Solitary Neurofibroma of the larynx in adults

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ABSTRACT
Neurofibromas are benign tumors with neural origin, most frequently found in neurofibromatosis. However, they can also occur as isolated lesions, which are extremely rare in the larynx. A case of a 56 years old patient is presented with complains of odynophagia, hoarseness, dysphagia and dyspnea. On otolaryngologic observation it was found a large pharyngolaryngeal mass compressing the airway, causing dyspnea with the need of a tracheotomy. A surgical resection of the tumor was performed and it was diagnosed a solitary laryngeal neurofibroma. Due to the rarity of the disease, we present the first case identified in the Portuguese population. It is performed a review of this entity in the adult, to contribute for a better understanding of the disease.
Keywords: neurofibroma; neural tumor; larynx; laryngeal

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INTRODUCTION

Neurogenic tumors of the larynx are extremely rare, accounting for only 0.1–1.5% of all benign laryngeal tumors[1]. Neurofibromas are benign neurogenic tumors with a peripheral nerve sheath comprising neurites, Schwann cells, and fibroblasts within a collagenous or mucoid matrix.[2] They are most frequent in the context of neurofibromatosis (NF; von Recklinghausen disease). However, they can also present as isolated lesions, without the other characteristics that define NF. Solitary neurofibromas of the larynx (SNLs) are very rare.[3]

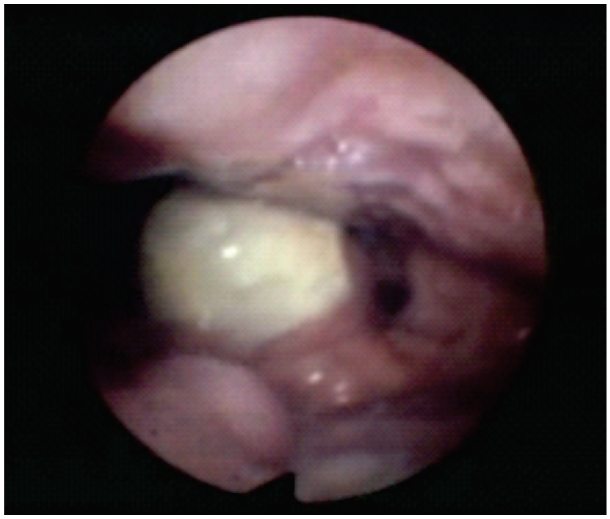
Considering the rarity of the disease, we describe a patient with SNL who was followed in the outpatient clinic of the Francisco Gentil Portuguese Oncology Institute in Lisbon, with the aim of contributing to a better understanding of the disease. We also searched PubMed for articles published in English about this entity in adults up to December 2019 using the terms “neurofibroma” AND “larynx” AND “laryngeal” AND “neurofibroma”, and manually reviewed patients identified in the references. Articles about pediatric SNL were excluded. The search yielded only 18 reports describing SNLs in adults, with the present patient being the first reported in Portugal.

CASE DESCRIPTION

A 56-year-old female patient with a history of asthma, acromegaly (as a result of a tumor of the hypophysis treated with surgery and radiotherapy at age 24 years), hypothyroidism, chronic anemia, and HIV infection (with controlled viral load) was regularly followed by Pulmonology, Endocrinology, and Infectious diseases. She was under regular inhaler therapy with fluticasone furoate and vilanterol, antiretroviral drugs, levothyroxine sodium, systemic corticosteroids, and salbutamol for rapid relief. She denied smoking cigarettes and consuming alcohol or drugs.

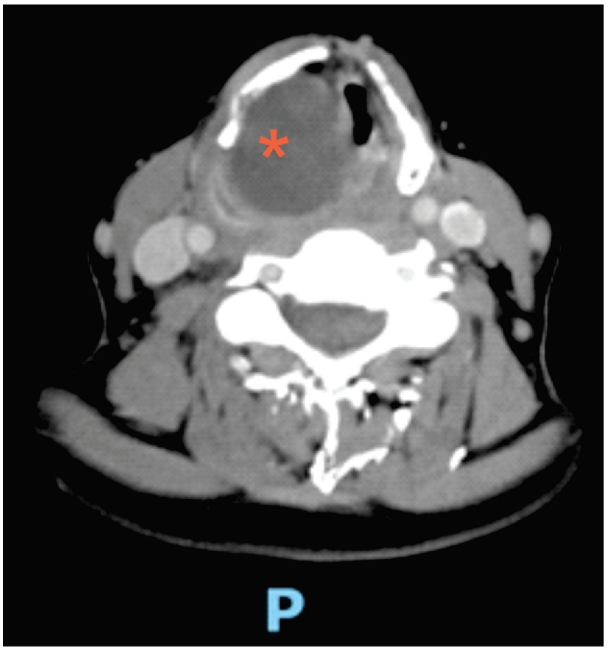
The patient was initially evaluated in the emergency department of the referring hospital due to a clinical presentation of dyspnea, which was initially interpreted as acute exacerbation of asthma. However, she also complained of associated odynophagia and a sensation of cervical tumefaction. Fiber nasolaryngoscopy revealed a large pearl-white laryngopharyngeal lesion located somewhat on the right but occupying the entire laryngeal vestibule, which preventing visualization of the vocal cords and glottic lumen (Figure 1). Neck palpation revealed no adenopathy. Computed tomography (CT) images of the neck showed a hypodense lesion (longitudinal, cross-sectional, and anterior-posterior dimensions of 40 × 35 ×

