5 Medical Management of Vascular Lesions: Current and the Future

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5.1 General Approach for Treatment

The treatment of hemangiomas should be individualized, based upon the size of the lesion(s), morphology, location, presence or possibility of complications, the potential for scarring or disfigurement, the age of the patient, and the rate of growth or involution at the time of evaluation [1, 2]. The potential risk(s) of treatment against the potential benefits is a consideration as detailed below. Medical management of infantile hemangiomas.

Consultation with a pediatric maxillofacial specialist, pediatric ophthalmologist, pediatric dermatologist, vascular anomalies team, or other knowledgeable specialists in pediatric hemangiomas with actual or potential risk for complications and when therapy is being considered [3]. Such children should be referred to as early as possible during the early proliferation phase (i.e., during the first few months of life).

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After clinical examination of the hemangioma, the family may need education regarding the natural course, potential complications; treatment indications; and risks, benefits, and expectations of available treatment options. Depending upon the type of lesion and the parents' level of concern, the patient may need to be re-evaluated frequently during the proliferative phase and again before school entry. Serial photographs of the lesion can help to monitor the clinical course.

The family's education should include information about the natural course, potential complications, treatment indications, and risks, benefits, and expectations of available treatment options for hemangiomas. Families can have realistic expectations about the duration of involution and the possibility of residual changes. The involution phase may continue up to the age of 10 years, although in some studies, complete involution has been known at a median age of 4 years [4, 5]. However, this timeline is highly variable and dependent on hemangioma size, morphology, and location. In many cases, involution does not result in normal-appearing skin. More than one-half of children with untreated hemangiomas experience residual changes such as scarring, atrophy, redundant skin, discoloration, and telangiectasia [6].

Finally, the family should have anticipatory guidance regarding responding to comments and queries from family members and strangers. Parents are commonly subject to inappropriate

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comments from strangers, including accusations of child abuse [7]. Other children, who are usually extremely curious about the hemangioma, are often satisfied to know that "It is a birthmark, it does not hurt, and it will get better" [7]. Addressing the psychosocial aspects of care and providing the parents' anticipatory guidance, emotional support, and reassurance is essential for the effective management of hemangiomas [1, 7].

Treatment modality depends upon the above factors and the availability of specific choices and treating clinicians' experience.

Indications for Intervention Intervention required for complicated lesions can interfere with a vital structure or function.

These include, but are not limited to:

- Very large, rapidly growing cutaneous hemangiomas.
- Lesions in the periorbital region.
- Lesions in the airway, liver, or gastrointestinal tract.

Besides, intervention indicated for lesions associated with other complications such as ulceration and increased risk of scarring or disfigurement [8]:

- Large, plaque-like segmental or nodular hemangiomas, especially in trauma-prone locations, can ulcerate, which invariably leads to scarring (Fig. 5.1a, b).
- Any lesion of the face, especially when large or segmental; hemangiomas of the lip), nose ("Cyrano nose"), and auricle are particularly prone to disfigurement.
- Large, nodular, superficial hemangiomas, especially those that exhibit a sharp, "cliff-like" border or pedunculated lesions (hemangiomas extending from a small base), have the

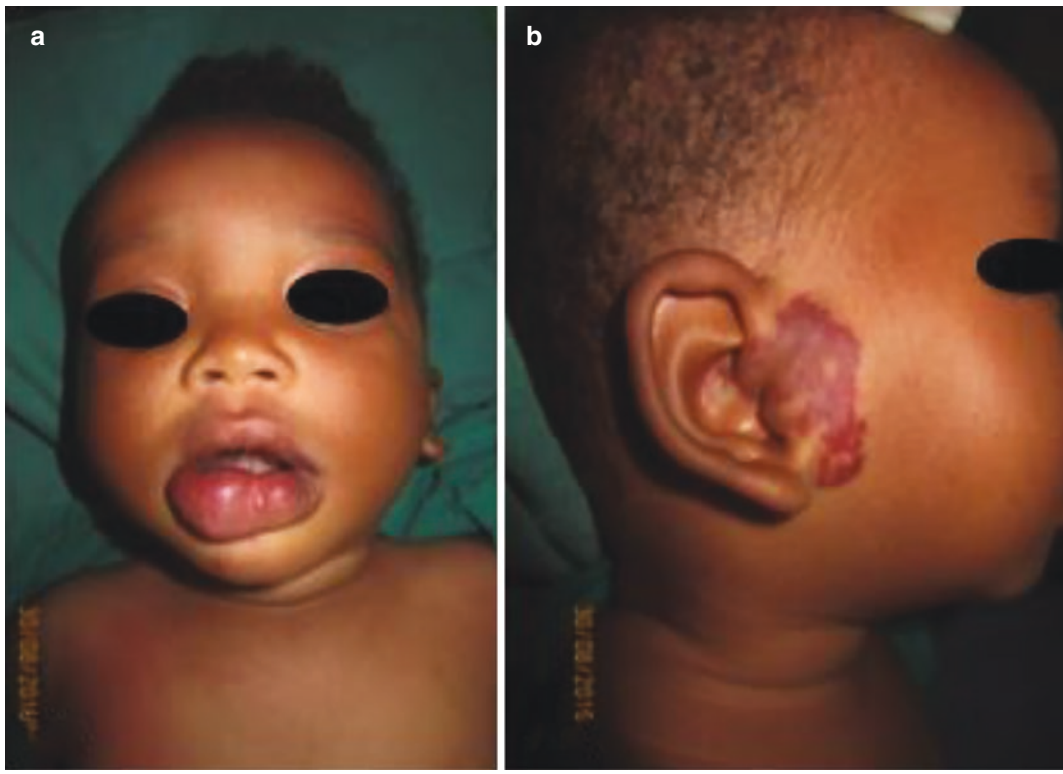


Fig. 5.1 (**a, b**) Lesions of the ear, lip, and nasal regions can cause significant deformity, including airway and vision compromise. These lesions can be amenable to medical management before surgical management. Courtesy: Dr. Amol Kulkarni, Senior Consultant OMF Surgeon, MDS, MOMS RCSEd, FIBCSOMS—ONC Kigali, Rwanda

most significant scarring risk. These lesions are also at risk for leaving residual fibrofatty tissue that may require surgical revision.

5.2 Goals of Treatment [1]

- Prevention or reversal of life-threatening or function-threatening complications.
- Prevention or minimization of a disfigurement from residual skin changes.
- Minimization of psychosocial distress for the patient and family.
- Adequate treatment of ulceration to minimize scarring, bleeding, infection, and pain.

5.3 Uncomplicated Hemangiomas

Serial observation is the mainstay of therapy for many uncomplicated, localized hemangiomas because hemangiomas involute spontaneously after the first year of life. The decision not to pursue medical and surgical therapy may not be necessarily a passive intervention since the growth and involution of the hemangiomas are monitored and the psychosocial implications, particularly facial hemangiomas, anticipated addressed [7]. Serial photographs of the lesion may be helpful to monitor the involution process and outcome.

Local Therapies Local pharmacotherapy is primarily used to treat small or superficial infantile hemangiomas and is not ideal for treating complex lesions. Data on topical therapies' efficacy, including topical beta-blockers, corticosteroids, and imiquimod, are limited.

Topical Beta-blockers Reports of successful treatment of hemangiomas with systemic propranolol led to the investigation of topical beta-blocker therapy to treat infantile hemangiomas [9, 10]. Topical beta-blockers in the treatment of small superficial hemangiomas (e.g., hemangiomas of minor cosmetic concern located on the face, small lesions in the anogenital area) as an alternative to observation, particularly if parents desire treatment.

