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CANDIDATE'S THESIS

The Biology and Management of Subglottic Hemangioma: Past, Present, Future

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Objectives/Hypothesis: **Objectives were 1) to review the presentation, natural history, and management of subglottic hemangioma; 2) to assess the affect of five variables (age, gender, degree of subglottic narrowing, location and extent of subglottic hemangioma, and lack or presence of other hemangioma) and the outcome of six different treatment modalities (conservative monitoring, corticosteroid, laser surgery, tracheotomy, laryngotracheoplasty, and interferon) in the management of subglottic hemangioma; and 3) to present specific guidelines to help determine the best possible treatment modality at the time of initial presentation.** ***Study Design:*** **Retrospective review in the setting of three tertiary care pediatric medical centers.** ***Methods:*** **Methods included 1) extensive review of the literature; 2) a systematic review with respect to age, gender, presentation, associated medical problems, location and degree of subglottic narrowing, initial treatment, need for subsequent treatments, outcome, complications, and prognosis; and 3) statistical analysis to determine the effect of five variables (age, gender, degree of subglottic narrowing, location and extent of subglottic hemangioma, and lack or presence of other hemangioma) and the outcome of six different treatment modalities (conservative monitoring, corticosteroid, laser surgery, tracheotomy, laryngotracheoplasty, and interferon).** ***Results:*** **In all, 116 patients with a mean age of 4.7 months were treated. The most common location of subglottic hemangioma was the left side. The range of subglottic narrowing was 10% to 99% (mean percentage, 65%). Twenty-six patients (22%) were managed with a single treatment modality, which included conservative monitoring (n = 13), corticosteroid (n = 11), and tracheotomy (n = 2). Ninety patients (78%) required multimodality treatments. Overall, the treatments included conservative monitoring (n = 13), corticosteroid (n = 100), tracheotomy (n = 32), CO_2 laser (n = 66), interferon (n = 5), and laryngotracheoplasty (n = 25). Complication rates included the following: conservative monitoring (none), corticosteroid (18%), tracheotomy (none), CO_2 laser (12%), interferon (20%), and laryngotracheoplasty (20%). The following variables showed statistical significance in the outcome of different treatment modality: 1) degree of subglottic narrowing ($P < .001$), 2) location of subglottic hemangioma ($P < .01$), and 3) presence of hemangioma in other areas ($P < .005$). Gender ($P > .05$) and age at the time of presentation ($P > .06$) did not show any statistical significance on the outcome of the treatments.** ***Conclusion:*** **Each patient should be assessed comprehensively, and treatment should be individualized based on symptoms, clinical findings, and experience of the surgeon. The authors presented treatment guidelines in an attempt to rationalize the management of subglottic hemangioma and to help determine the best possible treatment modality at the time of initial presentation.** ***Key Words:*** **Airway, hemangioma, corticosteroid, laser surgery, interferon, vincristine.**

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INTRODUCTION

Subglottic hemangioma is a rare condition with the potential to cause life-threatening complications in the newborn period. The most common presenting symptom is biphasic stridor, which is often exacerbated by crying and upper respiratory tract infection. Symptoms frequently present before 6 months of age. The natural history of this entity is characterized by progressive airway obstruction during the proliferative phase followed by resolution of symptoms during the involution phase. Since the early

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1970s, a number of treatment modalities have been advocated with variable success and morbidity.

Currently, there are no specific guidelines for the treatment of subglottic hemangioma, and most patients undergo several different treatment modalities during the course of their management. The purposes of the present study were to review the presentation, diagnosis, and natural history and to present guidelines in an attempt to rationalize the management of subglottic hemangioma and to help determine the best possible treatment at the time of initial presentation.

MATERIALS AND METHODS

Patients treated for subglottic hemangioma at three pediatric tertiary medical centers between 1980 and 2002 were identified. A systematic chart review was undertaken to determine the age, gender, initial presentation, significant medical and family history, location and degree of airway narrowing, involvement of other areas, initial treatment, need for subsequent treatments, efficacy of each treatment modality, and complications.

Six different treatment modalities (conservative monitoring, corticosteroid, laser surgery, tracheotomy, interferon, and laryngotracheoplasty [LTP]) were used in the management of our patients. We hypothesized that the outcome of each of these treatment modalities is based on the following variables: 1) age at the time of presentation, 2) gender, 3) lack or presence of other hemangioma, 4) degree of subglottic narrowing, and 5) location and extent of the subglottic hemangioma. We performed linear discriminant analysis[1] to determine the effect of these five predictor variables on the outcome of the six different treatment modalities just mentioned.

The five predictor variables were coded as follows: gender, male or female; age, months; location of subglottic hemangioma, unilateral = 1, unilateral with posterior extension = 2, bilateral = 3, and circumferential = 4; degree of subglottic narrowing, 0 to 100; and other hemangioma, yes or no. Complete data for the predictor variables were available for 82 patients. SAS software was used for all data management and analyses.[2]

RESULTS

In all, 116 patients with subglottic hemangioma were identified. There were 78 female and 38 male patients. Fifty-two patients were the product of a full-term pregnancy and normal delivery, 8 patients were born at less than 36 weeks of gestation, and no information was available on 56 patients. The age at the time of presentation ranged from 1 to 18 months (mean age, 4.7 mo). The most common presentation was biphasic stridor noted in more than 90% of patients. Other signs and symptoms included cyanosis, apnea, and retraction. Eighteen patients (16%) presented with other medical problems (Table I).

TABLE I.
Associated Medical Problems.

History	No. of Cases
Bronchopulmonary dysplasia	2
Hypospadias	1
Reflux	5
Ventriculoseptal defect	1
Right-side aortic arch	1
Aberrant left-side subclavian	1
Midline sternal cleft	1
Aberrant Innominate artery	1
Hyaline membrane myopathy	3
Left-side vocal cord paralysis	1
Hypoplasia of descending aorta	1

All patients underwent direct laryngoscopy and bronchoscopy. Diagnosis of subglottic hemangioma was based on endoscopic appearance of the lesion as a reddish-bluish submucosal mass. Lesions were described as bilateral (n = 25 [22%]), left-sided and posterior (n = 24 [21%]), circumferential (n = 24 [21%]), unilateral and left-sided (n = 19 [16%]), unilateral and right-sided (n = 7 [6%]), posterior (n = 6 [5%]), right-sided and posterior (n = 3 [2%]), unknown (n = 8 [7%]). The degree of airway narrowing ranged from 10% to 99% (mean percentage, 65%) in 88 patients and was unknown in 28 patients.

Twenty-six patients (22%) were managed with a single treatment modality, which included conservative monitoring (n = 13), corticosteroid only (n = 11), and tracheotomy only (n = 2). Ninety patients (78%) required multimodality treatments (Fig. 1 and Table II). The overall management of the 116 patients included conservative monitoring (n = 13), corticosteroid (n = 100), CO_2 laser therapy (n = 66), tracheotomy (n = 32), interferon (n = 5), and LTP (n = 25).