FIGURE 1
Fiber nasolaryngoscopy reveals a large pearl-white laryngopharyngeal lesion



33 mm, respectively) surrounded by a thin capsule at the glottic and supraglottic levels, apparently on the right. No malignancy was evident, but the lesion caused the airway to deviate to the left, which significantly reduced its diameter (Figure 2). Her clinical status worsened over the next two weeks with the development of dysphonia, dysphagia, and dyspnea on mild-to-moderate exertion, in addition to the extant odynophagia, indicating a need for emergency surgical tracheotomy. Lesion biopsy during the direct suspension laryngoscopy yielded inconclusive results. However, the findings of a repeat biopsy were compatible with a neural mesenchymal tumor, suggestive of neurofibroma. Magnetic resonance imaging showed a large, expansive, well-delimited lesion with longitudinal, cross-sectional, and anterior-posterior dimensions of 5.2 × 3.4 × 2.7 cm, respectively, a non-homogeneous hyperintense signal in T2-weighted images, and significant uptake of paramagnetic contrast. The lesion significantly obstructed the airway (Figure 3). Given the atypical clinical presentation and the rarity of the diagnosis, the patient was referred to the otorhinolaryngology department of the IPOLFG. Surgical

FIGURE 2
Axial CT image of neck, shows hypodense lesion on right side (asterisk) compressing the airway

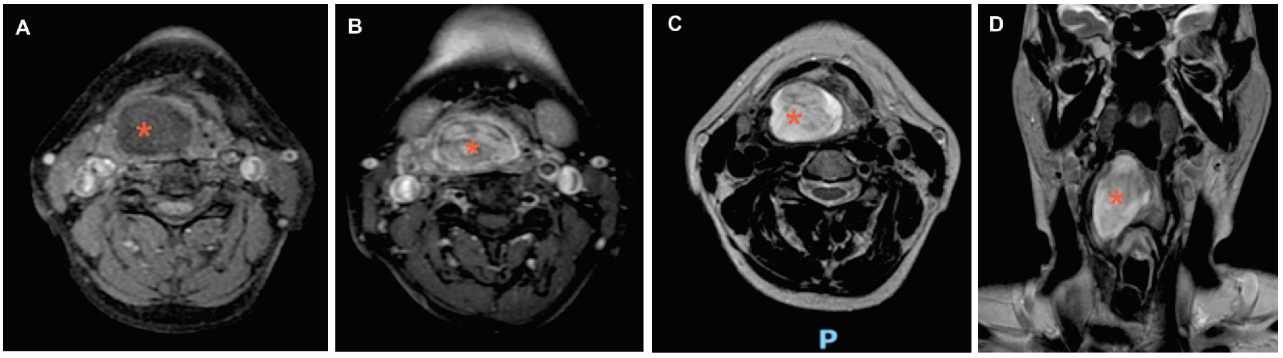


suspension laryngoscopy revealed a pedunculated lesion with a base at the level of the right aryepiglottic fold, lateral and posterior walls of the pharynx, and ipsilateral pyriform sinus. The lesion was completely removed piecemeal and the histological findings were compatible with neurofibroma. No serious postoperative complications developed and the tracheostomy tube was removed approximately 1 month after the surgery. She was left with the sequela of right hemilarynx paralysis, which remained at the time of her last assessment at 4 months after surgery. Signs of relapse were not evident.

