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Review

Laryngeal tubercolosis: a case report with focus on voice assessment and review of the literature

Tubercolosi laringea: case report con focus sulla valutazione della voce e revisione della letteratura

Andrea Migliorelli[1], Tommaso Mazzocco[1], Anna Bonsembiante[1], Daniele Bugada[1], Marco Fantini[2], Fabrizia Elli[3], Marco Stacchini[4]

[1] ENT & Audiology Department, University Hospital of Ferrara, Ferrara, Italy; [2] Otorhinolaryngology Service. Koelliker Hospital, Turin, Italy; [3] Division of Otorhinolaryngology, Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy; [4] ENT Department, M. Bufalini Hospital, Cesena, Italy

SUMMARY

Laryngeal tuberculosis (LTB) is a rare manifestation of tuberculosis (TB), accounting for 1% of all TB cases. Despite its rarity it is the most frequent laryngeal granulomatous disease. We performed a systematic literature review of the last 20 years on LTB and also present a case from our hospital with special focus on voice assessment. The literature review includes a total of 308 cases, involving studies from seven countries. In all, 64.3% of patients were males. At the time of diagnosis, the mean age range was 44.6-56.5 years. Odynophagia, hoarseness and dysphonia were the most frequent presenting symptoms. In 64 cases, the initial suspicion was laryngeal cancer. Most cases involved the true vocal folds. In about a third of cases a primary LTB with normal chest radiographic was found. Although it can be treated successfully, LTB may cause significant changes in voice quality. Nowadays, LTB is rarely diagnosed and may be confused with laryngeal cancer, it should also be included in the differential diagnosis with all other chronic benign inflammatory and non-inflammatory diseases of the larynx.

KEY WORDS: dysphonia, laryngeal tuberculosis, larynx, voice quality, voice assessment

RIASSUNTO

La tubercolosi laringea (LTB) è una rara manifestazione della tubercolosi (TB), e rappresenta l'1% di tutti i casi di TB. Nonostante sia una patologia di raro riscontro, rappresenta la malattia granulomatosa laringea più frequente. In questo studio riportiamo una revisione sistematica della letteratura degli ultimi 20 anni sulla LTB e descriviamo un caso clinico proveniente dal nostro ospedale, con particolare attenzione alla valutazione della voce. La revisione della letteratura comprende complessivamente 308 pazienti provenienti da sette diverse nazioni. Il 64,3% erano maschi. Al momento della diagnosi il range di età media era di 44,6-56,5 anni. Odinofagia, raucedine e disfonia sono i sintomi di presentazione più frequenti. In 64 casi il sospetto iniziale era di tumore laringeo. La maggior parte dei casi ha coinvolto le corde vocali vere. In circa un terzo dei casi è stata riscontrata una LTB primaria con una radiografia toracica non patologica. Anche se trattata con successo, la LTB può causare importanti cambiamenti nella qualità della voce.

Al giorno d'oggi la LTB è raramente diagnosticata e può essere spesso confusa con il cancro della laringe, inoltre dovrebbe essere considerata nella diagnosi differenziale delle malattie benigne croniche infiammatorie e non infiammatorie della laringe.

PAROLE CHIAVE: *disfonia, tubercolosi laringea, laringe, qualità vocale, valutazione della voce*

Introduction

Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium tuberculosis. It typically involves the lungs, but may also affect other organs such as the larynx. Occasionally laryngeal tuberculosis (LTB) can also be

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Correspondence
Andrea Migliorelli
Department of ENT & Audiology, University Hospital of Ferrara, via A. Moro 8 (Cona), 44100 Ferrara, Italy
E-mail: mglndr1@unife.it

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the first clinical manifestation of an asymptomatic active pulmonary TB. The pathogenesis of LTB and clinical syndrome was first described by Dworetzky [1] in 1941 and later by Auerbach [2] in 1946. Nowadays LTB is a rare presentation of TB, overall accounting for 1% of cases, while in the first decades of the 20th century it accounted for 25% [3,4]. Despite its low percentage of incidence, LTB is the most frequent granulomatous disease affecting the larynx [5].

