Biological Approaches to the Aggressive CVM Lesion (Antiangiogenic Therapy)

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AV Malformation (AVM)

The mechanisms for development and progression of AVM are incompletely understood, but have been most thoroughly studied in patients with familial AVM, especially hereditary hemorrhagic telangiectasia [HHT], known to be caused by mutations in endoglin, ALK1, and SMAD4, receptors for the transforming growth factor [TGF] beta superfamily. AVMs and similar vascular lesions have been created in animal models by creating mutations in ALK1, endoglin, and Notch in mice and zebra fish [4–6]. While the animal models do not exactly replicate human disease, it has been possible to study the development of AVMs and observe the effects of various interventions including drug treatment. In addition, studies of the molecular milieu of resected cerebral AVMs have shown inflammatory markers, and matrix metalloproteinases are increased in cerebral AVMs [7, 8]. Histochemical study of resected vascular malformations has also shown increased receptors to growth hormone and follicle-stimulating hormone [FSH] but not estrogen or androgens [9, 10]. Endothelial progenitor cells [EPCs] are also increased in higher stage AVMs, possibly in response to ischemia [11].

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Antiangiogenesis treatment for human AVMs has been based partly on findings in the animal models and human AVM tissue studies and partly on anecdotal observations.

Bevacizumab, which is an antibody to vascular endothelial growth factor [VEGF], was first used in patients with lung cancer who coincidentally had HHT. Initially, a patient with liver failure and cardiac overload due to hepatic AVM received treatment with bevacizumab and was found to have dramatic reduction in cardiac output and improvement in hepatic function. Subsequently, there have been some small clinical trials showing efficacy in epistaxis, GI bleeding, hepatic failure, and cardiac overload in patients with HHT [12–15]. Complications of the drug have been relatively infrequent, and it has been noted that patients with HHT require lower doses to achieve a result than patients with cancer [16].

Thalidomide, which is a beta FGF antagonist, has been used anecdotally in patients with sporadic AVM and more recently in patients with HHT who have GI bleeding and epistaxis [17]. Lenalidomide, an analog of thalidomide, has also been found to be effective in anecdotal cases of GI bleeding in HHT. Both drugs have been used successfully for epithelial hemangioendothelioma. Both drugs are teratogenic, and complications include peripheral neuropathy, somnolence, thrombosis, cytopenias, and pseudotumor cerebri.

Matrix metalloproteinase [MMP] inhibitors, such as doxycycline, minocycline, and marimastat, have been tried in patients with sporadic

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AVM, including brain AVMs. This approach is supported by findings of upregulation of MMPs 2 and 9 in brain AVMs and peripheral vascular malformations. In vitro and animal studies have shown that doxycycline and minocycline change the proteomic expression of endothelial cells and, in some cases, reverse the AVMs in animal models. In the brain AVM trial, there was a trend, not statistically significant, suggesting that MMP inhibition might reduce the risk of bleeding from cerebral AVMs [18]. A 3-year-old child with AVM of the forearm, resulting in significant progress of bone destruction and not responding to embolization, was treated with marimastat, a broad-spectrum MMP inhibitor with dramatic dose-related sustained response [19]. She has been taking this medication for 17 years without side effects. Unfortunately, this drug is not FDA approved and has not been available for compassionate use. Several centers prescribe doxycycline or minocycline to AVM patients, but as yet there is no conclusive data supporting its effectiveness. Tetracyclines are known to cause dental discoloration when administered chronically to children under 8 years of age. In addition, MMP inhibitors can cause allergic reactions, gastrointestinal distress, tendinopathies, and pseudotumor cerebri.

Cox-2 inhibitors [nonsteroidal anti-inflammatory drugs] have a mild antiangiogenic effect and are helpful in controlling pain in patients with AVM.

Venous Malformations (VM) and Lymphatic Malformations (LM)

Sirolimus [rapamycin] is an MTOR inhibitor that has been shown to be effective in reducing mass and symptoms related to the hamartomas in patients with PTEN mutations [3] and is also effective in decreasing symptoms and fluid leakage in patients with diffuse lymphatic malformations [1–2] [20–22].

Early studies also show benefit using sirolimus in patients with extensive venous malformations, including those with blue rubber bleb nevus syndrome [23]. A novel animal model showed that endothelial cells with TIE2 mutation, injected into mice, form vascular lesions resembling human venous malformations. Treatment of the cells and the mice with rapamycin resulted in decreased growth of the vascular lesions, by suppression of AKT. Patients with severely symptomatic venous malformations also improved. It has been noted that the response may require several months of treatment, but treated patients have shown significant improvement in pain, bleeding, lesion size, function, and coagulopathy. Unfortunately, symptoms recur quickly after discontinuation of treatment, but then improve on resuming treatment.

