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Laryngeal sarcoidosis: a case-control study

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Abstract. *Introduction:* We undertook a study on a series of laryngeal sarcoidosis (LS), a very rare and often threatening localization to better specify laryngeal manifestations, sarcoidosis clinical expression and long-term follow-up. *Methods:* This was a retrospective case-control study. All LS patients from two French centers were included and compared to sarcoidosis patients without laryngeal localization with two controls for one patient. *Results:* Twelve consecutive LS patients were recruited between 1993 and 2011. LS revealed sarcoidosis in eight cases (67%). The most common symptoms were hoarseness (77%), inspiratory dyspnea (38%) and dysphagia (38%). Epidemiological characterisics were not different. Extrapulmonary localizations were significantly more common in LS patients than in controls (92% vs. 54%, p=0.02), particularly lupus pernio (25% vs. 0%, p=0.03) and nasosinusal involvement (83% vs. 4%, p<0.01) while thoracic involvement was less frequent (58% vs 100%, p < 0.01). Treatment rates were higher in the LS group (92% vs. 58%, p=0.04), and treatment duration was longer (median: 81 vs. 13 months, p=0.04), with frequent long-term treatment (67%, N=8/12). Two patients underwent surgery. One patient needed temporary tracheostomy during the course of the disease; Remission rates were lower in LS patients (9% vs. 58% at 2 years p<0.01). Eventually, there was no death nor definitive tracheotomy. *Conclusions:* LS is a rare condition that is often associated to other loco-regional localizations. LS are often difficult to manage. Survival is good but may require a medico-surgical approach *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 227-234)*

Key words: Sarcoïdosis, larynx, sino-nasal, lupus pernio, multisystemic, upper airway

Abbreviations

ACE = angiotensin-converting-enzyme
DLCO = carbon monoxide diffusion capacity
ENS = ear, nose and throat
FIV1 = forced inspiratory volume in 1 second
LS = laryngeal sarcoidosis
PFT = pulmonary function test
SNS = sinonasal sarcoidosis

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Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology. Most patients present with pulmonary, lymphatic, ocular, and cutaneous involvement, though virtually any organ can be involved (1). Certain sarcoidosis localizations may be life-threatening, involve functional prognosis, and require systemic treatment. Laryngeal involvement is very unusual, as it was reported in only 13 of 2,319 sarcoidosis patients (0.6%) seen at the Mayo Clinic from 1950 through 1981.(2) Clinical features and prognosis of LS are still unclear while laryngeal localizations often are considered as a severe manifestation of sarcoidosis. According to the literature, 10 to 20% of patients may undergo tracheostomy or suffer from acute distress syndrome during the course of LS and death due to laryngeal sarcoidosis has been reported (Table 5)(3–5). We present a retrospective case-control study involving 12 consecutive LS cases. The objective of our study was, first, to describe these cases' clinical features, and then to compare their features and prognoses to 24 sarcoidosis patients without known LS and to reports from the medical literature.

Methods

Case and control definition

This retrospective case control study was conducted in 2011 in the chest departments of two French Parisian university hospitals (Hôpital Avicenne and Hôpital Tenon). All LS cases were retrieved from the clinical databases of both departments. We also used the pathologists' databases, in which were registered, the main characteristics of the pathological lesion (*i.e.,* "sarcoid granulomatosis"), along with the affected organ *(i.e.,* "larynx and/or pharynx").

Cases were included only if the following criteria were met: 1) the clinical and radiographic features were compatible with a diagnosis of sarcoidosis; 2) non-caseating granuloma was histologically confirmed by laryngeal biopsy or otherwise; 3) other causes of granulomatosis were excluded by means of tissue biopsies that were negative for fungi and acid-fast bacilli, as were other clinical and paraclinical granulomatosis cases, including Wegener granulomatosis, tuberculosis, syphilis, and lepromatous leprosy; 4) the signs and symptoms related to laryngeal or pharyngeal involvement were confirmed by an ear, nose and throat (ENT) specialist.

Controls were drawn from the same clinical databases. For each case, we retrieved two controls with no known LS that matched the LS cases in terms of the date of admittance (+/- 2 months). Published cases of sarcoidosis with laryngeal involvement were identified by means of a Medline search covering the years 1980 to 2012, using the following keywords: [MESH sarcoidosis] AND [laryngeal].

The Institutional Review Board of the French Society for Respiratory Medicine *(Société de Pneumologie de Langue Française*) approved this observational, non-interventional analysis of medical records.

