Arteriovenous Malformation

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Introduction

Arteriovenous malformation (AVM) is a fast-flow vascular malformation consisting of a network or nidus of abnormal blood vessels supplied by feeding arteries draining into veins. The lesional extent and angioarchitecture are extremely variable, as is the magnitude of the arteriovenous shunt. Unlike tumors, AVMs appear to replace the capillary bed of the affected tissue, causing an infiltrating lesion. AVM causes localized venous hypertension, reducing perfusion pressure to the involved and adjacent tissues, causing symptoms and signs of tissue ischemia. During childhood, AVM is usually associated with symmetrical overgrowth of the affected tissue, often with a capillary stain of the overlying skin (Fig. 11.1). Evolution occurs at a variable rate (Table 11.1, Schobinger staging system), although it is well-known that progression is stimulated by a number of events that stimulate somatic and angiogenic growth factors, such as trauma, puberty, and pregnancy [1, 2]. Over time, shunting increases, causing tissue ischemia with pain followed by tissue ulceration with bleeding (Schobinger stages III and IV) (Figs. 11.2 and 11.3). Extensive AVMs and those with large fistulas cause cardiac volume overload, potentially leading to high-output cardiac failure. AVMs outside of the central nervous system typically present with tissue overgrowth, pain, and ulcerative bleeding.

Most AVMs are somatic lesions and when located extracranially are usually the result of an *MAP2K1* mutation in endothelial cells [3]. AVMs are most frequently located intracranially often leading to neurological symptoms and/or hemorrhage; intracranial lesions are typically the result of a somatic *KRAS*

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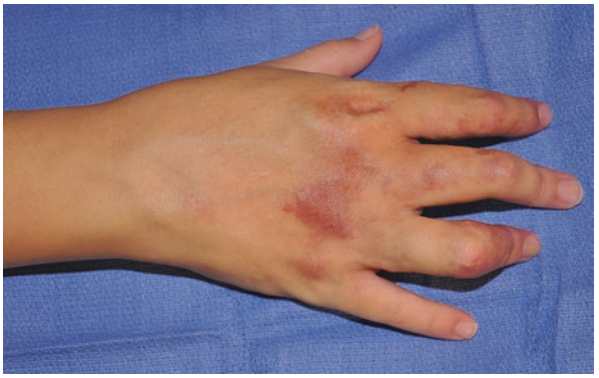

Fig. 11.1 Diffuse Schobinger stage III AVM of right hand of a 10-year-old girl who has undergone several embolizations. She has tissue overgrowth, swelling, patchy red stains, and dilated superficial veins. Flexion contractures of several fingers caused by ischemia. The diffuse AVM could not be embolized effectively

Table 11.1 Natural history of AVM

Stage 1	Warm, skin discoloration, fast-flow on Doppler
Stage 2	Growth, palpable pulsations, enlarged veins
Stage 3	Ulceration, bleeding, pain
Stage 4	Congestive heart failure

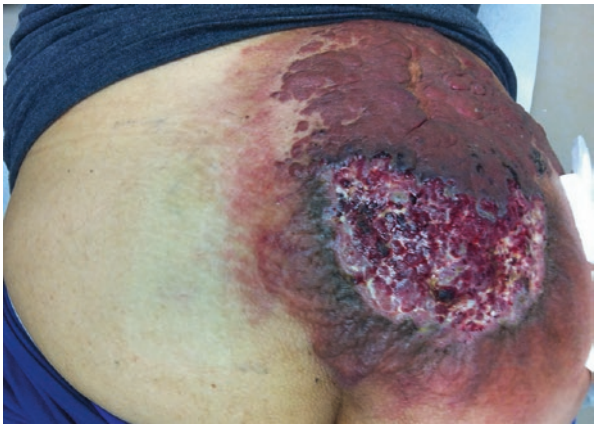

Fig. 11.2 Ulcerated, bleeding Schobinger stage III diffuse AVM of the right buttock in a 16-year-old girl, who was asymptomatic until 2 years earlier