Topical timolol gel-forming solution, 0.5%, can be used to treat lesions. One drop is applied two to three times per day for 6 to 12 months or until stable improvement.

A systemic review has espoused topical propranolol 1% or topical timolol 0.5% efficacy. And meta-analysis and a large retrospective cohort study [11, 12]. Topical timolol is generally well tolerated. However, data on its safety are limited.

- A retrospective study of 22 high-risk infants (young or preterm infants, infants were receiving more than two drops/day, or infants receiving application to a site with potential increased systemic absorption) with hemangiomas predominantly located in the periocular area treated with topical timolol. They received continuous cardiac monitoring for at least 24 hours [13]. Two infants developed symptomatic bradycardia associated with apnea or hypothermia requiring discontinuation of timolol; both were preterm (weighing <2500 grams) and had a history of symptomatic bradycardia before the initiation of timolol treatment.

High-potency topical corticosteroids (e.g., clobetasol propionate cream) have been used in the past for small, superficial hemangiomas at risk for ulceration or small periocular lesions [14]. They are now infrequently used since the introduction of topical timolol. Topical corticosteroids may be helpful for the treatment of minor but recurrent ulcerations. Adverse effects of long-term use of topical corticosteroids include skin atrophy, hypopigmentation, and hypertrichosis.

The use of intralesional corticosteroids such as triamcinolone acetonide 10 to 40 mg/mL is limited to small, well-localized, deep hemangiomas [15]. Individual doses should not exceed 3 mg/kg. A response usually is noted within two weeks, with the continued response over the ensuing six to eight weeks [16]. Serial injections administered at four-week intervals are sometimes needed.

Adverse effects of intralesional corticosteroids most commonly include local skin atrophy from leaks or inadvertent application to the normal surrounding skin. Adrenal suppression from systemic absorption is also possible, even with localized use [17–19].

5.3.1 Orbital, Mucosal and Maxillofacial Vascular Tumors/Infantile Hemangiomas

Orbital, mucosal, airway, and maxillofacial vascular lesions with rapid growth can cause significant ulceration, bleeding, pain, secondary infection, significant anatomical asymmetry, and psychological effects on the infant and the parents. Many of these infants and children need an inpatient setting. Especially considering cardiovascular or syndromic correlations need care too. Adequate care is taken as the skin is thin in infants. Desiccated mucosa can ulcerate, and topical medication absorption is high along with a further propensity to ulcerate.

5.3.1.1 Beta-blockers

The anti-angiogenic effect of Beta-blockers is a documented therapeutic. In the British journal of dermatology, 2010, Storch et al., espoused the inhibition of signal transduction pathway by beta-blockers in the proliferative vascular endothelial cells. Other actions of propranolol and beta-blockers have been reported to suppress beta FGF, VEGF, MMP-o2, MMP-9 through adrenoreceptor blockade. As we have alluded to in the chapter about etiopathogenesis, the mutational makeup of vascular lesions and oncologic mutational pathways are similar but produce a varied effect. An increased level of matrix metalloproteinases (MMP) is seen in sinonasal malignancy. The MMP levels seen a decrease with beta-blocker therapy compared to an increase with beta-adrenergic receptor agonist norepinephrine.

Propranolol at an Oral dose of 1.0–1.5 mg/kg per day- deep-seated lesions, multiple periodic doses with monitoring of cardiovascular and systemic effects as mentioned below during the proliferative phase (Fig. 5.2a, b).

Timolol maleate 0.5% ophthalmic solution, 25 mg per five mL-effective for topical superficial hemangiomas; applied as coats twice daily to minimize systemic absorption or peripheral runoff loss.

Beta-adrenergic nonselective blocker (propranolol) was a serendipitous therapy intervention for infantile hemangiomas, including orbital lesions. Leaute- Labreze et al., a French group,

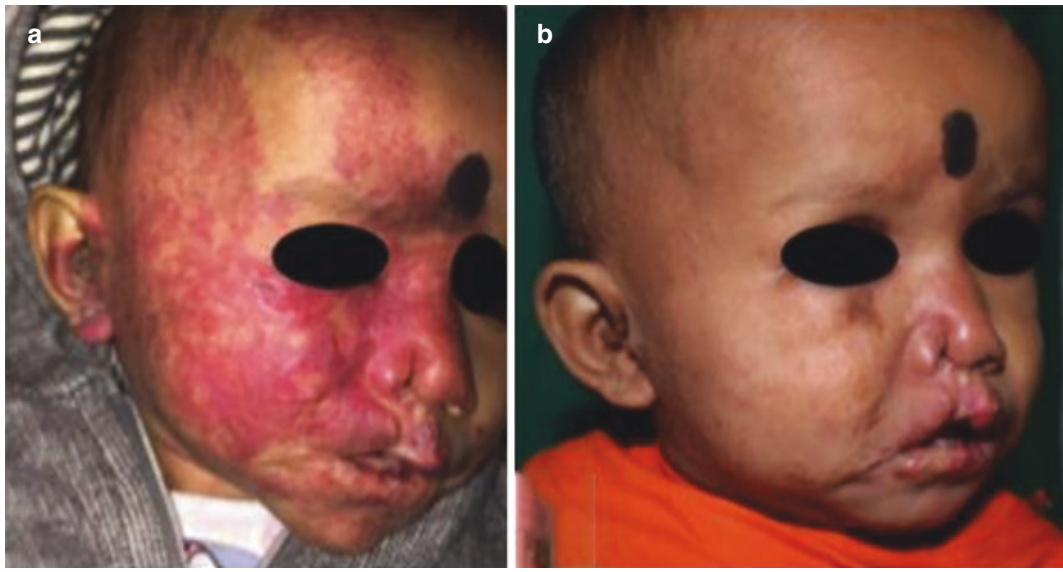


Fig. 5.2 Rapidly involuting congenital Hemangioma (RICH) of right face treated with propranolol therapy ((**a**) pre-treatment, (**b**) post-treatment)

unwittingly utilized propranolol in a couple of infantile maxillofacial hemangioma patients with impending cardiac failure. There was a significant resolution of the rate of growth and size regression of hemangiomas in these children while being used for cardiac symptoms. The group's findings are published in the New England Journal of Medicine in 2008. The use of topical timolol was reviewed by Puttgen et al. in the "Pediatrics" in 2016. Similar studies are in the maxillofacial literature.

The mechanism is poorly understood; the current literature reports growth factors (fibroblast growth factor- FGF, especially betaFGF) and matrix metalloproteinases (MMP 2 & 9) upregulation in these rapidly growing hemangiomas of the maxillofacial and periorbital areas. The beta-blocker therapy can be monitored with a reduction in urine excretion of the FGF and MMP as detected by enzyme-linked immunosorbent assay (ELIZA) and zymography tests.

Beta-blocker adverse reaction of hypoglycemia, hypotension, bradycardia, bronchial constriction, peripheral cyanosis, EKG changes, gastrointestinal symptoms (anorexia, diarrhea, vomiting), sleep changes, drowsiness, skin erythema, and exfoliation are all cared for appropriately, especially in infants. Cardiovascular and vital sign monitoring must be undertaken in an inpatient setting (3–7 days), especially when therapy is at the proliferative phase. Duration of the entire treatment can last between 1 and 8 weeks during the proliferative phase. Low doses of oral beta-blocker are advised during combination therapy with topical beta-adrenergic therapy in mitigating adverse effects.