Conservative Monitoring Group

Thirteen patients with a mean age of 6 months presented in the conservative monitoring group (Fig. 1 and Table II). All patients presented with mild stridor without any evidence of apnea, cyanosis, or feeding difficulty. The most common location of subglottic hemangioma was unilateral and left-side with or without posterior extension. None of the patients had a circumferential lesion. Subglottic narrowing ranged from 10% to 30% (mean percentage, 22%) in 11 patients and was unknown in two patients. Two patients presented with a small cutaneous hemangioma in other areas of head and neck. All patients were monitored conservatively, because of the lack of any major respiratory or feeding difficulty. There were no complications with a mean follow-up time of 21 months.

Systemic Corticosteroid Group

The systemic corticosteroid group (Fig. 1 and Table II) contained 47 patients (41%) who were treated with corticosteroid therapy as the initial treatment modality. Thirty-three of these patients were started on a corticosteroid regimen before our evaluation. The age at the time of initial presentation ranged from 1 to 10 months (mean age, 4 mo), and degree of airway narrowing ranged from 20% to 95% (mean percentage, 66%).

Corticosteroid was successful as the only treatment modality in 11 of these patients (Fig. 1) (Table II). These 11 patients had a mean age of 4 months at the time of presentation with a range of subglottic narrowing of 20% to 75% (mean percentage, 46%). Only two of these patients had a percentage of subglottic narrowing greater than 50%. The most common location of the subglottic hemangioma was either bilateral or unilateral with posterior extension. None of the patients had a circumferential le-

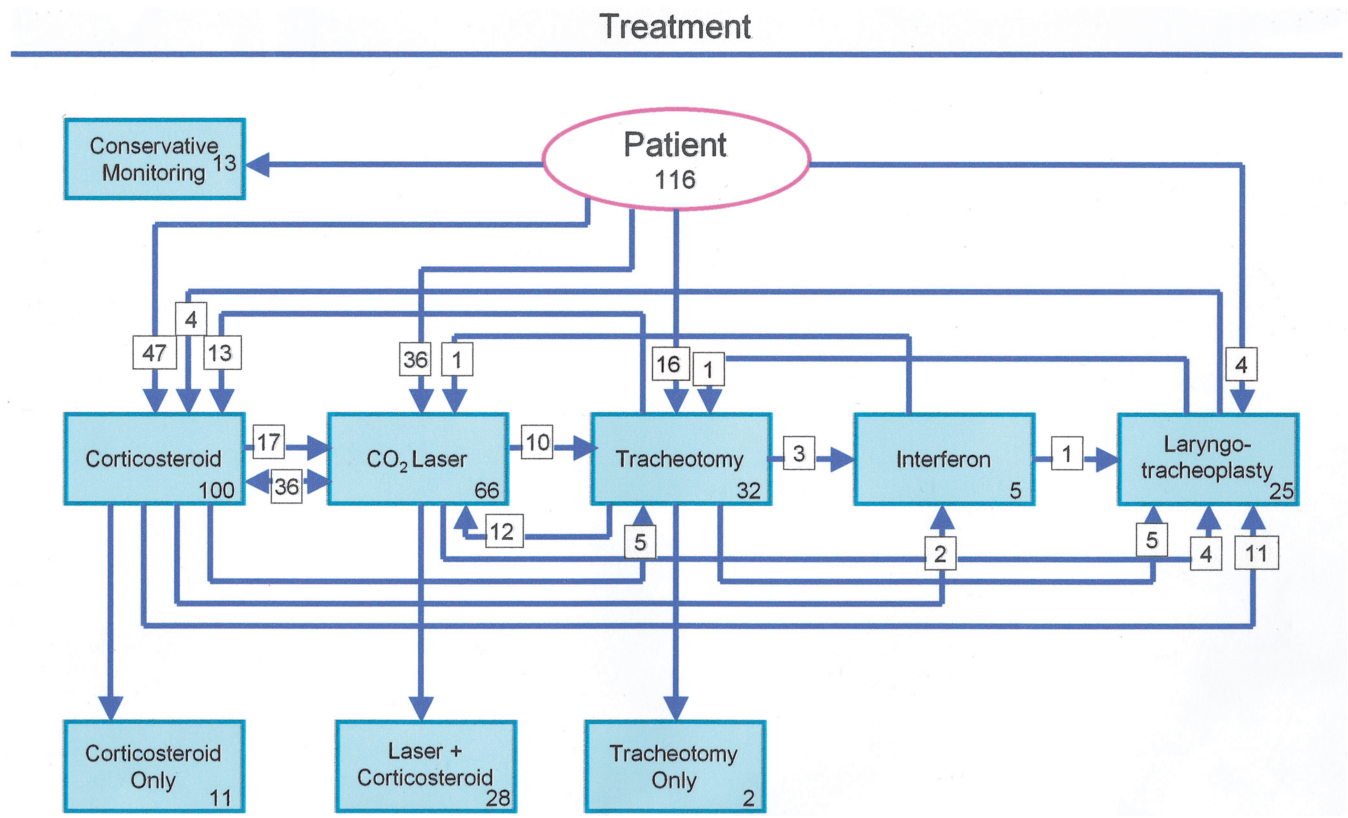

Fig. 1. Treatment.

sion. Three patients presented with another hemangioma in the head and neck. The mean follow-up time was 26 months.

Thirty-six patients (77%) with a mean age of 4 months did not respond adequately to the initial systemic corticosteroid (Fig. 1) (Table II). The most common initial presentation was biphasic stridor and retraction for these patients. The most common location of subglottic hemangioma was either circumferential or bilateral. The degree of subglottic narrowing ranged from 40% to 95% (mean percentage, 72%) in 33 patients and was unknown in 3 patients. Only three of these patients had subglottic narrowing of less than 60%. Fifteen patients presented with other hemangioma in the cervicofacial area. All 36 patients required other treatments in addition to systemic corticosteroid. The total course of corticosteroid treatment was available for 20 patients. These patients received 2 to 3 mg/kg per day of prednisolone for a duration range of 5 to 390 days (mean duration, 86 d); only five patients received steroid therapy for a period of less than 20 days. The mean follow-up time for these patients was 32 months. Four patients were lost to follow-up.

Overall, systemic corticosteroid was used as part of treatment in 100 patients (86%), as initial treatment in 47 patients, and during the course of treatments in 53 pa-

TABLE II.
Overall Treatments and Complications.