Presently, no benefit has been shown in patients with sporadic AVM treated with sirolimus. Octreotide, a somatostatin analog, has been used in a small series of patients with angioectasias of the bowel [24].

Sildenafil appeared to be effective in a few patients with lymphatic malformation, but subsequent trials did not show a benefit. A larger clinical trial is underway.

Antiestrogen drugs such as tamoxifen and raloxifene have been studied in patients with HHT with possible improvement of epistaxis.

At the time of this writing, the only active clinical trial for drug treatment of patients with AVM with is a European multicenter trial using sirolimus.

Summary

Early studies support the effectiveness of pharmacotherapy for certain vascular malformations, especially extensive lymphatic malformations [rapamycin], hamartomas associated with PTEN mutation [rapamycin], and AVMs associated with ALK1 and ENG mutations [bevacizumab, thalidomide]. As we learn more about the molecular pathways involved in development and progression of vascular malformations, it is likely that new pharmacologic approaches will be identified (Figs. 46.1 and 46.2).

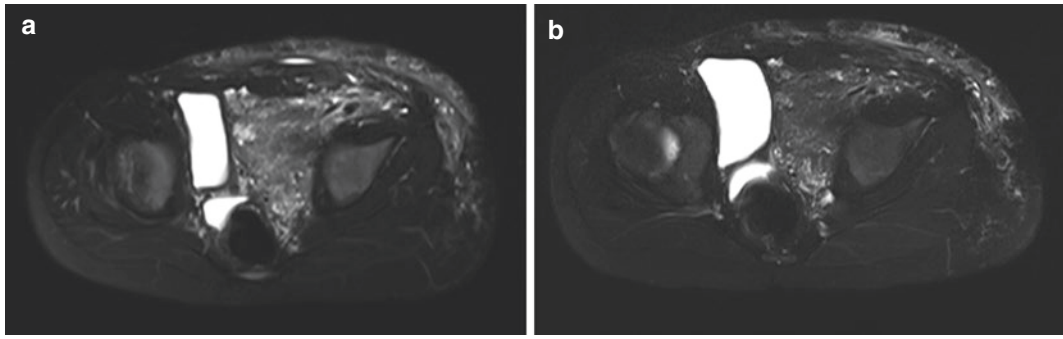

Fig. 46.1 Rapamycin treatment of symptomatic LM in 3-year-old patient with CLOVES syndrome. Patient had bulky overgrowth and leakage from lymphatic vesicles associated with cellulitis. (**a**) Axial STIR of pelvis shows overgrowth and microcystic LM with displacement of bladder. (**b**) After 2 years of rapamycin, the fluid leakage and cellulitis had resolved. MRI shows mild improvement in the bulkiness and fluid content of the LM

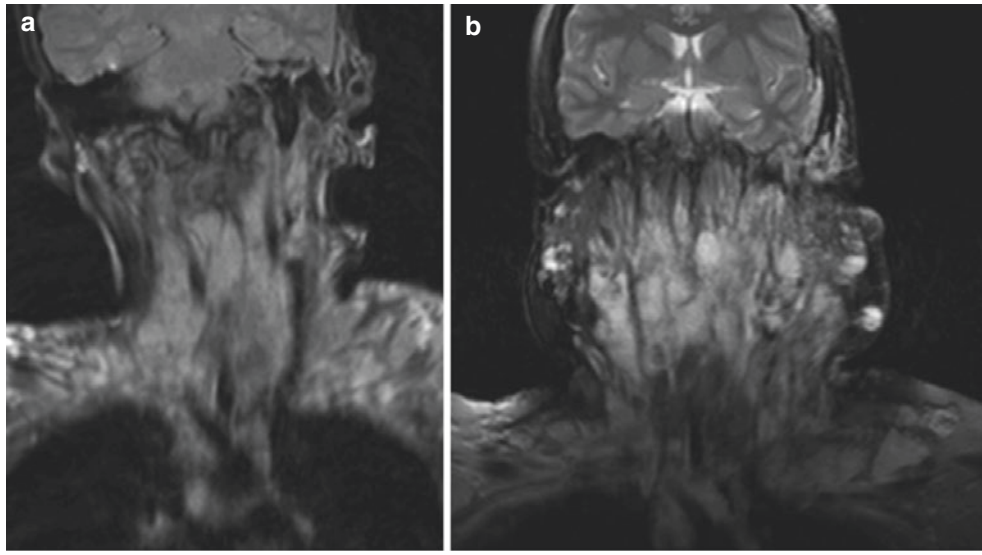

Fig. 46.2 Diffuse VM of the neck, face, airway, scalp, thoracic inlet, and shoulder, presenting with airway obstruction at 4 years of age. VM grew aggressively over childhood and early adulthood. Patient did not do well on rapamycin due to poor compliance. This case shows the need for biological treatment. (**a**) Coronal T2-weighted image at 4 years of age showing the extensive VM. Patient was treated with tracheostomy, extensive percutaneous embolization, and partial resection. Patient did not tolerate ethanol. Treatment continued twice a year after initial hospitalization. (**b**) Five years after presentation, VM still present. Treated with laser therapy, partial resection, and additional sclerotherapy using STS foam. Decannulated.