Over the last 20 years there has been a worldwide recrudescence of tuberculosis, mostly connected to the spread of AIDS and other immunodeficiency conditions. Other risk factors are poor quality of life, malnutrition, alcohol abuse and smoking [4,6,7]. The male to female ratio for LTB is around 2.5:1 with a mean age of 49.5 years. The most frequent symptoms are hoarseness, dysphonia, weight loss, cough, dysphagia and odynophagia [3,7,8].

LTB infection determines an exudation in the subepithelial space with subsequent infiltration of round cells which results in fibrosis. This scarring leads in most cases to irreversible changes in vocal fold structure, with consequent alteration of glottic vibration and dysphonia [9].

Misdiagnosis is not rare because endoscopic examination is often characterised by a exophytic and/or ulcerous lesion surrounded by erythema, mimicking malignant laryngeal disease.

Case series have found that both diseases can affect the larynx simultaneously [6,10]. Clinicians should be aware of this unusual localisation of TB in differential diagnosis.

Herein, we performed a systematic literature review of the last 20 years on LTB. In addition, we describe a case diagnosed and treated in our hospital with special focus on voice assessment.

Materials and methods

In accordance with the European Laryngological Society (ELS) guidelines, the phoniatric protocol in our centre includes the use of modified GRBAS scale (Grade, Roughness, Breathiness, Asthenia and Strain) for auditory perceptual voice assessment. The evaluation is performed by two experienced phoniatricians. We adopted the Voice Handicap Index-10 (VHI-10) administration for subjective voice evaluation and Maximum Phonatory Time (MPT) calculation as aerodynamic index [11-14]. In addition, jitter and shimmer were collected from acoustic analysis of the voice. Moreover, we provided a morphological and dynamic evaluation of the vocal folds, with flexible digital fiberoptic endoscopy and stroboscopy. The vascular pattern of the lesion was evaluated with Narrow Band Imaging (NBI). The equipment used consisted of: Video Rhinolaryngoscope Olympus ENF-VQ, stroboscopy by ATMOS (Endo Stroboscope L video Stroboscopy Otolaryngology) and NBI by Olympus (Visera Pro CLV-S40Pro).

A detailed search in PubMed and Medline on LTB from January 2000 to December 2021 was performed. The search yielded a total of 357 relevant articles. We included only papers in English language containing a series of 15 or more patients. The number of cases, sex, age, country, clinical presentation, larynx localisation, fibre-endoscopic findings, pulmonary active or inactive TBC, voice analysis, therapy and follow-up were collected and compared in the present review.

Articles in which these data were missing have been excluded from the study. Ten case series were included in the analysis, for a total of 308 cases.

Results

Case report

A 67-year-old Italian woman referred to the Otolaryngology Department of the M. Bufalini Hospital, Cesena, Emilia-Romagna, Italy. Her main complaint was one-year history of dysphonia that had worsened in the last two months. Her medical history included smoking (about 40 cigarettes a day for the past 15 years). She denied alcohol consumption and congenital or acquired immunodeficiency. She was unaware of TB contacts and had not travelled to endemic areas, while a possible exposition could have been related to her occupation, being a physician. The patient had no respiratory symptoms, weight loss, fever or other systemic manifestations. A laryngoscopy examination (Fig. 1) revealed a moderate Reinke's edema of the right vocal fold and a diffuse hyperplasic tumour-like aspect of the true left vocal fold, which extended posteriorly to the vocal process of the ipsilateral arytenoid. No granulomatosis or ulcerative lesions were detected. The laryngostroboscopy revealed a stiff left vocal fold with reduced mucosal wave, while motility and glottic closure were preserved [15]. Narrow Band Imaging (NBI) examination did not reveal any specific vascular patterns.

At the first visit the patient presented G2R2B1A0S2, VHI-10: 27, MPT 6 sec, Jitter 8.6% and Shimmer 18.59%.