Complicated Hemangiomas Complicated hemangiomas that require treatment include large hemangiomas at increased risk of scarring or disfigurement, life-threatening hemangiomas (e.g., airway hemangiomas), hemangiomas carrying operational risks (e.g., periocular hemangiomas), or hemangiomas with severe ulceration.

Propranolol Propranolol, a nonselective beta-blocker, is the first-line agent for hemangiomas with the potential to impair function or cause permanent disfigurement if there are no cardiac or neurovascular concerns [20].

Propranolol inhibits the growth and induces the regression of infantile hemangiomas [21] (Fig. 5.2a, b).

Efficacy In 2008, the serendipitous observation that propranolol to treat heart failure in two young children with infantile hemangiomas was associated with a color change, softening, and decrease in size hemangiomas led to the initiation of more extensive observational studies and randomized trials. All studies demonstrated improvement with propranolol [21–28].

Pretreatment Evaluation Treatment with propranolol should undertake in consultation with a pediatric dermatologist or another specialist with expertise in diagnosing and treating pediatric vascular tumors and using propranolol in children.

The pretreatment evaluation should include:

- History should focus on cardiovascular and respiratory abnormalities and family history of heart block or arrhythmia.
- Physical examination is with a cardiac and pulmonary assessment with measurement of heart rate and blood pressure.
- Electrocardiogram.
- Imaging studies, including cardiac ultrasound or cardiac magnetic resonance imaging (MRI), should be obtained in children with large facial hemangiomas at risk for PHACE to rule out the possibility of severe aortic coarctation, which is a contraindication to propranolol use.

5.3.1.2 Contraindications

- Cardiogenic shock.
- Documented chronic and significant sinus bradycardia.
- Documented chronic and significant hypotension.
- Greater than first-degree heart block.
- Heart failure.
- History of bronchospasm or wheezing.

- Hypersensitivity to propranolol.
- Preterm infants with corrected age < 5 weeks (postnatal age in weeks minus number of weeks preterm).

Treatment is usually started with oral propranolol at 0.5–1 mg/kg per day in two or three divided doses with feeds. If tolerated, the dose is then gradually increased (i.e., in increments of 0.5 mg/kg per day) over one to two weeks to the target dose of 2 mg/kg per day, given in two or three divided doses with feeds. Administering propranolol with feeds reduces the risk of hypoglycemia.

Monitoring Parents are educated about recognizing signs of serious adverse effects, including hypotension, bradycardia, wheezing, and hypoglycemia [29]. Early clinical signs of hypoglycemia include:

- Sweating.
- Jitteriness.
- Irritability.
- Cyanosis.
- Poor feeding.
- Hypothermia.
- Lethargy.

All these clinical signs, which are masked by beta-blockers except sweating, are paramount in treatment. Thus, sweating may be the most reliable early sign of hypoglycemia to watch.

Assessment of response and treatment duration — Children with infantile hemangiomas treated with propranolol should be followed up at one- to three-month intervals for response assessment and dose adjustment for weight gain. The treatment duration typically ranges between 6 to 12 months (or until the child is a 12- to 18-month-old) but maybe longer, depending upon the hemangioma's size and location, and response to treatment. Lack of response to treatment with propranolol is rare.

Rebound Growth Rebound growth after propranolol discontinuation was noted in approximately 14–25% of children [30–32]. The factors associated with the risk of relapse are not entirely understood. Some children with rebound growth may need a second course of propranolol. Topical beta-blockers may be used to treat mild to moderate relapses. However, mild relapses do not require treatment in most cases, and parents should be educated about the lesion's eventual involution.

Adverse Effects Serious adverse effects of propranolol therapy for hemangiomas, including hypotension, bradycardia, hyperkalemia, bronchospasm, and hypoglycemia, are infrequent [28, 33, 34]. Restless sleep, constipation or diarrhea, and cold extremities are more commonly reported [34]. Thus, children treated with this drug need close monitoring.

Of the potentially severe adverse effects, hypoglycemia is the most worrisome—risk reduction by daytime administration of propranolol with a feeding shortly before or after administration. Propranolol is discontinued during periods of illness or inadequate oral intake [20, 29, 35].

Other Beta-blockers A few small trials suggest that nadolol and Atenolol may be as effective as propranolol for the treatment of proliferative hemangiomas, potentially with a lower rate of adverse effects such as Broncho reactivity and sleep disturbances [36, 37]. However, these findings are preliminary and need to be confirmed by more extensive trials.

Systemic Corticosteroids Treatment with systemic corticosteroids remains a treatment option for patients with complicated hemangiomas, in whom treatment with beta-blockers is contraindicated.

Systemic corticosteroids were as effective as propranolol in a small randomized trial [38].

Dosing The starting dose for prednisolone is 2 to 3 mg/kg per day. A single, morning dose is preferred to minimize adrenal suppression. A response is usually seen within the first few weeks [39, 40]. Treatment is generally continued for several months or more, depending upon the indications for treatment, the response, and the child's age at initiation.

Prednisone should be slowly discontinued since abrupt discontinuation or rapid tapering of glucocorticoids while a hemangioma is still in its active growth phase may result in rebound proliferation.

Adverse Effects Adverse effects of systemic corticosteroids are more likely to develop with higher doses and courses of six months or longer, and they resolve with drug tapering.

Cushingoid facies, personality changes, delayed skeletal growth, gastric upset occurs in some cases. Serious corticosteroid complications, such as aseptic necrosis of the femoral head, hypertension, osteoporosis, and cataracts, are infrequent in children [41].

Other Systemic Therapies Vincristine and interferon alfa are alternative systemic agents for treating complicated hemangiomas but are rarely used since the advent of propranolol.

STEROID THERAPY
SYSTEMIC STEROIDS—Prednisolone in proliferative phase
FOCAL STEROIDS—Triamcinolone (40 mg/ml), Betamethasone (6 mg/ml)
VINCRISTINE FOR LIFE-THREATENING LESIONS
INTERFERON THERAPY- ALPHA 2a and BETA (serious side effects)
Beta-blockers – 2 mg/kg body wt. (propranolol)

Surgical Therapies When a hemangioma poses primarily cosmetic concerns, therapeutic interventions are tailored individually. In addition to systemic, topical, and intralesional medications, therapeutic options include laser therapy and surgery.

5.4 Special Situations

Periocular Hemangiomas Periocular hemangiomas can compromise vision and cause amblyopia, astigmatism, or strabismus. These hemangiomas can be evaluated by an ophthalmologist experienced with hemangiomas and their treatment [16]. Surgical excision also may be an option for small, localized lesions [42–45].

5.4.1 Ulcerated Hemangiomas (Fig. 5.3a, b)

Wound Care Gentle and meticulous local wound care is the mainstay of ulcer therapy and is particularly important for lesions in locations subject to trauma and infection, such as the perineum. Local wound care reduces pain and helps to prevent secondary infection [46]. Commonly used therapies include topical antibiotics, barrier creams, and non-stick dressings [47]. Very gentle debridement of crusted wounds with saline soaks two to three times daily may also be helpful since crusting prevents re-epithelization and favors infection.

Topical metronidazole gel, often used in combination with topical mupirocin, has proved to be safe and efficacious for ulceration, particularly in intertriginous or moist areas such as the lip and perineum [46]. When clinically indicated, broad-spectrum oral antibiotics are also occasionally used.