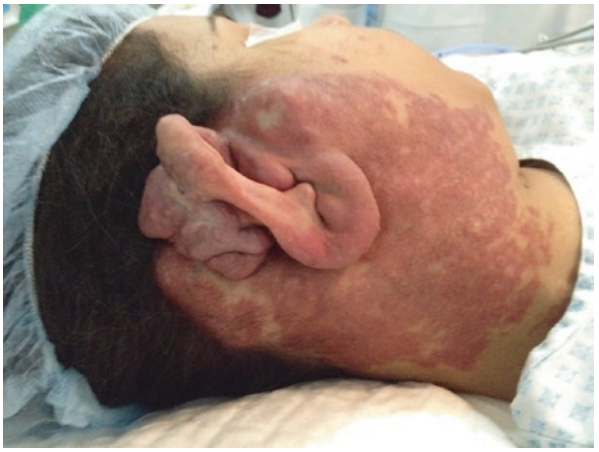

Fig. 11.3 Schobinger stage IV AVM of the pinna. A 20-year-old male with cardiac failure, ulceration, and bleeding. Note the huge varices behind the ear

mutation [4]. Congenital arteriovenous fistula [AVF] is a type of AVM, in which shunting occurs directly from artery to vein, without an intervening nidus. AVF can occur as an isolated defect or within a complex AVM. AVM and AVF are generally sporadic, although a small percentage of patients have hereditary forms. Hereditary forms are caused by germline mutations in *ACVRL*, *ENG*, *RASA1*, *EPHB4*, and *PTEN* [5]. AVM should be distinguished from vascular tumors that can contain arteriovenous shunts, such as infantile or congenital hemangiomas and certain malignancies. Usually, clinical and imaging features clearly differentiate AVM from tumor.

Diagnosis of AVM

Clinical findings in patients with AVM vary according to the extent and clinical stage. Generally, there is evidence of increased flow with prominent proximal pulsations, engorgement of draining veins, and increased skin temperature. With a large shunt, soft tissue pulsatility and/or venous thrill can be felt. The skin can be involved with a diffuse or patchy flat red stain. Over time, dark red keratotic macules called pseudo-kaposiform change may develop, especially in the lower extremities. The stain of AVM can easily be distinguished from isolated capillary malformation because of increased temperature. A portable Doppler probe can be used in the clinic to detect increased flow in the underlying tissues.

MRI with time-resolved contrast-enhanced MRA is the best diagnostic test to demonstrate extent and flow characteristics. Typically, standard MR images show some enlargement of the affected tissue with vascular flow voids representing dilated feeding arteries and draining veins (Fig. 11.4). With a few exceptions, the AVM does not have significant signal abnormality or mass effect. The lack of distinct soft tissue mass on fluid-sensitive sequences helps distinguish AVM from tumors. AVMs within a confined space, such as intramuscular AVMs, may demonstrate increased signal on T2-weighted sequences. Contrast enhancement may also be seen in AVMs composed of small channels. 2-D time-of-flight MRA is not reliable for diagnosing AVM, but may show enlargement of the feeding arteries. Time-resolved contrast-enhanced MRA, which obtains 3-D data sets every few seconds after intravenous contrast injection, is the best sequence to show arteriovenous shunting [6] (Fig. 11.5). In this study, veins draining an AVM will appear much sooner than normal veins. Unlike hemangioma, contrast washes out of the AVM quite quickly.

Ultrasonography with Doppler interrogation is a good method to confirm the presence of arteriovenous shunting. Involved tissue may appear normal or more echogenic than normal due to fibrofatty infiltration or edema. Feeding arteries will be dilated, with low-resistance waveform. Draining veins typically have turbulent, high velocity flow.

Catheter angiography is the best technique to delineate the specific angioarchitecture but, at least in children, is usually not performed unless intervention is planned during the same procedure. MRI often demonstrates tissue overgrowth and enlarged vascular flow voids, usually without a focal mass. MRA is helpful to show the anatomy of feeding and draining vessels. 2-D and 3-D time-of-flight MRA gives

good resolution of the vascular anatomy, while dynamic time-resolved contrast-enhanced MRA confirms the present of a shunt, as well as better depiction of the venous anatomy. Knowledge of the angioarchitecture of an individual AVM is necessary to plan endovascular treatment and predict the likelihood of complete occlusion [7, 8]. A number of angiographic classifications have been proposed, based on an early paper describing dural AVMs [9]. There are three basic types of AVM angioarchitecture: direct arteriovenous fistula, arteriolovenous fistula, and arteriolovenular malformation. The direct arteriovenous fistula can be cured by placing an appropriate occluding device in the arteriovenous communication, either through a trans-arterial or transvenous approach. The arteriolovenous fistula is composed of