Chest X-Ray did not show any pathological findings. A neck CT scan with Contrast Enhancement (CE) (Fig. 2) was also performed and confirmed thickening and CE at the level of the posterior superior third of the left hemilarynx involving the false cord and the left true vocal fold, with obliteration of the ipsilateral laryngeal ventricle and paraglottic space invasion. Despite a large and deep extension of the lesion, the CE was modest and superficial. No erosion of the hyoid bone and laryngeal cartilages was noticed. The anterior commissure was preserved.

A direct microlaryngoscopy was performed. During the procedure, careful laryngeal exploration revealed a lesion of the left hemilarynx that extended from the posterior third of the true vocal fold to the floor of the ventricle and to the arytenoid.

Due to the deep extension of the disease revealed by CT and the lack of superficial lesions, in order to avoid taking a non-diagnostic biopsy sample, four deep biopsies were collected with a CO2 laser.

The histopathological report described chronic focally necrotising granulomatous inflammation. Additional histopathological investigations included Ziehl-Neelsen staining for alcohol-acid fast bacilli, Congo red staining and cytokeratin immunohistochemistry for squamous cell carcinoma: all were negative.

Considering the biopsy findings and the most probable inflammatory granulomatous laryngeal diseases [16] (TB, sarcoidosis, fungal laryngitis and Wegener granulomatosis), the patient was evaluated by a pneumologist who prescribed a sputum test even if alcohol-acid fast bacilli research and X-Ray of the lungs were negative. The sputum test and the culture examination revealed the presence of acid-fast bacilli. The patient was then referred to an infectious disease specialist, who clinically suspected an active pulmonary TB, confirmed by pulmonary High-Resolution CT (HRCT) scan.

The treatment was completed in 9 months and consisted of: ethambutol, pyrazinamide, rifampicin and isoniazid for 2 months, and then rifampicin and isoniazid. Following the latter treatment which caused hepatoxicity, isoniazid was discontinued and restarted at a lower dose [17].

After the specific therapy for TB, the patient had complete resolution of the lung and laryngeal pathology confirmed by negative CT scan. A laryngoscopy examination at 12 months from the biopsy and three months from the end of systemic treatment was performed (Fig. 1). The left vocal fold appeared diffusely scarred and slightly swollen. Laryngostroboscopy showed a slightly reduced mucosal wave, while vocal folds motility and glottic closure were preserved. NBI examination was analogous to pre-treatment evaluation.

Voice evaluation after treatment revealed a substantial improvement of all parameters, suggesting significant voice improvement: G1R1B0A0S0, VHI-10: 2, MPT greater than 10 sec, Jitter 5.12% and Shimmer 13.86%.

Literature review

Ten articles regarding LTB were identified in the English literature that matched our inclusion criteria, with a total of 308 cases (Tab. I).

The sample was very heterogeneous in terms of country of origin: 3 studies were from China, 2 from Japan and 1 from Taiwan, South Korea, India, Poland and Brazil each.

Of the 308 patients, 198 (64.3%) were males and 110 (35.7%) were females. At the time of diagnosis, the mean age range was 44.6-56.5 years.

Odynophagia or pharyngodynia (174/308), hoarseness (130/308), dysphonia (125/308) and cough (119/308) were the most frequent presenting symptoms.

Occasionally, the first reported symptoms were dysphagia (35/308), shortness of breath/dyspnoea (35/308) or systemic symptoms (19/308), one patient presented to clinical observation with stridor.