Oral Propranolol We suggest oral propranolol in addition to meticulous wound care and appropriate analgesia for the treatment of ulcerated hemangiomas.

A beneficial effect of propranolol on ulcerated hemangiomas has also been reviewed in several case series [48–51].

Analgesia The pain associated with ulceration can be severe. Affected infants commonly suffer from sleep disturbance and increased irritability. Use of oral acetaminophen (without codeine) or a topical anesthetic agent (i.e., lidocaine hydrochloride 2 to 5% ointment) may be warranted.

Airway Hemangiomas (Fig. 5.4a–c) Because of the infant airway's small caliber, a growing airway hemangioma can lead to life-threatening airway obstruction.

Systemic propranolol is generally the first line of therapy for children with symptomatic airway hemangiomas [22, 52]. Laser ablation is an occasional second-line therapy [53]. Rarely, a tracheotomy may be required. Adult hemangiomas of the airways are reviewed with flexible endoscopy (Fig. 5.4a–c) frequently if asymptomatic.

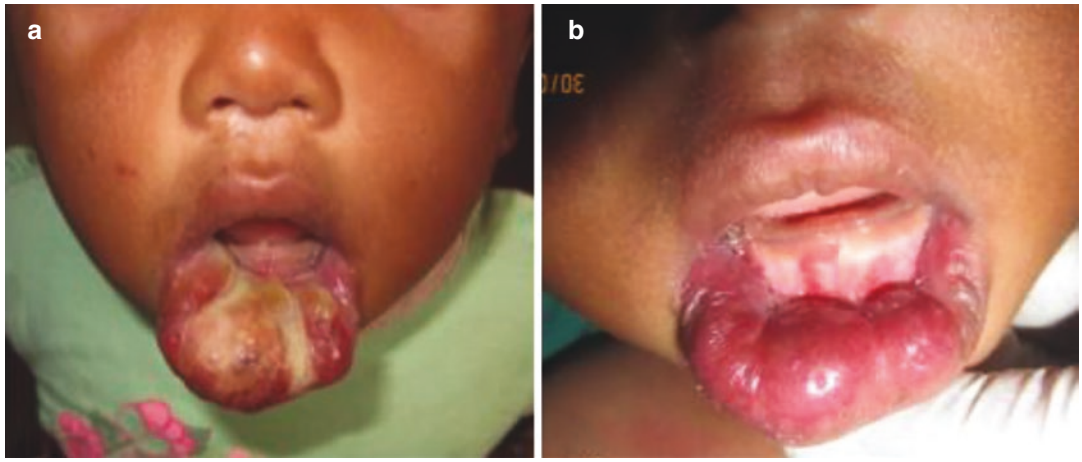


Fig. 5.3 (**a, b**) Pre- and post-op of lip with ulceration and progressive increase in the size and thickness. Therapy was with an intralesional Injection of Bleomycin 1 IU / Kg weight. There is no safe dosage for this useful and readily available chemotherapeutic agent called Bleomycin. It is known to cause pulmonary, hepatic dysfunction even in the smallest doses. (Pictures Courtesy: Dr. Amol Kulkarni, Senior Consultant OMF Surgeon, MDS, MOMS RCSEd, FIBCSOMS—ONC Kigali, Rwanda)

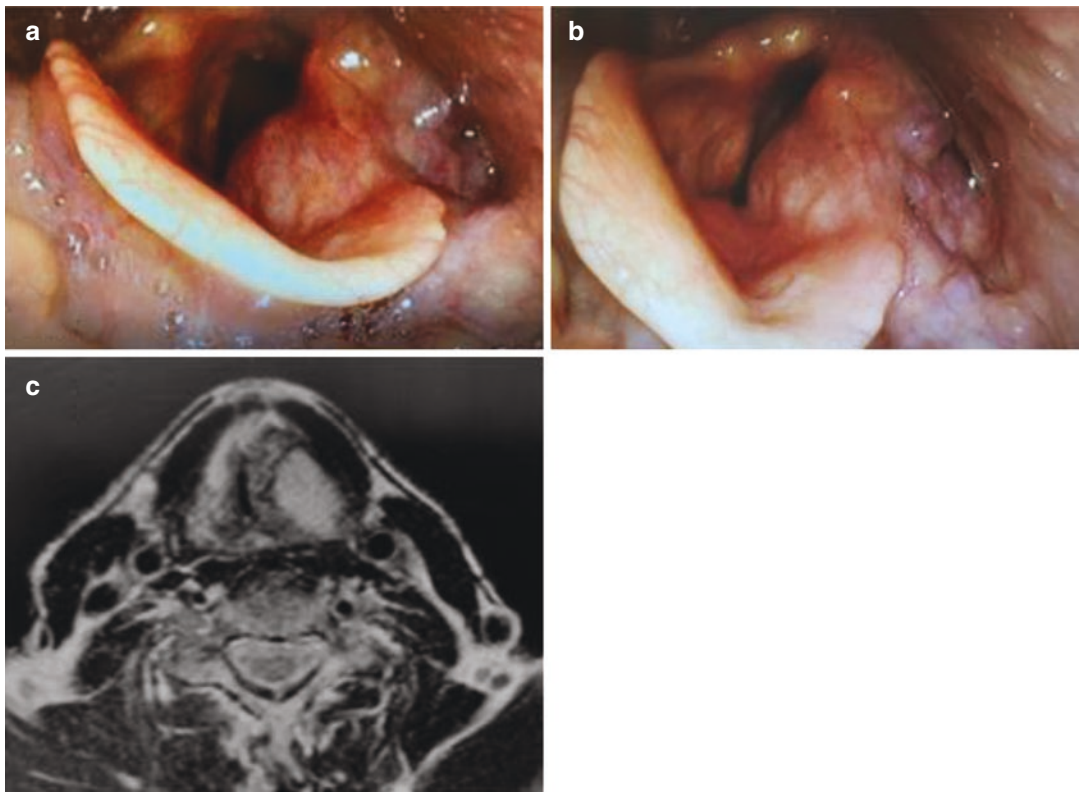


Fig. 5.4 (**a, b**) Endoscopic images of left laryngeal area showing low flow vascular lesion of the pyriform fossa, (**c**) MRI scan image of the same lesion with intense contrast uptake in left pyriform with vocal cord deviation in the laryngeal area

Surgical resection is a consideration in noted obstructive or bleeding episodes. Sclerotherapy as described can be utilized for management.