Type of Treatment	No. of Patients: Initial Treatment	No. of Patients: Only Treatment	No. of Patients: Total	Complication Rate (%)	Type of Complication
Conservative monitoring	13	13	13	None	
Corticosteroid	47	11	100	18	Cushinoid, decrease growth
Tracheotomy	16	2	32	None	
CO_2 laser and corticosteroid	36	28	66	12	Subglottic stenosis
Interferon	0	0	5	20	Spastic diplegia
Laryngotracheoplasty	4	0	25	4	Failure: required tracheotomy; granulation, scar
				16	

tients. Complications associated with use of corticosteroid were noted in 18 patients (18%) and included cushingoid features (n = 8), decreased growth (n = 4), pneumonia (n = 3), and gastric ulcer (n = 3) (Table II).

Tracheotomy Group

Sixteen patients (14%) with a mean age of 2.8 months underwent tracheotomy as the initial treatment modality (Fig. 1 and Table II). Biphasic stridor and retraction were the most common presentation. The most common location of subglottic hemangioma was either circumferential or bilateral. Degree of subglottic narrowing ranged from 60% to 99% (mean percentage, 84%) in seven patients and was unknown in nine patients. One patient presented with a cervicofacial hemangioma. Tracheotomy as the only treatment modality was successful in two of the patients. Fourteen patients required other treatments because of concern for the degree of airway narrowing and the reserve airway in case of obstructed or displaced tracheotomy tube (Fig. 1).

In all, 32 patients (28%) underwent tracheotomy as part of their treatment. Sixteen patients underwent tracheotomy as the initial treatment, and 16 patients underwent tracheotomy during the course of treatments. Age at decannulation ranged from 1 to 3 years (mean age, 22 mo) in 24 patients and was unknown in 7 patients. No complications, subglottic stenosis or death, were reported with a mean follow-up time of 36 months.

Laser Surgery

The laser surgery group (Fig. 1 and Table II) contained 36 patients (31%) with a mean age of 5 months who were treated with CO_2 laser therapy as the initial treatment. Degree of airway narrowing ranged from 50% to 80% (mean percentage, 68%) in 17 patients and was unknown in 19 patients.

Twenty-eight patients (Fig. 1 and Table II) responded well to CO_2 laser excision followed with systemic corticosteroid. A unilateral subglottic hemangioma was the most common presentation for these patients. Degree of airway narrowing ranged from 50% to 80% (mean percentage, 66%) in 14 patients and was unknown in 14 patients. The number of laser surgeries for these patients ranged from 1 to 4 (mean number, 2).

Eight patients (Fig. 1 and Table II) did not respond to CO_2 laser surgery and systemic corticosteroid and required either tracheotomy or LTP, or both. The most common location of subglottic hemangioma was either circumferential or bilateral. Degree of airway narrowing ranged from 70% to 80% (mean percentage, 77%) in three patients and was unknown in five patients.

Overall, CO_2 laser surgery was used in 66 patients (57%) as part of the treatment with a mean number of 2 procedures per patient. Eight patients (12%) presented with subglottic stenosis following laser surgery, four patients required tracheotomy followed with LTP, and four patients were monitored conservatively with resolution of symptoms (Table II).

Interferon Group

Five patients (4%) with a mean age of 2.4 months were treated with interferon (Fig. 1 and Table II). The locations of the subglottic hemangioma were circumferential (n = 3), bilateral (n = 1), and unknown (n = 1). The degree of subglottic narrowing ranged from 70% to 90% (mean percentage, 80%) in three patients and was unknown in two patients. All five patients presented with extensive hemangioma in other areas of head and neck. All patients required a combination of treatment modalities (Fig. 1). All patients responded well to interferon with an average treatment duration of 8 months. One patient presented with spastic diplegia at 8 months after initiation of treatment, which resolved after termination of therapy. No other complication was noted with a mean follow-up time of 36 months.

Laryngotracheoplasty Group

The LTP group (Fig. 1 and Table II) contained 25 patients (22%) with a mean age of 4 months who underwent LTP for excision of their lesion. The most common location of the hemangioma was either circumferential or bilateral (72%). The range of airway narrowing was 60% to 99% (mean percentage, 82%). Thirteen patients (52%) presented with hemangiomas in other areas of head and neck. Twenty-one patients (84%) were treated with either systemic corticosteroid or other surgical intervention (CO_2 laser, tracheotomy), or both, before LTP (Fig. 1). Twenty-one patients had augmentation of the subglottis using costal or conchal cartilage. One patient (4%) failed LTP and required a tracheotomy. Four patients (16%) presented with minimal granulation tissue postoperatively, which was treated with CO_2 laser excision. No other complication was noted with a mean follow-up time of 47 months.

Statistical Analysis

We are fully aware of inherent difficulties in the analysis of our data, which include change of treatment protocols since the early 1980s, surgeons with different management philosophies, and improvement of surgical and medical techniques. We have presented 116 patients with subglottic hemangioma who underwent six different treatments (conservative monitoring, corticosteroid, laser surgery, tracheotomy, interferon, and LTP). We hypothesized that the outcome of a treatment modality is determined by the following variables: age, gender, degree of subglottic narrowing, location of subglottic hemangioma, and lack or presence of other hemangioma. We performed linear discriminant analysis[1] to determine the effect of these five variables on the outcome of the six different treatment modalities. Figure 2 outlines the results of statistical analysis.

The degree of subglottic narrowing caused by hemangioma was a significant predictor variable ($P < .001$). All patients who were monitored conservatively had a subglottic narrowing of less than 30% (mean percentage, 22%). Patients who were treated successfully with corticosteroid alone had a mean subglottic narrowing of 45%, and only two of these patients had subglottic narrowing of more than 50%. Patients who required further interven-

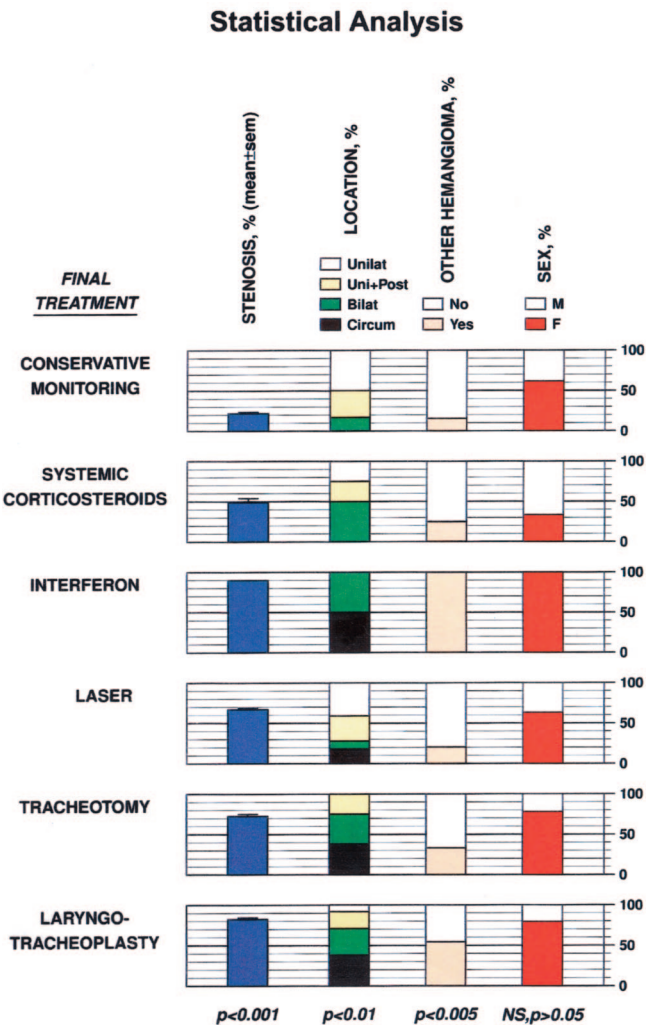

Fig. 2. Statistical analysis.