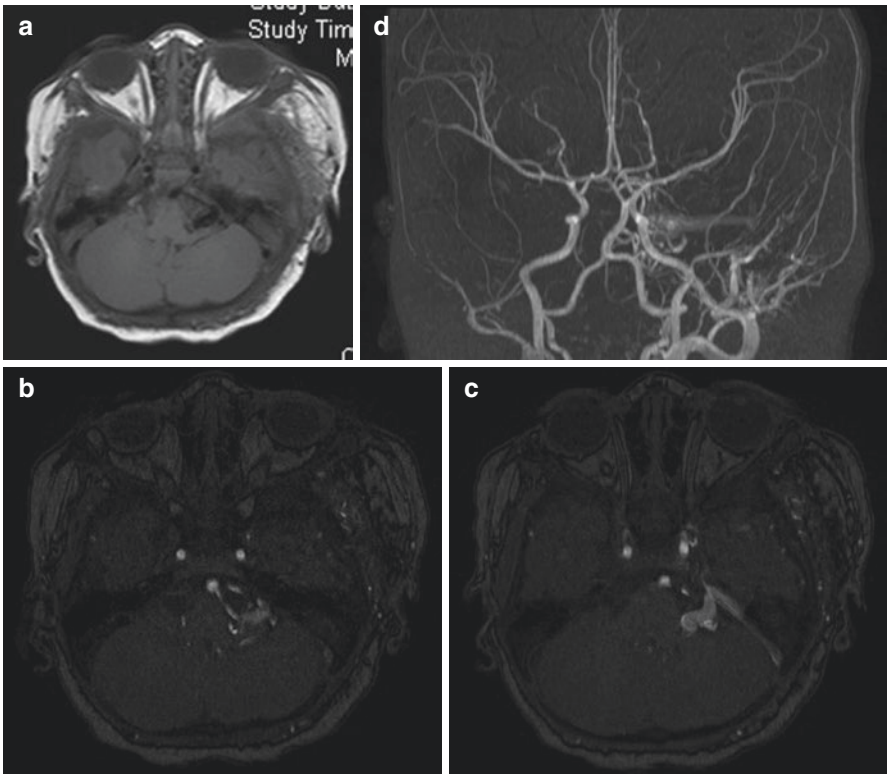

Fig. 11.4 Imaging of a patient with CM-AVM who had multiple CMs, Schobinger stage I small vessel AVM [arteriolovenular], and intracranial AVFs. (**a**) T1-weighted MR image through the face and posterior fossa shows dilated flow voids to the left of the brainstem representing AVF and increased thickness of temporalis muscle and subcutaneous fat in the left cheek. (**b**, **c**) Flow-senstive images through the posterior fossa show dilated vessels in the AVM and AVF. (**d**) 2-D time-of-flight MRA shows the dilation of the left external carotid branches, as well as visualization of an intracranial venous channel. (**e**) Right vertebral angiogram shows AVF in the left posterior fossa. (**f**–**h**) Serial angiographic images demonstrate the diffuse AVM of the left face

