

Case Report

Bronchoscopic high-frequency electrode excision combined with cryotherapy for infantile tracheal hemangioma: a case report and literature review

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Abstract: Infantile tracheal hemangioma is a rare disease in which airway hemangiomas potentially cause airway narrowing and respiratory distress. In this report, we present a case of a 9-month-old boy with infantile hemangioma in the middle of trachea that was successfully removed using bronchoscopic high-frequency electrode excision combined with cryotherapy and review of the literature. The effect of drug treatment for infantile hemangioma is uncertain and may eventually require surgical intervention. Bronchoscopic high frequency electrode excision combined with cryotherapy is an effective, safe, and minimally invasive therapy for tracheal infantile hemangioma, which needs further exploration for the application.

Keywords: Tracheal infantile hemangioma, high frequency electric excision, cryotherapy, bronchoscopy

Introduction

Hemangiomas are the most common tumors caused by mesoderm normal vascular tissue with excessive proliferation. These tumors have been estimated to occur in 2.6%~9.9% of infants [1, 2]. Airway hemangiomas are rare, and there is no epidemiological data at present. Airway hemangiomas potentially cause airway narrowing and respiratory distress. Untreated, these lesions carry a mortality of nearly 50 percent [3]. Currently, bronchoscopic interventional techniques have been used for the treatment of endobronchial hemangiomas in adolescents [4, 5]. However, there is no report of bronchoscopic high-frequency electrode excision combined with cryotherapy for the treatment of tracheal infantile hemangioma. We report a case of tracheal infantile hemangioma in an infant treated by combination therapy of high-frequency electrode excision and cryotherapy with bronchoscope. We further reviewed the literature to date.

Case report

A 9-month old boy was admitted because of wheezing for 3 months and aggravation for 3

days. 3 months ago, the patient started to have wheezing, was getting worse, and the symptoms were more obvious with shortness of breath. One month ago, computed tomography (CT) examination at another hospital displayed a respiratory tract neoplasm, and the patient was then transferred to the intensive care unit (ICU) of our hospital. Blood gas analysis showed: pH 7.10, PO₂ 7.6 kPa, and PCO₂ 11.9 kPa, with continuous positive airway pressure (CPAP) ventilation treatment. High resolution computed tomography (HRCT) revealed a round-like occupying lesion within the middle segment of trachea (around 6.5 mm × 7.1 mm × 8.3 mm). Three dimensional reconstruction of airway displayed localized filling defect of trachea and no definite vascular supply. Abdominal CT displayed multiple intrahepatic round-like low density foci, with the largest one at the S7 segment of the right lobe of the liver (around 3.2 mm × 3.1 mm × 3.0 mm). The diagnosis considered hemangioma in the middle of the main bronchus and multiple hemangiomas in the liver (**Figure 1**). Bronchoscopy discovered a mass in the middle segment of the trachea, of which the base was located on the right wall of the trachea, with plentiful blood vessels on the surface, and the airway lumen was almost blocked

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Figure 1. A-C. Chest high resolution CT exhibited soft tissue imaging at the middle segment of the main bronchus (pointed by arrows) (size of around 6.5 mm × 7.1 mm × 8.3 mm), which was almost completely obstructed the airway lumen, with the CT value of around 25 Hu and conspicuous intensification by enhanced scanning (CT value of around 128 Hu), indicating hemangioma; D. Local filling defect sign was shown in 3 dimensional airway reconstruction (pointed by arrows); E. Abdominal CT displayed multiple intrahepatic round-like low density foci (pointed by arrows), with the largest at the S7 segment of the right lobe of the liver (size of around 3.2 mm × 3.1 mm × 3.0 mm), and the CT value of around 44 Hu, and evident intensification by enhanced scanning (CT value of around 182 Hu), indicating hemangioma.