Data collection

Complete information was obtained from hospital and referring physician medical files and retrospectively reviewed by the authors (BD and AL). One physician (BD) used a standard form in order to record patient characteristics from the medical files. The form comprised the following items: 1) epidemiological characteristics (age, gender, race, and smoking history); 2) characteristics of sarcoidosis (pulmonary and extrapulmonary symptoms, as well as physical signs on admission; time between onset of sarcoidosis, onset of laryngeal sarcoidosis, and admission; serum angiotensin-converting-enzyme (ACE) levels; chest radiographic staging (0 to 4), as recommended by DeRemee *et al.*(6); pulmonary function test (PFT) results, including blood gas levels on room air and carbon monoxide diffusion capacity (DLCO); 3) outcome data derived from regular assessments (physical findings, PFT data, and chest imaging), at time intervals depending on clinical status from diagnosis to cut-off date analysis in September of 2012. Remission was defined as the complete resolution of all sarcoidosis symptoms, without disease recurrence for at least 2 years without treatment.

At the time of LS diagnosis, all patients were seen by an ENT specialist and pulmonologist from the respective university hospital. Nasopharyngolaryngeal and bronchial endoscopies were performed

Table 1. Epidemiological characteristics of laryngeal sarcoidosis patients and controls

	Cases (N=12)	Controls (N=24)	P
Epidemiology	N (%)	N (%)	
Age, yr (mean +/-SD)	39.5+/-16.3	40.5 +/-12.6	0.64
Men/women	5 /7 (%)	14 /12 (%)	0.34
White	4 (33)	11 (42)	0.72
Black	4 (33)	8 (33)	0.99
North African	4 (33)	5 (22)	0.44
Smoker (current and former)	3 (25)	12 (46)	0.28
Berrylium, silica or asbestosis exposure	0 (0)	2 (8)	0.99

Yr = year

on every patient. All control had bronchial fibroscopy for the diagnosis of sarcoidosis. None had laryngeal abnormality.

Statistical Analysis

Analysis was performed using GraphPrism 5.04. Results were expressed as mean ± standard deviation or median (range). Groups were compared using unpaired student's t-test, Mann- Whitney test, or Chi-squared test, according to appropriateness. The probability of remission from sarcoidosis was estimated using the Kaplan-Meier method and compared with the log-rank test.

Results

Among the sarcoidosis patients seen between January 1992 and September 2011 in the two centers, 12 fulfilled the inclusion criteria. In one center, 1,800 new patients with sarcoidosis were recruited between 1999 and 2011, six of whom had LS, resulting in an estimated LS involvement of 0.33% (mean 0.31/100 sarcoidosis/year +/- 0.12) Two patients were not included: one with concomitant non-tuberculosis mycobacterial infection; the other presented with pulmonary sarcoidosis and laryngeal symptoms, but exhibited complete improvement following compressive cervical lipoma surgery.

Epidemiological and clinical LS characteristics

Epidemiological and clinical characteristics are provided in Tables 1, 2, and 3. Cases and controls were similar as to age (39.5 *vs.* 39.0, p=0.64), gender (H/F=0.71 v. 1.17, p=0.34), ethnic origin (Caucasian 33% *vs.* 42%, p=0.72), and dust or mineral exposure (asbestosis or silica). There were no cases of familial sarcoidosis.

Symptoms related to LS revealed sarcoidosis in eight patients (67%), but only one had sarcoidosis confined to the larynx. The time interval between

Table 2. Ear nose and throat characteristics of laryngeal sarcoidosis patients (n=12)

FEATURES	N (%)
Symptom	
- Hoarseness	10 (77)
- Dyspnea (inspiratory)	5 (38)
- Dysphagia	5 (38)
- Cough	1(8)
- Sleep disorder / snoring	2 (15)
- Life-threatening symptom	3 (23)
Localization	
- Supraglottic	10 (77)
• Upper rim	4 (31)
• Arytenoids	4 (31)
• Epiglottis	3 (23)
• Ventricular fold	1 (8)
- Glottic	4 (31)
- Subglottic	2 (15)
Local examination	
- Infiltration	5 (38)
- Vocal cord abnormal mobility	2 (15)
- Edema	6 (46)
- Reddish granulomatous lesions	3 (23)
- Ulceration	2 (15)
- Chondritis	1 (8)