DISCUSSION

Neurofibromas of the larynx are rare, accounting for only 0.03–0.1% of all benign laryngeal tumors.[1] A review of pediatric reports reveals that > 80% of these tumors occur in the context of neurofibromatosis type 1 (NF-1; von Ricklinghausen syndrome)[4]. Neurofibromas occurring

FIGURE 3
Neck MRI shows lesion (asterisk) compressing airway. Axial plane in FSE T1-weighted image shows a) hypointense lesion and b) lesion after gadolinium enhancement. Axial c) and coronal d) planes in T2-weighted image of hyperintense lesion.



solely in the larynx is extremely rare and are distributed equally between children and adults, according to Zhang et al.[3]

We identified only 18 published reports of SNL in adults[3,5–15]. The present report describes the first patient in the Portuguese population with a laryngeal neurofibroma. Table 1 presents a summary of the clinical data described herein and in the 18 published reports along with the clinical results. The mean age of the patients was 44 (19–78) years, indicating that these lesions could occur at any age in adults, and 53% and 47% were men and women, respectively, indicating no sex predominance.

Clinical presentation

Solitary neurofibromas of the larynx typically grow slowly and their clinical manifestations depend mainly on their size and location3. They can be completely asymptomatic (5.3%), which may result in them being being underdiagnosed, or manifest with symptoms such as dysphonia (78.9%) and dyspnea (47.4%) that sometimes occurs only on exertion, cervical discomfort

TABLE 1
Summary of clinical data of patients with SNL

Author (year)	Age/ Sex	Clinical presentation	Size (cm)	Location	Treatment	Complications	Relapse (Follow-up)
Present report (2021)	56 / f	Dyspnea, dysphonia, dysphagia, odynophagia, dyspnea, stridor	5,2x3,4x2,7	Aryepiglottic fold and hypopharynx	LDS (Cold Instrumentation)	Vocal paralysis	WR
Zhang (2017)[3]	26 / f	Dyspnea, wheezing	0,6x0,8x1,0	Interarytenoid	LDS	n.d.	WR (n.d.)
Son (2013)[15]	56 / f	Dyspnea (with nocturnal apnea)	2x1,3cm	Arytenoid (+ parapharynx)	LDS (LASER CO2)	Vocal paralysis	WR (2 years)
Liu (2013)[1]	78 / m	Dysphonia, odynophagia	0,8x0,6	Vocal cord	LDS (Cold Instrumentation + LASER CO2)	n.d.	WR (6 months)
Gstottner (2005)[14]	35 /m	Dyspnea on exertion	1,8x1,5x2	Subglottic	Surgery (LASER CO2)	n.d.	R at 4 years
Koc (1996)[13]	45 / m	Asymptomatic	n.d.	Bilateral ventricles	LDS	n.d.	WR (1 year)
Puri (1997)[12]	40 / f	Dysphonia, dyspnea	n.d.	Aryepiglottic fold	Lateral pharyngotomy	n.d.	n.d.
Hisa (1995)[11]	23 / f	Dysphonia	1,5x1,1x0,9	Ventricle	LDS (Cold Instrumentation + LASER CO2)	n.d.	WR (2 years)
Cummings (1969)[10]	69 / m	Dysphonia, dyspnea, Sensation of cervical tumefaction	n.d.	Ventricular band and base of the epiglottis	LDS (Cold Instrumentation)	n.d.	n.d.
	61 / m	Dysphonia	n.d.	Vocal cord	Lateral thyrotomy	n.d.	n.d.
	52 / f	Dysphonia	n.d.	Arytenoid	n.d.	n.d.	n.d.
	30 / m	Dysphonia	n.d.	Arytenoid	LDS		R at 2 and 4 years
ZoBell (1963)[9]	23 / m	Dysphonia	8x5,5x5	Aryepiglottic fold	Lateral pharyngotomy	n.d.	WR (2 months)
Figi (1953)[8]	49 / f	Dysphonia	0,3x0,8	Vocal cord	LDS (Cold Instrumentation)	n.d.	WR (3 years)
	19 / f	Dysphonia, Dyspnea on exertion, throat discomfort	2,8	Aryepiglottic fold	LDS (Cold Instrumentation)	n.d.	WR (10 months)
Fisher (1949)[7]	23 / m	Dysphonia, cough	0,7x0,3	Aryepiglottic fold	LDS (Cold Instrumentation)	n.d.	WR (6 months)
	75 / m	Dysphonia, Dyspnea, Cough, Sensation of cervical tumefaction	n.d.	Vocal cord	LDS (Cold Instrumentation)	n.d.	WR (5 years)
Oliver (1948)[6]	45 / f	Dysphonia, dysphagia, stridor	2	Aryepiglottic fold	LDS (Cold Instrumentation)	n.d.	WR (22 months)
Smith (1944)[5]	26 / m	Dysphonia, cough, throat discomfort	3x2.5x2	Ventricular band	Laryngofissure	Hemilarynx paralysis	WR (n.d.)

