ORIGINAL ARTICLE

The Biology and Management of Laryngeal Neurofibroma

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Objectives: To review the presentation of laryngeal neurofibroma, including its association with neurofibromatosis types 1 and 2, and present guidelines for its management.

Design: Retrospective study.

Patients: Five pediatric patients with laryngeal neurofibroma, 4 girls (80%) and 1 boy (20%), were treated at a tertiary pediatric medical center from 1973 through 2003. Recorded data included age at initial presentation, sex, symptoms, significant medical and family history, preoperative evaluation, location of the tumor, surgical procedure, complications, outcome, and recurrence.

Results: The 5 patients presented with stridor and café-au-lait spots at or shortly after birth. All patients were diagnosed as having neurofibromatosis type 1 by the established criteria. Studies evaluating the disease processes included plain radiography, computerized tomography, magnetic resonance imaging, barium swallow, and laryngoscopy and bronchoscopy under anesthesia. Pathologic examination of biopsy specimens from all patients showed neurofibromas with plexiform and/or diffuse features. Treatments included tracheotomy (n=4), carbon dioxide laser excision (n=4), modified neck dissection (n=3), partial pharyngectomy (n=1), supraglottic laryngectomy (n=1), and endoscopic hemilaryngectomy (n=1). Three patients were successfully decannulated. Follow-up ranged from 1 to 15 years. One patient was lost to follow-up. No evidence of malignant degeneration was noted.

Conclusions: Neurofibroma of the larynx is a rare condition that should be considered in the differential diagnosis of children with a submucosal laryngeal mass. In our series, all patients had associated neurofibromatosis type 1. Complete surgical excision is the treatment of choice in cases of localized small lesions. To prevent debilitating outcomes due to aggressive surgery, minimally invasive procedures (partial excision via endoscopic approach) may be preferable for larger lesions that infiltrate the surrounding vital structures. Long-term follow up of these patients is essential owing to the possibility of malignant transformation.

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WELL-KNOWN CAUSES of pediatric airway obstruction and stridor include croup, supraglottic laryngitis, laryngomalacia, and subglottic stenosis. Although benign tumors occurring in the peripheral nerves are seen in almost all parts of the body, neurogenic tumors arising primarily from the larynx are rare and include neurofibroma, schwannoma, and malignant peripheral nerve sheath tumor. When neurofibromas occur in the larynx, they may be solitary and nonsyndromic or, most commonly, associated with neurofibromatosis (NF) type 1 or 2.

Also known as von Recklinghausen neurofibromatosis, NF1 is an autosomal dominant, neurocutaneous, systemic disease. Patients with NF1 present with multiple café-au-lait spots, skeletal defects, learning disabilities, endocrine abnormalities, and tumors of ectodermal and mesodermal tissues such as cutaneous neurofibromas and central nervous system tumors. Although NF1 is transmitted as an autosomal dominant trait, there is a high rate of spontaneous mutation. While the estimated incidence of NF1 is between 1 in 2500 and 1 in 3300 live births, its prevalence in the population is approximately 1 in 4000.

Central NF, or NF2, is also an autosomal dominant condition, having a reported incidence of 1 in 40 000 live births and a prevalence of 1 in 210 000. Manifestations of NF2 include acoustic neuroma, neurofibroma, meningioma, glioma,

Table 1. Presentation of Laryngeal Neurofibromas in 5 Patients

Patient No./Sex/ Age at Presentation	Presenting Symptoms	Workup	Tumor Site at Presentation
1/F/at birth	Stridor, café-au-lait spots	Plain radiography, barium swallow, laryngoscopy, bronchoscopy, biopsy	Arytenoid, hypopharynx, upper esophagus
2/M/15 wk	Stridor, café-au-lait spots, feeding difficulty, hoarseness	Laryngoscopy, bronchoscopy, biopsy	Neck, arytenoid, post-cricoid
3/F/1 y	Stridor, café-au-lait spots	Plain radiography, CT, barium swallow, laryngoscopy, bronchoscopy, biopsy	Pharynx, aryepiglottic fold, arytenoid
4/F/10 d	Stridor, café-au-lait spots, feeding difficulty	Plain radiography, CT, MRI, laryngoscopy, bronchoscopy, biopsy	Posterior commisure, arytenoid, mediastinum
5/F/at birth	Stridor, café-au-lait spots, feeding difficulty, hoarseness	CT, MRI, laryngoscopy, bronchoscopy, biopsy	Aryepiglottic fold, arytenoid

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

schwannoma, and juvenile superior subscapular lenticular opacity. In common with NF1, 50% of cases represent new sporadic gene mutations.