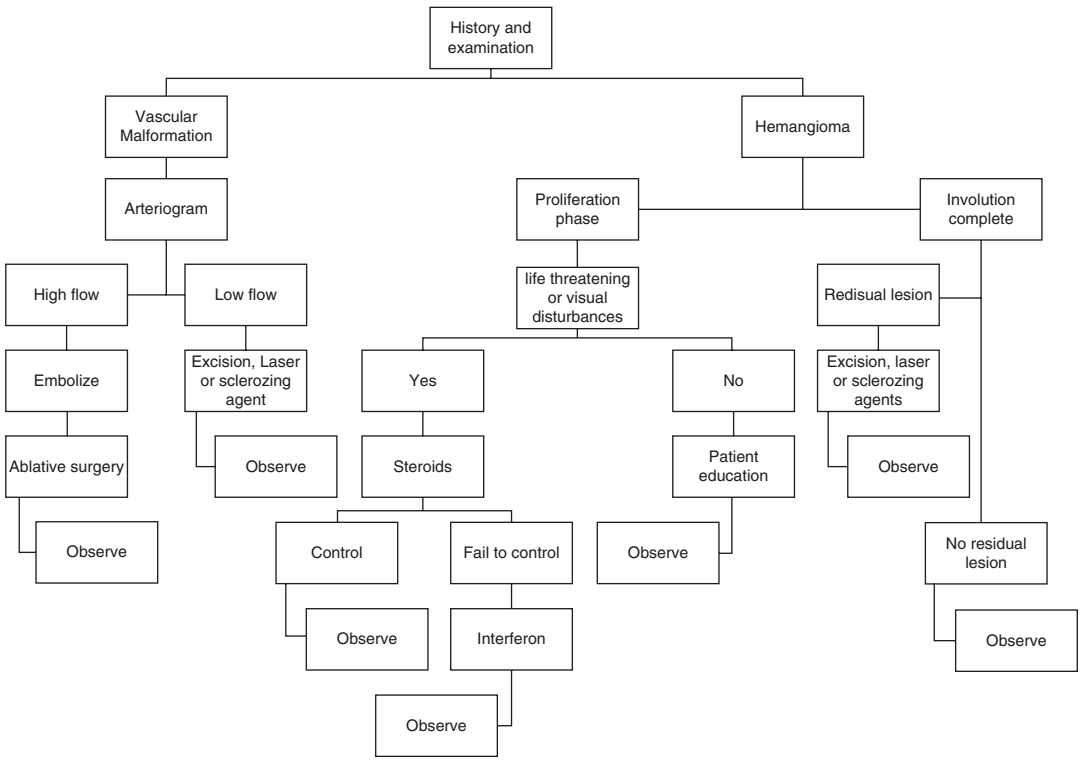
PHACE Syndrome The presence of severe arterial anomalies may restrict propranolol in some patients with PHACE syndrome [54]. In addition to large facial hemangiomas, patients with this disorder exhibit coarctation of the aorta and abnormalities of the aortic arch's cerebral and cervical vasculature and vessels. A small percentage of patients with severe cerebral or cervical anomalies develop acute arterial ischemic stroke, most often during infancy or toddlerhood [55].

Consensus guidelines recommend that infants with PHACE syndrome be thoroughly evaluated with magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) of the head and neck and cardiac imaging to include the aortic arch before starting propranolol treatment [20].

The risks and benefits of propranolol treatment for patients with PHACE syndrome who have high-risk MRA features are reviewed for treatment and in consultation with neurology and cardiology specialists [20].

Lymphatic malformations are treated depending on the type and location in the head and neck. As mentioned previously, these lesions can cause pressure on the airway, aerodigestive tract, and enlarge due to repeated infection or hemorrhage into the lesion. In the majority of patients with macrocystic LMs, sclerotherapy with *Picibanil (OK-432)* has shown good results. Patients may develop inflammation at the site of injection and fever, which is managed symptomatically. Microcystic LMs may require systemic therapy with *Sirolimus* or surgery as they do not always respond to Picibanil. Sirolimus is a natural macrolide secluded from the Streptomyces genus (Streptomyces hygroscopicus). It causes a decrease in the vascular endothelial growth factor (VEGF) and is a key regulator in lymphangiogenesis and angiogenesis.

Algorithm for management of vascular anomalies (Adapted from: R. Mattassi, D.A. Loos and M. Vaghi for congenital vascular anomalies. Fonseca RJ, Turvey RD, Timothy A, Marciani RD, Turvey TA. Surgical pathology. Philadelphia: Saunders; 2000.)



5.4.2 Sclerosing Agents (Table 5.1)

PYM, also known as Bleomycin A5, is the most used single-drug therapy for the treatment of cervicofacial malformations. Transient fever and swelling are commonly seen side effects. Skin ulceration and subcutaneous tissue atrophy are scarcely seen complications.

Absolute ethanol causes alteration in cellular proteins and hence damages the endothelium of the vascular wall leading to obliteration of its lumen. Common complications include nerve injury, necrosis, and ulceration of skin.

OK-432 is a lyophilized preparation of low-virulence bacteria, group- A Streptococcus pyogenes, incubated with benzylpenicillin. It causes,

Table 5.1 Table for use of medical therapy in vascular lesions (Adapted from: S.C.Nair, Vascular anomalies of the Head and Neck region. Journal of Maxillofacial and Oral Surgery. https://doi.org/10.1007/s12663-017-1063-2)

Sclerosing agent	Important facts	Advantage	Disadvantages
Bleomycin	First used by Yura and coworkers in 1977 [25]	Can absorb systemically at very low levels, even if administered locally [25]	Development of fatal pulmonary fibrosis even in low doses [26] hyperpigmentation
Pingyangmycin	Chemical structure similar to Bleomycin A5, this anticancer drug can be extracted from gram +ve streptococci	Most effective in treating vascular malformations of size less than 5.0 cm and for superficial lesions. Percutaneously, it is very simple and effective	Allergic reactions, cutaneous or mucosal necrosis and sensory nerve or motor nerve injuries
5% sodium morrhuate	Earlier, it was successfully used	May remain in lesion, causing sclerosis and involution for a longer duration	Irritating and has tendency for the induction of severe reactions like tissue necrosis
Absolute ethanol	Clinical application over the decades used globally, even in complicated and extensive lesions [27]	Low cost, remarkable results, quick metabolism and lower recurrence rates [28]	Ethanol sclerotherapy is painful and requires general anesthesia. Facial palsy and allergy
Lauromacrogol aethoxysklerol or polidocanol	Most effective sclerosing agents with low risk of complications and contains 95% hydroxyl polyethoxydodecane with 5% ethyl alcohol	Injection technique is simple, safe and time-saving, painless, rarely allergic, and well tolerated by patients	It may cause necrosis and ulceration, if solution leaks out into mucosa or skin
OK-432	OK-432, also called picibanil, is a biological preparation of lyophilized powder containing Streptococcus pyogenes Su strain cells (group A, type 3) treated with benzylpenicillin potassium [29]	No perilesional fibrosis [30]Possibility to perform multiple subsequent injections with additional shrinkage response Low complication rate Better esthetics results [30]	The main disadvantage of OK-432 is that some lesions require more than one injection to shrink satisfactorily. Other complications include fever, allergy, erythema and swelling [31]
Detergent sclerosants (sodium tetradecyl, the most commonly used sclerosant, ethanolamine and polidocanol	Detergents came into use in the 1930s they work by a mechanism known as protein theft denaturation	Addition of air results in a microfoam which is felt to be more effective than the bland solution. A reasonable dose limit for image-guided sclerotherapy is 0.5 ml/kg or 30.	It is painful to inject, but effective and relatively nontoxic

induction of various cytokines. The inflammatory response caused by this remains localized and causes endothelial damage. The complications include local swelling and transient facial nerve palsy.

Ethanolamine oleate is an emulsion of fatty acids, which induces thrombosis and damages the endothelium. Complications like ulceration and necrosis of skin are known but infrequently observed.

Polidocanol is a non-ionic detergent, causes absorption at the cell membrane and leads to lysis of endothelial lining. Superficial necrosis of skin or mucosa is a known complication with Polidocanol.

Doxycycline belongs to the tetracycline group of antibiotics. Its mode of action is not yet clear, but its effects are known to be due to inhibition of matrix metalloproteinases and cell proliferation. It also causes suppression of vascular endothelial growth factors during angiogenesis and lymphangiogenesis. This further leads to dense adhesions and fibrosis due to collagen and fibrin deposition. Macrocystic LM's show a better response to treatment with doxycycline in comparison to microcystic LMs. Hemorrhage, cellulitis, pain, and transient edema are commonly seen complications. Scarring, skin excoriation, and Horner syndrome are seen less commonly. These adverse effects are self-limiting and likely to be related to the sclerosing effect rather than a side effect of the medication itself.

