Management of Subglottic Stenosis and Subglottic Stenosis in Systemic Disease

António Bugalho

Contents

Abstract

Subglottic stenosis (SGS) is a challenging therapeutic problem for the interventional pulmonologist. Depending on the etiology it can be classified as congenital or acquired. Acquired causes are often due to iatrogenic injury but can also result from tumors, infections, and rare diseases such as granulomatosis with polyangiitis, relapsing polychondritis, and amyloidosis. Flexible bronchoscopy is essential for the diagnostic and pre-interventional evaluation of these patients. Bronchoscopic procedures such as radial incisions, dilation, local adjuvant drugs, and airway stents have been used alone or in combination to treat SGS. Endoscopic treatment has a high success rate for simple stenoses and is a valid option for patients who are unsuitable candidates for surgery. Complex stenoses often require a multidisciplinary approach. There is no universally accepted treatment

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strategy that will consistently relieve symptoms and prevent recurrence in all patients. Treatment must be individualized according to the pathological findings and the patient's health status. Current minimally invasive techniques performed wisely and proficiently allow the interventional pulmonologist to restore airway patency and improve the quality of life of patients with SGS.

Keywords

Larynx · Vocal cord · Laryngotracheal stenosis · Subglottic stenosis · Endoscopic treatment · Endotracheal intubation · Balloon dilation · Relapse polychondritis

1 Introduction

The management of central airway obstruction is a frequent problem for the interventional pulmonologist. In contrast, subglottic stenosis (SGS) remains a relatively rare condition; however, one of the most challenging and difficult to treat.

The subglottic airway is a vulnerable site for symptomatic stenosis because it is one of the narrowest regions of the respiratory tract and is formed by a complete non-expandable ring. Once SGS is identified, a wide range of treatments can be proposed. The therapeutic process involves a choice between conservative, endoscopic, and surgical procedures, but the results are not always satisfactory. A multidisciplinary approach is usually recommended, as the decision for a specific intervention is dictated by the needs of each patient and requires a high degree of expertise and collaboration between interventional pulmonologists, thoracic surgeons, and otolaryngologists.

Depending on the etiology and severity, a combination of endoscopic tools and techniques can be used to successfully manage SGS. In most cases, these minimally invasive procedures are able to provide good outcomes in this high morbidity condition.

2 Subglottic Definition and Anatomy

SGS is a congenital or acquired narrowing of the subglottic airway. An advanced knowledge of the anatomy, configuration, size, and proportions of the larynx is vital for all interventional physicians to manage SGS correctly (see chapter ▶ "Airway Anatomy"). Briefly, the precise anatomical boundaries of the subglottic area, are defined in the craniocaudal direction by the inferior arcuate line of the vocal cords—the transition from squamous epithelium to high columnar respiratory epithelium—to the inferior margin of the cricoid cartilage. In the lower horizontal plane, the subglottic diameter in the full-term neonate is 4.5–5.5 mm, and in adults, the mean diameter of the cricoid is 17 mm in males (range 13–23 mm) and 13 mm in females (range 11–19 mm) [1, 2]. Disruption of the normal gross anatomy and tissue architecture of the subglottis tends to reduce the circumference of the lumen and cause significant obstruction (Fig. 1).

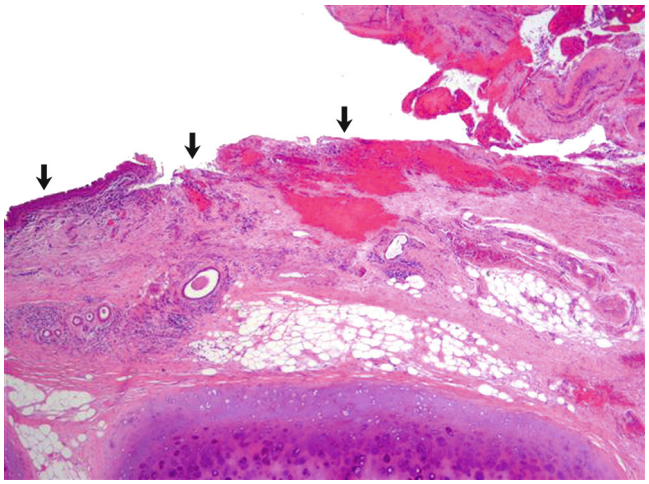

Fig. 1 Injured subglottic airway displays mucosal ulceration and incomplete re-epithelialization (*arrows*) with hemorrhagic areas and collagen deposition. This altered healing process may lead to airway stenosis

3 Etiology and Pathogenesis

In the early decades of the twentieth century, infections and external airway trauma were the main causes for SGS. In the late 1960s, the incidence of acquired SGS began to increase as a result of prolonged intubation and other invasive airway procedures. Currently, the most common etiologies leading to SGS are endotracheal intubation, tracheotomy, previous airway surgery, neoplasia, and radiation for oropharyngolaryngeal tumors [3]. Other causes, although rare, are important to consider when evaluating SGS of unclear etiology (Table 1).

SGS can be classified into congenital and acquired forms. The acquired form is much more common than the congenital type and can be subdivided into traumatic, inflammatory, infectious, and tumor related. In addition, a poorly characterized female population suffers from idiopathic SGS (ISGS).

3.1 Congenital SGS

Although this type of stenosis is rare, it is the third most common congenital airway problem. Malformation of the cricoid cartilage is linked with inadequate recanalization of the laryngeal lumen after completion of the normal epithelial fusion at the end of the third month of gestation. Patients may present with various degrees of atresia, stenosis, or webbing

Table 1 Types and causes for subglottic stenosis

Congenital	Membranous	Increased fibrous connective tissue, hyperplastic submucous glands, granulation tissue
	Cartilaginous	Cartilage deformity (small or elliptical cricoid, large anterior or posterior lamina, generalized thickening, submucous cleft), trapped first tracheal ring
	Combined	Membranous and cartilaginous stenosis
Acquired	Trauma	Post-intubation, previous airway surgery (high tracheotomy, percutaneous tracheotomy, cricothyroidotomy, prior surgery), accidental (foreign body, thermal, or caustic inhalation, radiation, blunt, or penetrating trauma)
	Infection	Tuberculosis, syphilis, leprosy, diphtheria, bacterial tracheitis, croup, typhoid fever, histoplasmosis, scarlet fever, laryngeal scleroma
	Inflammatory and autoimmune	Granulomatosis with polyangiitis, relapsing polychondritis, amyloidosis, sarcoidosis, systemic lupus erythematosus, inflammatory bowel disease, immunoglobulin G4-related disease, gastroesophageal reflux
	Tumor	Carcinoma, hemangioma, lymphoma, papilloma
Other	Idiopathic	Unknown cause