(**Figure 2A**). Oral propranolol (2 mg/kg/d, t.i.d) was administered, stridor gradually reduced at one week after therapy, and gas analysis showed carbon dioxide pressure dropped to normal with improvement in oxygen partial pressure. Therefore, the patient succeeded in weaning from the ventilator and 10 days after therapy, the patient was successfully removed from oxygen inhalation. The lesion was smaller than before (4.6 mm × 2.8 mm × 2.5 mm) on CT at the 17th day of propranolol therapy. Oral propranolol (2 mg/kg/d, t.i.d) was continued after discharge, and stridor was still present, particularly during activity. Three days prior, the stridor had deteriorated and was accompanied with fever and dyspnea. Therefore, the patient was admitted again. The patient is the 2nd child by spontaneous delivery, with 38 weeks of gestational age, and a healthy past, without a family history of similar diseases.

Physical examination on admission showed a body temperature of 36.1°C, heart rate of 138 beats per minute, breathing rate of 56 times per minute, blood pressure of 90/52 mmHg, and a body weight of 8 kilograms. The patient presented with mental fatigue and “three depression signs”, with audible biphasic wheezes. The abdomen was flat, and the liver was palpable 3 cm below rib, showing a soft texture and sharp edge.

The admission diagnoses were: 1) tracheal hemangioma; 2) multiple hepatic hemangioma; 3) respiratory tract obstruction. Blood gas analysis after admission showed: pH 7.19, PO₂ 7.73 kPa, and PCO₂ 11.13 kPa, and chest CT displayed an increase in size of original hemangioma within the middle segment of the trachea (around 6.8 mm × 6.9 mm × 7.6 mm). Oral pro-

pranolol (2 mg/kg/d, t.i.d) was continued for 17 days, and symptoms of wheezing and dyspnea were not alleviated. Dexamethasone (0.5 mg/kg/d, q.d) was administered for 4 days, still without relief of wheezing or dyspnea. After multidisciplinary consultation within our hospital, and the approval of parental consent, bronchoscopic high-frequency electrotome excision combined with cryotherapy was performed under general anesthesia and extracorporeal membrane oxygenation (ECMO). After general anesthesia through trachea intubation, the 12Fr catheter was inserted into the beginning of Brachio Cephalic Trunk (BCT) via the carotid artery, and the 14Fr catheter was inserted into the right atrium via the jugular vein, followed by according connection of catheters with the artery and vein end of ECMO, prior to bypass circulation and full establishment of the ECMO (A-V mode). The endotracheal tube was then removed, and #1.5 laryngeal mask was placed, via which, bronchoscopy (Japan, Olympus P260F, the head diameter of 4.0 mm, and the working channel diameter of 2.0 mm) reached the lesion site, showing that the lumen of the middle trachea was almost completely blocked by hemangioma, and not able to pass through. The ERBE VIO 200D respiratory endoscopy workstation (Germany) was then applied for the procedure, and ENDO CUT Q mode (effect 3, cutting width 1, cutting time interval 6, peak voltage 770Vp) was chosen. Specifically, through a bronchoscopic working channel, the electrotome (Olympus, model SD-7C-1) was launched when arriving at the proximal side of the tumor, and the tumor was trapped, followed by adjustment of the bronchoscope and snare to ensure trapping at the tumor base, prior to slowly tightening the snare for resection of hemangioma (**Figure 2B**), withdrawing the snare,

