Int J Clin Exp Med 2020;13(2):1014-1022
www.ijcem.com /ISSN:1940-5901/IJCEM0098907

Case Report

Clinical diagnosis and oral propranolol curative effect analysis of infant subglottic hemangioma

Xiaofang Ding, Lili Zhong, Bing Zhang, Lin Lin, Han Huang, Min Chen, Xiaojuan Lin, Sangzi Wei

Children's Medical Center, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha 410005, Hunan, P. R. China

Received June 25, 2019; Accepted October 9, 2019; Epub February 15, 2020; Published February 28, 2020

Abstract: Objective: To investigate the diagnosis of subglottic hemangioma in infants by bronchoscopy combined with laryngeal imaging and the therapeutic effect of oral administration of propranolol. Methods: A retrospective analysis was performed for 16 pediatric patients who were admitted to the Children's Medical Center of Hunan People's Hospital from November 2012 to May 2018 and were diagnosed with subglottic hemangioma. The diagnosis was confirmed by bronchoscopy combined with laryngeal enhanced CT or MRI. Clinical data was extracted from the medical records and further ascertained by physician interviews. Results: All clinical cases had respiratory symptoms, mainly showed as laryngeal stridor, coughing, and wheezing. Bronchoscopy indicated limited smooth and soft subglottic tumors showing dark red or purple, which resulted in local lumen stenosis. After taking propranolol orally for 24-48 hours, the symptoms of laryngeal wheezing or obstruction were alleviated, and 3 children with laryngeal obstruction were successfully removed from mechanical ventilation after 3-5 days. One case of hemoptysis with lower right basal stem hemangioma was given an interventional closure. After 6 months of oral Propranolol, 6 cases of tumors had completely faded, 8 cases of tumors had significantly reduced. In 12 cases, the treatment was stopped after 6 to 12 months when the obstructive symptoms improved, and the obstructing mass in the subglottis was less than 10% of the diameter; 11 cases in this group had no any evidence of recurrence, but 1 case had a slight increase in the past drug withdrawal after the 6 month review. Conclusions: Oral propranolol has definite curative effects, less side effects, and less trauma; therefore, it could be used as the main treatment for infantile subglottic hemangioma.

Keywords: Hemangioma, subglottis, infants and young child, bronchoscopy, propranolol

Introduction

Subglottic hemangioma in infants is a rare laryngotracheal disease found in clinic, accounting for 1.5% of all congenital laryngeal deformities [1]. The common symptoms include laryngeal stridor and feeding intolerance, and the condition is likely to be misdiagnosed as laryngomalacia. As the tumor mass grows rapidly and obstructs the trachea, the infants may suffer from shortness of breath and dyspnea. When there is concurrent upper respiratory infection, acute respiratory distress may occur. Unless properly handled, this critical condition is highly dangerous or even lethal to the infants [2]. However, due to the hidden position of the tumor mass, the rate of being missed diagnosis is high for subglottic hemangioma, and early accurate diagnosis and fast clinical intervention are necessary. So far, there is no standard treatment protocol for this disease. In this study, we reviewed 16 infants with subglottic hemangioma, who were treated at Children's Medical Center of Hunan Provincial People's Hospital from November 2012 to May 2018. These cases were diagnosed by bronchoscopy combined with laryngeal imaging, and were given oral propranolol and assessed by bronchoscopy. All of them achieved satisfactory outcomes.

Materials and methods

Patients

Sixteen infants with subglottic hemangioma were treated at Children's Medical Center of Hunan Provincial People's Hospital from November

2012 to May 2018, including 10 males and 6 females. The cases aged 15 days to 8 years old, with 3 cases aged below 2 months, 6 cases between 2-4 months, 4 cases between 4-6 months, and 3 cases above 6 months. All of them received bronchoscopy with contrast-enhanced CT or MRI scans of the neck. The present study was approved by the Medical Ethics Committee in Hunan Provincial People's Hospital, and written informed consent was provided by the parents of the patients.