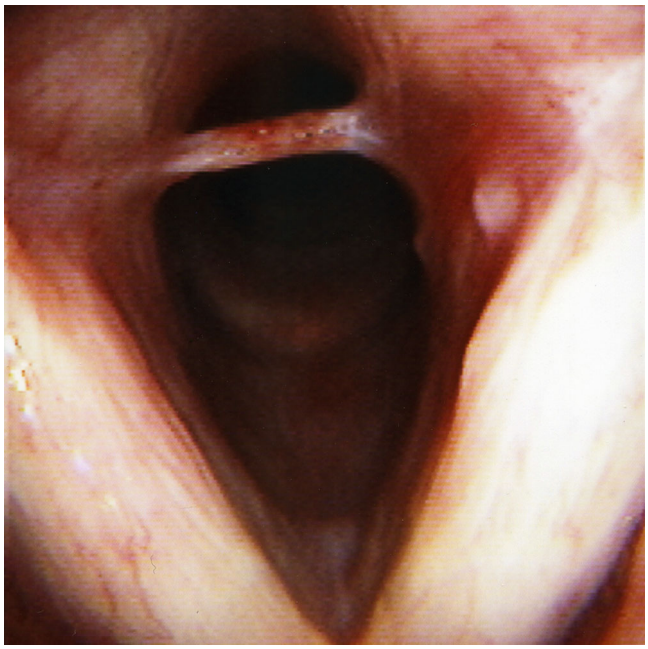

Fig. 2 Congenital subglottic web with Myer-Cotton grade I cricoid cartilage stenosis. This thin web was mechanically broken

can be found in these patients (Fig. 2). Histopathologically, congenital SGS is divided into cartilaginous and membranous types. The cartilaginous type results from a thickened or distorted cricoid cartilage, creating an anterior subglottic shelf extending to the posterior region. It is often more severe than the membranous type and is rarely successfully treated with endoscopic techniques. The membranous form is more common, circumferential, often involving the true vocal cords, and is characterized by fibrous soft tissue thickening.

3.2 Laryngeal Trauma

Trauma is the most frequent cause of acquired laryngeal stenosis in children and adults. Internal subglottic trauma is usually iatrogenic (e.g., endotracheal intubation, tracheotomy, or previous tracheal instrumentation). External trauma may be caused by contusion, penetrating wound, or inhalation injury.

In SGS caused by intubation, stenosis may occur as a late complication and can take weeks to months to develop after the initial insult. Several risk factors have been identified, including prolonged intubation, large-caliber endotracheal tubes, traumatic intubation, multiple re-intubations, local infection while intubated, frequent displacement of the endotracheal tube, and the concomitant presence of a nasogastric tube (Fig. 3a). The COVID-19 pandemic era reflects this paradigm, where trauma associated with difficult intubation (decreased visualization caused by personal protective gear), prolonged intubation, high frequency of reintubation, cuff overinflation, and prone positioning, among other factors, contributed to an increased rate of laryngotracheal stenosis in critically ill patients.

Gastroesophageal reflux disease has also been implicated as a risk factor in children and adults, and obesity and diabetes are thought to contribute to the risk for post-intubation SGS.

The pathogenesis of this form of acquired SGS is not fully understood. The most widely accepted theory is that high pressure from a tube or cuff exceeds the capillary pressure of the airway wall, causing biomechanical stress and ischemia of the mucosa and cartilage (Fig. 3b). Uncontrolled wound repair develops in response to airway injury and results in four overlapping phases: hemostasis, inflammation (initial injury produces edema and vascular congestion with recruitment of cells and mediators, occasionally ulceration and infection may occur), proliferation (re-epithelialization, neovascularization, increased fibroblast activity, granulation tissue), and airway remodeling (collagen deposition, scar formation, contracture, and loss of structural integrity leading to stenosis).

Postoperative SGS may occur as a complication of previous tracheotomy, percutaneous tracheotomy, cricothyroidotomy, and surgical treatment for airway neoplasms. Stenosis after

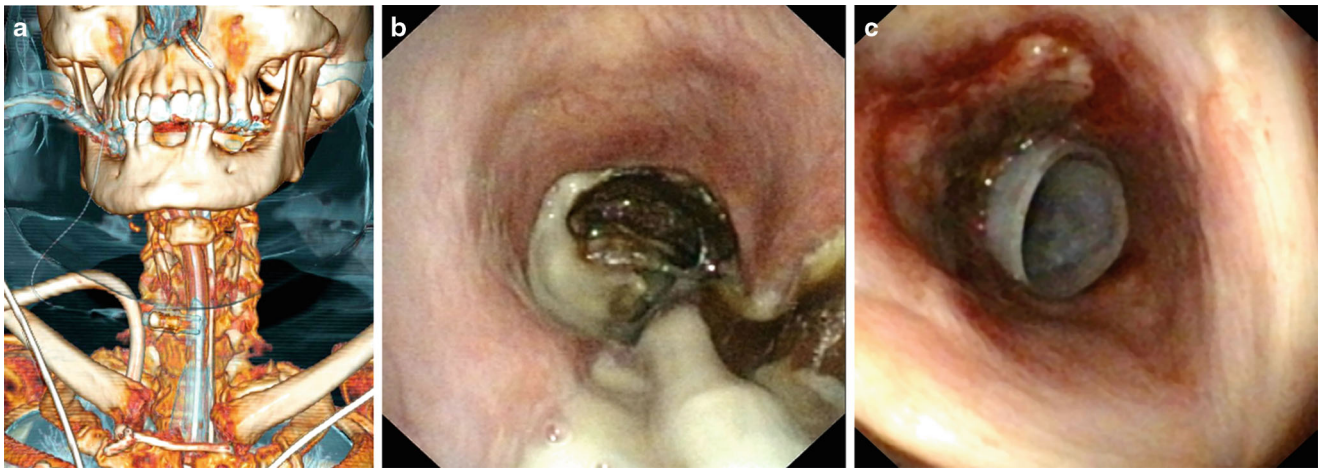

Fig. 3 CT reconstruction of a 78-year-old female with subglottic stenosis caused by prolonged endotracheal intubation (**a**). Multiple comorbidities, high position of the tube, excessive cuff pressure, and the presence of a nasogastric tube contributed to extensive mucosal and cartilage damage (**b**). A straight silicone stent 12/40 mm was deployed (**c**)

tracheotomy may occur above the stoma, at the same level as the stoma, at the cuff site, and at the tip of the cannula. In addition to ischemic mucosal injury and chondritis, cartilage fracture is an important factor for SGS in these patients. Damage to the cartilage above the stoma is the most common cause of stenosis after emergency tracheotomy performed with a poor technique.

The incidence of traumatic SGS can be radically reduced if high tracheotomy and cricothyroidotomy are only performed in extreme emergencies; aggressive endoscopic manipulation for benign laryngeal lesions is avoided; intubation and endoscopy are performed gently; and factors contributing to laryngeal trauma after intubation are recognized and prevented when possible.

3.3 Infection

Acute laryngotracheobronchitis, an acute viral respiratory illness common in children, can cause subglottic narrowing. Croup is most frequent in children aged 6–36 months, and it is rare after the age of 6. Acute bacterial tracheitis can also cause thick, purulent secretions and mucosal edema which can origin symptoms of upper airway obstruction.

SGS secondary to chronic infection is rare, except in certain endemic geographical areas, and it has been described in patients with tuberculosis, syphilis, diphtheria, typhoid fever, scarlet fever, leprosy, and laryngeal scleroma.

Although rare, subglottic and endotracheal tuberculosis may result in significant obstruction related to the initial lesion or subsequent stricture formation. Some degree of stenosis may still develop despite appropriate antituberculosis chemotherapy.