tion had a mean subglottic narrowing of more than 60% (CO_2 laser, 66%; tracheotomy, 84%; interferon, 80%; LTP, 82%).

The location of subglottic hemangioma was also a significant predictor ($P < .01$). The most common location of hemangioma for the patients who were treated conservatively or with corticosteroid alone was unilateral or unilateral with posterior extension. None of the patients with circumferential lesion was treated successfully with conservative monitoring or corticosteroid alone. All patients who presented with circumferential lesion required multimodality treatments (Fig. 1 and Table II).

The lack or presence of a hemangioma in other areas of head and neck was also a significant variable ($P < .005$) (conservative monitoring, 15%; corticosteroid only, 27%; CO_2 laser, 18%; LTP, 52%; and interferon, 100%. However, gender ($P > .05$) and age at the time of presentation ($P > .06$) did not appear to be a significant variables with regard to the outcome of the different treatment modalities.

DISCUSSION

The field of vascular anomalies has been obscured by its own nomenclature and confusing descriptive and histological terms. This confusion has led to improper diagnosis and treatment. In 1982, Mulliken and Glowacki[3] helped resolve the confusion with the terminology of vascular anomalies by presenting a biologic classification based on clinical characteristics, natural history, and cellular features. This initial classification was slightly modified and accepted at the 1996 biennial meeting of International Society of the Vascular Anomalies in Rome.[4] On the basis of cellular kinetics and clinical behavior, there are two major categories of vascular anomalies: *tumors* (lesions that arise by endothelial hyperplasia) and *malformations* (lesions that arise by dysmorphogenesis and exhibit normal endothelial turnover).[5]

Infantile hemangioma is the most common vascular tumor. It is a lesion that grows rapidly in early infancy, is characterized by endothelial proliferation, and invariably undergoes slow regression. The precise incidence of endangering and life-threatening complication of hemangioma is unknown; however, it is estimated to be approximately 10%.[6] Complications such as ulceration, bleeding, visual obstruction, airway obstruction, congestive heart failure, are of concern.

There are rare variants called *congenital hemangioma,* defined as tumors that are fully developed at birth and do not exhibit the usual postnatal rapid proliferation.[7] There are two types of congenital hemangioma. The term "rapidly involuting congenital hemangioma" (RICH) defines the group of tumors that rapidly regress by one year of age.[8] The second type fails to regress, grows in proportion to the child, and is called noninvoluting congenital hemangioma (NICH). The difference in clinical behavior differentiate RICH, NICH, and common infantile hemangioma. Other vascular tumors are the intermediate-grade hemangioendotheliomas and high-grade angiosarcomas.

Vascular malformations are localized or diffuse errors of embryonic development. They are present at birth, are characterized by normal rate of endothelial cell turnover, and grow commensurately with the child. The classification of these anomalies is based on the clinical and histological appearance of the abnormal channels. It is clinically useful to separate the vascular malformations into *slow-flow anomalies* (capillary, venous, lymphatic, or combined forms) and *fast-flow anomalies* (arteriovenous fistula and arteriovenous malformation).

The stages in the life cycle of hemangioma have been documented by light and electron microscopy and immunohistochemical techniques (Fig. 3). Proliferation is characterized by increased levels of basic fibroblast growth factor and vascular endothelial growth factor. Involution is characterized by endothelial apoptosis and the downregulation of angiogenesis and is correlated with the accumulation of mast cells and the increase of the tissue inhibitor metalloproteinase.[5] The biological factors that initiate proliferation and the molecular mechanisms of regression are unknown. North et al. discovered that erythrocyte-type glucose transporter protein, GLUT 1, is highly expressed by infantile hemangioma at all stages. This immunohistochemical marker is highly specific and

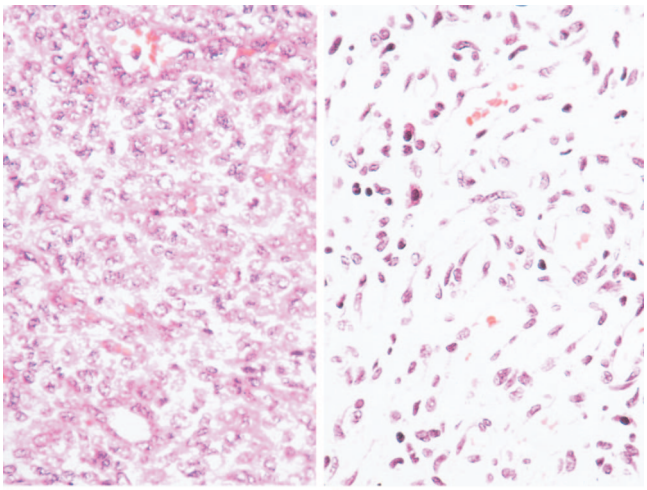

Fig. 3. (**A**) Hemangioma: proliferative phase. Closely packed, plump endothelial cells and pericytes with small vascular lumina are evident (H&E stain, original magnification ×400). (**B**) Hemangioma: involuting phase. Less closely packed, plump endothelial cells and pericytes with thick vascular basement membrane are evident. The channels are separated by delicate connective tissue (H&E stain, original magnification ×400).

is not observed in other vascular tumors or vascular malformations.[9] There is preliminary evidence that the risk of hemangioma is 10-fold higher in children of women who undergo chorionic villus sampling.[10] Viral origin and genetic alteration have also been postulated.[5]

Presentation

Subglottic hemangioma is the most common neoplasm of the infant airway. In 1871, Mackenzie was the first to describe a hemangioma of the larynx.[11] Phillips and Ruh[11] presented the first description of infantile subglottic hemangioma in 1913. The most common presentation is biphasic stridor, which is exacerbated by crying and upper respiratory tract infection and often presents before 6 months of age. Recurrent episodes of croup may indicate the possible diagnosis of subglottic hemangioma. Hoarseness, cough, dysphasia, and hemoptysis are uncommon. The natural history of subglottic hemangioma is unpredictable. The majority of lesions are characterized by progressive airway obstruction shortly after birth during the proliferative phase, followed by resolution of symptoms after the first year of life during the involutive phase. Although subglottic hemangioma is a benign condition, it can be associated with a fatal outcome. Without proper diagnosis and treatment, a 30% to 70% mortality rate has been reported.[5,12]

Cutaneous hemangioma is present in approximately 50% of affected children. However, the absence of cutaneous hemangiomas does not preclude the presence of a subglottic hemangioma.[13] Although the biological basis for the association of cervicofacial and subglottic hemangioma is unknown, this relationship has been reported in the past.[8] Orlow et al.[13] reported a 63% association between the presence of cutaneous hemangiomas distributed in the "beard pattern" (preauricular, chin, lower lip, neck) and the presence of symptomatic hemangioma in the upper airway or subglottis (Fig. 4).