Accessary examination

(1) Electronic bronchoscope: Olympus CLV260 BF-XP260F (outer diameter 2.8 mm, Japan); (2) Contrast-enhanced CT scanner: Philips Brilliance 16-slice CT scanner; contrast medium: 37% Iopamidol (Iopamiro, Shanghai Bracco Sine Pharmaceutical Corp. Ltd.); (3) MRI scanner: Siemens Trio Tim 3.0T MRI scanner (Germany); contrast medium: Magnevist (Bayer Healthcare Co., Ltd.).

Examination methods

(1) Preoperative assessment: ① The infants were stable. Emergency preparation for bedside percutaneous tracheostomy and laryngeal mask airway was ready for one case with difficulty in endotracheal intubation and tube removal. Blood transfusion, medication and microscopic hemostasis, or even interventional closure was ready for one case with hemoptysis. ② Preoperative examination: The infants underwent routine blood tests, blood coagulation test, routine blood test before transfusion, and ECG. ③ Assessment of respiratory system development: The respiratory tract diseases were preliminarily assessed by imaging of the neck and chest. Those suspected of combined respiratory tract stenosis and hemoptysis received 3D reconstruction of the bronchial tree and blood vessels of the cardiopulmonary system. The stenosis, bleeding site, adjacency relation and distal respiratory tract were assessed. ④ The informed consent for bronchoscopy was signed by the guardians of infants. (2) Bronchoscopy procedures: The infants received local anesthesia, and the bronchoscope was inserted into the nasal cavity concomitantly with the anesthetic procedures. ① The infants took a supine position, and oxygen supply was given to the left nasal cavity via a nasal catheter. The bronchoscope was inserted into the right nasal cavity until reaching the glottis. The tumors were observed with respect to size, number, position, morphology, and color. The degree of respiratory tract stenosis caused by the tumor and the relation with the surrounding tissues were also observed. The bronchoscope was further inserted if it was able to observe whether there was hemangioma in other positions or respiratory tract dysplasia. ② Congestion and edema of the narrow positions in the glottis, or even dyspnea might occur after bronchoscopy. The infants were given 2.5-5 mg dexamethasone and 1 mL 1:10,000 adrenaline before withdrawing the bronchoscope. After the procedures, the infants were given nebulized budesonide with or without 1:10,000 nebulized adrenaline to relieve local edema. ③ The respiratory rate, heart rate, blood pressure and other vital signs were monitored during and after the bronchoscopy procedures. (3) Contrast-enhanced CT or MRI of the neck was performed postoperatively to assist the diagnosis [3, 4]. The tumor position, number, size, morphology and adjacency relation were observed.

Treatment

Infants with tumors confirmed by bronchoscopy with contrast-enhanced CT or MRI of the neck received oral propranolol, along with dynamic assessment with bronchoscopy. Before the medication therapy, the infants received routine examinations, including routine blood tests, routine urine test, blood biochemistry, myocardial zymogram, and ECG. Those without contraindications were given oral propranolol tablets [propranolol hydrochloride tablets (Jiangsu Yabang Epsom Pharmaceutical Co., Ltd., 10 mg/tablet)]. The initial dose was 0.5 mg/(kg·d) after meals, tid. The heart rate, blood pressure and 1-hour post prandial glucose were monitored continuously. At day 3, the dose was increased to 1.0 mg/(kg·d), and the blood glucose was monitored once daily. After another 3 days, the dose was further increased to 2.0 mg/(kg·d) and maintained until the symptoms were alleviated. The infants were discharged after the vital signs were stable, and the medication was continued at home. The infants underwent further monitoring of the heart rate and blood pressure at home once daily, and monitoring of blood glucose 2 to 3 times per week. All infants had return visits regularly, that is, at 2 weeks, 1 month, 3 months

and 6 months of treatment, for 3-15 months. The return visits covered assessment of alleviation of laryngeal stridor, cough with wheeze and dyspnea. The hemangioma size, texture and color were observed under the bronchoscope. The dose was adjusted according to changes in body mass and the adverse reactions were properly handled. The medication was discontinued when the clinical symptoms basically disappeared, the hemangioma receded under the bronchoscope and the respiratory tract stenosis was relieved. Generally, the medication therapy lasted for at least 6 months, and applied to those aged above 1 year old. The infants continued to have return visits after discontinuance. Bronchoscopy was indicated to exclude the relapse of hemangioma if laryngeal stridor, voice hoarseness and dyspnea recurred.