The purpose of the present study is to review our experience in the management of laryngeal neurofibroma at The Children's Hospital, Boston, Mass, with emphasis on the presentation, role of preoperative imaging, surgical approach, pathologic features, and rate of recurrence. On the basis of our experience and review of the literature, we present our recommendations for the management of laryngeal neurofibroma.

METHODS

This is a retrospective study of 5 patients with neurofibroma of the larynx treated at The Children's Hospital, Boston, from 1973 through 2003. We recorded data including the child's age at initial presentation, sex, presenting symptoms, significant medical and family history, preoperative workup, site of the tumors, surgical procedures, complications, functional results, and recurrence. Pathologic features of all tumors were reviewed. Gross evaluation included review of recorded gross features and all available photographs. Hematoxylin-eosin–stained slides were examined in all cases.

RESULTS

The patients included 4 girls (80%) and 1 boy (20%). Their clinical presentations, evaluation results, and disease findings are summarized in **Table 1**. All 5 patients presented with café-au-lait spots and stridor at birth or within the first year of life. Three patients experienced feeding difficulty, and 2 patients had hoarseness (Table 1). The studies conducted to evaluate the disease process included plain radiography, computed tomography (CT), magnetic resonance imaging (MRI), and barium swallow (Table 1). Airway endoscopy (laryngoscopy and bronchoscopy) under general anesthesia and biopsy were performed on all patients. The most common locations of laryngeal involvement were the arytenoids and aryepiglottic folds (Table 1). All patients were diagnosed as having NF1 using the following diagnostic criteria:

The patient should have 2 or more of these findings:

1. Six or more café-au-lait spots:
   1.5 cm or larger in postpubertal individuals
   0.5 cm or larger in prepubertal individuals
2. Two or more neurofibromas of any type or 1 or more plexiform neurofibroma
3. Axillary or groin freckling
4. Optic glioma
5. Two or more Lisch nodules (benign melanotic iris hamartomas)
6. A distinctive bony lesion:
   Dysplasia of the sphenoid bone
   Dysplasia or thinning of long bone cortex
7. A first-degree relative with NF1

The data regarding the type and number of surgical treatments are listed in **Table 2**. Due to the extent of the lesions and their infiltration into surrounding soft tissues and vital structures, complete excision and preservation of laryngeal function was not possible in all patients. Four patients required tracheotomy (Table 2). Initially, all 5 patients were treated conservatively with partial excision to improve patency of the airway and to preserve laryngeal functions. Carbon dioxide laser excision was implemented in 4 of the 5 patients.

Patient 1 (Table 2), who was not treated with laser, first underwent surgery in the early 1970s. This patient initially required tracheotomy and neck dissection followed by a partial pharyngeal resection and excision of neurofibroma involving the arytenoids. She presented with recurrence within a year and required more extensive pharyngeal resection. She remains dependent on her tracheotomy.

Patient 2 (Table 2) underwent carbon dioxide laser resection of the neurofibroma involving the arytenoids and postcricoid area. This patient was lost to follow-up owing to geographic relocation. Patient 3 (Table 2) required tracheotomy and underwent multiple laser excisions of the laryngeal mass followed by a supraglottic laryngectomy. This was followed by neck dissection with preservation of cranial nerves. Further laser excisions of residual tumor led to a final procedure of decannulation.

Patient 4 (Table 2) required tracheotomy and laser excisions of the laryngeal neurofibroma followed by neck dissection. This patient was successfully decannulated.

