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REVIEW ARTICLE

Laryngeal Involvement in Connective Tissue Disorders. Is it Important for Patient Management?

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Abstract Connective tissue disorders (CTDs) involve multiple organ systems and may have a significant impact on the overall health and quality of life of the affected individuals. The present paper aims to review the current knowledge on the laryngeal manifestations of CDTs, and describe the available diagnostic and treatment options. Systematic literature review in Medline and other database sources. Information from related books was also included. Prospective controlled, double-blind prospective, prospective, and transversal cohort studies, case series, case reports, systematic reviews, and consensus papers. Laryngeal involvement mostly occurs in rheumatoid arthritis (13–75% of patients). It is not uncommon in active and progressive clinical course, though can also occur in silent or inactive CDTs. The crico-arytenoid joint is the most commonly affected site. Common symptoms include throat pain, dyphonia and hoarseness. Careful clinical assessment of the larynx by flexible naso-endoscopy, video-stroboscopy, or direct laryngoscopy, and appropriate imaging are required for pertinent patient management. Stridor is a sign of a life-threatening condition, and may require prompt surgical intervention. However, mild symptomatology may mislead clinicians, and the related diagnosis may be significantly delayed. The current evidence as identified in the present study suggest that laryngeal manifestations of CDTs are often underdiagnosed, due to a range of non-specific symptoms. A multidisciplinary team approach with ENT input is necessary to improve the overall patient management.

Keywords Laryngeal · Stroboscopy · Connective · Rheumatoid · Arthritis · Lupus

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Introduction

Connective tissue disorders represent a rather heterogeneous spectrum of overlapping pathologies, which have as a common feature the involvement of multiple organ systems. Though generally uncommon, they represent lifelong conditions, which are often coupled with various immunologic disorders, thus significantly affecting the overall health and quality of life of the affected individual.

The classic connective tissue disorders include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, Sjogren's syndrome, and the mixed connective tissue disease. Laryngeal involvement is not an uncommon characteristic of connective tissue diseases, with the crico-arytenoid joint representing the most commonly affected site. Failure to recognize laryngeal manifestations of connective tissue disorders may lead to severe and life threatening complications, usually due to airway compromise.

The aim of the present paper is to review the current knowledge on the laryngeal manifestations of connective tissue disorders, and describe the available diagnostic and treatment options. Implications for appropriate multi-disciplinary management will also be discussed.

Materials and Methods

An extensive search of the literature was performed in Medline and other available database sources, using the keywords "larynx", "rheumatoid arthritis", "Sjögren's syndrome", "lupus erythematosus", and "scleroderma". The keyword larynx was considered primary and was combined to each of the other keywords individually. In addition, reference lists from the retrieved articles were manually searched. Language restrictions limited the search to English-language articles only. Information from related books was also included in the analysis of data.

Results

Four prospective controlled studies, one double-blind prospective, one cross sectional prospective, and five prospective studies, one transversal cohort study, three case-series, 31 case-reports, 11 systematic reviews, one consensus paper, and 10 books met the defined criteria and were included in study selection.

Discussion

Connective tissue disorders predominantly affect women, with a varying incidence. The prevalence of Sjögren's syndrome ranges between 0.5 and 3% [1], whereas RA occurs in 0.5 to 1% of the population [2]. The prevalence of laryngeal involvement in RA ranges from 13 to 75% in different series and between 45 and 88% in postmortem studies [3–14]. Laryngeal involvement is uncommon in Sjögren's syndrome. The world literature reports only 4 cases. SLE, on the other hand, is less common, with an estimated prevalence between 15 and 50 cases per 100,000. The female to male ratio of this disease is 6–10:1, in the age group between 15 and 40 years [1]. However, laryngeal involvement in SLE is also scarcely described in the literature, and reportedly occurs in 0.3% to one-third of patients [15–18]. Systemic sclerosis occurs even more rare, with an estimated incidence between 4.5 and 18.7 new cases per million in the USA and Europe [1], and a female to male ratio of 3:1 [19].

The target of pathology in connective tissue disorders is the connective tissue of the body; the diseases may have both genetic and environmental causes.

The synovial membrane and the pressure sustaining areas of the small peripheral joints are the primary target sites of the chronic inflammatory process in RA, causing joint damage and bone destruction [20–23]. The clinical course of RA is variable, often progressive and disabling, with stages of remission and exacerbations.