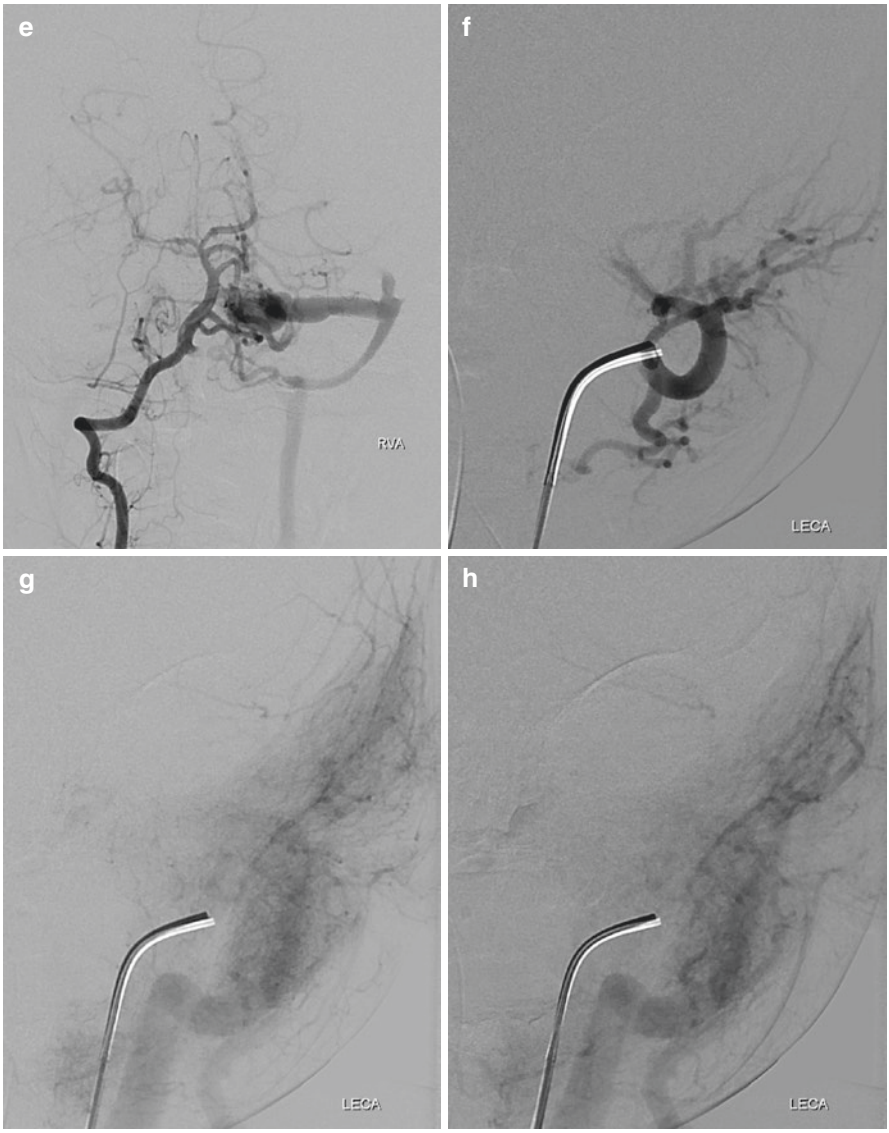

Fig. 4 (continued)

numerous arterial connections to a single outflow vein. It is best treated by packing or closing the immediate draining outflow vein, either by direct puncture or transvenous approach. This type of AVM also has a high rate of permanent occlusion. The arteriolovenular malformation, consisting of numerous arteries, nidus, and numerous draining veins, is usually managed transarterially or by direct puncture and has the lowest rate of complete occlusion by endovascular treatment.