Laryngeal scleroma is also an uncommon chronic infectious disease caused by *Klebsiella rhinoscleromatis*. It is prevalent in certain regions such as Africa, Asia, Central and South America, and Central and Eastern Europe. It typically affects the nose but can also affect other parts of the respiratory system. Subglottic involvement is reported in 23% of cases [4]. Following the initial infection, three sequential phases are described: exudative stage, with active inflammation, edema, congestion, and necrosis; proliferative stage characterized by multiple erythematous nodules; and fibrotic stage with cicatricial tissue. The CT scan normally shows concentric irregularities and narrowing in the subglottic space. Definitive diagnosis requires biopsy specimens, usually taken during the proliferative phase, which show a recognizable histological pattern with clusters of vacuolated histiocytes—Mikulicz cells. Treatment should be based on the clinical stage, severity, and anatomical location. In the proliferative phase, long-term antibiotics are the treatment of choice. In the fibrotic stage, if the patient is symptomatic and there is mild subglottic involvement, endoscopic procedures can be valid therapeutic options. Open surgical techniques have been attempted for extensive SGS.

3.4 Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA) is a multisystemic disease characterized by necrotizing vasculitis and granuloma formation with a predilection for the upper and lower respiratory tracts and kidneys. Its etiology is unknown, and it affects both males and females with a peak between 40 and 55 years of age. The course of GPA varies widely, from localized to multisystemic, from mild to life-threatening disease. Nasal and sinus findings are present in a high percentage of cases (e.g., chronic sinusitis, epistaxis, septal perforation, and saddle nose deformity). SGS may occur

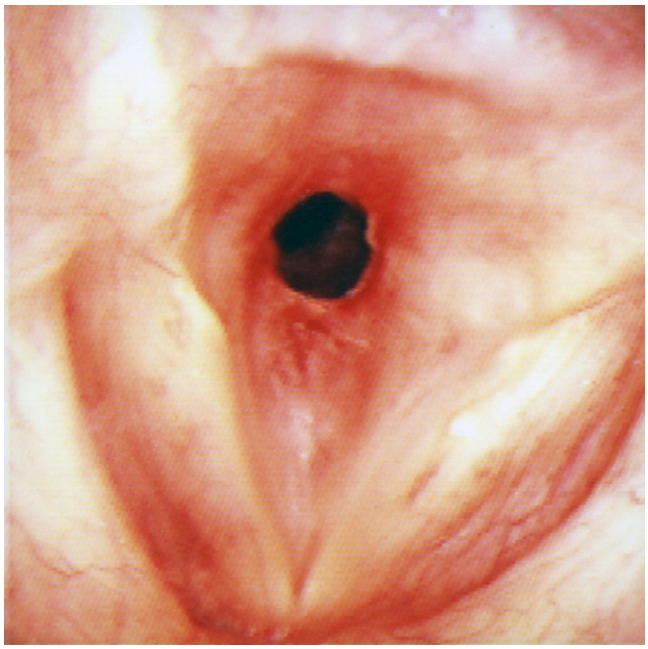

Fig. 4 Subglottic stenosis in granulomatosis with polyangiitis. One can notice the red inflammatory friable tissue circumferentially narrowing the subglottis

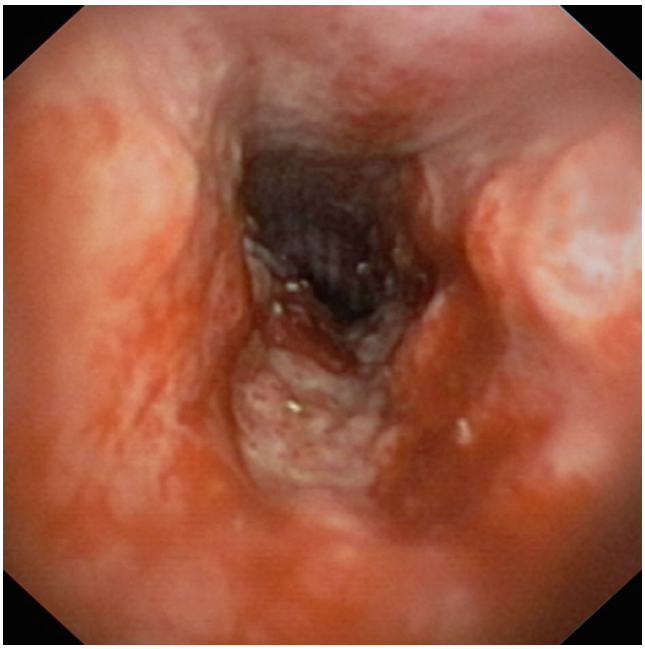

Fig. 5 Bronchoscopic appearance of laryngotracheal amyloidosis in a 37-year-old female patient. Amyloid deposits infiltrate the mucosa and reduce airway caliber

either as a presenting feature or as a late manifestation of the disease and is reported in 12–23% of patients with GPA [5] (Fig. 4). It often occurs independently of other features of disease activity and frequently does not improve with systemic treatment. Laboratory studies may show a positive antineutrophil cytoplasmic autoantibody (ANCA-c) test, although this should be interpreted with caution because ANCA-c may be positive in other diseases and GPA can be present in the face of a negative ANCA test. Chest radiographs and CT scans may show pulmonary infiltrates and/or cavitary nodules. Biopsy remains the gold standard for the diagnosis, but specimens from the larynx and trachea often do not show the characteristic inflammatory infiltrates with multinucleated giant cells, granuloma formation, and vasculitis of the small and medium vessels. Systemic immunosuppressive therapy is the mainstay of treatment in GPA. Endoscopic management of subglottic lesions (laser resection, serial dilations, topical corticosteroids, local mitomycin-c) is an important aspect in those who remain symptomatic, despite appropriate medical management.

3.5 Amyloidosis

Amyloidosis is a disease characterized by the deposition of fibrillar proteins in extracellular tissues and can affect virtually any organ or system. It may be idiopathic or associated with inflammatory, hereditary, or neoplastic diseases. Respiratory tract amyloidosis may be part of a widespread or local process. Sites in the larynx with a predilection for nodular or polypoid amyloidosis include the ventricles, false cords, aryepiglottic folds, and the subglottis [6]. Pulmonary manifestations include tracheobronchial infiltration, persistent pleural effusions, and parenchymal nodules. There may be diffuse narrowing and wall thickening, circumferential airway involvement, often with ossification of the amyloid deposits (Fig. 5). Bronchoscopy displays multiple plaques or localized tumor-like masses. Tissue biopsy stained with Congo red and examined under polarized light shows the characteristic submucosal extracellular deposits of amyloid protein, confirming the diagnosis. Bronchoscopy-based techniques (laser therapy, stenting) have been suggested as a possible method for treating subglottic obstructive lesions. Excision, when possible, remains the treatment of choice in localized forms of amyloidosis.