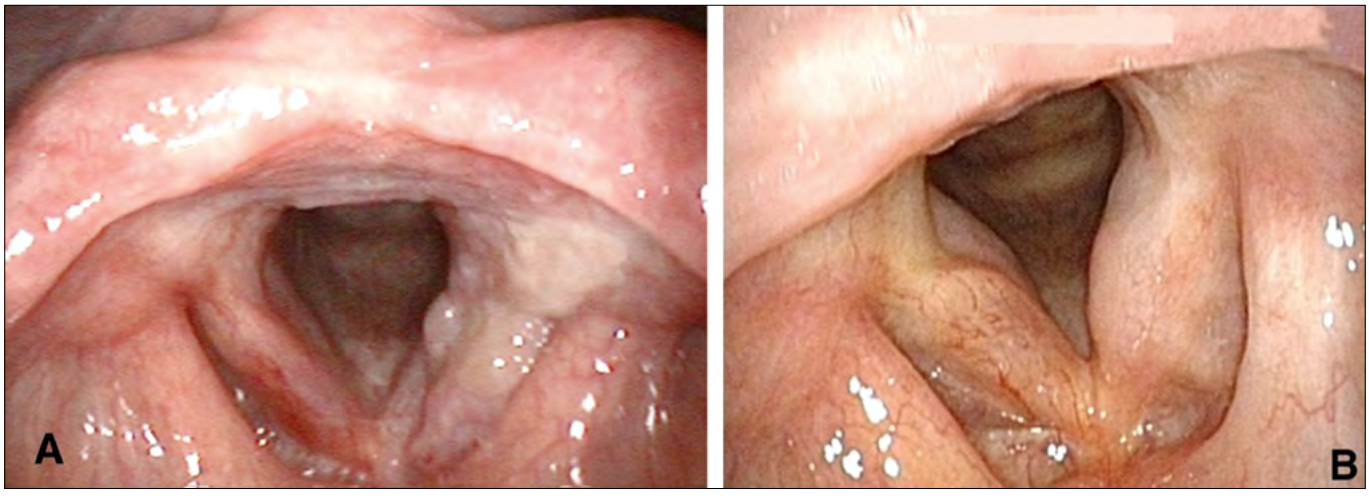

Figure 1. Laryngoscopy: (**A**) pre-treatment laryngoscopy showed a moderate Reinke's oedema of the right vocal fold and a diffuse hyperplasic tumour-like aspect of the true left vocal fold, extended posteriorly to the vocal process of the ipsilateral arytenoid; (**B**) laryngoscopy after three months from the end of the systemic treatment revealed a scarred and tumefied left vocal fold.

Table I. Literature review.