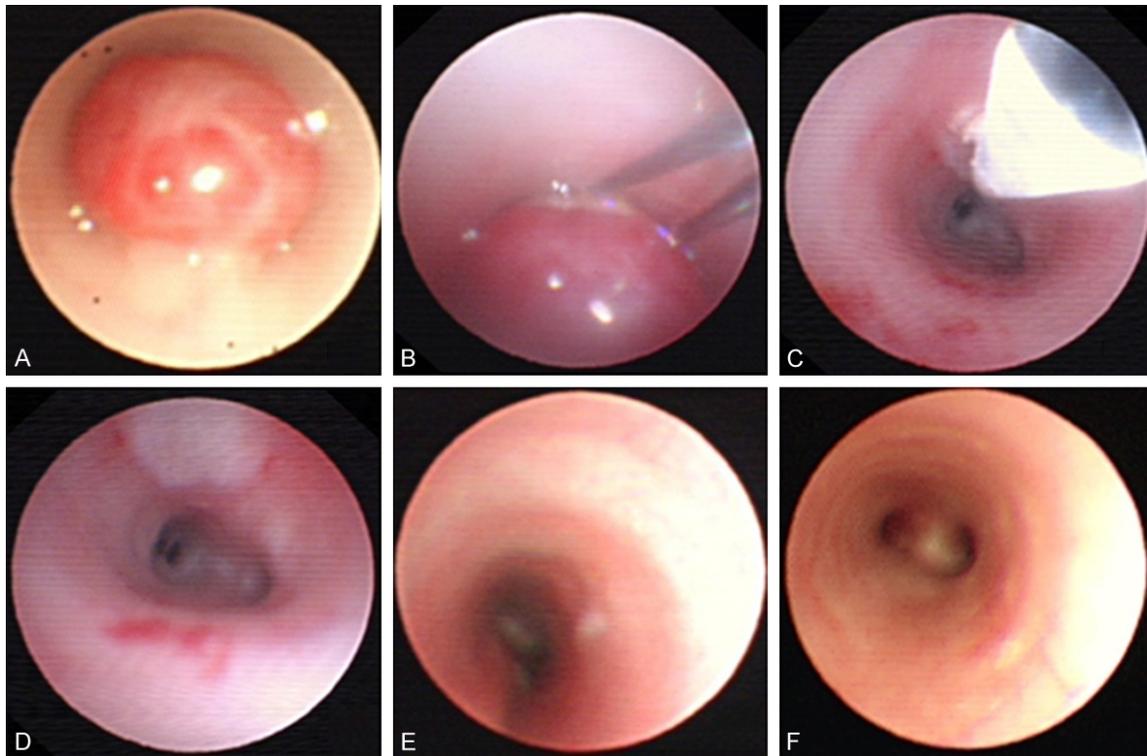


Figure 2. A. Bronchoscopy displayed a bright red mass within the middle segment of the main bronchus, with the base on the right wall and plentiful blood vessels on the surface, which almost completely blocked the airway lumen; B. Bronchoscopic high-frequency electrotome excision of hemangioma; C. Lesion residue after electric resection of hemangioma and cryotherapy for wound; D. After high-frequency electrotome excision combined with cryotherapy, it showed disappearance of the hemangioma, patency of lumen, and local mucosal edema of the wound covering the necrotic tissue; E. Bronchoscopy at 1 week after surgery revealed patency of lumen, no evident edema of the wound, necrotic surface of foci, and no relapse of hemangioma; F. Bronchoscopy at 3 months after surgery exhibited patency of lumen, smooth local mucosa, and no relapse of hemangioma.

and retrieving the mass with a pair of foreign body forceps. After tumor excision, the wound was not smooth, and had some bleeding. Again, via the bronchoscopic working channel, the cryosurgery probe (Germany ERBE company, Erbokryo CA cryotherapy instrument, 20416-037 new type soft freezing probe, diameter of 1.9 mm, L900 mm, freezing gas of CO₂) was inserted, and freezing started when its metal end got close to the wound (**Figure 2C**). Freezing lasted 10-30 seconds, followed by release of the pedal and waiting for melting of ice and frost on the probe, which was then moved to another spot for freezing multiple spots, with 1-3 cycles of freezing and thawing for each spot. After operation, the lumen was unobstructed and the wound was clean (**Figure 2D**), and oral propranolol was continued, and ventilator was withdrawn on the same day. Pathology examinations exhibited bulky capillary hyperplasia, and immunohistochemistry staining of CD31

(+), D2-40 (-), GLUT-1 (+) and CD34 (+), with the pathological diagnosis of infantile hemangioma (**Figure 3**). Bronchoscopy re-exam at 1 week post-surgery showed no bleeding at the local wound, with mucosal focal ulcer, and no recurrence of hemangioma (**Figure 2E**). The patient was discharged from hospital 9 days after surgery and continued to take oral propranolol. Follow-up at 3 months showed no symptoms of wheezing, and bronchoscopy re-check showed absence of local scar, hemangioma relapse, and tracheal stenosis (**Figure 2F**).