3.6 Relapsing Polychondritis

Relapsing polychondritis (RP) is a multisystemic immune-mediated disease characterized by recurrent episodes of inflammation of cartilaginous structures. RP is most likely to occur between the ages of 40 and 60, although it can occur in younger patients. One third of cases develop in association with another recognizable condition, particularly systemic vasculitis or connective tissue disease. Auricular chondritis is the usual initial presentation, but the disease may also involve the nose, laryngotracheobronchial tree (malacia and/or stenosis),

peripheral joints, and other organs. In the active stage, there is a red, warm, painful swelling of the cartilage. After the inflammatory episode, significant destruction may occur. The definitive diagnosis is based on the presence of three of the following criteria or at least one of them together with a confirmatory biopsy showing inflammatory changes in the cartilage: recurrent bilateral auricular chondritis, non-erosive inflammatory polyarthritis, nasal cartilage chondritis, ocular inflammation, respiratory chondritis, and cochlear or vestibular damage. CT and bronchoscopic findings include diffuse smooth thickening of the larynx, trachea, and proximal bronchi; thickened, densely calcified cartilaginous rings with sparing of the posterior tracheal membrane; tracheal wall nodularity; diffuse narrowing of the tracheobronchial lumen, large airway collapse due to destruction of the cartilaginous rings (Fig. 6). It is difficult to predict the clinical course of the disease which may be indolent or fulminant. It is therefore important to diagnose and plan treatment promptly before irreversible damage occurs. Medical management of RP focuses on suppressing the acute inflammatory process. Ernst and colleagues have shown that it is possible to treat these patients by endoscopic procedures (e.g., dilation, stenting) [7]. The majority experience improvement in respiratory symptoms although occasionally, involvement of the glottis and subglottic regions may require tracheotomy.

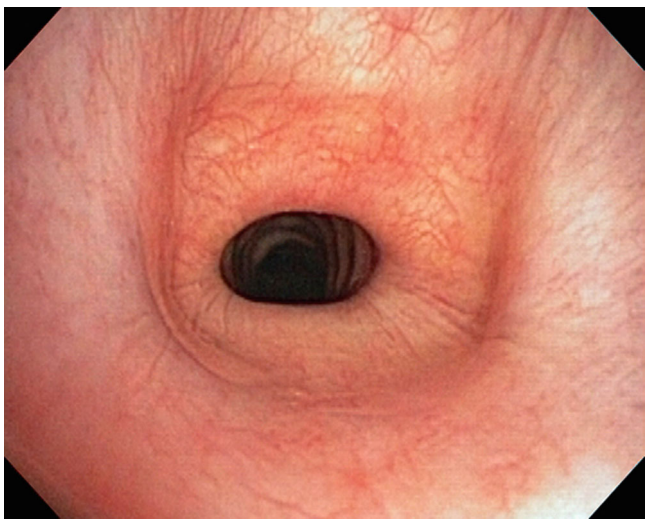

Fig. 6 Firm thickening of the subglottis in a patient with relapsing polychondritis. (Courtesy of Armin Ernst, M.D.)

3.7 Tumor

Direct extension of a locally advanced tumor and/or extrinsic compression may cause SGS (e.g., laryngeal cancer, thyroid tumors). Primary laryngeal and tracheal tumors are extremely rare in children, with papillomas, hemangiomas, and granular cell tumors being the most common [8]. In adults, squamous cell carcinomas followed by adenoid cystic carcinomas are the most frequent and may cause SGS. Other less common tumors in adults include hemangiomas, neurogenic tumors, lymphomas and papillomas.

Recurrent papillomatosis results from infection of the upper respiratory tract by the human papilloma virus (HPV). This disease is most common in children but, as mentioned above, can also occur in adults. Infection often occurs at birth, and laryngeal papillomas can lead to contamination of the trachea and lungs. On bronchoscopy, the papillomas have a polypoid appearance and may involve the larynx, trachea, or bronchi (Fig. 7). Endoscopic interventions are crucial, as repeated treatment is usually necessary due to recurrence.

3.8 Idiopathic Subglottic Stenosis

ISGS is a rare inflammatory process of unknown cause, usually confined to the subglottic region and the first two tracheal rings.

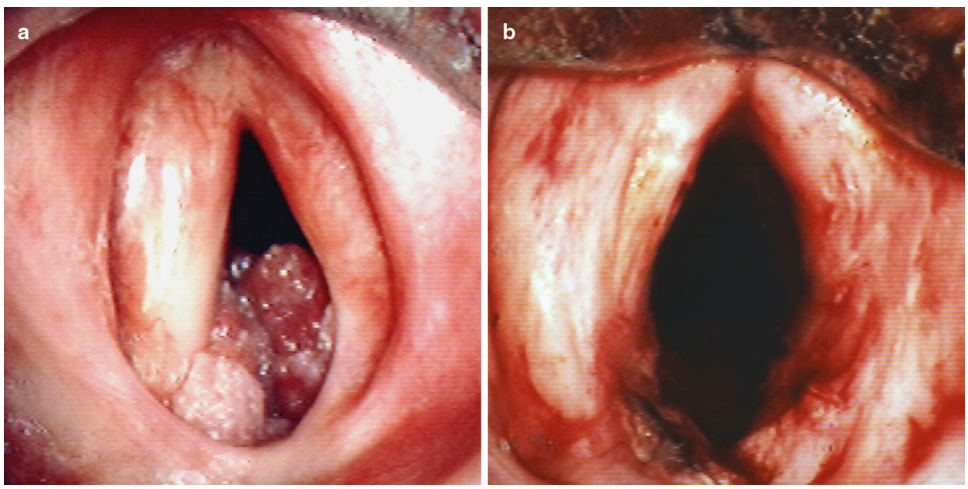

Fig. 7 Glottic and subglottic cauliflower-like tumors with smooth surface, corresponding to recurrent papillomatosis in a 42-year-old (**a**). There was a marked improvement in airway caliber after laser treatment (**b**)

It is a diagnosis of exclusion, based on the absence of recent intubation or trauma, and other rare diseases that can affect the subglottis. The majority of patients are females, Caucasian, with a mean age of 50 years, and no previous diseases. In 63 tracheal resections performed in patients diagnosed with ISGS, Mark et al. found extensive fibrosis, dilation of the mucous glands, relatively normal cartilage and, in most cases, positive staining for estrogen and progesterone receptors in fibroblast cells [9]. Another hypothesis suggests abnormal mucosal inflammatory responses with fibroblast proliferation through chemokine and cytokine production. It is not yet known what the initial insult is, that leads to the disease. One theory is that severe coughing episodes may cause mechanical trauma, intermittent disruption of blood supply to the cricoid, and scarring in the subglottic area leading to ISGS [10]. Recent studies have focused on changes in the microbiome, and samples from ISGS patients have shown strong associations with *Moraxella* and *Acinetobacter* genera, which may contribute to the pathogenesis [11, 12]. Laryngopharyngeal reflux as a potential etiological is still controversial, with conflicting results between studies and poor response to anti-gastroesophageal reflux medications [11]. Dilation, laser incisions, intralesional steroids, mitomycin-c, and airway stenting have all been used for the initial management of ISGS.

4 Diagnosis and Pre-interventional Assessment

4.1 Clinical Evaluation

SGS is usually suspected on the basis of clinical findings. Congenital SGS normally presents early in life with symptoms of respiratory distress and laryngeal involvement: feeding difficulties, stridor, abnormal or absent cry, and hoarseness. If the stenosis is severe, the neonate has major respiratory distress at birth. Congenital SGS is often associated with other malformations, and the presence of other causes for respiratory compromise should always be assessed. Adults with mild congenital stenosis are usually asymptomatic and are diagnosed after a difficult intubation or during bronchoscopy for other reasons (Fig. 2).

Patients with acquired mild to moderate SGS often have a history of previous intubation. They are asymptomatic or present with mild symptoms that may include chronic cough, wheezing, dyspnea on exertion or dysphonia. Early manifestations may be mistaken for other obstructive airway diseases (e.g., asthma, COPD). Progressive or more severe or SGS can lead to dyspnea at rest or on light exertion, stridor, and functional limitations, depending on the severity of the stenosis. The Medical Research Council Scale is an approved tool for assessing the degree of dyspnea and treatment response in patients with SGS. Voice should also be assessed at baseline, for example using the GRBAS (grade, roughness, breathiness, asthenia, and strain) scale.