The laryngeal manifestations of RA do not always correlate to the stage of the disease [8]. These manifestations can be either secondary to vocal cord lesions (rheumatoid nodules), or involvement of the crico-arytenoid joint, or, more rarely, secondary to amyloidosis or Sjogren's syndrome (as also mentioned later in the text) [3]. There are two stages of laryngeal involvement in RA [6]. An active acute phase, when the larynx is tender, and a chronic phase, which is primarily characterized by crico-arytenoid joint involvement.

SLE, on the other hand, is essentially a multisystem autoimmune disorder, characterized by the production of excessive autoantibodies, which can cause inflammation in various organ systems (i.e. arthritis, pleuritis, pericarditis, nephritis, and CNS involvement) [24]. The pathophysiology of laryngeal inflammation in SLE is not well understood, although the tissue deposition of immune complexes with activation of the complement pathway represents the most likely cause [25].

In addition, Sjögren's syndrome represents a rather diffuse connective tissue disorder, which mainly involves the exocrine glands. The disorder is characterized by lymphocytic infiltrates of the lacrimal and salivary glands, and systemic production of autoantibodies to the ribonucleoprotein particles SS-A/Ro and SS-B/La [26]. Although xerophthalmia and xerostomia are main characteristics of both primary and secondary Sjögren's syndrome, only the latter case is associated with other connective tissue disorders [27].

Finally, scleroderma is a rare connective tissue disorder, of unknown nature, characterized by progressive fibrosis of multiple organ systems. It may present in two forms; limited systemic sclerosis (previously called CREST syndrome), which typically shows cutaneous involvement, and diffuse systemic sclerosis/scleroderma, which is rapidly progressive and additionally affects at least one internal organ [28, 29]. The diagnosis is made clinically and histopathologically with biopsy of the involved site (Fig. 1). Laboratory findings are not diagnostic for scleroderma, although most of the patients are positive for anti-nuclear antibodies [19, 30]. The pathophysiological mechanism of arthritis resulting in cricoatytenoid joint fixation in scleroderma resembles RA. The synovium is infiltrated by lymphocytes and plasma cells, and fibrin deposits in the joint space lead to fibrous ankylosis [31].

General treatment strategies in connective tissue disorders aim to reduce inflammation and autoimmune response. Medications commonly used for these purposes are NSAIDs, corticosteroids and immunosuppressive drugs, depending on the symptoms and signs.

Despite early reports in the literature [32, 33], laryngeal involvement in connective tissue disorders is usually overlooked in everyday clinical practice. The main reason

Table 1 Laryngeal manifestations in connective tissue disorders

Disease	Symptoms	Findings
Rheumatoid arthritis	Fullness-tension of throat	Mucosal edema-erythema
	Foreign body sensation	Cricoarytenoid joint arthritis
	Hoarseness	Rheumatoid nodules
	Odynophagia	Cricoarytenoid joint ankylosis/deformity
	Pain	Interarytenoid fibrosis
	Cough	Fixation of arytenoids
	Dyspnoea-stridor	Fixation of vocal cords
		Epiglottitis
Systemic lupus erythematosus	Dysphonia	Mucosal edema
	Hoarseness	Mucosal ulceration
	Throat pain	Submucosal haemangiomas
	Dyspnoea	Laryngitis-corditis
		Cricoarytenoid joint arthritis
		Epiglottitis
		Mucosal thickening
		Laryngeal scarring
		Laryngeal stenosis
		Thickened vocal cords
		Vocal cord palsy
Sjogren's syndrome	Dysphonia	Cricoarytenoid joint arthritis
	Hoarseness	Vocal cord nodules
	Dyspnoea	Supraglottic/glottic scarring
	Inspiratory stridor	Swelling of false vocal cords
Scleroderma	Dysphagia	Dilated blood vessels
	Weak/breathy voice	Postcricoid edema
	Respiratory distress	Postcricoid erythema
	Biphasic stridor	Vocal cord nodules
		Bilateral vocal cord palsy

is that such patients are primarily seen by Rheumatologists, which in turn may not be familiar with the methods of examination of the larynx (flexible naso-endoscopy, direct laryngoscopy, video-stroboscopy), and the available treatment options. ENT surgeons, on the other hand, may not be able to appreciate the dynamics of connective tissue disorder-associated pulmonary disease, and the impact that these conditions may have on the overall respiratory system. The toxicity of some of the administered drugs in patients with connective tissue disorders can only perplex the clinical picture, and make patient management even more challenging. Hence, ENT involvement in the assessment and treatment of patients with connective tissue