Efficacy assessment

(1) Alleviation of respiratory tract stenosis after taking the medicine; (2) Scope of hemangioma and degree of respiratory tract stenosis under the bronchoscope. The grading system proposed by Myer et al. in 1994 is most commonly used [5], which is applied to calculate the percentage of stenotic area on the plane of stenosis to the normal lumen area: grade I was defined as stenotic area ≤50%, grade II 51%-70%, grade III 71%-99%, and grade IV complete obstruction; (3) Drug-related adverse reactions such as hypoglycemia and cardiovascular system reactions were monitored during treatment.

Results

Clinical manifestations

Two cases were admitted to the pediatric intensive care unit (PICU) of our center due to severe pneumonia, respiratory failure and grade III-IV laryngeal obstruction, and received endotracheal intubation and assisted mechanical ventilation. One of them received an endotracheal intubation at another hospital due to acute laryngotracheitis and grade IV laryngeal obstruction. After 3 days of large-dose hormone therapy and anti-infection therapy, this case was suspected of a subglottic abscess. The other case was combined with hemangioma in the skin and right parotid region. The causes of laryngeal stridor in 10 cases remain unknown. These cases presented with laryngeal stridor, inspiratory dyspnea, and intermittent episodes of laryngeal obstruction. However, they responded poorly to symptomatic treatment such as calcium and vitamin AD supplement. The causes of cough with dyspnea were unknown in 3 cases, they presented with repeated cough and wheezing and responded poorly to routine atomization therapy and anti-infective therapy. The symptoms were temporarily relieved after hormone therapy (dexamethasone or methylprednisolone). Among the above-mentioned 13 cases, 3 cases received NCPAP due to grade II laryngeal obstruction; 2 cases were combined with hemangioma of skin, and one of them was also combined with hemangioma of the pharyngolaryngeal cavity. Another case was combined with right lower basilar hemangioma, which was not diagnosed until the appearance of hemoptysis at the age of 8 (**Table 1**).

Bronchoscopic findings

The subglottic hemangiomas were located in the left lateral wall in 7 cases, right lateral wall in 1 case, bilateral lateral walls in 3 cases, posterior wall in 2 cases, left posterior wall in 2 cases and circumferentially in 1 case (**Table 1**). The typical manifestations of hemangiomas in different locations under the bronchoscope are shown in **Figure 1**: restricted dark red or purplish red bulges in the subglottic mucosa, leading to local luminal stenosis; the lesions having a smooth surface, soft texture and size of 1 mm×1 mm-4 mm×5 mm under the bronchoscope. There were grade I (18.75%), II (43.75%) and III (37.5%) stenosis of the tracheal entrance in 3, 7 and 6 cases, respectively (**Figure 2**; **Table 1**). One case was combined with hemangiomas of the epiglottic fold and tongue base, 1 case with abnormal vascular network in the larynx, 4 cases with laryngomalacia, 1 case with hemangioma of right lower basilar trunk, and 1 case with glottal granulation tissues after endotracheal intubation.