Table 2. Management of Laryngeal Neurofibromas in 5 Patients With Neurofibromatosis

Patient No./ Age at Tracheotomy	Surgical Intervention	Histopathologic Findings	Decannulation	Persistence of the Disease	Follow-up, y
1/3 y	Neck dissection, partial pharyngectomy and excision of laryngeal mass, revision partial pharyngectomy	Neurofibroma	No	Yes	10
2/ND	Carbon dioxide laser excision (n = 1)	Neurofibroma	NA	Unknown	1
3/12 y	Carbon dioxide laser excision (n = 11), supraglottic laryngectomy, neck dissection, carbon dioxide laser excision (n = 2)	Neurofibroma	Successful	No	15
4/19 d	Carbon dioxide laser excision (n = 1), neck dissection, carbon dioxide laser excision (n = 1)	Neurofibroma	Successful	Yes	5
5/2.75 y	Carbon dioxide laser excision (n = 4), endoscopic hemilaryngectomy	Neurofibroma	Successful	No	7

Abbreviations: NA, not applicable; ND, not done.

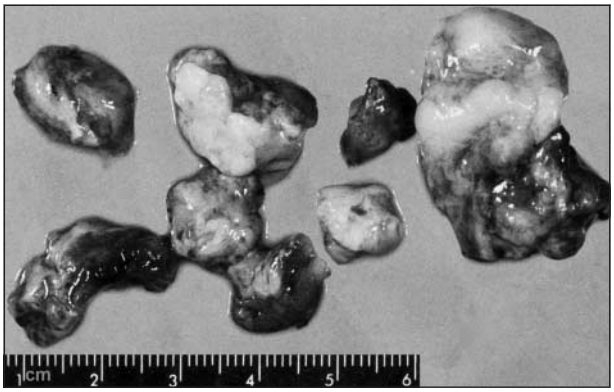

Figure 1. Gross examination of 1 of the larger specimens showed ropy cords of tan-white, rubbery, slightly myxoid tissue.

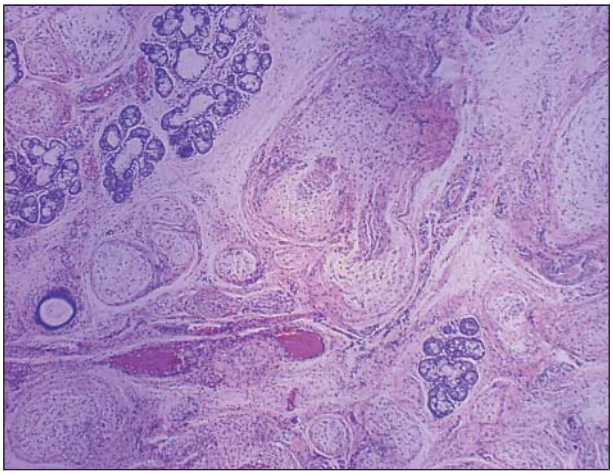

Figure 2. Histologic section showing nerves expanded in a plexiform pattern, interdigitating around preexisting mucosal glands (hematoxylin-eosin, original magnification ×40).

Patient 5 (Table 2) underwent tracheotomy and multiple carbon dioxide laser excisions followed by endoscopic hemilaryngectomy. She has been successfully decannulated and shows no evidence of recurrence. Patients 1, 3, 4, and 5 are able to eat and swallow without aspiration and have socially acceptable voices. There was no perioperative mortality.

Gross pathologic specimens ranged from minute mucosal biopsy specimens to bulky tumor up to 5 cm in aggregate. Sectioning of larger specimens revealed plexiform features of ropey white cords and areas of solid, firm, white tumor (**Figure 1**). The diagnosis of neurofibroma was confirmed histologically in all cases. Sections showed proliferation of small, delicate, wavy, spindle cells as well as a variable accumulation of myxoid ground substance and delicate collagen fibers. These components expanded preexisting nerves in a plexiform pattern and also showed areas with a diffuse pattern of growth (**Figure 2**).

COMMENT

Neurofibroma of the larynx is extremely rare.[1,2] In 1929, Jackson and Coates[3] reported the first case of laryngeal neurofibromas. In 1987, Fukuda and colleagues[4] reviewed the available world literature and reported 57 cases of laryngeal neurofibromas. These tumors may occur in isolation, but more commonly they are associated with NF1 or NF2.

PATHOGENESIS

The most common sites of laryngeal involvement include the aryepiglottic folds and the arytenoids, areas of the larynx rich in terminal nerve plexuses. It has been postulated that this location implies a tumor origin from the superior laryngeal nerve and/or from anastomoses between the superior laryngeal nerve and the recurrent laryngeal nerve.[5-7] In 1849, Robert W. Smith[8] first published a review of the disease and suggested that the origin of the tumors was the connective tissue surrounding small nerves. In 1882, Friedrich von Recklinghausen[9] recognized that the tumors included both neural and fibrous tissue derived from peripheral nerves and introduced the term *neurofibromatosis*.