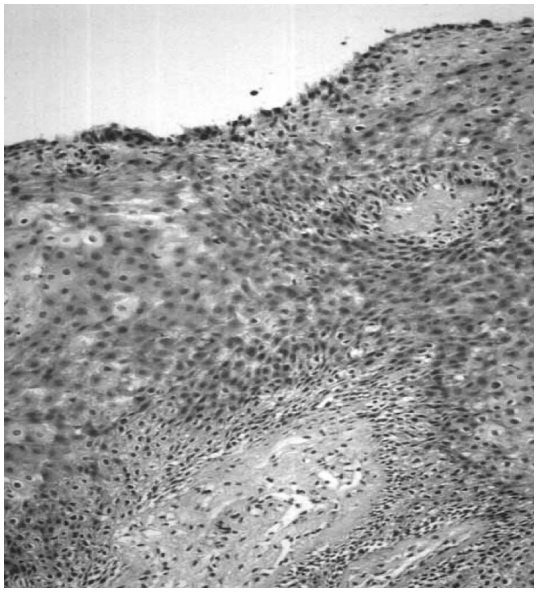

Fig. 1 Photomicrograph of laryngeal biopsy demonstrating mucosal and submucosal infiltration with chronic inflammatory cells in a patient with scleroderma [66]

disorders in the context of a multidisciplinary approach is necessary to ensure appropriate patient management and counseling, when laryngeal manifestations are present.

The laryngeal involvement in RA is usually subclinical. In the active phase, the larynx is tender and erythematous on examination. In contrast, the mucosa appears relatively normal in the chronic phase but the crico-arytenoid joint is ankylosed and deformed. Common symptoms in the early stages of the disease include fullness or tension in the throat, and foreign body sensation (Table 1). As the laryngeal involvement progresses, hoarseness [34], odynophagia, pain, cough, and dyspnoea may occur [9]. Dyspnoea and/or stridor may result either from the inflammation and oedema of the arytenoids and posterior commissure, when the crico-arytenoid joint is acutely inflamed, or from crico-arytenoid joint ankylosis in chronic cases. The ensuing respiratory distress can lead to pulmonary and cardiac complications in severe cases [35].

Flexible naso-endoscopy may reveal mucosal oedema (Fig. 2) and diffuse or localized inflammation (epiglottitis, redness in the arytenoid cartilages), or be suggestive of crico-arytenoid arthritis, inter-arytenoid fibrosis and fixation, and impaired mobility of the vocal cords. The latter is usually seen in chronic cases, along with decreased vocal cord tension during phonation. Rheumatoid nodules can also be seen.

Involvement of the cricoarytenoid joint is a common finding in RA, occurring in 17–70% of patients [4], either as acute or chronic arthritis. However it's not exclusively seen in RA. The differential diagnosis includes SLE, gout, mumps, tuberculosis, syphilis, gonorrhea, Tietze's syndrome and

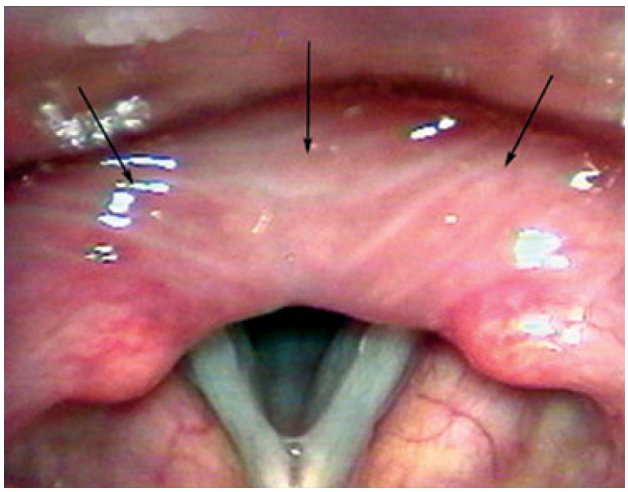

Fig. 2 Oedema of the post-cricoid area in a patient with rheumatoid arthritis [67]