Radiologic manifestations

Contrast-enhanced CT or MRI of the neck: There was a soft tissue mass in the subglottic region, which protruded into the lumen and caused luminal stenosis. The mass was apparently enhanced upon the contrast-enhanced scan and abundant blood supply was shown (**Figure 3**). One case was combined with hem-

Table 1. Clinical data for the patients enrolled in this study

No	Sex	Age	Duration	Clinical performance	Tumor location	Stenosis	Complication	Effect after treated for 6 months	long-term effect
1	Male	21 Days	2 Days	laryngeal stridor, laryngeal obstruction (II), cough	Circumference	II	Hemangioma in skin and upper segment of larynx and trachea	I	Recrudescence
2	Female	10 Months	10 Months	laryngeal stridor, laryngeal obstruction (II)	Left	III	Laryngomalacia, malnutrition	I	Ok
3	Female	15 Days	1 Day	laryngeal stridor, laryngeal obstruction (II)	Left rear	II	Hemangioma in skin, epiglottic fold, and lingual base	Tumor regression	Ok
4	Male	2 Months	1 Month	laryngeal stridor, anhelation	Left	III	Laryngomalacia	Tumor regression	Ok
5	Female	2 Months	1 Month	laryngeal stridor, dyspnea, choking	Bilateral	III	Laryngomalacia	I	Ok
6	Male	1 Year	2 Months	laryngeal stridor, cough, fever	Right	I	Left aortic foreign matter	Tumor regression	Ok
7	Male	2 Months	1 Month	Asthma, dyspnea	Left	II	None	Tumor regression	Ok
8	Male	8 Months	4 Months	Asthma	Rear	II	None	Tumor regression	Ok
9	Female	1 Month	10 Days	laryngeal stridor, cough	Left	II	Laryngeal anomalous vascular network	I	Ok
10	Female	6 Months	1 Week	Asthma, fever	Rear	I	Laryngomalacia	Tumor regression	Ok
11	Female	2 Months	2 Months	laryngeal stridor, laryngeal obstruction (III-IV)	Bilateral	III	Right parotid hemangioma	I	Ok
12	Male	4 Months	2 Months	laryngeal stridor, laryngeal obstruction (III-IV)	Left rear	III	Glottic granulation	I	Ok
13	Male	4 Months	1 Month	laryngeal stridor	Left	II	None	I	Intrafraction
14	Male	3 Months	2 Months	laryngeal stridor	Bilateral	III	None	Intrafraction	
15	Male	8 years	20 Days	Hemoptysis, cough	Left	I	Hemangioma of right lower basal trunk	Intrafraction	Intrafraction
16	Male	2 Months	1 Month	asthma, dyspnea	Left	II	None	I	Intrafraction