Table 3. Thoracic imaging, spirometry, and extra-respiratory manifestations in patients with or without laryngeal sarcoidosis

	Cases (N=12)	Controls (N=24)	P
Altered general condition >10% loss of total weight	4 (33)	3 (12)	0.19
Thoracic involvement	7 (58)	24 (100)	<0.01
Acute respiratory distress	4 (33)	0 (0)	<0.01
Initial chest radiographic stage*			
Stage 0	5 (42)	0 (0)	<0.01
Stage 1	2 (17)	4 (17)	0.99
Stage 2 and 3	1 (8)	15 (63)	<0.01
Stage 4	4 (33)	6 (23)	0.70
Pulmonary function test			
Normal spirometry	8 (67)	13 (54)	0.72
Obstructive pattern	1 (8)	2 (8)	0.99
Restrictive pattern	3 (25)	10 (42)	0.47
Mixed pattern	0 (0)	1 (4)	0.99
Extrarespiratory localization			
Presence of extrarespiratory localization†	11 (92)	13 (54)	0.02
Number of extrarespiratory localizations (mean+/- SD)	2.7 +/- 1.5	0.93 +/- 1.26	<0.01
- Ophthalmic (refractory to local treatment)	3 (25)	0 (0)	0.03
- Symptomatic Heart involvement	3 (25)	1 (4)	0.10
- Chronic hepatic cholestasis	2 (17)	0 (0)	0.10
- Kidney	0 (0)	1 (1)	0.99
- Sinonasal involvement	10 (83)	1 (4)	<0.01
- Lupus pernio	3 (25)	0 (0)	0.03
ACE Increased (>2 fold)	7 (58)	12 (50)	0.30

** Chest radiographs were classified according to the standard statement on sarcoidosis: 0: normal; I: bilateral hilar lymphadenopathy with normal lung parenchyma; II: bilateral hilar lymphadenopathy with pulmonary infiltrates; III: pulmonary infiltrates without hilar lymphadenopathy; IV: pulmonary fibrosis/fibrocystic parenchymal changes*

† All features were based on patient's condition at presentation except for extrarespiratory localization of sarcoidosis, which could be either at presentation or during follow-up.

initial LS symptoms and LS diagnosis ranged from 3 months to 2 years, and was longer than 6 months in 75% of cases. The main symptom at diagnosis was hoarseness, followed by inspiratory dyspnea. Three had acute respiratory failure occurring during the evolution of sarcoidosis, one of which required a tracheostomy for 3 years. Endoscopy examination most frequently revealed infiltration without edema (in five cases; 38%) (Figure 1). The most frequent localization was the supraglottic upper rim, arytenoids, and epiglottis.

LS diagnosis was confirmed on laryngeal biopsy in nine patients (75%). The other three had laryngeal macroscopic typical lesions during laryngoscopy. For them, other diagnoses were excluded, and lymph node or bronchial biopsies revealed non-caseating granulomas.

The two groups were statistically different with respect to the presence of thoracic involvement (58%

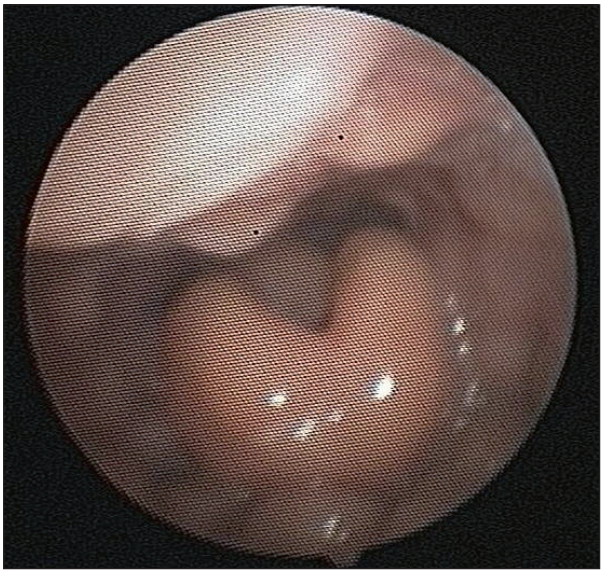

Fig. 1. A laryngoscopic picture showing sarcoidosis of the epiglottis. Supraglottic structures are enlarged, pale pink, and edematous

vs 100% p<0.01) and the presence (92% *vs.* 54%, p=0.02) and number (2.7 *vs.* 0.93, p<0.01) of extra-respiratory manifestations (Table 3). Among these extra-respiratory manifestation ophthalmologic sarcoidosis refractory to local treatment (25% *vs.* 0%, p=0.03), Cardiac involvement (25% *vs.* 4%, NS) and liver chronic cholestasis (17% *vs.* 0%, NS) were or tended to be more commonly observed in LS patients. *Lupus pernio* (25% *vs.* 0%, p=0.03) and symptomatic nasosinusal involvements (83% *vs.* 4%, p<0.01) were also more frequent in LS patients.