F, female; LDS, laser diffraction spectroscopy; m – male, ND, not documented; R, relapse; WR, without relapse.

(21.1%), cough (15.8%), odynophagia, dysphagia, wheezing, stridor (10.5%), and nocturnal apnea (5.3%), (Figure 4). Because symptoms can easily be confused with those of other respiratory diseases, as in our patient and the patient described by Zhang et al.[3], a thorough ORL assessment is important to avoid progression to a more severe respiratory obstruction.

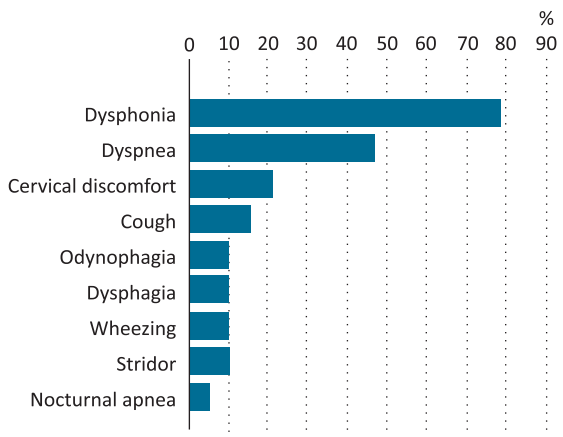
Macroscopically, SNLs can be reddish, yellow, white, or grayish and surrounded by mucosa that is usually intact, unless disrupted by trauma such as a biopsy or an attempt to excise the lesion.[9] The size of tumors varies from infracentimetric[1,7,8] to approximately 8 cm (largest axis)[9]. The 5.2-cm lesion in our patient is the second largest reported to date, at 5.2 cm. Tumors can be located in the subglottis (5%), in the glottis (21%), and in the supraglottis (74%), where the most common sites are the aryepiglottic and arytenoid folds (Figure 5). This distribution can be explained by the fact that sensory fibers are more frequently affected than motor fibers and the supraglottis is innervated by a rich nerve plexus of the superior laryngeal nerve, which is the main sensory pathway from the larynx.[11] Thus, supraglottic and subglottic neurofibromas might arise from the sheath of terminal branches of the superior laryngeal nerve, and the recurrent laryngeal nerve, respectively[3]. Only one patient had a bilateral lesion, located in the laryngeal ventricles[13]. Another patient had a synchronous parapharyngeal neurofibroma[15]; however, NF was clinically excluded in both patients.

We highlight that anamnesis combined with a thorough physical examination of these patients is important to exclude manifestations that define NF, namely other neurofibromas, café-au-lait spots, axillary or inguinal freckling, optic nerve glioma, Lisch nodules, specific bone lesions, or a family history of NF[16].

Imaging assessment

CT and MRI are important for evaluating laryngeal anomalies, and CT is particularly recommended for large obstructive lesions that can cause rapid respiratory movements or coughing because evaluation is less time-consuming. However, the sensitivity of MRI for tissue differentiation, as well as its multiplanar capacity, allow better characterization of tumors and their extension, despite the disadvantage of entailing a longer acquisition time. Neurofibromas appear on CT images as homogeneously hypodense lesions, without contrast uptake.[15-17] T1- and T2 weighted MR images show lesions as areas of low or intermediate intensity, and hyperintensity, respectively.[14,17-19]

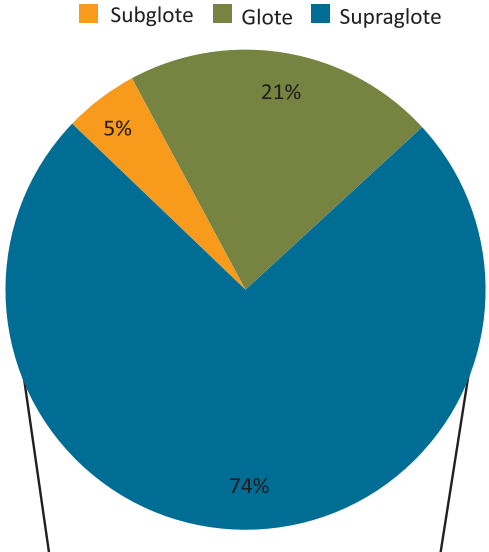
FIGURE 4
Clinical manifestations of solitary neurofibromas of the larynx in adults