Evaluation

Diagnosis of subglottic hemangioma is based on the history and physical examination. Diagnosis is confirmed by endoscopic examination, which reveals a submucosal lesion that is compressible in the subglottic area (Fig. 5). The color ranges from red to blue depending on the thickness of the overlying mucosa and degree of vascularity. Biopsy is required only if findings on endoscopy are not diagnostic. The most common location of subglottic hemangioma is on the left side. It may also present as circumferential, bilateral, or unilateral with or without posterior extension (Fig. 5).

Imaging

It has been reported that asymmetrical narrowing of the subglottic airway on frontal radiographs of the neck is pathognomonic for hemangioma.[14] However, Copper et al.[15] reported that only 50% of subglottic hemangiomas presented asymmetrical narrowing, whereas others presented as symmetric narrowing. We recommend workup with magnetic resonance imaging (MRI) if there is suspicion for cervical or intrathoracic extension of hemangioma (Fig. 6). Hemangioma appears to be solid tissue of intermediate intensity on T1-weighted spin-echo images and of moderate hyperintensity on T2-weighted spin-echo images. One may also see flow voids within the hemangioma that could indicate shunting between feeding arteries and draining veins.[5]

Treatment

A multitude of medical and surgical modalities has been proposed for the management of the subglottic hemangioma, and no single approach has received universal acceptance.

Conservative monitoring. Because of the concern for possible airway obstruction and the high mortality rate associated with subglottic hemangioma, it is essential to

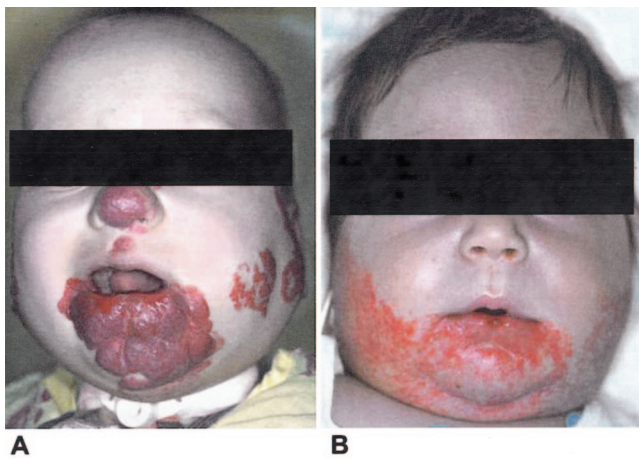

Fig. 4. (**A**) Hemangioma involving the cervicofacial area, parotid, and nose. (**B**) Hemangioma involving the "beard distribution" (periauricular area, chin, neck).

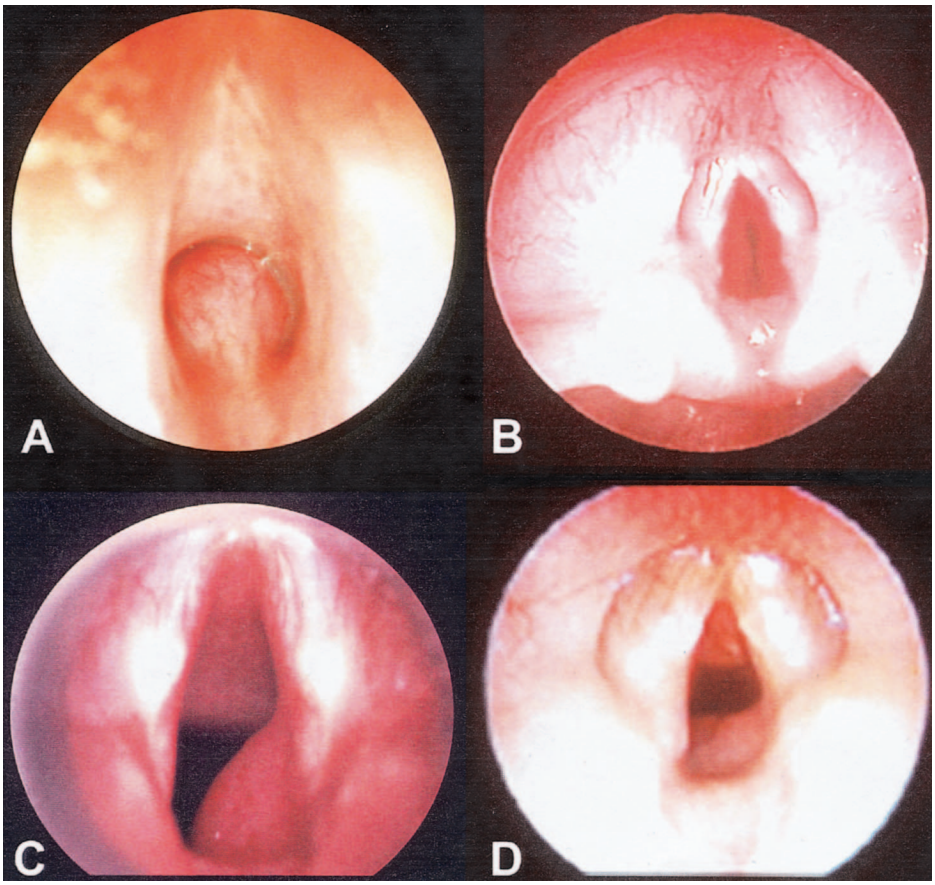

Fig. 5. Subglottic hemangioma. (**A**) Unilateral lesion causing complete obstruction of subglottic area. (**B**) Circumferential lesion. (**C**) Unilateral right-side lesion with posterior extension. (**D**) Isolated posterior lesion.

intervene with a treatment or initiate close monitoring after the initial diagnosis. We have presented 13 patients who were monitored conservatively without any complication. Based on our data, patients who present with a subglottic hemangioma that causes less than 30% subglottic narrowing without any significant respiratory or feeding difficulty may be monitored conservatively (Fig. 7). However, it is essential that these patients have close follow-up and access to immediate medical care in case of change in symptoms.

