fibrotic (see Fig. 7.2) [32].

Capillary Malformation-Arteriovenous Malformation

CM-AVM shares most of the histopathological features that are found in non-syndromic AVM.

PTEN-Associated Vascular Anomaly

Similar to non-syndromic AVM, PTEN-AVA shows tortuous arteries with transmural muscular hyperplasia and clusters of abnormal veins with variable smooth muscle [18]. However, skeletal muscle infiltration with adipose tissue, fibrous bands, and lymphoid aggregates is unique to PTEN-AVA.

Treatment

Pharmacological therapy does not exist for AVM. Problematic lesions are embolized and/or resected. The goal of treatment usually is to control the lesion; cure is rare. Interventions focus on alleviating symptoms (e.g., bleeding, pain, ulceration), preserving vital functions (e.g., vision, mastication), and for improving a deformity. Asymptomatic AVMs should be observed unless they can be managed with minimal morbidity; embolization or subtotal resection of an asymptomatic malformation may provoke it to enlarge and become problematic. Therapy is determined by the (1) size and location of the lesion, (2) patient's age, and (3) Schobinger stage. Resection of a non-problematic Stage I AVM offers the best chance for long-term control. However, intervention must be individualized based on the deformity that would result from excision and reconstruction [1, 3]. For example, a large Stage I AVM in a non-anatomically important location (e.g., trunk, proximal extremity) may be resected without significant morbidity, before it progresses to a higher stage when excision is more complicated and the recurrence rate is greater [1, 3]. Similarly, a small, well-localized AVM in a more difficult location (e.g., face, hand) may be removed for

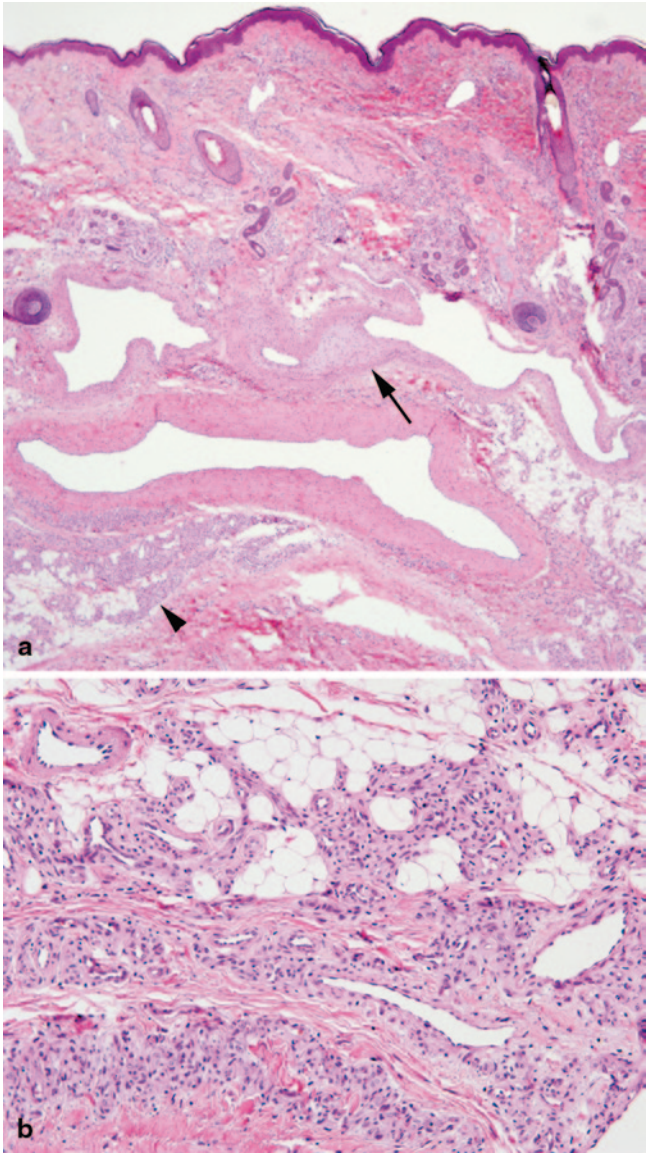

Fig. 7.2 Arteriovenous malformation, scalp. **a** Malformed large arteries and veins occupy superficial and deep dermis as well as subcutaneous tissue. A venous channel with high flow, hypertensive changes, is indicated by arrow. Arrowhead on the bottom left indicates small vessel component. **b** Small vessel component of AVM in subcutaneous tissue at higher magnification is characterized by groups of small channels in close proximity to each other and lined by plump endothelium

possible "cure" before it expands and complete extirpation is no longer possible [1, 3].

In contrast, a large, asymptomatic lesion located in an anatomically sensitive region (e.g., face) is best observed; especially in a young child not ready for a major procedure [1, 3]. Resection may cause a worse deformity and the malformation can recur. Some children (17.4%) do not experience morbidity from their AVM until adulthood [3].