Occasionally, SGS may present as a patient in the ICU who fails extubation. It is imperative to review the characteristics of previous intubations: date, duration, size of the endotracheal tube, number of subsequent intubations, and whether any intubations were traumatic.

If laryngeal trauma is not the cause, other etiologies should be investigated and ruled out, otherwise, recurrence of the disease may lead to repeated treatment failures.

A full clinical assessment should be performed in all patients as many of the above conditions may have systemic implications. It is also important to assess for major comorbidities (e.g., pulmonary, cardiac, metabolic and neurological diseases) or significant congenital anomalies, as these may influence therapeutic decisions and outcomes. For example, gastro-esophageal reflux, diabetes mellitus, immunodeficiency or chronic infection can reduce the rate of healing after treatment.

4.2 Endoscopic Assessment

Flexible bronchoscopy is the gold standard for the evaluation of these patients as it is an effective method of obtaining preliminary information prior to any interventional attempts. It allows the detection of supraglottic/glottic and subglottic abnormalities, length and severity of stenosis, assessment of vocal cord mobility, distance from the vocal cords, dynamic assessment of the airway, assessment of cartilage involvement, and degree of scar maturity. The tracheobronchial tree should always be examined for secondary lesions and the suprastomal area if the patient has a tracheotomy or a tracheotomy is planned. Flexible bronchoscopy can be performed in the awaked patient under local anesthesia, under mild to moderate sedation or general anesthesia, depending on the goals.

Rigid bronchoscopy under general anesthesia allows a more accurate and reliable measurement of the length and diameter of the stenotic airway and is ideal for planning appropriate treatment. The insertion of progressively larger endotracheal tubes has been used to assess the degree of SGS. Caution should be taken with this method as it may cause further iatrogenic injury to the airway.

Endoscopic classifications of laryngotracheal stenosis have been proposed to predict interventional success (Table 2). The Myer-Cotton system applies to firm circumferential stenosis confined to the subglottis with four staging degrees based on the percentage of reduction in cross-sectional area [13]. It must be emphasized that this classification has some limitations as it was applied to all laryngotracheal stenoses and relies on the skills and judgment of the interventional pulmonologist. As this system was developed for pediatric patients, but has been used in adults, and in order to standardized the reporting system, a consensus paper by Monnier and colleagues was published in 2015 to complement the Myer-Cotton grade,

Table 2 Subglottic stenosis classification systems

	Myer-Cotton	McCaffrey	Lano
Grade/stage I	<50% obstruction of the lumen	Subglottic or tracheal lesion	Lesion involves one subsite (glottis, subglottis, or trachea)
		<1 cm long	
Grade/stage II	51–70% obstruction of the lumen	Lesion confined to the subglottic area	Lesion involves two subsites
		>1 cm	
Grade/stage III	71–99% obstruction of the lumen	Subglottic and tracheal lesions not involving the glottis	Lesion involves all three subsites
Grade/stage IV	100% obstruction of the lumen	Glottic involvement	

which includes a letter (a-d) according to the number of laryngeal subsites involved in the stenosis, and a plus sign to indicate the presence of severe comorbidities or congenital anomalies.

McCaffrey suggested that treatment success depends on the subsites involved and the length of the stenosis but did not consider the degree of luminal reduction [14]. Lano and coworkers proposed a method based on the number of subsites involved (glottis, subglottis, and trachea) and the degree of stenosis to better predict patient prognosis which is determined by successful decannulation and absence of disease recurrence [15]. They reported a negative correlation between management success and the number of sites affected.

In general, stage I lesions have the highest success rate while stage IV lesions have the lowest. As no staging system allows a true comparison of patients, treatment modalities, and outcomes between different centers, Freitag and colleagues proposed a new classification of central airway stenosis based on the type, degree, location, and transition zone [16]. Further studies are needed to confirm the usefulness of this system, particularly in SGS.

SGS can also be classified according to the morphological bronchoscopic aspects into simple or complex stenosis, with management and prognostic implications. Simple stenoses are web-like, short segment (<1 cm), membranous, concentric, without cartilaginous lesions. Complex stenoses are characterized by an extensive endoluminal occlusion (≥1 cm), circumferential contraction scarring, and/or associated malacia or loss of cartilaginous support and have a lower endoscopic treatment success rate compared to simple stenoses [17]. In addition, the European Laryngological Society distinguishes between fresh incipient SGS (resulting from acute or subacute post-intubation airway narrowing with edema, ulceration, granulation tissue) and mature cicatricial SGS (well-established airway narrowing that can be a therapeutic challenge) [18].

4.3 Radiological Evaluation

Standard neck and chest radiographs with anteroposterior and lateral views of the subglottic and tracheal air column have gradually been replaced by high-resolution CT and magnetic resonance imaging (MRI) because these modalities provide detailed information about the airway and adjacent structures (e.g. differentiation between intrinsic and panmural stenosis); are able to assess the size, location, and extent of airway lesions; and show areas beyond high-grade stenotic segments (Fig. 8). Dynamic expiratory CT also helps to detect excessive airway collapse, which may be associated with SGS. MRI may be indicated to assess vascular compression of the airway secondary to congenital cardiovascular anomalies or the mediastinal extent of a tumor.

4.4 Other Exams

The evaluation of SGS patients should include functional (e.g., lung function, swallowing), serological (e.g., ANCA-c, angiotensin-converting enzyme) and reflux exams (e.g., 24 hour esophageal pH-impedance test, esophagoscopy), which are essential for good treatment outcomes.

Spirometry provides information about the level (e.g., extra vs. intrathoracic) and degree of obstruction (e.g., mild vs. severe) [19]. The ratio of forced expiratory volume in 1s (FEV_1) to the peak expiratory flow (PEF) >0.50 can discriminate between extrathoracic airway obstruction and asthma or COPD, supporting the diagnosis of SGS. The flow-volume loops and spirometric values allow post-intervention results to be compared with pre-intervention values to assess therapeutic efficacy (Fig. 9).

5 Management

5.1 Overview

The primary goals in the treatment of any patient with upper airway obstruction are to ensure adequate oxygenation, ventilation, and management of the underlying disease. Treatment must be individualized according to the pathological findings and the patient's health status. Management options include observation, systemic and/or topical drug therapy, intubation/reintubation, tracheotomy, endoscopic treatment,