Literature review

The key words of tracheal, bronchial, hemangioma, and infant were utilized to search literature in PubMed database and in the Chinese database of Wanfang, and infantile tracheal and bronchial hemangioma was reviewed in the perspectives of clinical features, clinical man-

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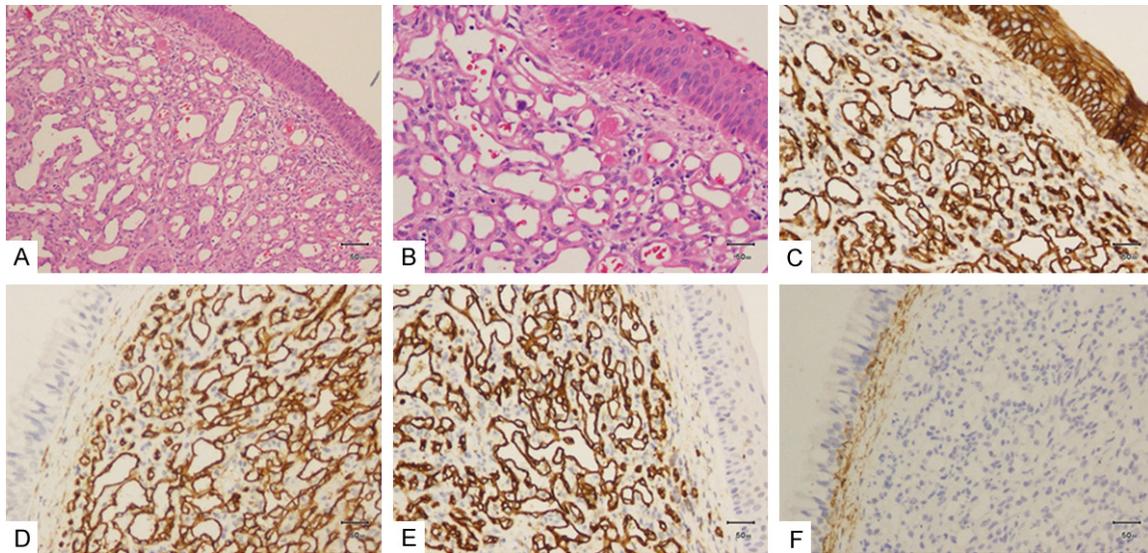


Figure 3. A, B. Pathology of the mass (HE staining, magnification of 10×20 and 10×40) showed that the mass surface was covered with stratified squamous epithelium and pseudostratified ciliated columnar epithelium, and a large number of capillary vessels with lobulated hyperplasia were seen in sub-epithelium and dermis, presenting homogeneity in size of vascular endothelial cells, without obvious pleomorphism; C. GLUT-1 immunohistochemistry (IHC) staining (SP method, magnification of 10×20) showed large amounts of positive endothelial cells in the mass, indicating high expression of GLUT-1; D. CD34 IHC staining (SP method, magnification of 10×20) showed large amounts of positive endothelial cells in the mass, implying expression of vascular endothelial cell biomarker, CD34; E. CD31 IHC staining (SP method, magnification of 10×20) showed many positive endothelial cells in the mass, with expression of vascular endothelial cell biomarker, CD31; F. D2-40 IHC staining (SP method, magnification of 10×20) showed no positive cells in the mass, implying the absence of expression of the lymphatic endothelial cell biomarker, D2-40.

agement and prognosis. One reference [6] was retrieved from Wangfang while 16 international references from PubMed [7-22], in which, 13 were case report [6, 7, 9-13, 15-18, 20, 22] and 4 were retrospective case analysis [8, 14, 19, 21], with a total of 21 cases of infantile tracheal or bronchial hemangioma (**Table 1**). In summary of those cases, the disease onset age was between newborn and 9 months, with primary clinical manifestation of wheezing, 17 cases of baby girl, 3 cases of baby boy, and 1 of unknown gender. The lesion location included main bronchus in 14 cases, left main bronchus in 3, right main bronchus in 2, and each of the left and right upper lobe bronchi in 1. According to the Cotton classification of airway obstruction [23] (grade I: obstruction of lumen by lesion at less than 50%; grade II: obstruction of lumen at 51%-70%; grade III: obstruction of lumen from 71% to 99%; grade IV: lesion obstructing lumen, without visible lacunae, or, full stenosis of the respiratory tract), 7 cases were at grade II, 13 cases were at grade III, and 1 cases was at unknown level. In the perspective of clinical management, 5 cases were treated with steroids and/or propranolol + surgery, 3 cases with steroids and/or propranolol + laser, 5 cases