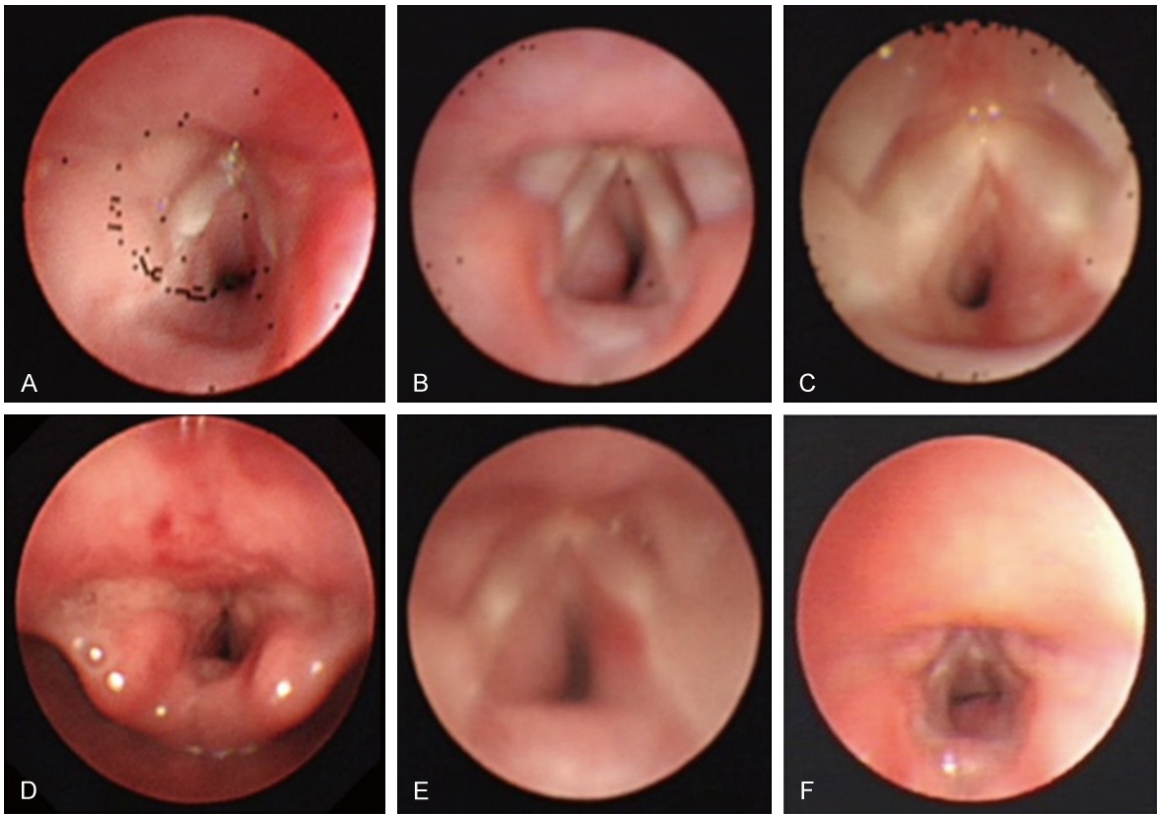

Figure 1. Subglottic hemangioma at different sites. Circumferential type (A), left side wall (B), right side wall (C), left back wall (D), bilateral wall (E), and rear wall (F).

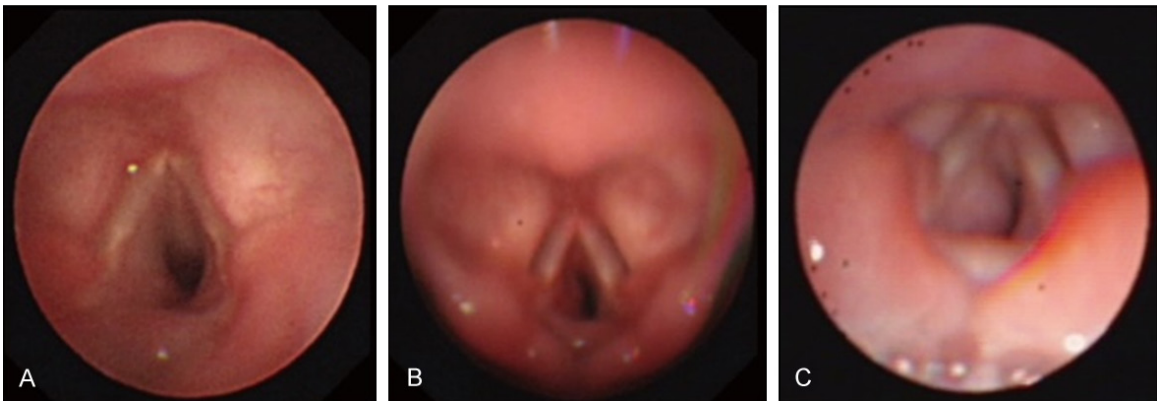

Figure 2. Assessment of the degree of airway stenosis caused by subglottic hemangioma. Grade I stenosis (A), grade II stenosis (B) and grade III stenosis (C).

angiomas in the nasal cavity, pharynx and upper part of trachea; 1 case was combined with hemangiomas of epiglottic fold and tongue base; 1 case was combined with abnormal vascular network of the larynx; 1 case was combined with hemangioma in the right lower basilar trunk; 1 case was combined with hemangioma in the right parotid gland; the remaining 11 cases had lesions confined to the subglottis and were not affected in the trachea. The bronchoscopic results agreed well with those of contrast-enhanced CT and MRI.