STS, also known as *sotradecol*, causes denaturation of proteins like clotting factors due to disruption of the normal architecture of the lipid bilayer in cell membranes of endothelial cells. This causes fibrosis and occlusion of vessels. It is not known to have any major complications so far.

5.4.3 Bleomycin

As it is available and inexpensive this drug has been effectively used for cystic lymphatic lesions to scar them to reduce the volume of macrocyctic lesions.

Bleomycin is used widely for the treatment of VMs and microcystic lesions too.

It inhibits DNA synthesis and has a non-specific inflammatory reaction on the endothelial cells. Adverse effects of bleomycin are minimal and transient (Fig. 5.5a, b), mostly being localized pain and swelling. Skin infections around injection are seen less commonly. Some people report occasionally severe nausea.

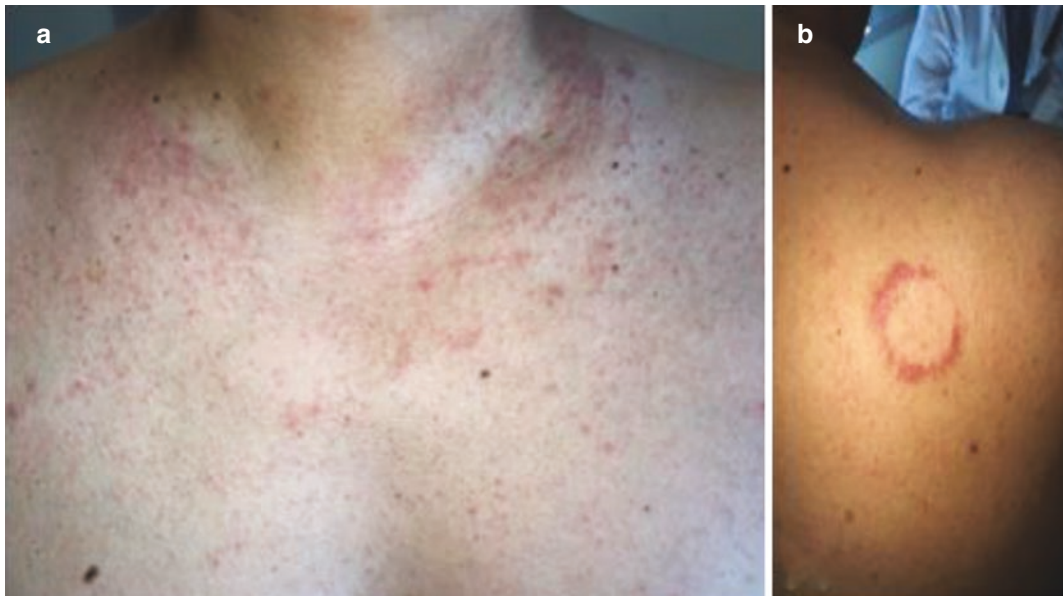


Fig. 5.5 (**a**) Koebner phenomenon after bleomycin injection for a vascular cystic lesion, with rash around the neck due to friction irritation of clothing. (**b**): shows annular or ring-like erythema of the area of electrocardiogram lead sticker

It has been used along with OK-432 and alone. Large lymphatic lesions treated with intralesional Injection of Bleomycin 1 I.U / Kg weight. There is no safe dosage for this effective and readily available chemotherapeutic agent called Bleomycin. It is known to cause pulmonary hepatic dysfunction even in the smallest doses.

mechanism of action on microcystic disease is not completely understood and may involve derangement of tight junctions between endothelial cells or induction of endothelial mesenchymal transition. The overall response is a favorable but complete response is seen in only about 20–57%.

The authors follow a protocol of intralesional injection of 15 IU Bleomycin in 5 ml of fresh normal saline, administered every 15 days. Most patients show a response in 3–4 sittings (Fig. 5.6a–c).

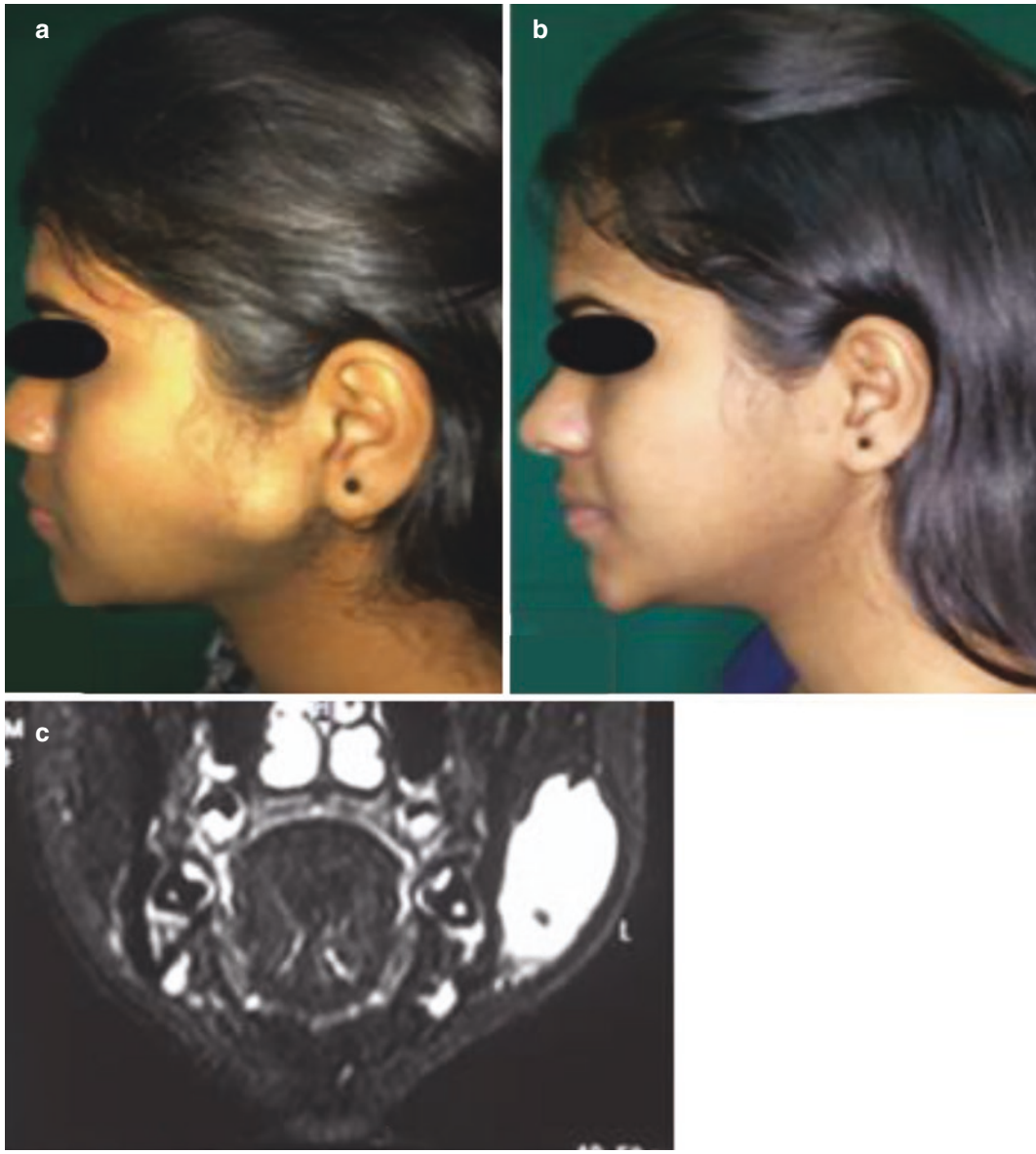


Fig. 5.6 Venous malformation-Left cheek (**a**) before sclerotherapy, (**b**) after sclerotherapy, (**c**) pretreatment T2-weighted MRI image