Intervention for Stage II AVMs is similar to Stage I lesions. However, the threshold for treatment is lower if an enlarging malformation is causing a worsening deformity or if functional problems are expected [1, 3]. Treatment for Stage III and IV AVMs is necessary to control pain, bleeding, ulceration, or congestive heart failure [1, 3].

Non-Operative Management

For superficial AVMs, patients should apply hydrated petroleum to prevent desiccation and subsequent ulceration [1]. Compression garments for extremity lesions may reduce pain and swelling, but can also worsen symptoms [1]. If bleeding occurs it is readily controlled by compression; further intervention is rarely necessary [1].

Embolization

Delivery of an inert substance, through an arterial catheter, occludes blood flow and/or fills vascular spaces. Fibrosis may further reduce arteriovenous shunting and shrink the lesion. Even if significant volume reduction is not obtained after embolization, symptoms are reduced [1]. Embolizing the arterial inflow to the nidus is contraindicated because recannalization occurs, and the lesion becomes inaccessible for future embolization [4]. Patients and families are counseled that the AVM is likely to re-expand; additional embolizations may be required in the future.

Liquid (n-butyl cyanoacrylate [n-BCA], Onyx, ethanol) or solid (polyvinyl alcohol particles [PVA], coils) may be used for embolization [4]. The choice of agent depends on whether embolization is utilized as a primary treatment or as a pre-operative adjunct to excision [1, 4]. For primary treatment, permanent liquid agents capable of permeating the nidus (ethanol, n-BCA, Onyx) are used. Our institution prefers Onyx, an ethylene-vinyl alcohol copolymer (EV3 Neurovascular, Irvine, CA) that precipitates on the surface after contact with blood [1, 4, 33]. It maintains a non-adhesive liquid core that allows multiple injections of different compartments. For pre-operative embolization, temporary occlusive substances (gelfoam powder, PVA, embospheres) are used. Delivery of different particle sizes permits the initial occlusion of small, distal vessels followed by blockage of more proximal branches with larger emboli. Our institution is now using Onyx for pre-operative embolization [1, 4, 33].

Patients are typically observed overnight in the hospital. If swelling is a concern, dexamethasone can be administered peri-operatively [1, 4, 33]. If airway or orbital lesions are embolized, post-treatment swelling may require close monitoring. Embolization of deep extremity lesions are at risk for compartment syndrome. Ulceration is the most common complication of embolization, especially in superficial lesions [1, 4, 33]. Wounds are allowed to heal secondarily with local wound care.