Therapeutic outcomes

The symptoms of laryngeal stridor and dyspnea were improved at 24-48 h after taking oral propranolol. Grade II laryngeal obstruction was

Figure 3. Enhanced CT findings of subglottic hemangioma. The left paraglottic wall of the larynx became thicker, the laryngeal cavity was narrowed, and enhanced markedly (the intensity was basically at the same level of vascular shadow). The lower segment of the lesion involved the left inferior segment of the trachea. Horizontal position (A), coronal position (B) and sagittal position (C).

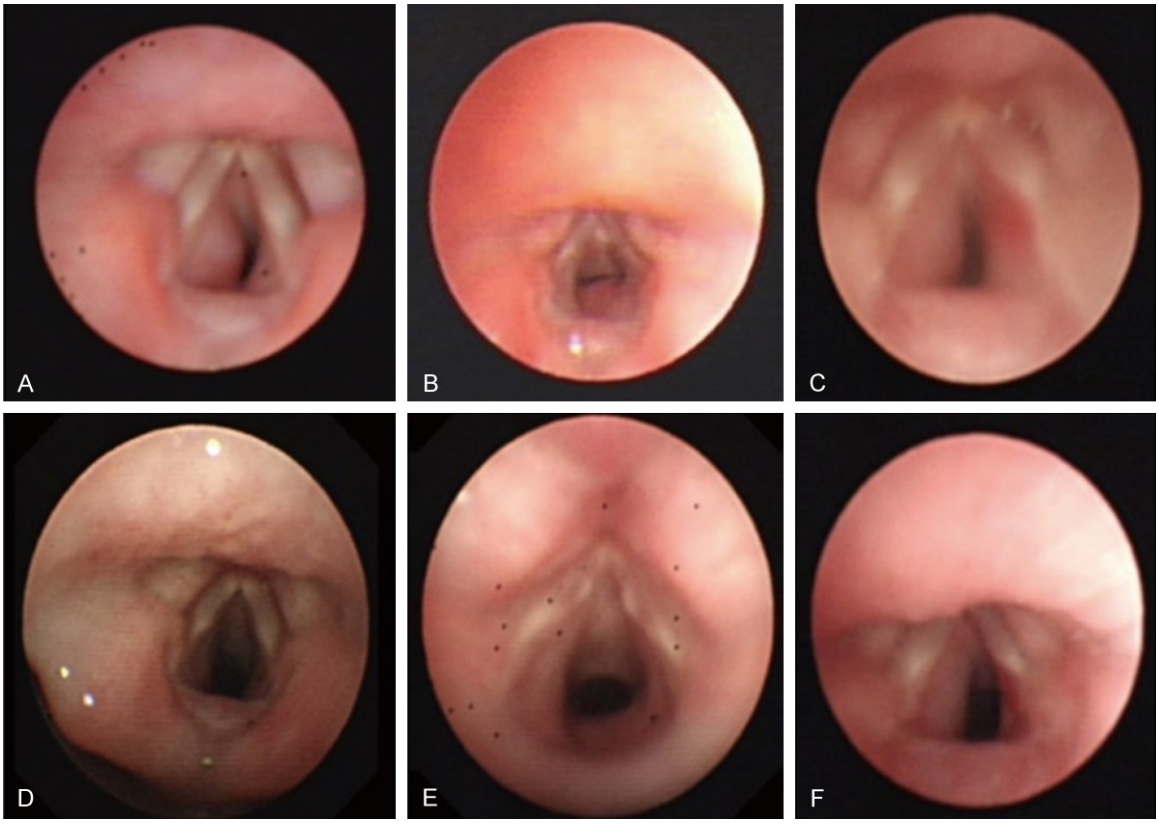

Figure 4. Contrast chart of subglottic hemangioma before (A-C) and six months after (D-F) propranolol treatment. For case 1 (A before treatment, D after treatment) and case 2 (B before treatment, E after treatment), the hemangioma subsided basically, and for case 3 (C before treatment, F after treatment) the hemangioma was reduced from grade III to grade I.