Author	Country	No.	Sex (M/F)	Mean age (yrs ± DS)	Symptoms	Fibroscopic findings	Single/ Multiple (S/M)	Larynx localization
Nishiike, 2002 [8]	Japan	15	M: 11 F: 4	51.1 ± 3.7	Hoarseness: 11 Cough: 10 Odynophagia or pharyngodynia: 9 Systemic symptoms: 7 Dysphagia: 4	Ulcerative lesions: 7 Granulomatous lesions: 5 Nonspecific inflammatory lesions: 3	S: 6 M: 9	Epiglottis: 8 True vocal fold: 10 False Vocal fold or Ventricle: 8 Arytenoid: 7
Lim, 2006 [23]	South Korea	60	M: 39 F: 21	49.7	Hoarseness: 58 Cough: 31 Odynophagia: 24	Granulomatous: 22 Ulcerative: 11 Polypoid: 16 Nonspecific: 11	S: 37 M: 23	True vocal fold: 46 False vocal fold: 18 Epiglottis: 12 Arytenoids: 7 Posterior commissure: 10
Wang CC 2007 [20]	Taiwan	26	M: 19 F: 7	47.11 ± 18.23	Hoarseness: 22 Cough: 12 Odynophagia: 8 Shortness of breath: 5 Sistemic symptoms: 3 Cervical lymphoadenopathy: 2 Stridor: 1	Mucosa white lesion: 10 Ulceration: 13 Granulomatous tumours: 13 Nonspecific inflammation: 7	M: 8 S: 18	True vocal fold: 21 Posterior commissure: 10 False vocal fold: 10 Epiglottis: 7 Subglottis: 1
Ling L 2010 [30]	China	19	M: 15 F: 4	44.6	Hoarseness: 12 Sore throat: 3 Odynophagia: 6 Systemic symptoms: 3	Polypoid lesion: 4 Diffuse congestion: 3 Rough tumour-like lesion: 4 Diffuse papillary lesion: 8	S: 11 M: 8	One vocal fold with irregular closure gap: 4 Epiglottis: 3 One true vocal fold: 4 Multiple lesions in bilateral false vocal folds and true vocal folds: 8
Bruzgielewicz, 2014 [21]	Poland	20	M: 14 F: 6	56.5 ± 8.5	Hoarseness: 18 Cough: 9 Dysphagia: 4 Dyspnoea: 2 Systemic symptoms: 6	Ulcerative tumour: 8 Papillomatous tumour: 7 Chronic hypertrophic laryngitis: 5	S: 15 M: 5	Vocal folds: 12 Posterior commissure: 8 Vestibular folds: 5
Kurokawa, 2015 [24]	Japan	17	M: 9 F: 8	51.4 ± 14.0	Hoarseness: 15 Odynophagia: 7 Abnormal sensation syndrome of the throat: 4 Cough: 13	Perichondritic: 3 Ulcerative: 6 Granulomatous: 6 Polypoid: 1 Nonspecific inflammatory: 1	S: 1 M: 16	True vocal fold: 16 Arytenoids: 6 False vocal fold: 4 Epiglottis: 4
Reis, 2016 [31]	Brazil	36	M: 28 F: 8	47.08 ± 14.75	Dysphonia: 32 Cough: 32 Odynophagia: 27 Dyspnoea on exertion: 19 Dysphagia: 11 Dyspnoea at rest: 5 Reflex otalgia: 2	Granulomatous lesion: 24 Nonspecific inflammatory lesion: 19 Ulcerated lesion: 14 Erosive lesion: 8	S: 8 M: 28	Epiglottis: 21 Aryepiglottic fold: 22 Arytenoid region: 18 Interarytenoid region: 12 False vocal fold: 24 True vocal fold: 32
Zhao, 2017 [18]	China	61	M: 23 F: 38	47.7	Voice problems and aphonia: 57 Sore throat and painful swallowing: 49 Both hoarse voice problems/aphonia and sore throat/painful swallowing: 42 Cough and sputum production: 20 Dysphagia: 9	Pale edema: 24 Hyperplasia: 34 Ulcerative lesion: 3	-	Vestibular folds: 4 Vocal folds: 20 Aryepiglottic folds: 8 Epiglottis: 4

continues ▶

Table I. Literature review (*follows*).

Author	Country	No.	Sex (M/F)	Mean age (yrs ± DS)	Symptoms	Fibroscopic findings	Single/ Multiple (S/M)	Larynx localization
Agarwal, 2019 [32]	India	15	M: 12 F: 3	49	Hoarseness: 6 Odynophagia: 6 'Change in voice': 3	Ulceroproliferative lesion: 10 Exophytic growth: 5	S: 15 M: 0	Epiglottis: 8 True vocal fold: 4 false vocal fold: 1 Anterior commissure: 1 Pyriform sinus: 1
Zang, 2020 [33]	China	39	M: 28 F: 11	47.5 ± 15.8	Dysphonia including hoarseness and aphonia: 33 Sore throat including odynophagia: 26 Dyspnea: 4 Dysphagia: 7	Nonspecific inflammatory lesion: 22 Ulcerative lesion: 47 Exophytic lesion: 55	S: 8 M: 31	Vocal folds: 33 False vocal folds: 22 Arytenoid region: 23 Aryepiglottic fold: 17 Interarytenoid region: 11 Epiglottis: 25 Subglottis: 2

Granulomatous lesion was found at laryngeal fibroendoscopy in 104 cases, ulcerative lesion in 119 findings and non-specific inflammatory pattern in 92 cases. Less frequently, laryngeal lesions had a polypoid (n = 21), papillomatous tumour (n = 12), or mucosal white lesion appearance (n = 10). A single lesion was found in 119 patients, whereas multiple lesions were identified in 128 cases. In 64 cases, the initial suspicion was for laryngeal cancer, and a biopsy was performed.