Histopathology

A definitive diagnosis is based on anatomopathological findings. However, preoperative biopsies may be difficult to obtain due a fibrous capsule, the elastic consistency of the tumor, and risk of hemorrhage. Thus, a diagnosis is often determined based on immunohistochemical findings of surgically excised lesions using the S-100 protein marker that is characteristic of neural tumors.[3,11,12] Neurofibromas histologically comprise plexiform and non-plexiform subtypes. Non-plexiform neurofibromas are more common and consist of lesions that are clearly delineated from surrounding tissues. They comprise fusiform cells with abundant collagen surrounding the

FIGURE 5
Locations of solitary neurofibromas in the larynx of adults



7%	Interarytnoid region
14%	Ventricles
14%	Ventricular bands
21%	Arytenoid
43%	Aryepligottic folds

tumor nucleus, and can be completely excised surgically. Plexiform neurofibromas have a similar structure but are unencapsulated, more invasive, and indistinguishable from surrounding tissues. Because they can involve nerve fibers, their complete surgical removal is more challenging and associated with higher rates of relapse. According to Zhang et al., non-plexiform SNLs are more common than the plexiform type.[3,15,17]

Treatment

Complete surgical resection is the indicated treatment for SNLs.[3] Among several transoral to external surgical approaches, the selection depends on the size, location, histological subtype of the tumor, and the experience of the surgeon. Technological advancements have led to the application of less invasive techniques, such as transoral approaches by direct suspension laryngoscopy, with endoscopy or microscopy; the morbidity associated with these procedures is lower, particularly among patients with smaller SNLs[1,3,6-8,10,11,13-15]. Although SNLs have been treated using CO2 lasers, they can destroy nuclei, especially in smaller tumors, which hinders the histological diagnosis[14]. Therefore, excision with cold instrumentation and subsequent laser management of the surgical margins has been suggested.[3]

External approaches such as laryngofissure[5], lateral thyrotomy[10], and lateral pharyngotomy[9] allow direct visualization with better exposure. They are indicated for resecting larger and recurrent tumors, and when there is a risk of incomplete endoscopic resection, such as with plexiform subtypes, in which complete excision might require extended dissection. However, these more aggressive approaches are associated with higher morbidity and risk of complications, including a need for tracheostomy and vocal cord paralysis.[3,17,19] Nevertheless, Hisa et al., have questioned whether these techniques result in vocal impairment because they are usually applied to larger lesions that prevent proper preoperative evaluation of vocal mobility. Thus whether paralysis is extant before, or develops after surgery can be uncertain[11].

We excised a very large lesion piecemeal by suspension laryngoscopy using cold instrumentation without necessitating an external approach. The procedure resulted in vocal cord paralysis ipsilateral to the tumor. However, the size of the lesion hindered preoperative evaluation of vocal cord mobility, so whether it resulted from surgical iatrogeny or was extant before the surgery remains uncertain.

Prognosis and follow-up

The prognosis of patients with SNL is usually good after complete resection. The reports included in the literature review that described patient follow-up, indicated that only two patients relapsed at 2 and 4 years of follow-up, which led to repeated surgical resection in both (one had a second relapse that required a third intervention).[10,14] However, some reports describe patients with short follow-up periods and others do not mention the duration of follow-up; hence late relapse cannot be excluded. Malignant transformation of neurofibromas has been associated with NF-1, but so far, not in patients with solitary neurofibromas[20]. Despite the benign nature and slow growth of solitary neurofibromas, patient follow-up should be prolonged due to the possibility of relapse over the long term.

CONCLUSION

Adult SNLs are extremely rare and the first SNL detected in the Portuguese population is presented herein. The clinical presentation depends on the size and location of the tumor and symptoms can be confused with other respiratory diseases, which delays a diagnosis and places the life of patients at risk when lesions are obstructive. Obtaining a thorough patient history and conducting a detailed physical examination are important for the diagnosis, as they can exclude manifestations associated with NF. The final diagnosis is confirmed via histology. The definitive treatment is surgery, which has a good prognosis following complete resection, but long-term patient follow-up is important given the potential for late relapse.

Conflict of Interest

The authors declare no conflict of interest regarding this article.

Data confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Human and animal protection

The authors declare that the followed procedures complied with regulations established by the Ethics and Clinical Research Committee and according to the Helsinki declaration of the World Medical Association.

Privacy policy, informed consent and approval by the ethics committee

The authors declare having written consent for the use of patients' photographs in this article.

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Availability of scientific data

There are no publicly available datasets related to this study.

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