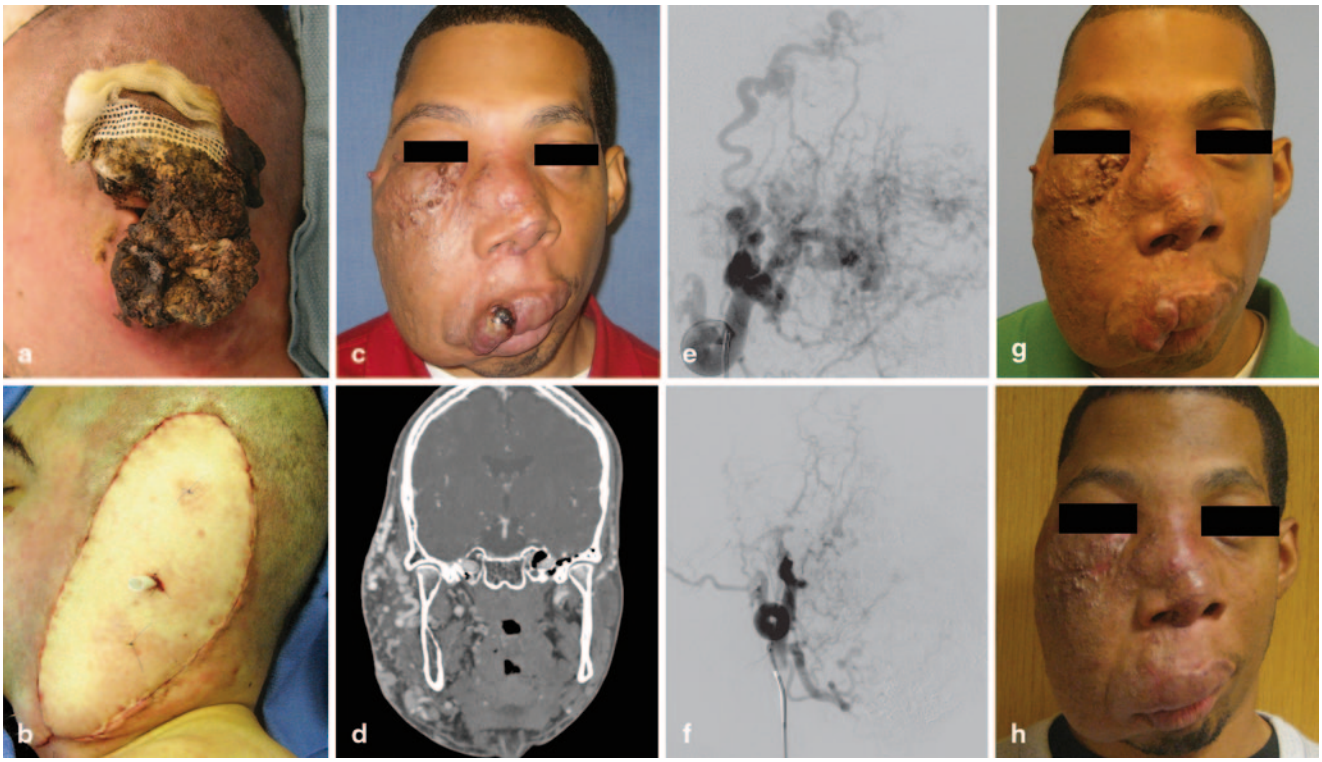

Fig. 7.3 Operative management of AVM. **a** Twenty-two-year-old male patient with a Stage III auricular AVM causing pain, bleeding, and infection. **b** Following embolization and wide resection, a free latissimus dorsi myocutaneous flap was used to close the defect. **c** Twenty-five-year-old male patient with a Stage III AVM causing a significant deformity, bleeding, pain, and ulceration. Because the lesion involved all structures of the face (including orbit, maxilla, mandible), radical resection would cause a greater deformity than the AVM. Embolization and subtotal resection of the ulcerated, bleeding lip and cheek lesions were performed. **d** Coronal computed tomography angiogram illustrates prominent, diffuse vascular anomaly with soft tissue enlargement. **e** Angiogram showing diffuse nidus. **f** Nonopacification of most of the AVM nidus after embolization. **g** Healed lip ulceration and resolution of bleeding following six embolizations. **h** Improved appearance after subtotal resection of the upper lip and cheek. Reprinted from Clinics in Plastic Surgery, 38/1, Greene AK, Orbach DB, Management of Arteriovenous Malformations, 100–101, 2011, with permission from Elsevier

Sclerotherapy

Transcutaneous injection of a substance into the malformation causes endothelial destruction and thrombosis. Subsequent fibrosis decreases the size of the lesion and improves symptoms. Sclerotherapy is reserved for an AVM that cannot be accessed transarterially, or for a well-localized lesion [1, 4]. Sclerosant use in a high-flow lesion is at risk for escaping into the systemic circulation [1, 4]. Sodium tetradecyl sulfate (STS) and absolute ethanol are the preferred scleroscents at our institution [1, 4]. Ethanol is more effective than STS, but has a higher complication rate; it should be used carefully in proximity to important structures (e.g., facial nerve) [1, 4].

Resection

Excision of an AVM has a lower recurrence rate than embolization, and is considered for localized lesions to correct a focal deformity (e.g., bleeding or ulcerated areas, labial hypertrophy) (see Fig. 7.3) [1]. Wide extirpation and reconstruction of a large, diffuse AVM should be performed with caution because (1) cure is rare and the recurrence rate is high, (2) the resulting deformity is often worse than the appearance of the malformation, and (3) resection can cause significant blood loss and iatrogenic injury [3].

Pre-operative embolization facilitates resection by reducing the size of the lesion and minimizing blood loss. Excision should be carried out 24–72 hours after embolization, before recannalization restores blood flow, especially if particulate agents, such as PVA, are used [3]. Infusing an epinephrine-containing local anesthetic throughout the operative field reduces blood loss. Small, well-localized AVMs or those that cannot be accessed for embolization may be treated by resection alone.

Surgical margins are best determined by assessing the amount of bleeding from the wound edges [2]. Most defects can be reconstructed by advancing local skin flaps. Skin grafting ulcerated areas has a high failure rate because the underlying tissue is ischemic; excision with

regional flap transfer may be required [1]. Free-flap reconstruction permits wide resection and primary closure of complicated defects but does not improve long-term control [2, 3, 12, 34].

Outcome

Embolization

Embolization does not remove the AVM; almost all lesions will eventually expand after treatment. Although studies suggest that multiple embolizations do not lower the rate of recurrence, newer embolic agents (e.g., Onyx) may offer more lasting results [3]. Stage I AVM has a lower recurrence rate than higher-staged lesions. Most recurrences occur within the first year after embolization and 98.0 % re-expand within 5 years; although this may reflect results obtained with older embolic agents [1, 3]. The recurrence rate after embolization in PTEN-AVA lesions seems to be higher than non-syndromic AVMs [1]. Despite the high recurrence rate, embolization can effectively palliate an AVM.

Resection

Despite subtotal and presumed "complete" extirpation, most AVMs recur [3]. Recurrences typically occur within the first year after intervention, and 86.6 % re-expand within 5 years [3]. It is our experience that PTEN-AVA has a higher recurrence rate compared to non-syndromic AVM, possibly because the loss of the tumor suppressor protein favors a more proliferative environment [1]. Patients not displaying recurrence 5 years following intervention are more likely to have long-term control [3]. However, 5.2 % will experience re-expansion more than 10 years post-operatively [3]. Patients and families are told that AVM is likely to recur following resection, and further intervention may be needed in the future.

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