Neurofibromatosis type 1 is inherited in an autosomal dominant manner, and although it shows almost 100% penetrance, there is variable expressivity with variation of clinical manifestations within a family. In addition, in 30% to 50% of cases, there is no family history, and the disease arises from a probable germ cell mutation.[5] The gene for NF1 has been localized to chromosome 17q11.2, spans over 350 kilobases (kb) of genomic DNA, and encodes a protein, neurofibromin, which contains 2818 amino acids. The pathogenesis of NF1 in-

volves a loss of neurofibromin, which appears to have a tumor suppressor role.[5] Mutations resulting in diminished levels of this protein result in development of the wide variety of tumors seen in the disease. Although 25% to 35% of neurofibromas are found in the head and neck, neurofibromas involving the larynx are rare.[6]

The gene for NF2 has been localized to chromosome 22q12.1, spans 110 kb of genomic DNA, and encodes a cytoskeletal protein known as Merlin or schwannomin. It seems that the NF2 gene acts as a tumor suppressor in NF2, sporadic meningiomatosis, and other neuroectodermal tumors.[5] The occurrence of laryngeal neurofibroma in patients with NF2 is extremely rare.

PRESENTATION

Neurofibromas may be classified as plexiform, diffuse, or both, based on their pattern of growth. A plexiform growth pattern is virtually diagnostic of NF. Plexiform neurofibromas are poorly localized and spread along preexisting nerve networks. They often have a slow growth rate and can remain symptom free for years or become symptomatic depending on size and location. In our 30-year experience with laryngeal neurofibroma, all patients had associated NF1.

The diagnostic criteria for NF1 have been summarized above. Patients with NF1 typically present in the first decade of life. Café-au-lait spots are the most common presentation, symmetrical, flat areas of skin hyperpigmentation with rounded edges. Their number and size increase during infancy. Most patients (70%) also show freckling of the intertriginous area of the axilla or groin. Lisch nodules (benign melanotic hamartomas of the iris) develop in 95% of individuals with NF1, usually after age 5 years. Also, distinctive bony lesions including scoliosis, dysplasia of the sphenoid wing, and thinning of long bones are among the diagnostic criteria for NF1. About 50% of patients have learning disabilities.[5] Other conditions that occur more commonly in the NF1 population include epilepsy, headaches, and growth disturbances.

Laryngeal neurofibromas are not, as a rule, associated with NF2. The diagnostic criteria for NF2 are as follows:

Bilateral eighth-nerve tumors diagnosed by biopsy or seen on imaging study (CT or MRI) or

A first-degree relative with NF2 AND either a unilateral eighth-nerve tumor OR 2 of the following: neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacity.

A defining feature of NF2 is the presence of bilateral acoustic neuromas.[5] Patients typically present with a gradual, sudden, or progressive and often asymmetrical hearing loss. Conductive hearing loss may be the consequence of ossicular and temporal bone deformity or tumor within the auditory meatus.

Owing to its slow growth and variability of location and size, laryngeal neurofibroma can remain symptom free for years or become symptomatic at birth (**Figure 3**). The first symptoms include stridor, hoarseness, dysphagia, dysphonia, and globus sensation and are usually of a progressive nature. All 5 of our patients presented at birth or within the first year of life. Other reported symptoms included dyspnea, hoarseness, and feeding difficulty.

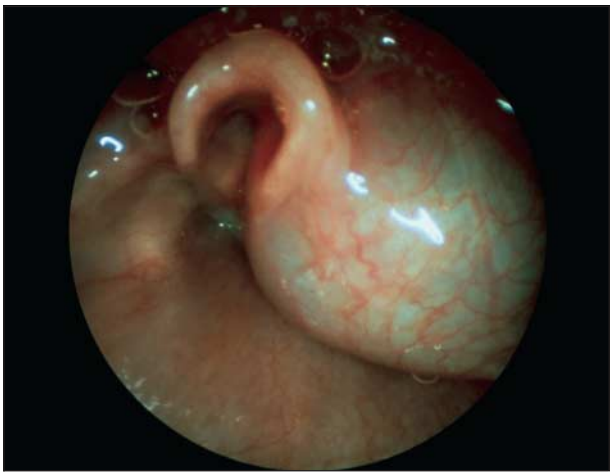

Figure 3. Endoscopic view of a neurofibroma projecting into the airway lumen, causing a bulging mass with prominent vasculature.