Radiation therapy. In 1919, New and Clark[16] reported the successful application of external-beam radiation for the treatment of subglottic hemangioma in two patients. In 1961, Ferguson and Flake[17] advocated the use of tracheotomy and radiation therapy for the management of subglottic hemangioma. They reported an average regression time of 9 months with the age range at decannulation of 1 to 2 years in 17 patients. Other studies have also reported success with the application of radioactive gold implant.[18,19] However, because of concerns for associated risk of damage to the normal airway mucosa and secondary malignancy, this treatment modality was abandoned in the late 1970s.

Cryotherapy. In 1972, Schechter and Biller[20] reported the application of cryotherapy and steroid use in two patients with only transient benefit. Jokinen et al.[21] reported five patients treated with cryotherapy with minor benefit. The depth of tissue destruction using cryotherapy is unpredictable, which could result in further complication such as subglottic stenosis. Overall, the application of cryotherapy in the management of subglottic hemangioma has been disappointing, and we do not recommend this treatment modality.

Tracheotomy. Tracheotomy with observation for involution was first described by Suehs and Herbur[22] in 1940. Many studies followed and recommended tracheotomy and waiting for spontaneous resolution.[23-25] However, it is important to recognize that tracheotomy does not influence the natural history of the hemangioma and often has to be in place for approximately 2 years. When considering tracheotomy, it is imperative to think about the degree of airway narrowing and the reserve airway because an obstructed or displaced tracheotomy tube could be life-threatening. A mortality rate of 40% to 60% has been reported because of tracheotomy tube plugging and accidental decannulation.[12,26] We recommend tracheotomy when the airway is compromised because of hemangioma in the area of 1) glottis and supraglottic, 2) multiple lesions of subglottis and trachea, and 3) a contraindication to another treatment modality (Fig. 7). When considering tracheotomy as a treatment option, factors such as adequate family teaching, availability of nursing and medical care, and communication and speech development must be taken into account.

Corticosteroids. In 1973, Cohen[27] reported on the use of systemic corticosteroids in the treatment of subglottic hemangioma. Many authors reported successful re-

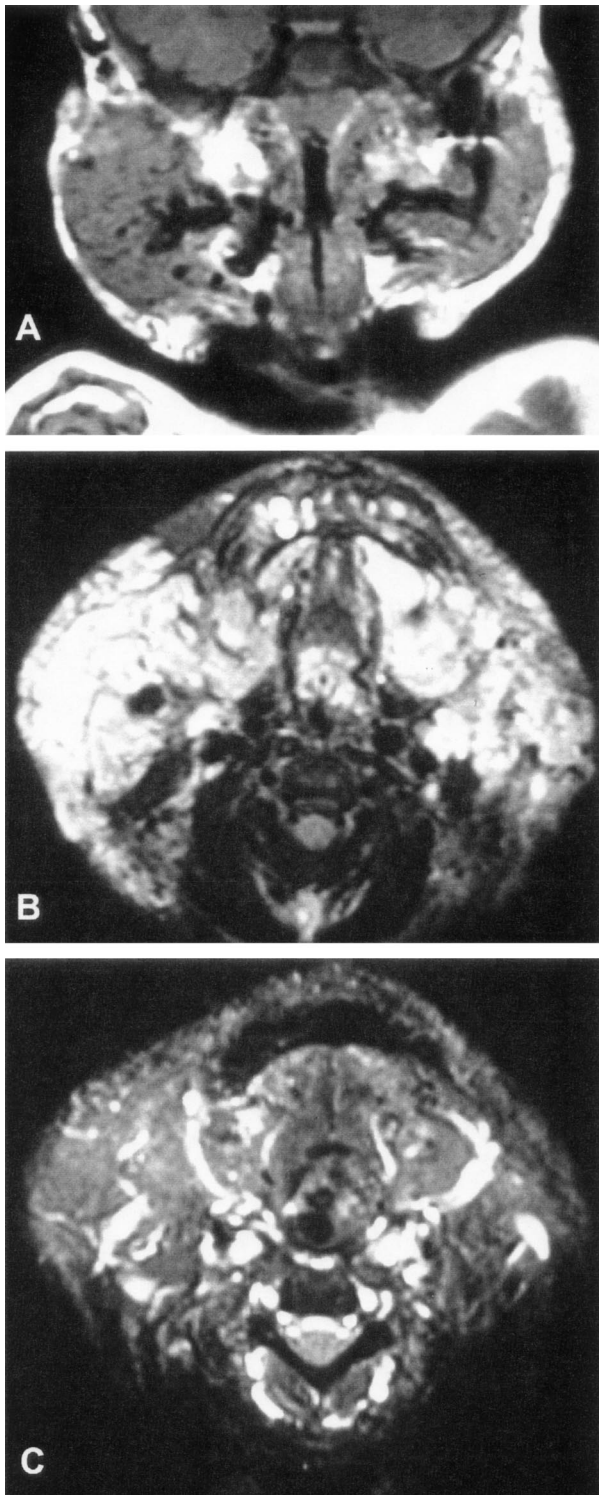

Fig. 6. Magnetic resonance imaging: cervicofacial hemangioma. (**A**) T1-weighted image without contrast showing large flow void within the lesion of parotid area. (**B**) T2-weighted image showing hyperintense, uniform, and well-marginated lesions. (**C**) Gradient sequence recall echo confirming high-flow nature of the lesion.

gression and resolution of airway symptoms with systemic corticosteroid.[5,12,28] Other investigators have reported a transient response with serious side effects.[20,29] It is truly difficult to properly assess the efficacy of the corticosteroid because it is often used in combination with other treatments in the management of subglottic hemangiomas. Also, the natural history of involution of hemangioma makes the picture more confusing when considering the prolonged duration of corticosteroid. When including hemangiomas of various sites, a positive response is seen in 30% to 60% of cases.[5] The mechanism of action of corticosteroid is unclear. However, it may increase the sensitivity of the hemangioma to physiological vasoconstriction. Its function may also be a result of blockage of estradiol receptors in the hemangioma, which are thought to enhance growth.

Intralesional injection of corticosteroids followed by endotracheal intubation has also been advocated.[30,31] In 1990, Meeuwis et al.[30] reported on successful treatment of six patients with a mean number of 2 injections (range, 1–5 injections) and an average intubation period of 19 days (range, 7–36 d). In 1997, Hoeve et al.[31] reported success in 14 of the 15 patients with a mean number of 3 injections (range, 1–12 injections) and an average intubation period of 37 days (range, 6–129 d). The need for repeated endoscopy and injections, prolonged intubation time, and the need for intermittent pharmacological paralysis and immobilization are of concern and may cause further morbidity.