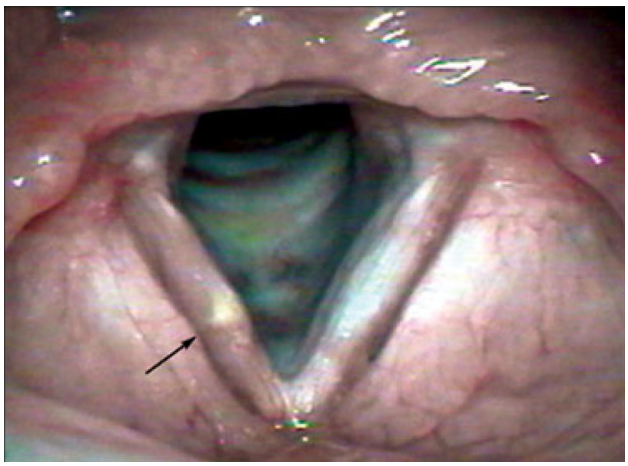

Fig. 4 Bamboo nodule on the middle third of the right vocal cord in a patient with rheumatoid arthritis [67]

trauma [36]. Histological examination of the crico-arytenoid joints shows synovitis, which can lead to the erosion of the joint cartilage, and finally ankylosis [14].

Rheumatoid nodules of the larynx can be found in different autoimmune diseases [37], and are present in about 20% of patients with RA (Fig. 3). Their presence may be a result of the course of the disease itself, or a side-effect of methotrexate use in the treatment of RA [38]. These nodules, often referred to as bamboo nodes, can be mistaken for vocal cord nodules or cysts (Fig. 4). However, the former can be found at the middle of the vocal cord and are most of the times asymmetrical, as they are not exactly opposing each other, whereas vocal cord nodules are usually found at the junction of the anterior and middle third, symmetrically in both cords. From a clinical point of view, rheumatoid nodules may cause voice instability and intermittent aphonia [39, 40]. The former can be detected on videostroboscopy, due to alterations in the vibratory pattern, which may include reduced or absent amplitude of the mucosal wave. However, voice changes may also be associated with cricoarytenoid joint involvement in up to two-third of cases [41–43], which, in turn, can result in an increase of the translaryngeal resistance during phonation [44, 45].

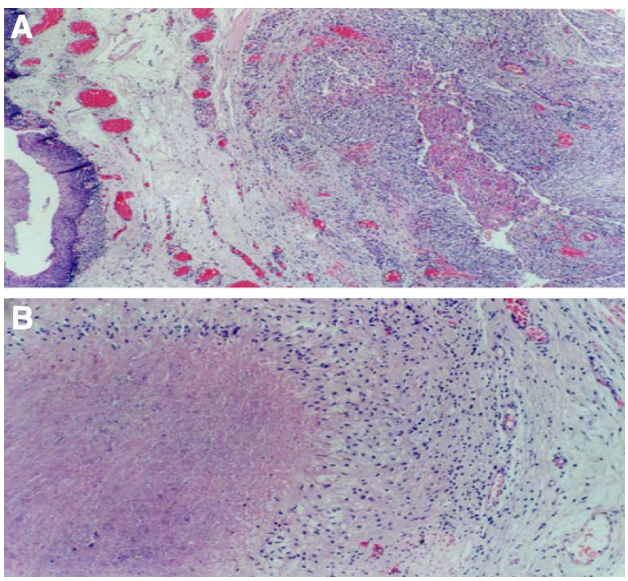

Fig. 3 Laryngeal biopsy specimen. **a** There is a formation of a rheumatoid nodule in the lamina propria composed of a central necrotic area surrounded by palisaded histiocytes. (H&E × 180) **b** The same rheumatoid nodule with extensive necrosis at higher magnification. (H&E × 320) [3]

Rheumatoid nodules have a characteristic appearance in stroboscopic light, especially when the patient phonates at high pitch, when the vocal folds are stretched. This appearance is consistent with soft swellings of the superficial layer, frequently as part of the vibrating mass, which sometimes tend to be incorporated in the mucosal wave during vibration. Vocal cord cysts, on the other hand, often appear as solitary rounded lesions, which may affect vibration in a similar way to the rheumatoid nodules. The bilateral appearance of the former and the transverse band formation on stroboscopy are the main findings that support the diagnosis.

In addition to clinical examination, imaging can be essential for the diagnosis of laryngeal involvement in RA.