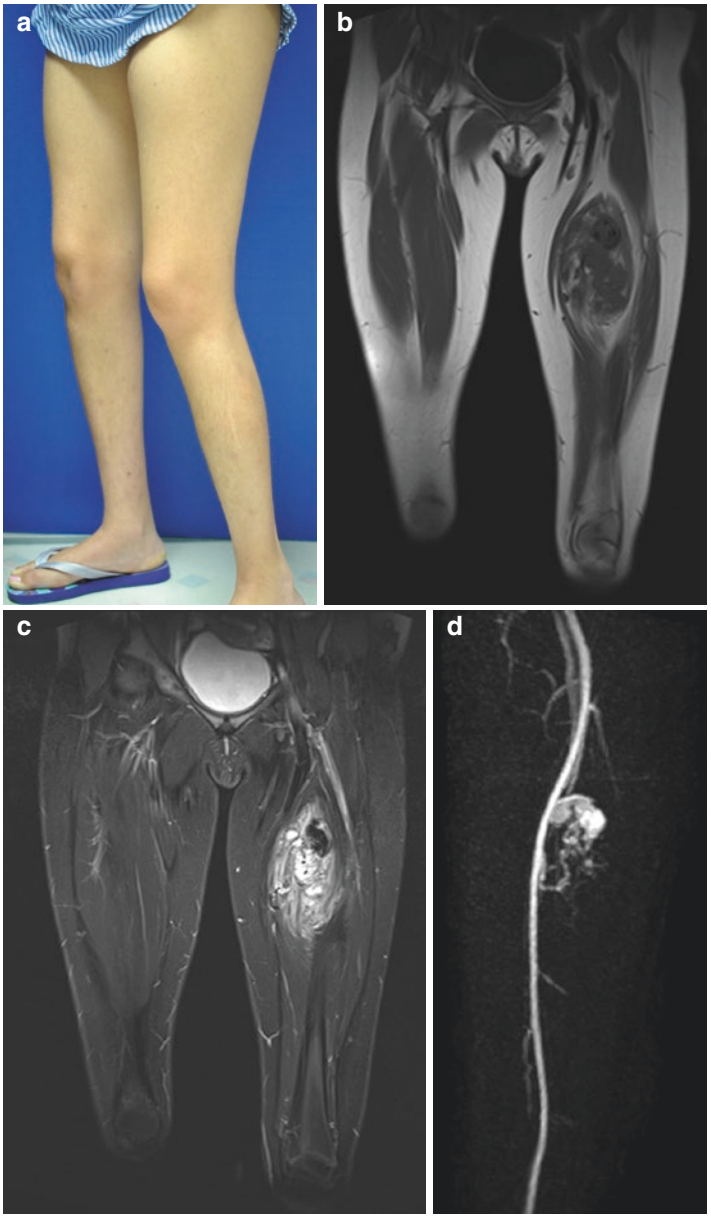

Fig. 11.5 PTEN tumor hamartoma syndrome in a 13-year-old girl with complex intramuscular AVM left thigh. (**a**) Photograph shows soft tissue mass of the anterior left thigh. (**b**) Coronal T1-weighted MR image of the thighs shows an intramuscular mass containing fat, soft tissue, and vascular flow voids. (**c**) Coronal T2-weighted image demonstrates increased signal within the mass and a large vascular flow void. Dilated left femoral vein confirms the presence of a shunt. (**d**, **e**) Early and late images from a contrast-enhanced time-resolved MRA show AVM with large varix draining to femoral vein. (**f**, **g**) Left femoral angiogram confirms AVM consisting of large AVF plus nidus. (**h**) Left femoral angiogram after embolization, using coils and NBCA in the venous components, and ethanol to close the remaining nidus, shows complete occlusion