Children presenting with plexiform neurofibroma may have extensive involvement of the neck, chest, and skull base. In our study, 1 patient (patient 4) presented with mediastinal neurofibroma. An estimated 5% of neurofibromas undergo sarcomatous degeneration. Most malignancies appear in the third to sixth decades and are characterized by sudden rapid growth with metastases in the lungs and bone. None of our patients has shown any clinical or pathogic changes suggestive of sarcomatous degeneration.

IMAGING

The decision about whether to obtain CT or MRI depends in part on the availability of each modality and the degree of soft tissue characterization required. Computed tomography provides useful delineation of tumor extent but provides limited soft tissue characterization. Magnetic resonance imaging provides superior soft tissue characterization and may delineate additional unsuspected synchronous tumors in patients with NF1 and NF2.

For CT, helical 3-mm-thick images should be obtained in the axial plane during the administration of a bolus of iodinated intravenous contrast medium (**Figure 4**). These initial images are acquired when there is dense contrast within the common carotid arteries and internal jugular veins, which allows for assessment of the patency of these vessels and their relationships to the tumor mass. Images can be retrospectively reconstructed with thinner slices, enabling the acquisition of 2-dimensional coronal and sagittal reformatted images. Scan times have been substantially reduced with the introduction of the newer-generation multislice CT scanners, which may preclude the need for general anesthesia. Neurofibromas appear hypodense prior to the administration of contrast and enhance moderately to intensely. Plexiform neurofibromas have a characteristic multilobulated appearance

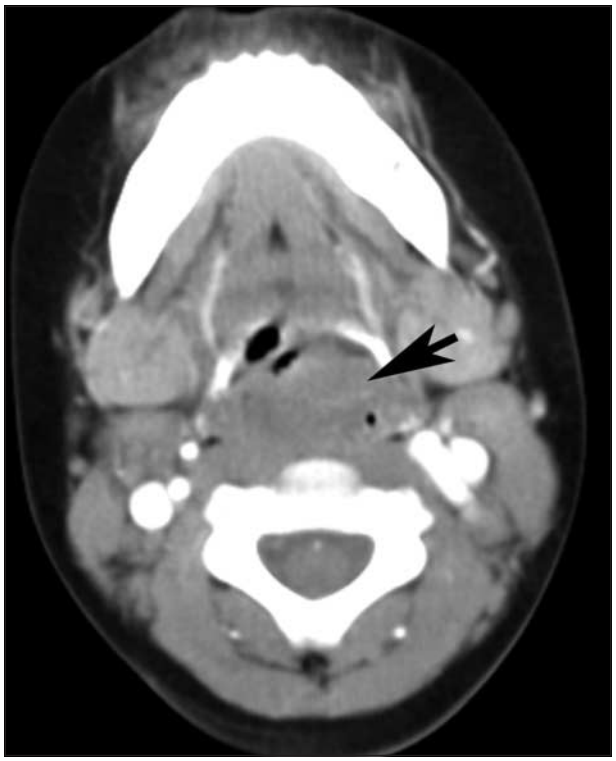

Figure 4. Axial contrast-enhanced computed tomographic image obtained at the level of the hyoid bone. A hypodense mass (arrow) fills the supraglottic airway.