Although plain x-rays may demonstrate erosive arthritis of the cricoarytenoid joint, HRCT of the neck is considered to be the investigation of choice [41]. The scans can also be helpful in the differential diagnosis from infections, inflammatory or granulomatous lesions. CT scan findings usually include crico-arytenoid prominence (46%), or density and volume changes (46%) in the area of the crico-arytenoid joint. Less commonly we can see crico-arytenoid

subluxation (39.9%), decrease in the cricoarytenoid joint space, erosion and ankylosis of the cricoarytenoid joint, and soft tissue changes, such as narrowing around the glottis and pyriform fossae (Fig. 5) [46, 47]. MRI scans can also be used [3]. Chest HRCTs can also be suggestive of obliterating bronchiolitis, or other RA-associated COPD, and should be performed in combination with the appropriate lung function tests in patients with shortness of breath.

If vocal cord palsy is developed in patients with RA, a CT scan of the area which extends from the skull base to the upper abdomen is initially performed, in order to exclude malignancy. In the absence of any suspicious pathology, EMG and palpation of the arytenoids under general anesthesia can assist in the differential diagnosis. Normal EMG findings of the thyroarytenoid muscle, and fixed cricoarytenoid joint on direct laryngoscopy, are suggestive of vocal cord palsy secondary to cricoarytenoid joint arthritis or cricoarytenoid joint subluxation [3, 48].

Thorough assessment of the laryngeal involvement in RA can be crucial in cases of planned surgery. Miyanohara et al. [49] reported a case of laryngeal RA aggravation, following the use of a laryngeal mask (LMA). The pressure that the LMA exerts on the arytenoids seems to increase the inflammation, and worsen the symptoms of post-operative hoarseness and stridor [49].

In the absence of airway compromise, the treatment of laryngeal RA is initially conservative. Early identification of the problem and administration of high dose intravenous steroids, or injection of topical steroids in the cricoarytenoid joint, can treat the inflammatory process [50]. Treatment with steroids shows good response, with patients being free of symptoms and having normal larynx on flexible nasoendoscopy even two years after an acute episode [3, 20]. Symptomatic rheumatoid nodules of the vocal folds can be removed with micro-laryngoscopy. Fixation of the cricoarytenoid joint can be treated either with cold-steel or laser arytenoidectomy. A surgical tracheostomy is reserved for life-threatening situations [28, 51–55].

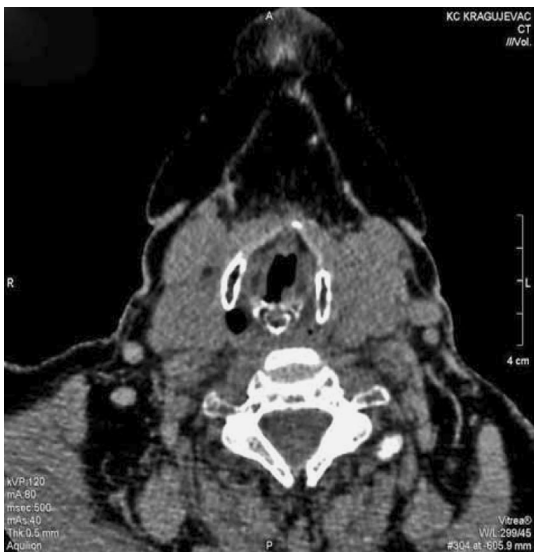

Fig. 5 Rheumatoid arthritis of the larynx. Sclerosis of the right arytenoid cartilage [47]

The laryngeal involvement in SLE mainly occurs in exacerbations of the underlying disease; very rarely have laryngeal symptoms been reported in cases of inactive SLE [56, 57]. The most frequently affected site is the glottis and crico-arytenoid joints, although other laryngeal compartments can also be involved.

The symptoms of laryngeal involvement in SLE include dysphonia, hoarseness, and throat pain, and may result from mucosal ulcerations, and oedema, or submucosal haematoma and impaired vocal cord vibration or vocal cord palsy [58, 59]. Mucosal oedema may also lead to epiglottitis [60]. Later effects of mucosal disease include mucosal thickening, laryngeal scarring and stenosis, laryngitis, vocal cord thickening and corditis [17, 61]. Perichondritis, cricoarytenoid arthritis and vocal cord paralysis, have been described as the presenting symptoms of SLE [16, 61]. Vocal cord palsy in SLE can be associated with mucosal oedema or ulceration, submucosal haematoma, vasculitis of the vasa nervosa, and pulmonary hypertension, or represent the only manifestation of vasculitis involving the cranial and peripheral nerves [62].