One hundred of our patients (86%) received systemic corticosteroid as part of their treatment. Eleven patients responded adequately to systemic corticosteroid alone as the initial treatment. These patients had either a unilateral or bilateral lesion with a mean degree of subglottic narrowing of 45%. Thirteen patients who had circumferential lesion did not respond adequately to corticosteroid alone and required further intervention. Based on our data, patients who present with subglottic hemangioma that causes less than 50% subglottic narrowing and do not have circumferential involvement respond well to an initial trial of systemic corticosteroid treatment (Fig. 7).

We recommend the dosage of 2 to 3 mg/kg per day of prednisone or an equivalent corticosteroid. Signs of responsiveness should occur within several days to 1 week of the initiation of the treatment.[5] One should see diminished rate of growth, softening of the tumor, fading of the color, and resolution of symptoms. If there is a response, the dosage should be tapered slowly and terminated when there is resolution of airway symptoms. Rebound growth is noted if the dosage is tapered too quickly or terminated prematurely. However, if corticosteroid fails to control the growth of hemangioma and does not result in resolution of symptoms in 2 to 3 weeks after treatment, it should be tapered quickly and stopped, and other treatment modalities should be considered. No factors have been identified that predict the response to corticosteroid treatment, and some hemangiomas appear to be nonresponders. Also, there are no data to support that higher dose or prolonged treatment improves response rate. Enjolras et al.[32] reported rates of 30% accelerated regression, 30% no response, and 40% equivocal response in 25 infants with life-threatening hemangiomas.

When considering corticosteroid treatment, it is essential to evaluate the risk-benefit ratio. Side effects with

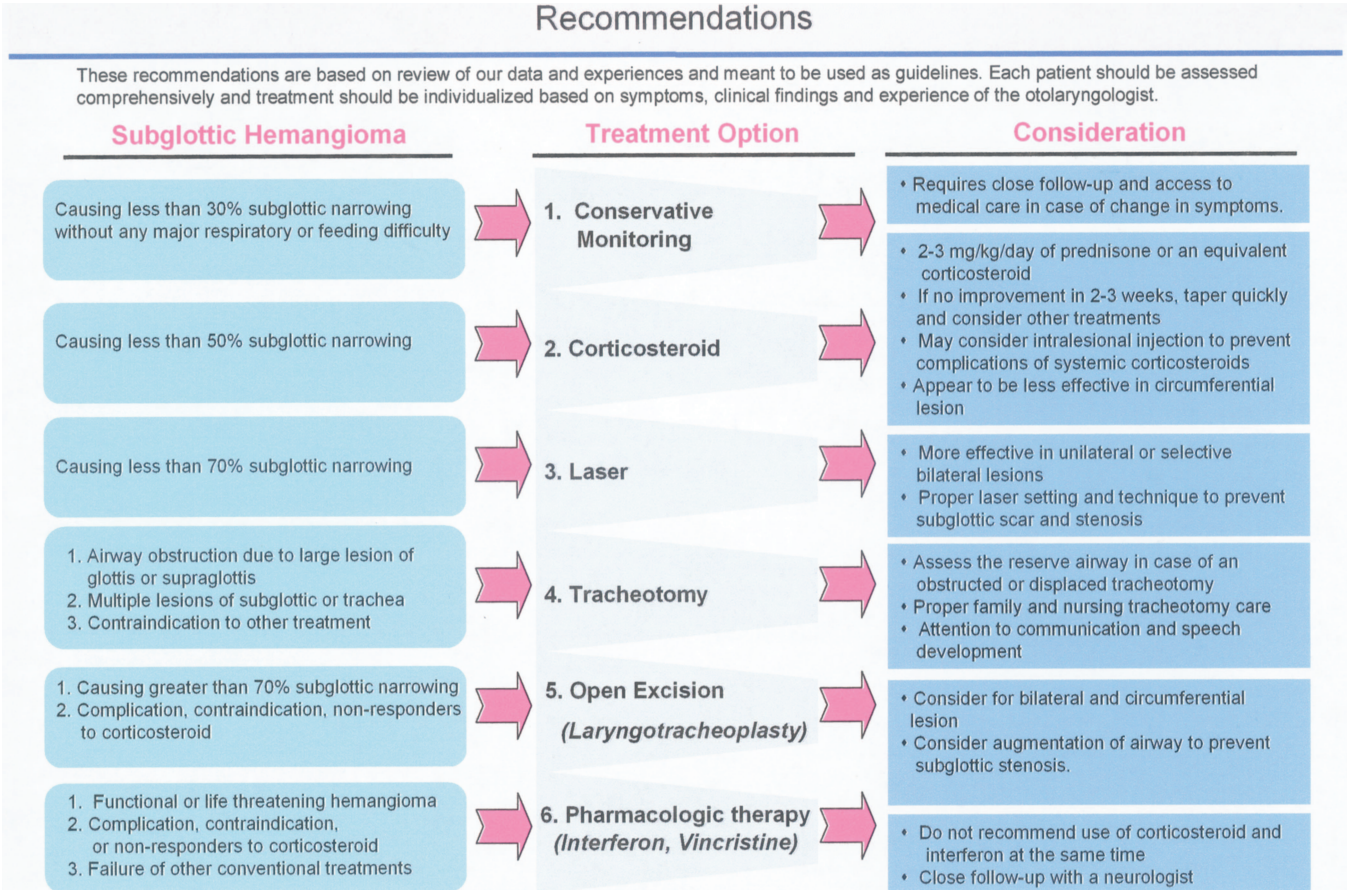

Fig. 7. Recommendations.

long-term use may include cushingoid features, infection, and growth restriction. Decreasing the maintenance dose, alternate-day treatment, and intralesional corticosteroid injection could diminish some of these risks.

Laser therapy. In 1979, Simpson et al.[33] reported the first case of CO_2 laser therapy in the management of subglottic hemangioma. In 1980, Healy et al.[34] presented the successful management of 11 patients with one or two CO_2 laser applications. Review of the literature revealed mixed results with regard to the efficacy of CO_2 laser treatment of subglottic hemangioma. Many authors have reported excellent success,[35–37] whereas others have reported minimum benefit and high complication rates.[12,29,38] Lack of long-term follow-up,[39] significant risk of scar formation and subglottic stenosis,[12,38] and limited application for lesions in the posterior subglottic area or distal trachea[40,41] have been reported.

The application of potassium-titanyl-phosphate (KTP) and neodymium: yttrium-aluminum-garnet (Nd:YAG) laser has also been reported with good success.[40–43] The KTP laser (wavelength of 532 nm) and Nd:YAG laser (wavelength of 1064 nm) are preferentially absorbed by hemoglobin, making them applicable to the treatment of hemangioma and other vascular tumors. Their tissue characteristics result in deep penetration with minimal disruption of the overlying mucosa. Theoretically, because there is less mucosal damage, there is a decreased risk of subglottic scar and stenosis. However, it is important to realize that the penetrating effects of KTP and Nd:YAG laser may cause thermal damage to the cricoid and tracheal cartilage. Overall, it is difficult to determine the efficacy of the laser treatment as a single treatment modality because most of the reported patients have also been treated with systemic corticosteroid.