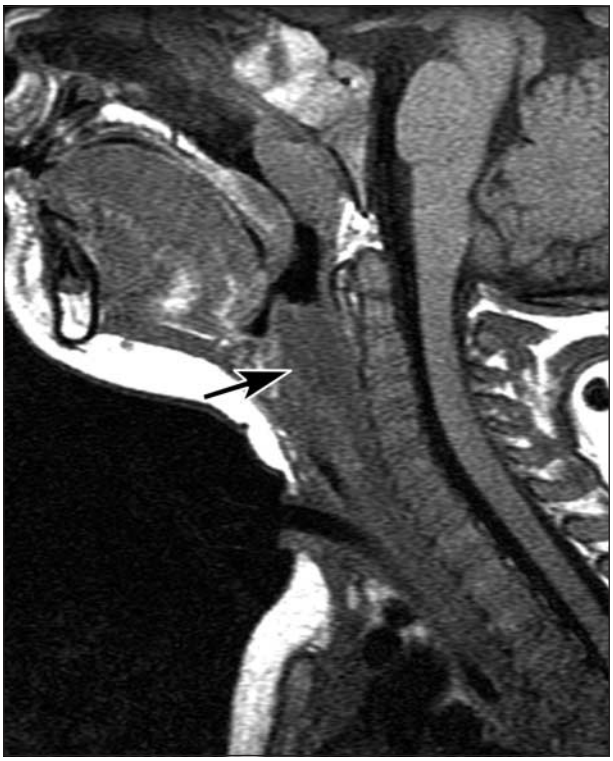

Figure 5. Sagittal T1-weighted magnetic resonance image reveals a tracheotomy tube in place. A tumor (arrow) abuts the inferior surface of the epiglottis and obliterates the supraglottic airway and larynx.

with a targetlike configuration with central enhancement and peripheral hypodensity.

Magnetic resonance images are acquired in the 3 orthogonal planes: coronal, axial, and sagittal (**Figures 5**, **6**, and **7**). Fast spin-echo T2-weighted images should be fat suppressed or substituted with fast spin-echo inversion recovery images. The gadolinium-enhanced, T1-weighted images should also be fat suppressed. However, there is often inhomogeneity of fat suppression when the neck is scanned. The appearance of solitary neurofibromas varies with high or low signal on T2-weighted images, depending on the admixture of fibrous tissue. Similarly, enhancement can be moderate and heterogeneous or homogeneous and intense.

PATHOLOGY

Neurofibroma is a benign proliferation of Schwann cells, perineurial cells, and fibroblasts. There are many subclassification schemes used to describe the patterns of growth and the degree of progression toward malignancy in neurofibroma.[10,11] The cells generally tend to grow in a plexiform pattern (expanding preexisting nerves), a diffuse pattern (growing as a nodule), or a combination of patterns. Approximately 30% of patients with NF1 have plexiform NF, which is histologically diagnostic of NF1.[5] These patients are also prone to malignant peripheral nerve sheath tumor, either de novo or degenerating from neurofibroma. Assessments as benign, atypical, or malignant may be made using a variety of factors such as cellularity, mitotic count, cellular pleomorphism, and necrosis.[11,12]

MANAGEMENT

Prudent history taking and thorough physical examination are essential for correct diagnosis. Further evaluation with CT and MRI aid the differential diagnosis and help determine the extent of the lesion. Genetic counseling and parental education should also be performed if there is any suggestion of NF1 or NF2. The final diagnosis of laryngeal neurofibroma is based on findings at the time of airway endoscopy and biopsy. Speech and swallowing evaluation should be a part of the patient's workup and treatment plan.[13]

Choice of treatment for neurofibroma of the larynx is based on the location, extension, and severity of symptoms. Complete resection of laryngeal neurofibroma and preservation of laryngeal functions are often impossible owing to the lesion's infiltrative nature. Currently there are no specific guidelines with regard to the management of these patients. A conservative approach is advisable when total resection is not possible and the patient has minimal symptoms. Subtotal excision has been the mainstay of therapy because of the propensity for diffuse involvement and poor margin control. Endoscopic laser excision is recommended for patients who present with a small, localized lesion that is accessible via suspension laryngoscopy. The difficulty lies in the patients who present with a large infiltrative lesion causing airway obstruction. Currently, there are no data comparing the long-term outcome of the open vs endoscopic approach in the management of NF. Often, tracheotomy may be required to establish a safe and adequate airway. Because of the propensity for diffuse involvement and poor