Clinical course and treatment of LS

cases

The clinical course and treatment are summarized in Table 4. LS cases were followed for a median of 8.3 years (range: 1.7–20.3 yrs.) after the diagnosis of sarcoidosis, and 5.7 years (range: 1.7–19 yrs.) after LS diagnosis. With a single exception treated by surgery alone, all cases required medical treatment because of LS symptoms, either exclusively (n=7) or because another sarcoidosis localization need treatment (n=4). Eleven patients received oral corticosteroids, either alone (n= 9) or in combination with immunosuppressive treatment (n=2). High corticosteroid doses (0.5 - 1 mg/kg/day) and long-term treatment for a median of 81 months (range: 0–168 months) were required. Corticosteroids were, in some cases, associated with at least one other drug, used as a corticosteroid-sparing treatment in four cases (33%; hydroxychloroquine: n=2, methotrexate: n=2), due to corticosteroid-resistant sarcoidosis in six cases (50%; hydroxychloroquine: n=3, methotrexate: n=5, thalidomide: n=3, cyclophosphamide: n=1, azathioprine: n=4, TNF inihibitor: n=2, mycophenolate mofetil: n=1, and pentoxifylline: n=1), or because of severe corticosteroid-related side-effects in one case (8.3%; methotrexate: n=1).

Seven out of 11 patients improved on physical and endoscopic examination (2 totally and 5 partially) on corticosteroids as first-line treatment. Maintenance treatment depended mainly on LS involvement in five patients, and on another localization involvement in three extra patients. In the 10 patients who received methotrexate in association with corticosteroids, we noticed response in eight cases (4 clinical improvement, 4 steroids decrease), failure in two and dose-limiting side effects in two cases. For the patients receiving azathioprine along with corticosteroids (N=4), we found an improvement in three and failure in one.

Two patients underwent LS surgery. For one woman, LS consisted of a single polypoid lesion,

Table 4. Clinical course and treatment of patients with laryngeal sarcoidosis and controls

	Cases (N=12)	Controls (N=24)	P
	N (%)	N (%)	
Follow-up, yr, median (range)	8.25 [1.7-20.3]	7,6[1,7-22,0]	0.60
Systemic treatment	11 (92)	14 (58)	0.04
Oral corticosteroids	11 (92)	12 (50)	0.01
Hydroxychloroquine	5 (42)	3 (13)	0.09
Non-steroidal immunosuppressants	10 (83)	8 (33)	<0.01
Methothrexate	9 (75)	3 (13)	<0.01
Azathioprine	4 (33)	7 (29)	0.99
Others	6 (50)	0 (0)	<0.01
Duration of systemic treatment in months, median [range]	81[0-168]	13[0-156]	0.04
Remission	3 (42)	17 (71)	0.01
Remission at 24 month			
Remission at 96 month	17		
31	58		
85	<0.01		

with no other sarcoidosis manifestation requiring

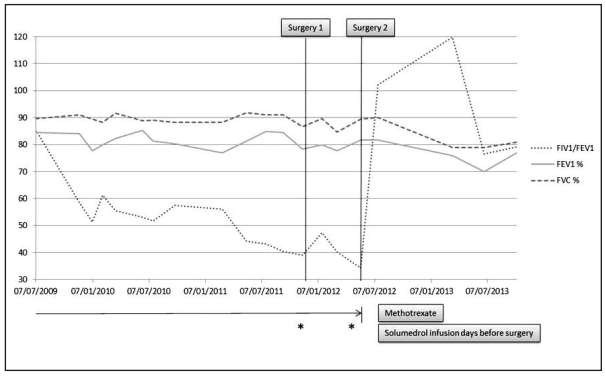

Fig. 2. Pulmonary function test results of one patient with laryngeal sarcoidosis under medical treatment and after laryngeal surgery. Note the dramatic improvement of FIMS.

treatment. No recurrence was noticed at 1-year follow-up. The second patient was corticosteroid-resistant and on methotrexate. She underwent two CO2 surgeries, with a good response and dramatic improvement of forced inspiratory volume in 1 second (FIV1) following a short follow-up of a few months (Figure 2).