The diagnosis of SLE from laryngeal findings is very difficult. However, it is important that SLE patients with upper airway symptoms undergo flexible naso-endoscopy, or micro-laryngoscopy. If biopsies of the larynx are taken in the latter case, the histology is indicative of infiltration with histiocytes, lymphocytes, plasma and mast cells, similarly to patients with subglottic stenosis [61]. Though not very specific for SLE, such findings can at least exclude diseases with similar manifestations, such as tuberculosis, or rhinoscleroma.

In contrast to patients with RA, in whom chronic involvement of crico-arytenoid joints occurs more commonly and often requires surgical intervention, patients with SLE typically present with acute arthritis of the crico-arytenoid joints and respond to corticosteroid therapy alone [56].

As mentioned earlier, laryngeal involvement in Sjögren's syndrome is uncommon. Laryngeal manifestations include crico-arytenoid arthritis and laryngeal scarring, nodules in the vocal cords, or oedema of the ventricular folds. Barrs et al. [63] reported a 62 year-old woman with a 10 year history of xerostomia and xerophthalmia, who presented with hoarseness, progressive dyspnoea, and inspiratory stridor. Indirect laryngoscopy was suggestive of diffuse thickening and scarring of the supraglottis and glottis. Histological examination revealed submucosal infiltration of plasma cells and lymphocytes, and confirmed

the diagnosis of Sjögren's syndrome. Prytz reported the case of a 31 year-old woman with a 4 month history of dryness in the eyes and oral mucosa and pharyngo-laryngitis, followed by hoarseness [64]. The patient underwent micro-laryngoscopy, which revealed bilateral vocal cord nodules. Biopsies showed hyperplastic epithelium and oedema of the lamina propria. Labial biopsy demonstrated lymphocytic infiltration consistent with Sjögren's syndrome. Ito et al. reported the case of a 42 year-old woman with Sjögren's syndrome and oedema in both the ventricular folds and epiglottis [65]. Biopsies revealed severe atrophic changes and cystic dilation of the ducts of the laryngeal glands, with marked lymphocytic infiltration and lymphoid hyperplasia. A rare case of Sjögren's syndrome and cricoarytenoid arthritis was reported by Seve et al. [66]. A 42 year-old woman with arthritis and dysphonia, who met the criteria of Sjögren's syndrome, responded to steroid administration with improvement of her symptoms.

Laryngeal involvement is not a common feature of scleroderma. Upper airway obstruction secondary to scleroderma is even more uncommon, and has only been reported once [67]. The patient was a 40 year-old woman with known scleroderma, who had symptoms of progressive dysphagia and respiratory distress, with biphasic stridor and weak, breathy voice. Flexible naso-endoscopy revealed bilateral immobile vocal cords in the median position, due to cricoarytenoid joint fixation, post-cricoid oedema and redness. Surgical tracheostomy was performed to avoid airway compromise. Biopsies showed nonspecific chronic inflammation.

Interestingly, a study conducted by Ramos et al. [68] showed all scleroderma patients ($n = 11$) to have alterations on video-stroboscopy. Alterations suggestive of gastroeosophageal reflux disease were also observed in all 11 patients, with clinical complaints in six. Two patients had prominent blood vessels in the vocal folds, two vocal nodules, whereas an additional patient presented with signs of laryngeal hypertrophy.

Conclusion

Connective tissue diseases are multi-organ disorders that may affect the larynx. Laryngeal involvement is not uncommon in active and progressive clinical course. However, it can also occur in silent or inactive disease. Taking into account that the related symptoms are often subtle or non-specific, the diagnosis of such an involvement may be missed or considerably delayed. Not only should Rheumatologists be aware of laryngeal involvement in connective tissue disorders, but also ENT surgeons should be actively involved in the management of these patients, as such involvement may become life threatening. The need for a multidisciplinary approach for appropriate patient management is therefore important. Stridor is not a symptom that only reflects pulmonary involvement. It may as well be attributed to laryngeal pathology, and requires ENT input and collaboration of specialties to be managed appropriately. ENT evaluation of patients with connective tissue disorders may also be crucial prior to any kind of surgery. Patients with laryngeal findings, such as cricoarytenoid joint arthritis, should be managed carefully by the anesthetist, and LMAs should be avoided.

Conflicts of interest None.

Disclosure This material has never been published and is not currently under evaluation in any other peer-reviewed publication.

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