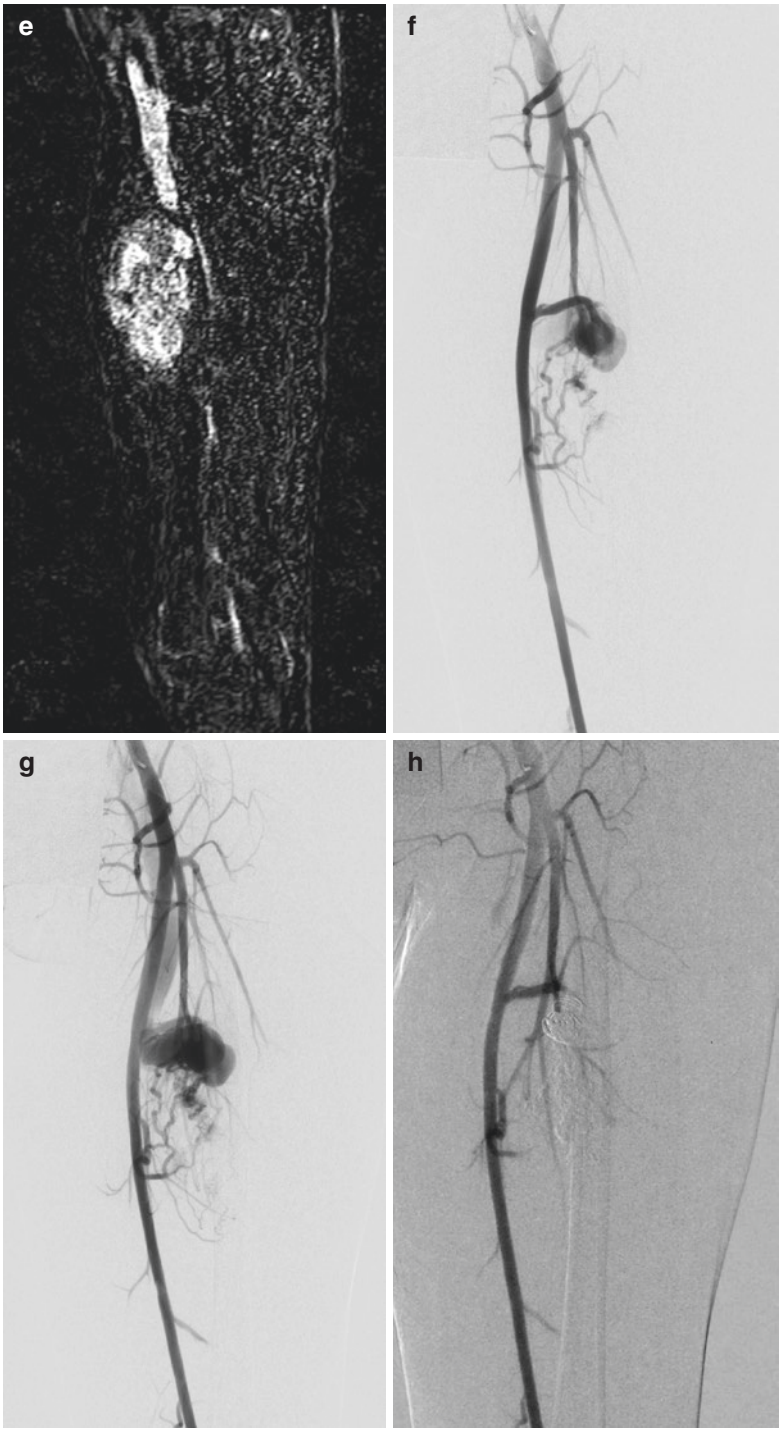

Fig. 5 (continued)

Natural History of AVM

AVM progresses over time and recurs after treatment. The evolution of AVM can be classified according to the Schobinger staging system (Table 11.1). Children with a stage 1 AVM have an approximately 50% risk of progression during childhood and an 82% risk during adolescence; 18% do not experience significant long-term growth until they are adults [10]. Diffuse AVMs are more likely to progress than localized lesions.

Despite subtotal and presumed "complete" extirpation, most AVMs re-enlarge after excision. Recurrence following resection typically occurs during the first year, and 86% will re-expand within 5 years. Patients not exhibiting regrowth 5 years later are likely to have long-term control. However, 5% will experience re-expansion more than 10 years postoperatively [10].

The cause of AVM enlargement is unknown. It may grow because of increased blood flow causing collateralization, dilatation of vessels, and thickening of adjacent arteries and veins. Arteriovenous shunts may open, stimulating hypertrophy of surrounding vessels from increased pressure. Alternatively, aneurysms might increase the size of these lesions. Because both males and females have a twofold risk of progression to a higher Schobinger stage in adolescence, circulating hormones during this period may promote expansion.

Endovascular Management of AVM

A variety of embolization materials and techniques are used for AVM treatment. It is inappropriate to compare results of embolization without consideration of the technique used. Transcatheter embolization of feeding arteries is the oldest technique, in which selective or supraselective catheterization of the arteries supplying the AVM is carried out. Embolization material, such as particles, microspheres, gelatin sponge, or NBCA glue, is injected with the goal of occluding the feeding arteries and decreasing flow. This technique is used preoperatively, 1 or 2 days before resection, to minimize blood loss. Because this method does not destroy or completely occlude the nidus and immediate draining veins, it has no long-term benefit and should not be used for palliative treatment without resection. Embolization of feeding arteries can lead to some ischemia of the surrounding tissue. Another technique that avoids proximal arterial occlusion is percutaneous embolization of the AVM nidus. Preoperatively, this is usually carried out with NBCA.

To achieve the best chance of long-term palliation or cure, endovascular treatment must selectively target the nidus and immediate draining veins. Absolute ethanol is the most effective agent for arteriolovenular malformations, because it penetrates the nidus and the immediate draining vein and destroys the endothelium. Ethanol can only be safely administered to the nidus. Any penetration of the normal capillary bed causes severe tissue destruction, leading to necrosis of the skin, soft tissue, and peripheral nerves. These procedures are time-consuming and, because of limits in ethanol volume per session, must be repeated numerous times. Ideally, embolization is repeated every month or every second month until the lesion is

completely closed. With proper technique, normal vascularity to the affected tissues is retained. Complication rates are high, however, including tissue damage, peripheral nerve injury, pulmonary thromboembolism, and cardiovascular collapse.

AVF can be closed through an arterial or venous approach, as long as the exact communication between artery and vein is occluded [11]. Numerous mechanical occlusion devices, such as plugs, coils, or micro-coils, are available. Detachable coils and microcoils can be positioned precisely before deployment. NBCA and Onyx are also effective in certain AVFs. Double-lumen balloon occlusion microcatheters are available for use with Onyx. Once a simple AVF is completely closed, recurrence is rare.

In arteriolovenous malformations, the single outflow vein is often occluded with a large number of coils, with or without additional ethanol or NBCA. This technique has excellent results, when applied to the appropriate lesion [12]. Permanent complete occlusion has been documented with 5-year and 10-year follow-up angiograms. Published series of patients undergoing primary embolization for peripheral AVM come mainly from the group at Samsung Medical Center in Seoul, Korea. This group reported an overall cure rate of 39%, with 10% major and 35% minor complications [8]. Extent of AVM and angiographic classification were the main predictors of outcome.