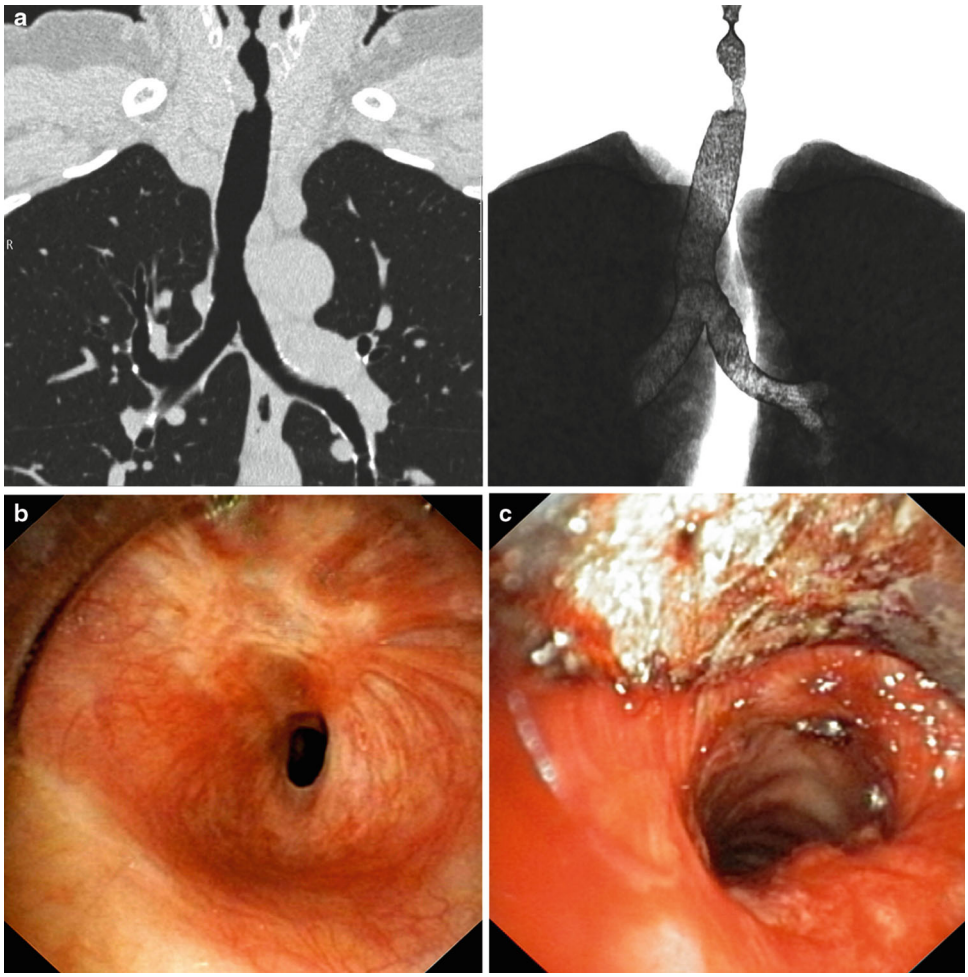

Fig. 8 CT coronal image and 3D reconstruction of a patient with >1-cm-length idiopathic subglottic stenosis (**a**). Bronchoscopy revealed a complex stenosis, Myer-Cotton grade III (**b**). Nd:YAG laser radial incisions followed by balloon dilation restored airway lumen (**c**)

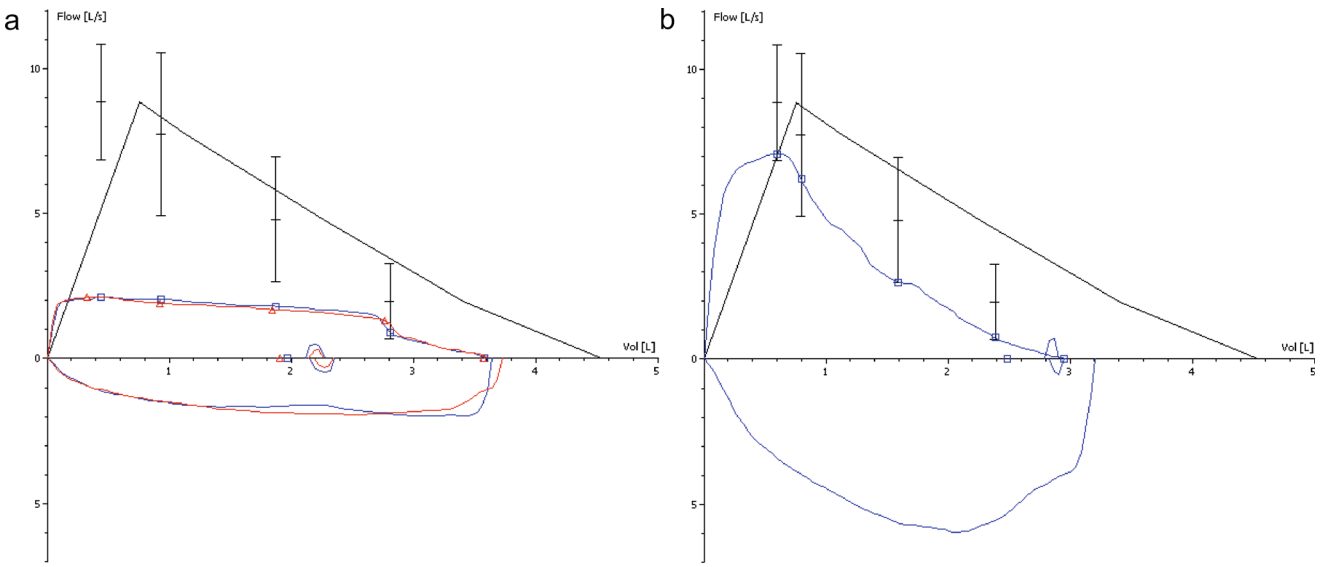

Fig. 9 Flow-volume curves of a patient with iatrogenic subglottic stenosis showing an initial fixed upper airway obstruction pattern (inspiratory and expiratory plateau) (**a**) and improvement after endoscopic treatment (**b**)

and open surgical management. Each patient requires a therapeutic plan that includes one or a combination of these modalities. A multidisciplinary approach involving interventional pulmonologists, otolaryngologists, thoracic surgeons, gastroenterologists, and speech language pathologists is used in many centers.

Whenever identified, medical causes need to be addressed (e.g., appropriate control of infection, treatment of inflammation in GPA, management of gastroesophageal reflux). A minimally symptomatic adult patient with stable non-progressive SGS, with no impact on quality of life, can be successfully managed with close monitoring. In a child with mild stenosis, conservative treatment, regular follow-up, and anticipation of growth may also obviate the need for further therapy. All therapeutic options must be discussed with the patient and their family in order to determine the safest approach that will give the best results.

5.2 Endoscopic Treatment

The more commonly used endoscopic therapeutic options include mechanical dilation, tissue resection (e.g., CO_2 laser, KTP laser, Nd:YAG laser, microdebrider, electrocautery, radiofrequency) with or without local adjuvants (e.g., mitomycin-c, corticosteroids), and in some cases airway stenting.

Endoscopic modalities may be the first option for short segment, membranous, benign, concentric SGS not involving the cartilage; for maintaining a safe airway while waiting for other treatments; and for treatment/palliation of symptoms in patients who are not surgical candidates due to the stenosis characteristics (e.g., extensive laryngotracheal stenosis), active local infection, severe inflammation, poor general medical status, and unstable coexisting diseases. They are also used to treat restenosis following open reconstructive procedures. Success rates for primary endoscopic treatment of SGS vary in the literature from 40% to 94% depending on the etiology, severity of stenosis and appropriateness of the indication [20].

Myer-Cotton Grade I stenoses are usually successfully managed endoscopically. Grade II and III lesions presenting as web-like diaphragms without loss of cartilaginous support are good candidates for an endoscopic treatment trial. From Grade I to Grade III, the success rate of endoscopic management decreases from 100% to 76% and the number of interventions required for treatment increases [21]. In moderate to severe cases of congenital and acquired SGS (grades III and IV), only a small percentage of cases can be successfully managed using endoscopic methods. When the cartilaginous framework of the larynx is significantly damaged, most patients require a tracheotomy to establish a safe airway and reconstructive repair.