There was no death at the end of follow-up. Three patients had recovered from all sarcoidosis symptoms. Between LS patients and controls, there was a difference in the rate at which systemic treatment was required (92% *vs.* 58%, p=0.04) and in the duration of treatment (81 months *vs.* 13 months, p=0.02). The probability of remission from sarcoidosis was significantly lower in LS patients than in controls (log-rank <0.01, 6-month remission rate 8% *vs.* 39%, 24-month remission rate 17% *vs*. 58%, and 96-month remission rate 31% *vs*. 85%, respectively).

Discussion

This study is the first case-control study with substantial follow up comparing patients with LS to paired sarcoidosis patients with no laryngeal involvement. The main conclusions of the study were: i) laryngeal involvement is initial in most cases but may be delayed for several years.; ii) despite the potential severity of such localization, there was no death nor permanent tracheostomy; iii) the clinical phenotype was original according to the unexpected low frequency of thoracic involvement and to the abnormally high frequency of extrapulmonary involvement, particularly at a regional level (quasi constant nasosinusal involvement; frequent *lupus pernio* and ophtalmologic localization) and to long duration of evolution; iv) treatment was necessary for several years with recourse to several medications and sometimes surgery.

We conducted a retrospective analysis involving two highly specialized tertiary care provider centers. We found a prevalence of 0.33% of laryngeal localization among sarcoidosis patients. This figure is in line with other uncontrolled and retrospective studies previously published. The Neel study conducted in the Mayo Clinic found that 13 of 2,319 sarcoidosis patients seen between 1950 and 1981 exhibited LS (0.6%).(2) In the Panselinas study, 21 out of 998 sarcoidosis patients seen between 1999 and 2006 had LS (2.1%).(7) In Yanardag's review of 546 sarcoidosis patients between 1964 and 2005, five (0.91%) having LS.(8)

In our study LS is often discovered at the same time sarcoidosis is diagnosed, revealing the sarcoidosis in most cases, as suggested in the literature.(4,9–12) Nevertheless LS can be discovered during the course of the disease until 7 years in our study.

Laryngeal sarcoidosis can be obstructive and life-threatening. In our series, three patients presented respiratory distress syndrome prompting in one patient a tracheostomia but we didn't have to deplore any death nor permanent tracheostomy despite a very prolonged follow-up. According to the literature, 10 to 20% of patients underwent tracheostomy or suffered from acute distress syndrome during the course of LS sometime with fatal outcome (Table 5).(3–5)

As previously reported,(2,4,8,13,14) the main symptom is hoarseness (73%). Inspiratory dyspnea can be revealing of the LS, particularly if there is no thoracic involvement on chest X-Ray. Endoscopic examination usually shows involvement of the supraglottis.(11,12) Impairment of function may be due to active granulomatous disease or secondary fibrosis. Classical features include edema, pale pink color, and diffuse enlargement of supraglottic structures. There is a turban-like thickening of the full and rounded rim of the epiglottis, aryepiglottic folds, and arytenoids. Granular areas or nodules may be observed, but are less common.

Table 5. Comparative data of previously published and current series

N=	4a	1b	6c	5d	39e	13f	6g	12h	N= 85
Hoarseness (%)	75	50	25	100	54	69	67	39.5	63
Dyspnea / stridor (%)	0	25	67	20	41	18	67	38	34
Cough (%)	0	67	0	0	5	5	0	8	11
Dysphagia (%)	50	33	0	100	10	13	83	38	41
Sleep disorder/snoring (%)	25	0	0	0	3	3	67	17	14
Subglottic (%)	50	42	0	0	ND	ND	ND	17	23
Supraglottic (%)	50	75	67	100	ND	ND	ND	83	73
Glottic (%)	0	0	33	0	ND	ND	ND	33	8
Life-threatening (%)	75	8	67	0	10	54	0	25	31
Isolated (%)	50	17	ND	ND	24	54	50	8	39
Histology-proven (%)	75	100	67	ND	56	85	100	75	80
Multivisceral >=3 (%)	25	75	ND	ND	54	31	17	83	40
Cure with treatment (%)	50	41	33	ND	ND	30	17	25	34