5.4.4 Protein Chain in a Vascular Cell that Transmits Signal from a Cell Surface Receptor to the DNA in the Cell Nucleus

Growth and differentiation of the vascular lesion and its endothelial cell proliferation or initiated at the cell membrane tyrosine kinase receptor with the RAS- RAF downstream to nucleus MAPK dependent gene transcription. The illustration demonstrates the potential therapy and inhibition of Src-tyrosine kinase family inhibitors; rapidly accelerated fibrosarcoma (RAF) inhibitors; mitogen activating pathway kinase-extracellular signal-regulated kinase (MEK) inhibitors; extracellular signal-regulated kinase is (ERK) inhibitors (Fig. 5.7).

5.4.5 Sirolimus/Rapamycin

Rapamycin is a chemotherapeutic agent derivative of *Streptomyces hygroscopicus* bacteria, a macrolide used for targeted therapy to block the PIK3CA

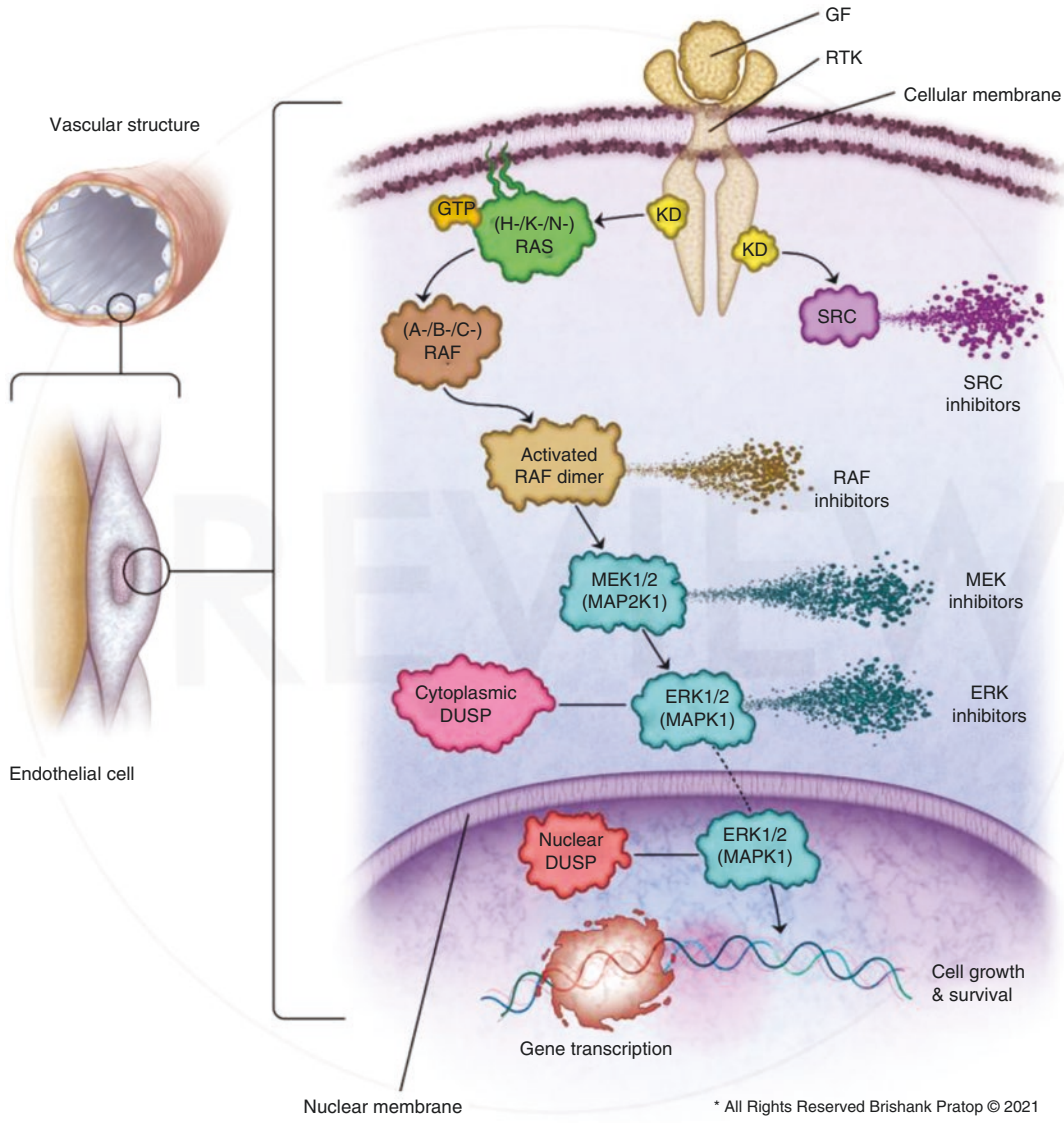


Fig. 5.7 MAPK/ERK pathway (well known as the Ras-Raf-MEK-ERK pathway) potential therapeutic inhibitors

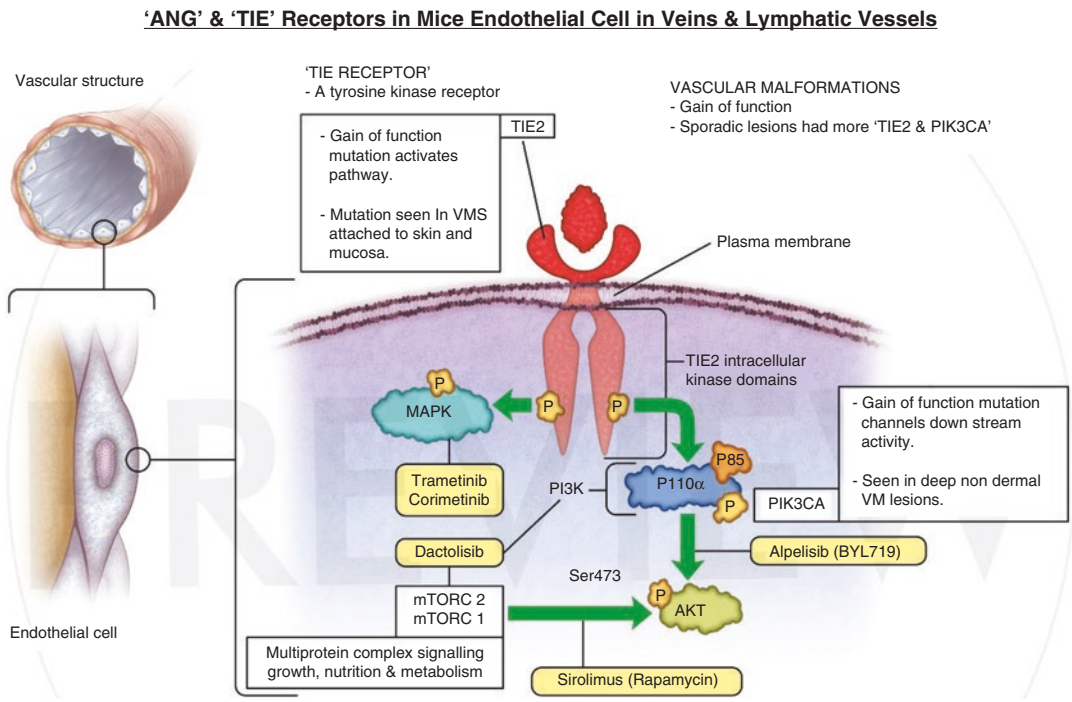


Fig. 5.8 Angiopoeitin (ANG) based two transmembrane tyrosine kinase receptors-TIE1 and TIE 2 (tyrosine kinase with immunoglobulin and epithelial growth factor (EGF) homology domain) homologous receptors have been identified in vascular and lymphatic endothelial cells leading to vascular malformations. This picture illustration represents the identified pathway and the potential therapeutic molecular therapies