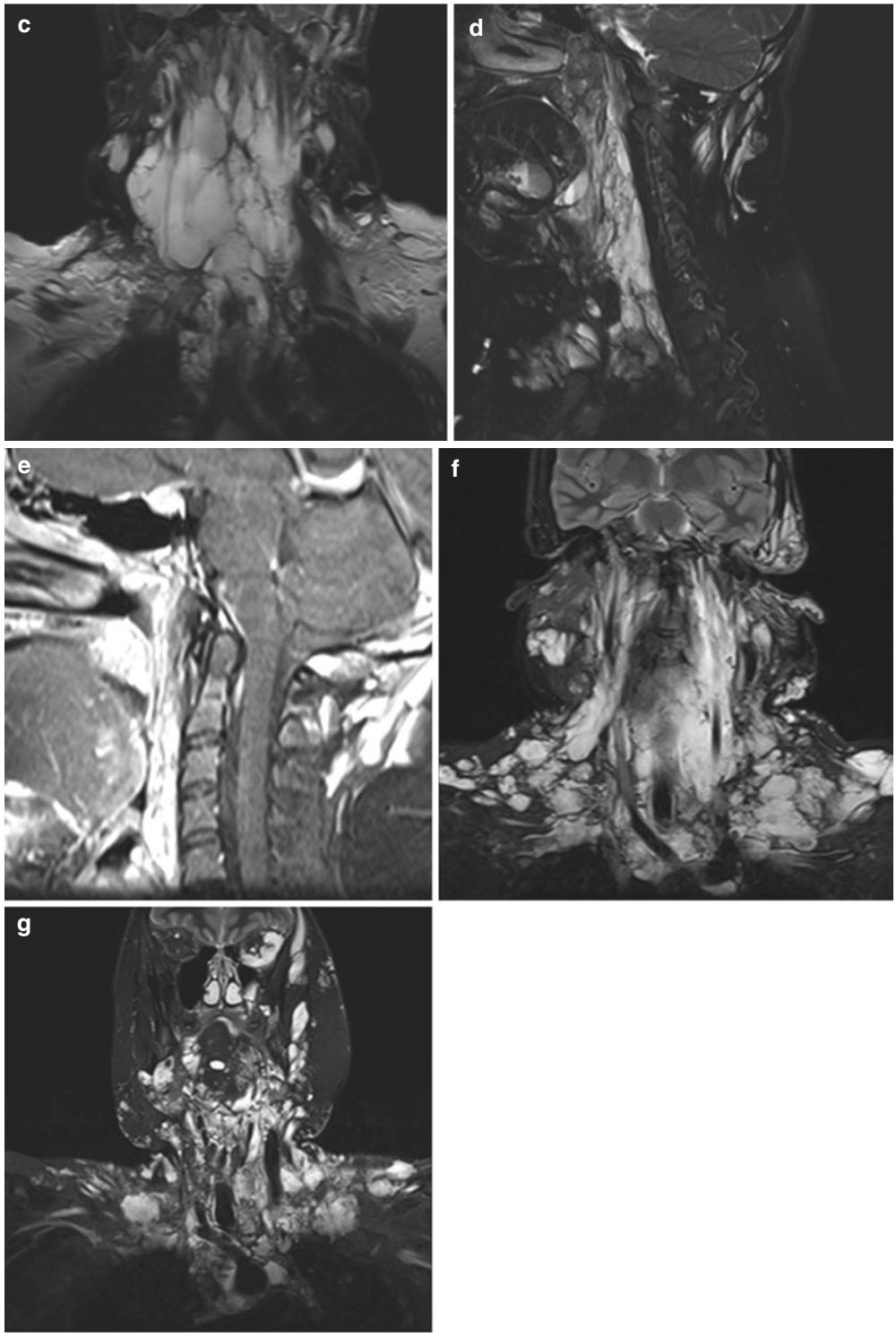

Fig. 46.2 (continued) (**c**, **d**) Six years after presentation, increased growth of VM. Emergency tracheostomy, started new series of sclerotherapy with foam and bleomycin. (**e**) Improved airway after three sessions of foam and bleomycin. (**f**) Eight years after presentation, increase growth of supraclavicular VM. (**g**) 14 years after presentation, after a trial of rapamycin with continued biannual sclerotherapy with foam and bleomycin. Improved but still having pain and tracheostomy dependence

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