The true vocal folds were involved in 163 cases, the false vocal folds and ventricle in 104 patients and the epiglottis in 92 cases. The remaining cases involved arytenoid (n = 61), aryepiglottic fold (n = 47), interarytenoid region (n = 23), posterior commissure (n = 28) and subglottis (n = 3).

Chest X-ray or high resolution computed tomography (HRTC) was performed in all patients and evidence of active lung TBC was confirmed in 164 cases. In 45 patients, an inactive TBC or signs of previous disease was detected. Primary LTB with normal chest radiography was found in 101 cases.

Where specified, the diagnosis was made by Purified Protein Derivative (PDD), sputum testing, or laryngeal tissue histopathology, and confirmed by isolation of Mycobacterium tuberculosis in laryngeal tissue culture.

Discussion

LTB is an uncommon finding in otolaryngology practice, although it is the most frequently reported granulomatous disease in the larynx [5]. LTB is a rare pathology, resulting in a limited number of cases in the literature. To the best of our knowledge, this is one of the most complete reviews in the literature on LTB, involving studies from seven countries and three continents.

In the literature, a predominance of males was described (M:F = 2:1), and only one article reported a higher percentage of females [18].

Two aetiopathogenetic mechanisms of LTB have been described to explain the cause of laryngeal localisation: the first is the bronchogenic one. The larynx is directly contaminated by bacilli-rich pulmonary secretions, and therefore laryngeal involvement occurs secondary to pulmonary involvement. The posterior larynx is the most affected area in secondary LTB because it is where infected secretions most frequently accumulate. The second is the haematogenic route. Blood or lymphatics carry bacillus to the larynx prevalently affecting the anterior region [19].

Known risk factors are HIV, poor quality of life, malnutrition, alcohol abuse and smoking habit [4,6,7].

Odynophagia or pharyngodynia, hoarseness and dysphonia were present in the majority of cases at diagnosis. Respiratory failure due to vocal fold immobility is a rare presenting symptom that can sometimes lead to emergency tracheotomy [20]. It is important to underline that the risk factors and main presenting symptoms of LTB are the same as those of laryngeal cancer. Furthermore, it should be kept in mind that the two diseases can also coexist [21].

In the suspicion of a LTB and even more in the suspicion of malignant laryngeal disease, fibrolaryngoscopy is mandatory. NBI can help in the diagnostic process. The physician should consider pathologies other than laryngeal cancer (such as LTB) if NBI is negative for a typical tumour pattern [22].

The lack of a universally-accepted fibroendoscopic classification makes evaluation and comparison of the presenting laryngeal lesions reported in the literature particularly difficult. According to Suetaka et al. [10], almost all studies refer to granulomatous, ulcerative and non-specific inflammatory lesions as the most frequently presenting laryngeal lesions. Other authors have added other lesional patterns to this classification such as polypoid or mucosal white lesions [20,23].

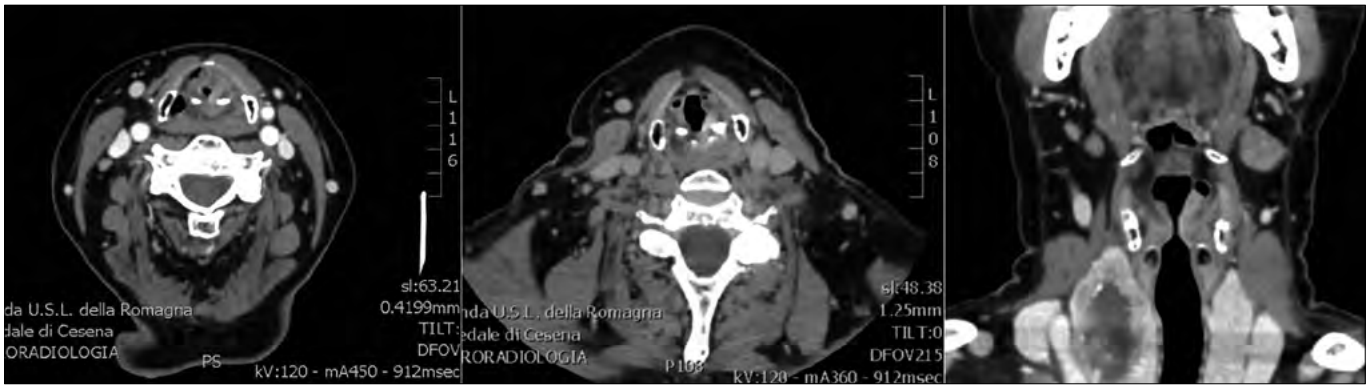

Figure 2. Neck CT scan with contrast enhancement.