pathway (Fig. 5.8). Rapamycin (Sirolimus) inhibits cellular proliferation. Sirolimus has varied success in vascular malformations therapy, but clinical outcomes have not been consistent. Authors here present personal experiences in use with syndromic patients has been with adequate caution. Multiple centers have used Sirolimus empirically, and mutational tests before using the therapy have not been consistent.

Sirolimus as a B & T cell suppressor is very well studied in transplant patients, as mentioned with useful utility. Its use in head and neck vascular lesions has shown a qualitative reduction in size and side effects of bleeding and vesicular discharge. Nevertheless, Sirolimus therapy has documented side effects for its use with complicated LM throughout the body. A reduction in cellulitis and hospitalizations with cellulitis-related complications documented with case reports and lesion management publications. Gastrointestinal, general metabolic toxicity, blood dyscrasias, bone marrow suppression (even though one of the treatment indications is dyscrasias of hematological and marrow-derived cell function) were the reported adverse effects of the medications.

The literature on Sirolimus and its efficacy is equivocal. The best candidate for this therapeutic advantage is not clear. Strychowsky et al., in the 2018 phase 2 trial using Sirolimus in patients, evaluated the benefits of its empiric use complicated LM. They reported a reduction in cellulitis and incidence of hospitalizations with cellulitis-related complications. The adverse effects of therapy were—Metabolic toxicity (3%), gastrointestinal disturbance (3%), and blood/bone marrow abnormalities (27%). Not all the patients receiving therapy had a genetic test for the PIK3CA mutation confirmed. So, treatment was based on clinical considerations. Other studies have reported on anecdotal success with Sirolimus. Sirolimus's current indications for

therapy are for pain, lesion enlargement, vesicular ulcerations, bone erosion and expansion, bleeding, airway compression, hematologic abnormalities, and complex symptomatic cases. Please also review the pathways of this therapy and references in Chap. 2 on mutational basis and etiopathogenesis of vascular lesions.

Many medications like interferons, bisphosphonates, and chemotherapeutic agents have been used by various groups of physicians with anecdotal evidence and with a lack of large clinical trials. Many of the patients have suffered long-term hepatic and renal impairment with such aggressive therapy in benign lesions. The molecular basis as being investigated (Fig. 5.9), will channel better therapeutic modalities for benign vascular lesions.

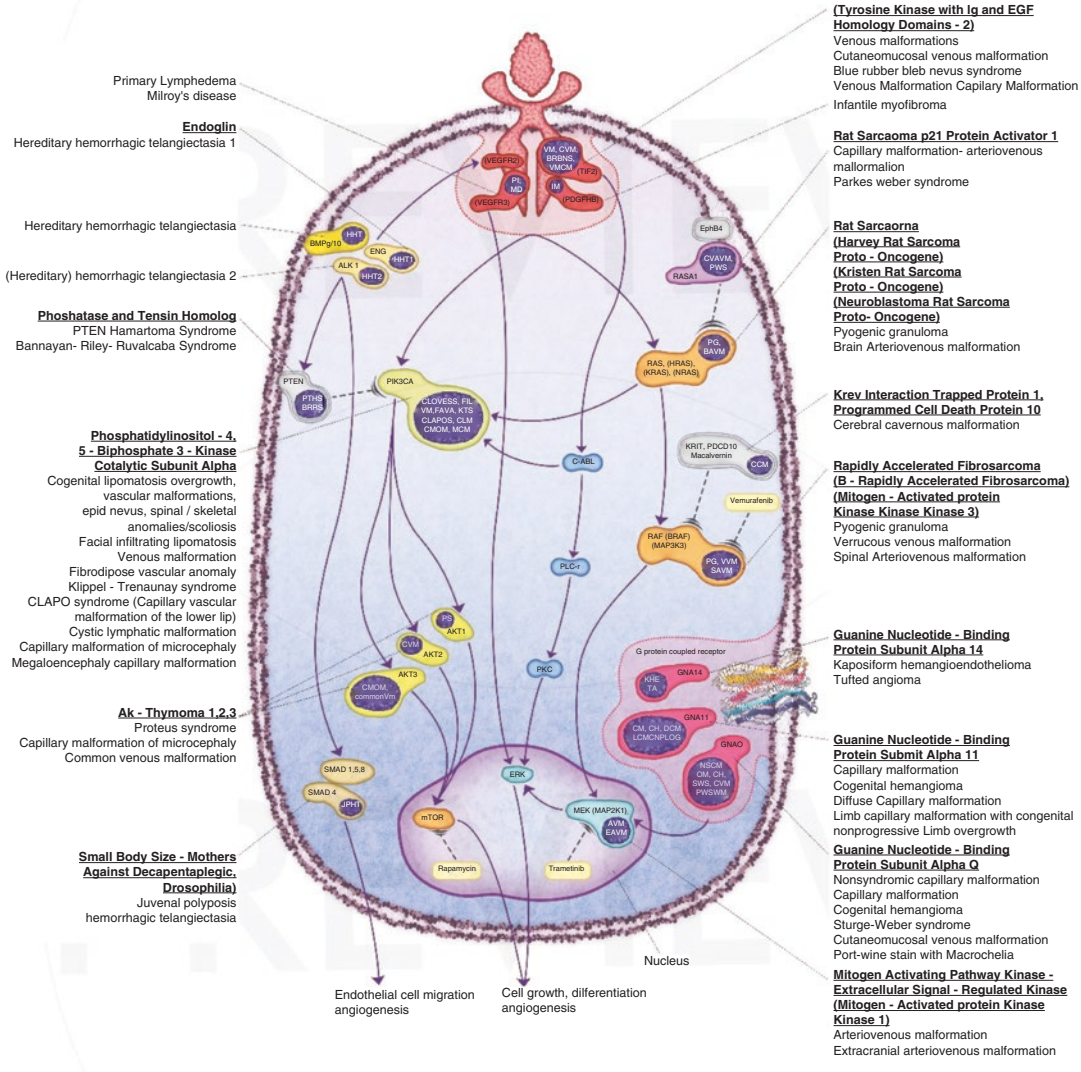


Fig. 5.9 Summary illustration of well-known genetic mutations based on that transmembrane tyrosine kinase MG protein-coupled signaling pathways. The protein mutations are abbreviated with the number's analogs. These vascular malformations caused by the mutations on the syndromic presentations are listed below the receptors which are mutated. Majority of these mutations are based on the well-known Ras-Raf-MEK-ERK and PIK3CA pathways. Adapted from Refs. [56–58]

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