with surgical operation, 2 cases with laser + steroids + IFN α -2a, and 1 case each with laser, or steroids, or steroids + cyclophosphamide, or steroids + propranolol + laser + vincristine, in addition to 1 case dying of abrupt massive bleeding with rescue failure, 1 case without treatment information. Among all cases, tracheotomy was required in 4 cases. Regarding concurrent diseases, 15 cases had multiple hemangioma, 7 with cutaneous hemangioma, 4 with mediastinal hemangioma, 4 with cervical hemangioma, and 1 with posterior fossa malformations-hemangioma-abnormal aortic artery narrow and/or heart defects-eye abnormalities-sternoschisis and umbilical cyst (PHACES) syndrome. Follow-up, lasting from 7 months to 7 years, demonstrated no relapse in 20 cases, and 1 death from tumor rupture and massive bleeding with rescue failure.

Discussion

Infantile tracheal hemangioma is a rare disease, and the severity of clinical symptoms is related to the obstruction degree of the respiratory tract, more obvious upon activity, crying and agitation, or the respiratory infection, whi-

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Table 1. Literature for infantile tracheal or bronchial hemangioma

Year	Author	Literature type	Age	Gender	Symptoms	Lesion site	Size/stage	Management	Concurrent lesion site	Follow-up ^a
1990	Weber et al. [21]	Case series	Newborn	NA	Wheezing	T	NA/NA	NA	None	NA
1990	Franks et al. [9]	Case report	3 months	Female	Wheezing, cyanosis	T	NA/II	Surgical excision after hormone therapy failure	None	NA
1991	Paul et al. [15]	Case report	5 months	Female	Wheezing, respiratory distress	RMB	NA/II	Sleeve resection after hormone therapy failure	Skin	2 years
1992	Messineo et al. [13]	Case report	3 months	Female	Wheezing	T	NA/III	Relapse of mediastinal lesion after surgical excision, tracheotomy, hormone	Mediastinum, right neck	7 years
			3 months	Female	Wheezing	T	NA/II	Relapse of mediastinal lesion after surgical excision, secondary surgery	Mediastinum, back skin	18 months
1994	Woolley et al. [22]	Case report	5 weeks	Female	Wheezing	T	NA/III	Laser, CO ₂ laser	Subglottis	1 year
1994	Ohims et al. [14]	Case series	3 months	Female	Wheezing	T	NA/III	Tracheotomy, hormone, laser, IFN α -2a	Subglottis, mediastinum, neck	NA
			7 months	Male	Wheezing	T	NA/II	Laser, hormone, IFN α -2a	Neck, subglottis, mediastinum	NA
			5 months	Female	Wheezing	T	NA/II	Hormone, cyclophosphamide	Subglottis	NA
2001	Kayser et al. [10]	Case report	3 months	Female	Shortness of breath, dyspnea	LMB	ϕ 5 mm/III	Sleeve resection	None	NA
2001	Link et al. [11]	Case report	3.5 months	Female	Wheezing	RMB	NA/III	Sleeve resection	None	NA
2003	McQueen et al. [12]	Case report	3 months	Female	Wheezing, dyspnea	T	NA/III	Nd:YAG laser	Chest skin	18 months
2003	Watters et al. [20]	Case report	9 months	Female	Shortness of breath	LMB	NA/III	Hormone	Scalp, skin, tongue, subglottis	8 months
2009	Buckmiller et al. [7]	Case report	2 months	Female	Wheezing	T	NA/II	Hormone, propranolol, CO ₂ laser, vincristine	Facial skin, subglottis	2 years
2010	Truong et al. [18]	Case report	1 month	Female	Dyspnea	T	NA/III	Systemic and local hormones, tracheotomy, propranolol	Neck, throat, parotid gland, glottis, subglottis	14 months
2010	Yang et al. [6]	Case report	17 days	Male	Sudden massive hemoptysis	RULB	ϕ around 6 mm/III	Rupture and bleeding, death following rescue	None	death
2011	Rameau et al. [16]	Case report	2 months	Female	Dyspnea	T	NA/III	Hormone, KTP laser	PHACES syndrome	15 months
2011	Sierpina et al. [17]	Case report	3 months	Male	Wheezing, dyspnea, cyanosis	LMB	8 mm \times 6 mm/III	Propranolol, KTP laser after hormone therapy failure	Facial skin	7 months
2014	Eyssartier et al. [8]	Case series	3 months	Female	NA	LULB	NA/III	Sleeve resection	None	2 years
2016	Vivas-Colmenares et al. [19]	Case series	1 month	Female	Wheezing	T	NA/III	Surgical excision, intercricothyrotomy	Subglottis	NA
			3 months	Female	Wheezing	T	NA/II	Hormone, laryngotracheal plasty	Subglottis	NA