Factors associated with high endoscopic failure are circumferential scarring; fibrotic scar tissue in the interarytenoid area of the posterior commissure; severe bacterial infection of the trachea; exposure of perichondrium or cartilage during laser excision, predisposing to perichondritis and chondritis; combined laryngotracheal stenosis; failure of previous attempts at endoscopic repair; vertical scar length >1 cm; and significant loss of cartilaginous support [21, 22].

Since the early years of interventional pulmonology, SGS has been treated with mechanical dilation alone using rigid dilators and scopes despite the need for multiple interventions and a high recurrence rate. Newer balloon dilators offer the advantage of gentle dilation without shearing the mucosa and exacerbating cicatricial stenoses. This method has been shown to be effective in the management of soft, short and isolated SGS, in adult and pediatric patients [23, 24]. In more extensive or firm SGS, there is evidence that endoscopic dilation alone is relatively ineffective in the majority of cases. However, combination with other procedures increases success rates.

A prospective multicenter study of 810 patients with ISGS showed that endoscopic dilation was the most common approach to ISGS [25]. The overall recurrency rate was 22.8% and endoscopic dilation had the highest recurrence rate (28%) compared to other procedures. Endoscopic resection with adjuvant medical therapy (e.g., antibacterial, inhaled corticosteroid, proton pump inhibitor) was associated with better disease control than endoscopic dilation [25].

With regard to endoscopic resection, a variety of heat techniques have been evaluated in SGS [21, 22, 26]. There is a consensus that the preservation of the airway epithelium with minimal trauma is essential for good outcomes, which means that argon plasma coagulation is not an option for SGS as it can cause uncontrolled tissue destruction. Laser has supplanted other techniques because the minimal energy delivered over a brief period of time allows scar tissue to be vaporized without causing significant bleeding or edema and its precision avoids trauma to the normal surrounding areas. The CO_2 laser is a precise cutting tool but has a limited coagulation effect compared to the Nd:YAG laser. The main disadvantage of the Nd:YAG laser is the greater depth of penetration. The operator's inability to control the depth of the laser or to keep it parallel to the wall at all times, may result in further damage to the mucosa and cartilage. Many authors have reported reliable results in the treatment of early or mild subglottic stenosis with CO_2 or Nd:YAG laser, although multiple procedures may be required to obtain the desired result [20, 22, 26, 27].

A careful use of the laser or the electrocautery knife in cutting mode, creating mucosal trapdoor flaps or radial incisions in three or four quadrants can release the constricting stenotic ring while preserving islands of intact mucosa between the incisions, allowing epithelial restructuring and resurface of the expanded lumen (Fig. 8). The combination of

this cutting method with gentle dilation may produce better long-term results [22], with a 75% success rate in selected cases (short, web-like stenoses). Monnier and colleagues used the CO_2 laser in patients with laryngotracheal stenosis and reported that the improvement to a near-normal airway decreased from 92% for grade I Myer-Cotton classification to 46% for grade II and 13% for grade III stenosis [20]. Based on these findings, a therapeutic algorithm was developed, stating that endoscopic interventions should be attempted first in the presence of SGS grade I/II, stenosis <1.5 cm in a craniocaudal direction, and membranous type with an adequate cartilaginous support. The same conclusions were drawn by Cavaliere et al., who achieved a 66% success rate in patients with post-intubation stenosis treated with laser, dilation, and stent, considering this a safe first-line therapy and reserving selected cases and relapsing stenoses for surgery [27].

5.3 Adjuvant Therapy

Ways to directly modulate airway wound healing have been intensively investigated to reduce the recurrence of SGS. Treatments have included topical corticosteroids, mitomycin-c, halofuginone, colchicine, tamoxifen, and 5-fluorouracil [28].

Steroids have long been known to interfere with the healing process and inhibit scarring and have been used topically in patients with SGS with inconsistent results. Several authors described the use of mechanical subglottic dilation followed by injection of a long-acting corticosteroid (e.g., methylprednisolone) into the stenotic lesion; however, patients often required multiple therapeutic sessions. Hoffman and coworkers reported that GPA patients with established laryngotracheal scarring required a mean of four intralesional corticosteroids and dilation procedures at a mean interval of 7 months to maintain patency, but none of the 21 patients required a new tracheotomy [29]. The best results were achieved when these endoscopic techniques were performed before other forms of surgery, which can lead to more scar tissue [30].

A systematic review published in 2023 evaluated the role of intralesional steroid injections in 55 patients with SGS and found that overall, patients received an average of 3.6 injections, and in 35 patients with multiple etiologies, the average procedure-free interval was approximately 219 days longer after corticosteroid injection, with a small but significant improvement in voice-related quality of life [31].

Although controversial, mitomycin-c has been used routinely after laser and/or dilation with reported positive results. Mitomycin-c inhibits fibroblast proliferation and activity, improving patency rates and reducing scarring. It is usually placed on a cotton pledge or sterile gauze at a concentration of 0.4 mg/ml and applied topically to the area of subglottic scar excision (2–3 applications of 2 min each or single application of 4–5 min). In 2010, Veen and Dikkers conducted a literature review on the side effects of mitomycin-c in the upper respiratory tract [32]. Forty-six articles were retrieved, and the authors concluded that topical application of this agent to a wound with subsequent irrigation with saline solution can be performed safely. The use of higher concentrations of mitomycin-c should be avoided as serious complications may occur. Care should be taken to avoid contact with unprotected skin or eyes and proper disposal protocols should be followed. Despite the belief that this antiproliferative agent is helpful, the conclusions of most clinical trials are limited by retrospective design, small populations or short-term follow-up. These studies also suggest that mitomycin-c may delay, but not prevent, the recurrence of symptomatic stenosis in the majority of patients with laryngotracheal stenosis.

Some authors advocate the use of long-term medical therapy to reduce the relapse rate, using anti-reflux management, high-dose inhaled corticosteroids, oral corticosteroids and/or daily trimethoprim-sulfamethoxazole, but there is a lack of prospective trials to confirm their effectiveness.

5.4 Airway Stenting

In some procedures, additional stenting is an important part of the therapeutic strategy. Possible indications for stenting in SGS include post-intubation SGS after failure of resection and/or benign complex stenosis in patients who are not surgical candidates (Fig. 3); benign stenosis due to inflammatory or infectious processes, while awaiting response to systemic therapy or open surgical resection; restenosis or anastomotic stricture after open surgery; extrinsic compression; expiratory airway collapse; and patient preference. Any endoluminal or intrinsic airway pathology that causes more than 50% lumen reduction after other treatments may be an indication for stenting. Active stenoses following burns or blast injuries and severe dysphagia are contraindications to the use of stents.

When selecting stents for SGS, the material, size, position and duration of stenting should be considered. Most often, the preferred option in SGS is to use the rigid scope to deploy a short and wide straight or hourglass silicone stent, followed by inflation of a balloon inserted into the folded stent to achieve complete opening and a more favorable anchoring. The subglottic location of the stenosis sometimes increases the difficulty of positioning the stent correctly. Once the proximal end of the stent is in the subglottic region, it can induce ulceration and granulation tissue formation with subsequent restenosis. Ko and colleagues analyzed stent complications, the influence of stent location, and stent-to-vocal fold distance on the risk of granulation formation in patients treated with Dumon stents and Montgomery T-tubes, below, at, or across the vocal cords [33]. The rate of granulation

formation was 63% for procedures with distances of ≤10 mm, 22% for those between 11 and 20 mm, and 11% for those ≥20 mm from the vocal cords. A distance of 10 mm from the vocal cords to the proximal end of the stent seems to be an acceptable safety margin, whenever possible [33].