lessened to grade I in 3 cases; the tracheal tube was removed in 2 cases with grade III laryngeal obstruction at day 3 and day 5, respectively, and these 2 cases achieved significant improvement of laryngeal stridor and dyspnea. 1 case of hemoptysis received interventional closure due to combined hemangioma in the right lower basilar trunk. The lesion began to shrink in size one week later under the bronchoscope, and the tumor color turned pale. The lesions completely receded in 6 cases after taking oral propranolol for 6 months, and they apparently shrank in size in 8 cases (**Figure 4**; **Table 1**). However, the other 2 cases did not

finish the 6-month treatment. For 3 cases combined with hemangioma of the skin, the lesions considerably shrank in size and the color turned pale after treatment.

Long-term efficacy

Twelve cases took medication for 6-12 months and all of them were aged above 1 year old. Their symptoms further improved, and drug was discontinued when the subglottic stenosis was not above 10% under the bronchoscope. Among them, 11 cases did not relapse after discontinuance, while 1 case showed a mild increase in lesion size after discontinuance for 6 months. The remaining 4 cases are still under treatment (**Table 1**).

Adverse reactions

None of the 15 cases showed apparent abnormalities on ECG, blood pressure detection and blood biochemistry test. One case had transient hypoglycemia after the initial dose, but returned to normal after fluid replacement and change of the feeding method.

Discussion

Subglottic hemangioma in infants is more often seen in those below 1 year old, and the age of onset is below 6 months old in 85% of the cases [6]. In the present study, the age of onset is below 6 months old in 13 infants, accounting for 81.25%. Another case, aged 8 years old, was not confirmed until the occurrence of hemoptysis due to hemangioma in the right lower basilar trunk. Subglottic hemangioma is believed to have consistent pattern of progression as hemangioma of the skin. That is, the lesion grows rapidly at 1-3 months after birth and begins to recede at about 1 year old [7, 8]. Because of its hidden position and fast growth, subglottic hemangioma may cause severe respiratory tract obstruction when combined with respiratory tract infection. The mortality is close to 50% if this critical condition is not properly handled [9]. However, blind endotracheal intubation may cause rupture of hemangioma, leading to bleeding and obstruction of respiratory tract and hence asphyxia or death.

Diagnosis of subglottic hemangioma is usually made based on medical history, electronic (fiberoptic) laryngoscopy and radiologic examinations. Damage of subglottic mucosa and symmetrical or asymmetrical neoplasm with smooth surface can be observed under the endoscope. Depending on the superimposed thickness of mucosal lesions, the neoplasm may be red or blue, with soft texture. The lesions are usually located on the left side, or sometimes on the right side, circumferentially or bilaterally. The lesions may extend towards the upper part of trachea [10]. However, the endoscopic findings are poor in specificity and differentiation is needed from other primary tracheal tumors or highly vascularized metastatic tumors [11]. Imaging examinations such as angiography, ultrasound, CT and MRI are conducive to the diagnosis of hemangiomas. Koplewitz *et al.* recommended dynamic contrast-enhanced CT as the preferred non-invasive detection [3]. Moreover, multiplanar reconstruction can better visualize the lesion's position and scope, stenosis degree and adjacent affected tissues. MRI is the preferred choice if it is suspected that hemangioma extends towards the neck or thoracic cavity. T1-weighted images can show isointense or hypointense soft tissue masses, while T2-weighted images usually present with uniformly hyperintense signals [10, 12]. However, radiologic examinations have some limitations in subglottic hemangioma in infants and the rate of missed diagnosis remains high. This is because the respiratory tract is narrow and the blood supply is abundant in infants. Subglottic hemangioma in infants is more likely to cause respiratory tract obstruction. Contrast-enhanced CT or MRI of the neck has to be performed under sedation, and the examination usually lasts for a long time. The symptoms of respiratory tract obstruction are even more severe for infants under sedation, and that is why radiologic examinations are not suitable at an early stage, which leads to delayed diagnosis. Besides, the radiologic examinations have some inherent defects. For example, resolution and contrast medium distribution may affect the imaging of blood flow, leading to missed diagnosis. In the present study, subglottic hemangioma was diagnosed by bronchoscopy combined with contrast-enhanced CT or MRI of the neck. Under the bronchoscope, restricted dark red or purplish red bulges were observed in the subglottic mucosa, leading to local luminal stenosis. The lesions had smooth surface and soft texture. The subglottic hemangiomas were located in the left lateral wall in 7 cases, right lateral wall in 1 case, bilateral lateral walls in 3