The success rate of the laser surgery is highly operator dependent, and techniques must be fully mastered because considerable damage can be caused by imprudent application of the laser. Sixty-six of our patients underwent CO_2 laser excision. Twenty-eight of these patients responded well to CO_2 laser followed by systemic corticosteroids. These patients presented with a mean degree of subglottic narrowing of 66% and, most commonly, a unilateral or bilateral lesion.

Based on our data, patients who present with unilateral or selected bilateral subglottic hemangioma that causes less than 70% subglottic narrowing respond well to CO_2 laser surgery (Fig. 7). We recommend using low power (2–4 W) with intermittent (0.1 s) mode slightly off focus to benefit from the vaporization and decrease the thermal effect of the CO_2 laser. It is important to use the intermittent mode of the laser because continuous mode may cause excessive overheating of the tissues. The proper setting for other lasers is also of paramount importance: Nd:YAG, 10–15 W,[42] and KTP laser, 5–7 W in a single-pulse or repeated-pulse mode at 0.5 s.[43] Despite all

of these measurements, laser surgery in the airway can create a burn, and it is important to provide intense humidification, careful suctioning, and close observation in the immediate postoperative care.

Open Excision and Laryngotracheoplasty. Sharp[44] reported successful excision of a tracheal hemangioma in a 5-month-old infant in 1949. In 1974, Evans and Todd[45] reported the successful excision of subglottic hemangioma in three patients. Since the early 1990s, there have been many reports of using the open approach for excision of subglottic hemangioma with good outcomes.[46–49] This procedure may be performed as a single stage modality with short-term endotracheal intubation or as a staged procedure with subsequent decannulation in cases in which a tracheotomy is left in place.

Twenty-five of our patients with a mean degree of subglottic narrowing of 82% underwent open excision of subglottic hemangioma. Twenty-one patients (84%) had been treated with other treatment modalities without any success before LTP. Eighteen of these patients (72%) presented with either bilateral (n = 8) or circumferential (n = 10) lesions. It is apparent from our patients and other reported cases in the literature[46–49] that an open approach (LTP) is a viable option in the management of selected patient with subglottic hemangioma. Based on our data, we recommend that this approach should be considered for patients who present with 1) subglottic hemangioma that causes more than 70% subglottic narrowing, 2) bilateral or circumferential lesion, or 3) in cases of a nonresponder, complication, or contraindication to prolonged corticosteroid therapy (Fig. 7).

Complications such as subglottic stenosis and recurrent laryngeal nerve injury are of concern. Different techniques have been reported to prevent subglottic stenosis, such as using a castellated incision and a silastic roll or placing a cartilage graft for augmentation of subglottic area.[47,48] Important factors for a successful outcome and decreased rate of complication are careful dissection of tissue under magnifying spectacles or microscope, meticulous suturing of laryngeal and tracheal tissue, and cartilage graft augmentation of subglottic area.

Interferon. In 1992, Ezedowitz et al.[50] reported the use of interferon alfa-2a for the treatment of life-threatening hemangiomas in infancy. The efficacy of interferon (INF) in the treatment of cervicofacial and life-threatening hemangiomas has been well reported.[51–53] The empiric dose for IFN is 2 to 3 million units/m^2, injected subcutaneously every day. It is important to adjust the dose as the infant gains weight. Duration of treatment is often 6 to 12 months. There is no evidence that IFN and corticosteroids are synergistic, and we do not recommend using them together.[5] Interferon may cause low-grade fever, reversible elevation of hepatic transaminase levels, transient neutropenia, and anemia. The most serious toxicity is spastic diplegia with an incidence of 5% to 20%. The mechanism for spastic diplegia is unknown, and it is potentially reversible.

The first apparent case of spastic diplegia in a patient with subglottic hemangioma was reported by Enjolras et al.[54] in 1996. In 1998, Barlow et al.[55] reviewed their experience with a group of 26 infants treated with IFN for potentially life-endangering hemangioma. They reported five cases complicated with spastic diplegia as a result of IFN therapy. Diplegia persisted in three infants; however, the remaining two infants showed significant recoveries after IFN was discontinued. Five of our patients with a mean degree of subglottic narrowing of 80% were treated with IFN. All five patients had other cervicofacial or airway hemangiomas. One patient (20%) presented with spastic diplegia that resolved after termination of INF.

The effectiveness of INF in the treatment of hemangioma is well reported.[51,52] However, because of reported neurological complications, it should be reserved for 1) functional and life-threatening hemangiomas, 2) contraindication, complication, or nonresponders to prolonged systemic corticosteroid, and 3) failure of other conventional treatments (Fig. 7). We recommend that all children on a regimen of INF should be monitored closely by a neurologist, and if there is any evidence of long-tract signs, termination or diminishment of the treatment.

Vincristine. Vincristine has recently become the second line medical management of life-threatening hemangioma.[56,57] In 1995, Payarols et al.[58] reported two patients with enlarging hemangioma and Kasabach-Merritt phenomenon who successfully were treated with a combination of corticosteroids and vincristine. Other investigators have also advocated use of vincristine for life-threatening hemangioma with excellent outcomes.[56,57] Vincristine is a naturally occurring vinca alkaloid. It inhibits mitotic spindle microtubules by binding to tubulin, resulting in inhibition of mitosis. Treatment is administered at standard doses (1–1.5 mg/m^2 or 0.05–0.065 mg/kg) in weekly intervals, and average time of response is 4 to 6 weeks.[59–61] Vincristine appears to be well tolerated; however, neurotoxicity is the most common reported complication. The indications for use of vincristine are 1) functional and life-threatening hemangiomas, 2) contraindication, complication, or nonresponders to prolonged systemic corticosteroids, and 3) failure of other conventional treatments. It appears that vincristine will be an increasingly important component of the therapeutic armamentarium for selected patients (Fig. 7).

CONCLUSION

Subglottic hemangioma is the most common neoplasm of the infant airway. Many medical and surgical treatment modalities have been proposed, and no single treatment option is acceptable for all patients. Treatment options aimed at decreasing the size of the lesion and resolution of symptoms must be judged against the natural history of gradual involution and the risk of causing further complications. An individualized therapeutic approach should be based on the symptoms, location, and extent of the subglottic hemangioma; the lack or presence of other hemangiomas; and experience of the surgeon. We have reviewed the natural history and presented guidelines in an attempt to rationalize the management of subglottic hemangioma and to help determine the best treatment modality at the time of initial presentation.

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