Small vessel AVMs [arteriolovenular] are the most difficult to treat. Localized small vessel AVMs can be treated with ethanol embolization. Staged bleomycin infiltration is also sometimes effective. However, diffuse small vessel AVMs do not respond well to embolization and often worsen.

Surgical Management of AVM

Operative Indications

Intervention for an AVM is not mandatory and should not leave a worse deformity than the appearance of the lesion [13]. Variables that determine whether an AVM should be resected are the stage, patient age, location of the lesion, and size of the AVM. If it is possible to completely resect a stage 1 or 2 AVM in an anatomically favorable area, then prophylactic excision and reconstruction should be considered before the lesion progresses [14]. However, if an AVM is located on the face and extirpation and reconstruction would leave a significant deformity, then it is generally best to wait until the lesion becomes very problematic before surgical intervention. Stage 3 and 4 AVMs require treatment for deformity, bleeding, pain, ulceration, and/or congestive heart failure.

Timing of Intervention

Stage 3–4 AVMs require immediate treatment, regardless of the age of the patient. Generally, an AVM should not be removed before 6 months of age. At this time the patient's risk of anesthesia is greater than for an adult. In addition, a young infant is less able to tolerate an operative procedure. If it is likely that a patient will require

an operation, a common time to intervene is between 3 and 4 years of age. Because long-term memory and self-esteem begin to form at approximately 4 years of age, removing an AVM at this time will improve a deformity before the child's self-esteem begins to form, and the patient will likely not remember the procedure. Another period to extirpate an AVM is during late childhood/early adolescence when the child is able to communicate whether he/she would like to have a procedure.

Operative Approach

The operative strategy for an AVM is based on whether the lesion is localized, regional, or diffuse. A localized AVM involves 1–2 tissue planes (e.g., skin and subcutaneous tissue), is well-defined, and theoretically able to be entirely removed with linear closure. These lesions can sometimes be excised without preoperative embolization because bleeding is not significant. AVMs located in anatomically sensitive areas should have minimal or no margins taken. If a lesion is located in a nonsensitive area, then larger margins can be included as long as they don't significantly complicate the procedure.

Regional AVMs are large and/or involve >2 tissue planes. They usually cannot be reconstructed using local tissue; grafts or free-tissue transfer typically are required. Regional AVMs are managed by subtotal resection of a symptomatic area or complete extirpation and reconstruction with distant tissue. Lesions should have preoperative embolization to reduce intraoperative blood loss and facilitate the procedure. Skin grafts are best placed on a recipient site that is free of disease. If the underlying area contains AVM, then a graft has a high chance of failure and flap reconstruction is preferred.

Diffuse AVMs are unable to be entirely extirpated without causing significant morbidity. Patients are managed using embolization for palliation of bleeding, pain, and ulceration or undergo subtotal excisions of symptomatic areas. When resection is planned, patients have preoperative embolization. Operative intervention for a diffuse facial AVM should be focused on improving the patient's symptoms/appearance with localized staged procedures without causing a significant deformity. It is critical to avoid facial nerve injury. Because all surgical planes are affected by AVM, resections cause more bleeding than removal of a regional AVM.

Medical Management of AVM

There are limited prospective studies on the medical treatment of AVMs. It is clear that medication has a role in high-risk patients with no other treatment options. With discovery of germline and somatic mutations in AVMs, precision medicine may play a large role in future therapy. In hereditary hemorrhagic telangiectasia (HHT), several medications are being investigated for symptom relief and control of the AVM. These include bevacizumab, tranexamic acid, tamoxifen, propranolol, sirolimus, thalidomide derivatives, and pazopanib [15–17]. Recent discovery of somatic mutations of

MAP2K1 and *KRAS* raises the possibility of treatment with MEK inhibitors and other agents in the *RAS* pathway [3, 4]. Most of these agents are presently used in oncology. Early studies are in development using some of these agents.

Syndromes Associated with AVM

Capillary Malformation-Arteriovenous Malformation (CM-AVM)

This autosomal dominant condition affects 1/100,000 persons and is caused by a mutation in *RASA1 or EPHB4*. Lesions usually are small, multifocal, round, and pinkish-red; 50% are surrounded by a pale halo. One-third of children also have either Parkes Weber syndrome, extracerebral AVM, or intracerebral/spinal AVM. A patient suspected of having CM-AVM should be evaluated for AVMs on physical examination, and MRI of the brain and spine is considered.