(a)Mayerhoff 201011 (b) Braun 200812 (c) Sims 20073 (d) Yanardag 20067 (e) Bower 198013 (f) Neel 19822 (g) Plaschke 201114 (h) Current series

The LS phenotype is original by different points. First, Thoracic localization is less common in LS than in controls. This observation is consistent with the findings of the study by Bower *et al.*, in which only 28 of 44 patients (47%) presented with thoracic localization (Table 5)(3). This low rate of thoracic involvement contrasts with data found in other severe localizations like cardiac, kidney, *lupus pernio*, or sinonasal sarcoidosis (SNS) cases (Table 5)(15–18). More interestingly, we found more extra-thoracic localizations in LS patients than in controls. Moreover, we found extra-thoracic localization to be associated with SNS and *lupus pernio*, which have been linked to poor prognosis.(8,16,19,20) A third of patients with *lupus pernio* had upper respiratory tract involvement.(9,16,21) Although the pathogenic mechanism of such an association is still unclear, it may result from the contiguous extension of granulomas. LS share with these involvements a particularly long course of evolution. Given these associations, it should be noted that some treatments, such infliximab(17) or thalidomide,(22) seem more efficient in *lupus pernio* cases. Finally, some manifestations seem more frequent in the LS group—especially eye, heart, and liver localizations. In previously published series, the main severe manifestation was the central nervous system (Table 5).(5,11,23)

Our results clearly show that LS patients present with a more severe illness in terms of number of extra-thoracic localizations, as compared to sarcoidosis controls. In our study, LS was associated with a significantly lower probability of remission and greater need for systemic treatment often for several years (Table 5). LS Pronostic remains unclear in the litterature. Although several studies reported spontaneous remission, (2,24) 95% of published cases received systemic, surgical, or local treatments. Approximately 65% of reported patients only partially improved or did not improve after treatment.

Therapeutic management of LS has never been clearly codified. In our series, oral corticosteroid therapy was the most frequently delivered therapy (Table 5). In a published series,(3) oral corticosteroid therapy was reported to be effective in 11 of 13 patients, but only with high-dose maintenance treatment and frequent side-effects. In another series,(24) six of 12 patients were remitted or stabilized using corticosteroids, with fewer side effects. In our series, each patient received additional treatment either for corticosteroid-sparing or due to corticosteroid-resistant sarcoidosis or severe corticosteroid side-effects.

Two of our patients underwent surgery. The first had an ablative surgery of one obstructive granulomatous mass, with complete symptom remission and no relapse. In contrast, the second had symptomatic corticosteroid-resistant sarcoidosis, with CO2 laser photo incision and vaporization of the arytenoids to create adequate airway. The surgery specimen contained only few granuloma, with mostly fibrosis. Surgery was

useful for restoring the airway after systemic treatment controlled the disease's inflammatory component. This patient's corticosteroid and methotrexate regimens were discontinued following surgery, with no relapse. Surgery was advocated for patients with well-localized mass lesions producing high-grade airway obstructions, and has proven effective in small series. Endoscopic resection, supraglottic laryngectomy, and laryngofissure with excision of subglottic tissue and skin grafting have produced good results in very selective patients,(11,13) often following systemic treatment. Surgery aims to create an adequate airway, avoid tracheotomy, and preserve the voice.

Our study suffered for possible biases include the estimated prevalence of LS involvement, in addition to the validity of the control group and the epidemiological specificity of our patients.

In conclusion, LS is associated with local and general severity of sarcoidosis, including disease dissemination, treatment resistance, and poor prognosis. We should look for it in the context of *lupus pernio* and SNS. This localization requires high corticosteroid doses for a prolonged duration, and may benefit from early administration of immunosuppressive agents. Surgery can be very effective in selected patients with low activity of sarcoidosis and airway obstruction. For all these reasons, the SL is a medical-surgical challenge requiring a multidisciplinary approach including physicians experienced in sarcoidosis and ENT specialists. Further multicenter studies are needed to assess the efficiency of corticosteroid-sparing treatments, and specify the most accurate time for surgery in the multimodal treatment course.

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Authors contributions: BD had full access to all data and takes responsibility for the integrity and accuracy of the data analysis.

JC, JMN, AL: contributed to the study concept, design, data interpretation; and the writing of the manuscript.

DV, SP, SB, ML, MK: contributed to the study design and reviewed the manuscript.

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