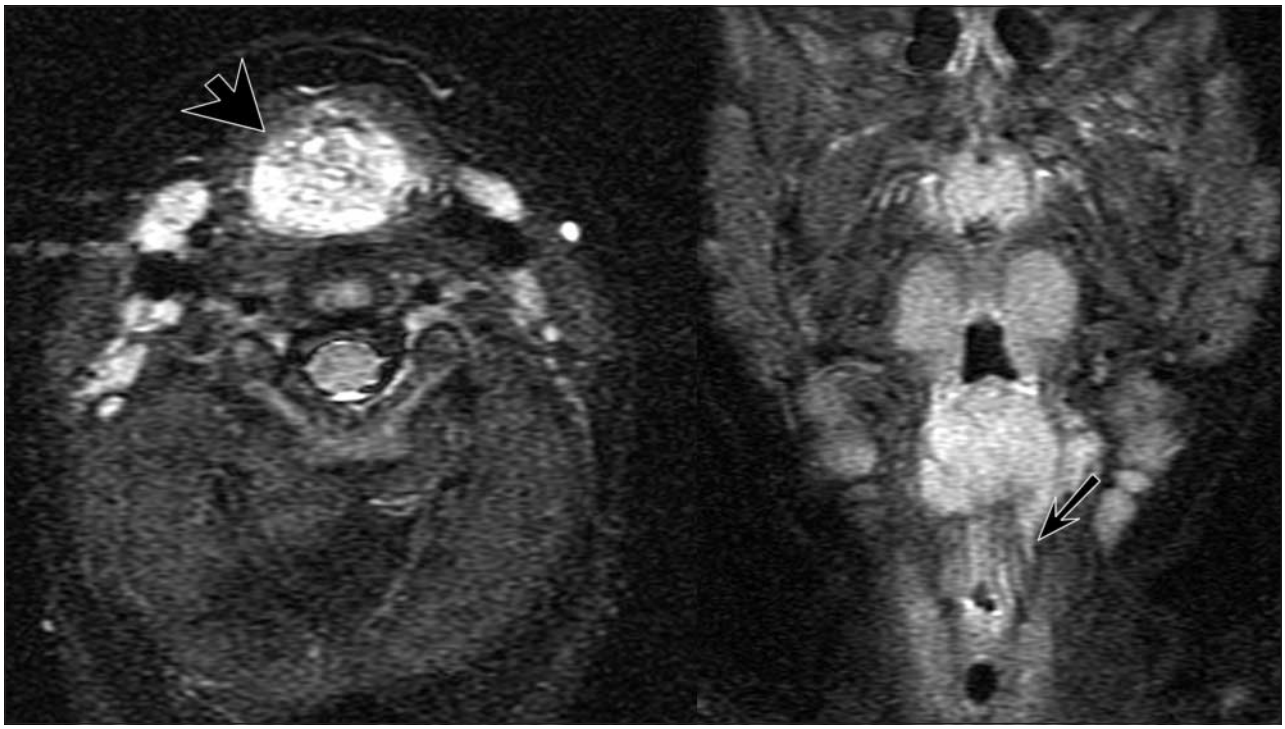

Figure 6. Axial (left) and coronal (right) fast spin-echo inversion recovery images demonstrate the hyperintense tumor filling the larynx (short arrow). The coronal image reveals tumor extending into the left pyriform sinus (long arrow).

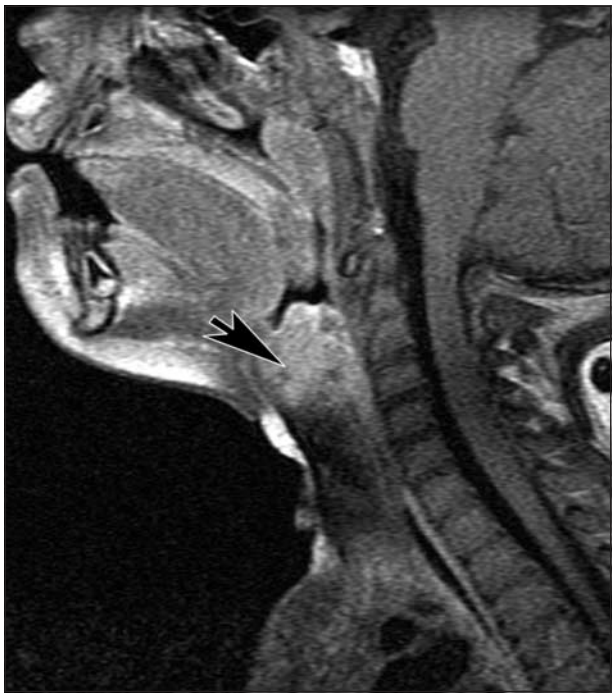

Figure 7. Fat-suppressed, gadolinium-enhanced T1-weighted magnetic resonance image reveals that the tumor is enhancing (arrow).