cases, posterior wall in 2 cases, left posterior wall in 2 cases and circumferentially in 1 case. Two cases were combined with hemangioma of the pharyngolaryngeal cavity, and 1 case had hemangioma extending to the upper part of trachea. The lesions were presented as soft tissue masses in the subglottic region on contrast-enhanced CT or MRI of the neck. They protruded into the lumen, causing luminal stenosis, and were enhanced with abundant blood supply upon the contrast-enhanced scan.

Many treatment options are available for subglottic hemangioma in infants, including hormone therapy, open surgical resection, intratumoral injection of a hardening agent, and plasma radiofrequency ablation at low temperature. However, there are neither criteria for the choice of appropriate treatment nor criteria for efficacy assessment so far. In 2008, Leaute-Labreze C et al. reported high tolerance and few adverse reactions after the use of propranolol for hemangioma of the face, which represents a new solution to hemangiomas [13]. In 2009, Denoyelle et al. reported the first successful use of propranolol for the treatment of subglottic hemangioma [14]. Later, propranolol gained increasing recognition for the treatment of subglottic hemangioma [15, 16]. However, propranolol may also cause adverse reactions, and the common ones include bradycardia, hypotension and hypoglycemia. Therefore, it is necessary to monitor blood pressure, blood glucose and heart rate before and after the medication. It has been reported that the symptoms of laryngeal stridor and dyspnea can be greatly relieved at 24 h-48 h after the initial dose and that the tumor size reduces considerably under the electronic laryngoscope. In the present study, the symptoms of laryngeal stridor and dyspnea were improved to varying degree in all 16 cases at 24 h-48 h after the initial dose of propranolol. One week later, the tumors shrank in size and became paler under the bronchoscope. The tumors completely receded in 6 cases after taking oral propranolol for 6 months. Eight cases showed an apparent reduction in tumor size. Fifteen cases did not show abnormalities of ECG, blood pressure and blood biochemistry tests during the medication. The remaining one case had transient hypoglycemia after the initial dose and soon recovered after fluid replacement and change of the feeding method. Twelve cases were medicated for 6-12 months and were aged above 1 year old. The drug was discontinued when the symptoms were further improved and the subglottic stenosis was not above 10% under the bronchoscope. Among them, 11 cases did not relapse after discontinuance, and 1 case had a mild increase in tumor size at 6 months after discontinuance. Schwartz T et al., once reported that the rebound rate of hemangiomas was 9% as the propranolol dose was reduced or after propranolol was completely discontinued [17]. This indicates that subglottic hemangioma may relapse after discontinuance of propranolol, and increasing the dose or surgical intervention may be needed. To conclude, oral propranolol can reduce the size of subglottic hemangioma and improve dyspnea within a short time. It is advantaged by fast acting, proven efficacy, small individual difference and few adverse reactions.

Acknowledgements

The present study was approved by the ethics committee of Hunan Provincial People's Hospital (Changsha, China) and informed consent was obtained from the aunt and the parents of the proband.

Disclosure of conflict of interest

None.

Address correspondence to: Lili Zhong, Hunan Key Laboratory of Pediatric Respirology, Children's Medical Center, Hunan Provincial People's Hospital, No. 61, Jie-Fang Road, Changsha 410005, Hunan, P. R. China. Tel: +86-0731-83929419; E-mail: 570047414@qq.com

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