NA: not available; T: tracheal; RMB: right main bronchus; LMB: left main bronchus; RULB: right upper lobe bronchus; LULB: left upper lobe bronchus; Nd:YAG laser: yttrium aluminum garnet crystal laser; KTP laser: Potassium titanyl phosphate laser; #: no recurrence except for death; ϕ : diameter.

ch usually presented with biphasic wheezing at 3-4 weeks after birth, especially at the inhalation phase [3]. Cases reported in references had the onset age within 9 months, and the onset primary manifestation of wheezing in most of them, with the respiratory tract obstruction degree above grade II, and maximum hemangioma of 6 mm × 8 mm [6-22]. The patients in our report had the disease onset age at 6 months, and onset symptoms of wheezing, biphasic wheezing of auscultation, with the mass size of 6.5 mm × 7.1 mm × 8.3 mm, up to 90% degree of lumen obstruction within the middle segment of the trachea detected under chest imaging and bronchoscopy, which belonged to grade III of the Cotton [23] classification of airway obstruction. Blood gas analysis indicated severe carbon dioxide retention and decompensation of ventilation function.

Most cases in the literature had concurrent subglottic hemangioma, some with facial and cervical hemangioma. Despite that cutaneous hemangioma is absent, our patient had multiple hepatic hemangioma. Diagnosis of the respiratory hemangioma is generally dependent on endoscopy, whereas CT or MRI is capable of determining the affected location and range. Diagnosis of all cases in the literature was carried out via CT or bronchoscopy, and radionuclide imaging or MRI was performed in some cases [15]. In our case, bronchoscopy exhibited a mass on the right wall of the middle segment of the trachea, with plentiful capillary vessels on the surface, and demonstrated by contrast-enhanced CT. Postoperative histopathological examination revealed bulky capillary hyperplasia and IHC of CD31 (+), D2-40 (-), GLUT-1 (+) and CD34 (+), by which infantile hemangioma was confirmed, with indication of the proliferative phase of hemangioma [24, 25].

Traditional therapeutic beliefs suggest that infantile hemangiomas may naturally subside during extinction, and that the best treatment is natural regression. But a study suggested that more than 1/3 of infants need to be treated for hemangiomas [26]. At present, it is necessary to treat infantile hemangioma with concurrent dysfunction and great bleeding risk, and there should be active rescue if there are life-threatening complications [27]. As indicated in the literature, all tracheal hemangiomas need interventions, even surgical measures for

most cases. In this regard, active treatment should be administered for infantile hemangiomas, that also have concurrent airway obstruction. The therapy duration and measures for tracheal hemangioma are determined by the obstruction degree of the respiratory tract, lesion location and affected range, availability of medical technology and the parents' will [27]. Therapeutic measures are comprised of drug and surgery [27]. Drugs include glucocorticoids and propranolol, and propranolol was suggested by some meta-analysis to be the first line regimen for infantile respiratory hemangioma [28]. Before clinical application of propranolol in infantile respiratory hemangioma, endoscopic laser ablation and surgical excision had been the regular measures. The indication for surgical excision is refractory hemangioma irresponsive to regular drugs. As reflected in our case and the literature, medications showed no superiority, and the possibility of disease progression or relapse caused by infection and other factors, eventually would lead to potential requirement of surgical intervention. Endoscopic subtotal resection or surgical total resection can be applied in tracheal hemangioma [29]. Bronchoscopic interventional therapy is less traumatic. Some study displayed that laser ablation of subglottic hemangioma possibly led to excessively deep destruction of local tissue and subglottic stenosis, especially for multifocal and annular lesions, with an incidence rate of 5-25% [30].