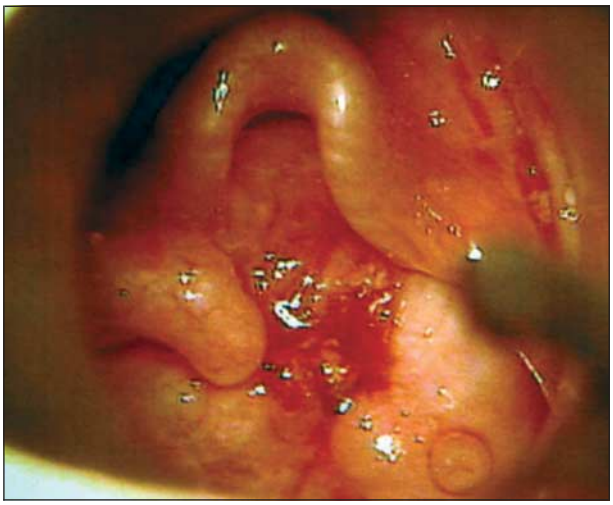

Figure 8. Endoscopic view of laryngeal neurofibroma with a serpentine shape bulging into the airway and causing obstruction (patient 5; Table 2).

margin control in NF, and to preserve laryngeal function, subtotal excision via endoscopic approach may be used to treat these patients.

An open approach (lateral thyrotomy, lateral pharyngotomy, or laryngofissure) for excision of laryngeal neurofibroma has also been advocated by some authors.[14] The open approach may provide a wider exposure and allows for more extensive removal of the tumors. However, regardless of surgical approach, there is significant likelihood of recurrence owing to the infiltrative nature of laryngeal neurofibroma.[14,15]

We advocate a conservative laryngeal procedure to establish an adequate airway and preserve laryngeal function (**Figure 8** and **Figure 9**). In cases of subtotal resection, endoscopic laser excision may be used to control the residual disease, maintain an adequate airway in a palliative measure, and preserve laryngeal functions. Complications of surgical excision of laryngeal neurofibroma include hemorrhage, scarring, vocal cord paralysis, and postobstructive pulmonary edema. Owing to the pos-

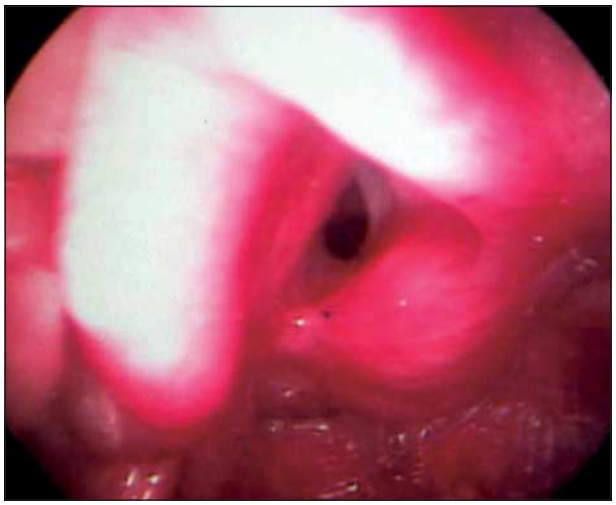

Figure 9. Endoscopic view of the larynx (patient 5; Table 2) after endoscopic hemilaryngectomy.

sibility of malignant transformation, close follow-up of these patients is essential. Malignant transformation must be considered in the case of a rapid increase in the volume of the neurofibroma and onset of pain. Treatment of malignant transformation is wide surgical excision followed by radiotherapy. In malignant transformation, the 5-year survival rate is between 20% and 50%.[16]

CONCLUSION

Neurofibromas should be considered as part of the differential diagnosis in a child presenting with a submucosal laryngeal mass, even without the other clinical signs of NF1 or NF2. A CT or MRI scan should be obtained with axial and coronal sections to determine the extent of the lesion. Diagnosis is confirmed by direct laryngoscopy and biopsy. We advocate a minimally invasive endoscopic approach for resection of the tumor with preservation of laryngeal function. Long-term follow-up is essential owing to high rate of recurrence or residual disease and the possibility of malignant degeneration.

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