Subglottic stents are prone to distal or proximal migration. This was reported by Martinez-Ballarin and colleagues in 18% of patients treated with Dumon stents for laryngotracheal stenosis [34]. Tracheotomy followed by insertion of a Montgomery T-tube is occasionally chosen to avoid migration and provide a safe airway. Other indications for Montgomery T tubes have been retrospectively evaluated by Carreta et al. [35] and include the treatment of patients with laryngotracheal stenosis with a permanent contraindication to surgery, a temporary preoperative measure in patients with a temporary contraindication to reconstruction, and the treatment of complications of tracheal surgery. In patients with pre-existing tracheotomies, Shapshay and colleagues showed that treatment with laser and T-tube stents can achieve a successful outcome in 67% of cases [36]. However, 75% of these patients required further treatment over a variable follow-up period of 1–5 years. In selected patients with SGS and malacia who are not candidates for surgical resection, tracheotomy, or Montgomery T-tube placement, or who have experienced repeated stent migration, external stent fixation may be performed [37].

Bronchoscopic surveillance is advisable to detect and treat stent complications and to monitor efficacy [33]. In some cases of benign disease, the stent can be removed after several months without symptomatic recurrence or restenosis. Expandable metallic stents should be avoided due to the significant long-term complications that are associated with the placement of permanent stents in benign conditions and should be reserved for palliation in malignant SGS etiologies. There is also the option of ordering customized 3D stents to fit the specific anatomy of a particular patient. In an attempt to avoid complications, biodegradable stents have been introduced but still need improvements (e.g., degradation time, resistance, radial force) before wider use in SGS patients.

5.5 Surgery

The optimal treatment of SGS remains unknown, and as the recurrence rate is high, the success of treatment is based on reducing disease recurrence and avoiding tracheotomy with a technique that causes the least morbidity. Endoscopic management is a valuable primary treatment in some cases, but open surgery plays a key role in the management of SGS, especially in cases of complex stenosis and multiple recurrences after endoscopic treatment [38]. The European Laryngological Society recommends that mature high-grade stenosis in adults should be treated primarily by open surgery, as the chances of success are generally best at the first procedure [18, 39].

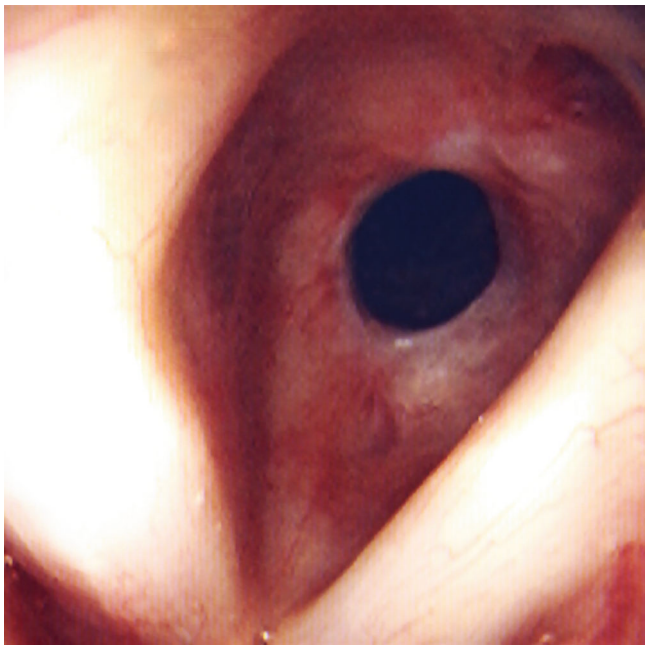

Fig. 10 Subglottic restenosis in a granulomatosis with polyangiitis patient 13 months after reconstructive surgery

There are two main categories of open airway procedures: resection (excise a diseased section of the airway), and expansion (increasing the diameter of the airway by using a graft) (see chapter ▶ "Techniques for Laryngotracheal Reconstruction").

A systematic review compared the outcomes of surgical and endoscopic approaches in SGS [40]. Overall, 32% of patients who underwent laryngotracheal resection received additional surgery and 89% were decannulated. In patients who underwent laryngotracheoplasty with expansion graft, 38% received additional surgery and 83% were decannulated. Patients who underwent endoscopic procedures had an additional surgery in 44% of cases. Regardless of approach, ISGS had the lowest rate of additional surgery (25%) compared to iatrogenic (35%) and traumatic (54%) etiologies.

In systemic diseases with persistent inflammation, such as GPA, invasive procedures should be performed with extreme caution, as certain surgical modalities have a greater tendency to aggravate the underlying vasculitis and cause restenosis (Fig. 10).

6 Follow-Up

Close follow-up and monitoring are essential. In different centers, the post-endoscopic approach includes the use of systemic antibiotics, depending on the extent of the wound and the status of the laryngotracheal mucosa, systemic corticosteroids and active anti-gastroesophageal reflux management, although, as mentioned above, there are no randomized control trials to prove the efficacy of these decisions.

Wound reassessment is performed regularly in the first few weeks after surgery (<2–4 weeks) to determine the status of airway healing, stent position and patency, and the need for further bronchoscopic interventions, as granulation tissue may develop and lead to reobstruction and scarring. Appropriate tracheotomy care is of paramount importance. In these circumstances, bronchoscopy is important to assess airway patency and plan decannulation.

For the first 1–2 years post-intervention, intermittent bronchoscopy is recommended because it allows long-term evaluation and detection of recurrent stenosis before it reaches a critical stage. In other patients, the duration of follow-up depends on the duration of stent placement and symptoms after stent removal. Bronchoscopy should be considered whenever the patient presents with symptoms of airway obstruction.

7 Conclusion

SGS is a major medical problem that can cause severe morbidity and life-threatening airway compromise. When identifying SGS, the etiology, the type of stenosis, its exact location and length, the degree of luminal obstruction, the patient's health status and comorbidities must be considered.

There is no standard treatment for all cases of SGS or for specific conditions that cause SGS. Current practice is still based on local resources and equipment, training and preferences of the interventional team.

Many authors have proposed therapeutic algorithms for the optimal management of SGS. Unfortunately, these have been developed on a single-center basis, with small numbers of patients included, short follow-up periods and no comparison between different treatment modalities or valid control groups.

Endoscopic procedures can be used to treat different types and grades of SGS. Scientific evidence suggests that they are the first choice for simple stenoses, whereas complex stenoses often need a multidisciplinary approach and may require surgery. Treatment of SGS can improve dyspnea and patient-reported quality of life, but there is no single procedure that can consistently relieve symptoms and prevent recurrence in all patients. It must always be remembered that major and repeated procedures themselves, if not thoughtfully planned as part of a management strategy, can cause additional injury and significant morbidity.

In recent years, promising work has been done in the treatment of SGS, but many questions remain unanswered. In the near future, a better understanding of the pathophysiology of this condition and the continued improvement of multimodality approaches and endoscopic techniques will help to prevent and treat SGS more effectively.

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