The infantile hemangioma in our case was located within the middle segment of the main bronchus, with a larger size, almost completely blocking the lumen and requiring mechanistic ventilation, and the mass presented with a shrinkage trend after oral propranolol. The mass expanded rapidly with concurrent infection, and the symptom of airway obstruction was not relieved by infection control and continued oral propranolol, or by additional administration of systemic glucocorticoids, indicating the need of surgical measures. If the regular open surgery was considered, tracheal sleeve resection would be the surgical modality, which is in operational difficulty and high risk, as well as with big trauma and the potential incidence of anastomotic stenosis, granulation hyperplasia, and other complications. The advancement of bronchoscopic interventional therapy for respiratory diseases provides more therapeutic options for tracheal hemangioma. In some reports,

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bronchoscopic gas argon or argon combined cryotherapy was applied for therapy of tracheal lobular capillary hemangioma in adolescents [4, 5]. Considering the big size of the infantile hemangioma in our case and limitation of its base within the right wall, single gas argon, or cryotherapy, or laser would be unable to rapidly excise or ablate the entire tumor in one procedure, and complications of massive hemorrhage or perforation of the trachea might occur. Therefore, high-frequency electrotome resection combined with cryotherapy was applied instead. The site for snare resection was at the base of hemangioma, and the resection was performed via the respiratory endoscopy workstation at the ENDO CUT Q mode, in which, alternative electrocoagulation was proceeded automatically, enabling the optimal hemostatic effect when excising. However, the electrocoagulation snare excision may not completely remove the mass, and the residual lesion may relapse, in addition to potential incidence of long-term restenosis reported in some study [31]. Cryotherapy was documented to cure tracheal stenosis, demonstrating efficacy and safety, no stimulation on tissue hyperplasia or scar formation, without proneness to relapse [32]. Hemangioma is enriched with water, with plenty of blood circulation, which reinforces sensitivity to freezing, and cryotherapy turns the intracellular water into ice, giving rise to cell disintegration, necrosis or apoptosis, and thus to hemangioma necrosis and breaking off. Cryotherapy was performed in our case for the wound and residual lesion, and no relapse was detected by bronchoscopy at 1 week and 3 months recheck.

Since our case had large size of hemangioma and severe airway obstruction, bronchoscopic interventional operation would affect ventilation, with the risk of exaggerating dyspnea and endangering life. Moreover, the hemangioma was rich in blood supply but no definite vascular supply, so that it is not suitable for embolization and massive hemorrhage would occur, whereas hemostasis under flexible bronchoscope is challenging, likely generating suffocation, which would call for hemostasis by rigid bronchoscopy, or even open thoracic surgery of lesion resection. Massive hemoptysis was reported to occur in a crying newborn when the venous indwelling needle was placed, leading to death following failed rescue. Upper lobe bronchial hemangioma was diagnosed by autopsy [6], indicating that infantile hemangioma

could rapidly expand under the condition of illness or stress, with potential life-threatening complications of tumor rupture and others. Surgical resection of lower respiratory tract hemangioma under the support of extracorporeal circulation was applied by Franks, and good safety was claimed [9], which guarantees oxygenation in patients, even in case of life-threatening complications, such as above massive hemorrhage, blockade of airway by hemangioma and others, and open thoracic surgery would be feasible for surgical intervention, making bronchoscopic interventional therapy proceed smoothly and ensuring the patient's safety.

In summary, infantile tracheal hemangioma has the primary onset manifestation of wheezing, and infection is potentially the important risk factor for tumor proliferation. Treatment with drugs doesn't show definite efficacy, so surgical intervention is the ultimate measure. Bronchoscopic high-frequency electrotome excision combined with cryotherapy is efficacious and safe, with less trauma, and is thus worthy of further exploration.

Disclosure of conflict of interest

None.

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