Cobb Syndrome

This term previously had been used for a midline capillary malformation of the posterior trunk with an underlying spinal AVM. Patients labeled with "Cobb syndrome" likely have either CLOVES syndrome or CM-AVM. One-fourth of patients with CLOVES syndrome have spinal/paraspinal AVMs, and truncal capillary malformations are common in this condition. *RASA1* mutations have been documented in patients with spinal AVMs and overlying capillary malformations (CM-AVM).

Hereditary Hemorrhagic Telangiectasia (HHT)

This autosomal dominant disease (also referred to as Osler-Weber-Rendu syndrome) affects 1/10,000 persons and is caused by mutations in endoglin (*ENG)*, activin A receptor type II-like 1 (*ACVRL1/ALK1)*, or *SMAD4*. These mutations affect transforming growth factor beta signaling. Clinical findings consist of epistaxis, mucocutaneous telangiectasias, and visceral AVMs. The patient may exhibit upper gastrointestinal bleeding, stroke from pulmonary arteriovenous shunting, cerebral hemorrhage, heart failure, portal hypertension, and/or chronic anemia. Patients undergo genetic testing, echocardiography for pulmonary AVMs, brain MRI, and abdominal ultrasound; endoscopy is indicated for patients with a *SMAD4* mutation to document whether polyps are present.

PTEN-Associated Vascular Anomaly (PTEN-AVA)

The PTEN (phosphatase and tensin homologue) gene encodes a tumor suppressor lipid phosphatase. Patients with PTEN mutations have the autosomal dominant PTEN hamartoma tumor syndrome (previously referred to as Cowden or

Bannayan-Riley-Ruvalcaba syndrome). One-half of individuals have a fast-flow vascular anomaly with arteriovenous shunting, referred to as a PTEN-associated vascular anomaly (PTEN-AVA). Unlike a typical AVM, PTEN-AVAs can be multifocal, are typically intramuscular, contain ectopic adipose tissue, and have disproportionate, segmental dilation of draining veins. Patients exhibit macrocephaly, and males have penile freckling; other features can include developmental delay, thyroid lesions, and gastrointestinal polyps. Surveillance is required particularly for the development of epithelial, endocrine, and gastrointestinal malignancies. PTEN-AVAs are managed similarly to non-syndromic AVMs (i.e., embolization and/or resection).

Wyburn-Mason Syndrome

This rare sporadic condition consists of retinal AVMs with or without brain AVMs and a facial vascular malformation (capillary malformation or AVM). The syndrome also is referred to as Bonnet-Dechaume-Blanc syndrome or retinocephalofacial vascular malformation syndrome [18]. One-third of children do not contain a cutaneous lesion but exhibit AVMs of the retina and have neurological symptoms with or without brain AVMs. One-half of patients have retinal AVMs without cutaneous or brain lesions.

Parkes Weber Syndrome (PWS)

PWS consists of a diffuse AVM of an extremity (typically one leg) causing soft tissue and/or bony overgrowth. The cutaneous stain of the affected limb is warmer than a typical capillary malformation. PWS can be sporadic or familial due to a mutation in *RASA1* (CM-AVM1) or *EPHB4* (CM-AVM2) [19]. Patients have subcutaneous and intramuscular microshunting, often with cardiac volume overload, and can develop congestive heart failure. MRI is obtained to confirm the diagnosis and determine the extent of the malformation. Dilated feeding and draining vessels are illustrated as flow voids. The enlarged limb muscles and bones exhibit abnormal signal and enhancement. Most patients are observed until symptoms necessitate intervention. Children are monitored by an orthopedic surgeon for axial overgrowth. Embolization may be useful for pain, ulceration, or congestive heart failure, in those patients with discrete shunts, but the typical infiltrating small vessel AVM does not respond and may actually worsen with embolization. Occasionally, amputation is necessary [13].

Conclusion

Arteriovenous malformations are complicated vascular anomalies associated with germline and somatic mutations. Overall the natural history favors progression over time and in the most severe patients leads to life-threatening complications. These

anomalies need to be treated by skilled practitioners in an interdisciplinary center. In the future, targeted medications will complement the surgical and interventional treatments and improve the overall outcome for these patients.

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