In our opinion, endoscopic classification should go beyond the three most frequent lesions mentioned above, considering that in countries where the incidence of LTB is lower, the disease may occur with less common presentations, as in the case we described.

Considering the site of presentation, in 163 cases the LTB affected the true vocal fold, while the other most common sites were false vocal fold (n = 104), epiglottis (n = 92) and arytenoid (n = 61). LTB can also compromise motility and mucosal vibration of the vocal cords. The literature suggests that laryngeal lesions can be multiple or single without substantial differences in terms of incidence. Jae-Yol Lim et al. [23], in a review of 60 patients, reported that multiple lesions are mostly associated with the ulcerative type. Granulomatous, polypoid and non-specific inflammatory types are usually associated with single lesion presentations.

In addition, other authors believe that protracted disease may involve multiple areas of the larynx with the expression of more than one lesion [24].

If LTB is suspected, all diagnostic and therapeutic procedures should be performed while wearing an FFP3 face mask to reduce the risk of infection to operators [3].

According to the literature, once suspicion of LTB is established by fibre endoscopic examination, a chest radiograph or preferably HRTC should be performed to detect pulmonary TB. In most cases, active TB is diagnosed, whereas the finding of a primary LTB is less frequent.

As previously mentioned, laryngeal tuberculosis and laryngeal cancer may have similar clinical and endoscopic findings and clinicians should always consider LTB, even in non-endemic areas. Furthermore, it should be emphasised that LTB has to be included in differential diagnosis with all other inflammatory and noninflammatory benign chronic diseases of the larynx. Among the granulomatous diseases affecting the larynx, those which are more clinically relevant are TB, sarcoidosis, fungal laryngitis, Wegener granulomatosis, leprosy, syphilis and rhinoscleroma [16].

As a consequence, biopsies represent an essential tool to make a proper differential diagnosis between a suspected cancer, laryngeal tuberculosis, or other granulomatous diseases. The next step for correct diagnosis is bacteriological and histological examination on laryngeal biopsies [25,26]. The first examination can detect the bacterium (Mycobacterium tuberculosis) with Ziehl-Neelsen staining. In some cases, it is also possible to achieve slow-growing colonies with an ivory-white cauliflower aspect if the specimen is placed on a special culture medium known as Lowenstein-Jensen. On the other hand, histological examination should detect the tuberculous follicle characterised by a peripheral zone made up of Langhans cells, epithelioid cells and lymphocytes, and a central caseous zone [6,25,26]. Furthermore, we believe that even when the alcohol-acid fast bacilli research and X-Ray of the lungs are negative, if histologic findings are suggestive of chronic inflammatory pathology, further investigation and research including a sputum test should be performed, as in the case we described.

Finally, we want to emphasise that although LTB is rare and insidious, correct and rapid diagnosis can be achieved thanks to the collaboration of several healthcare professional including an ENT, pulmonologist, infectious disease specialist, pathologist and microbiologist.

As reported in our case and in agreement with the literature, treatment involves the use of the 4 antituberculosis drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) with posology and dosage reported in the guidelines of each individual centre.

Dysphonia is one of the main symptoms and most invalidating for the patient's quality of life. Despite this, little focus has been placed on evaluation of post-treatment voice outcomes to date.

We believe that it is very important to perform accurate

and multidimensional voice analysis both before and after phonosurgical procedures for all laryngeal disorders. In our hospital, according to ELS recommendations, subjective (VHI-10 and GRBAS) and objective (MPT, Jimmer and Shimmer) measures were collected before and after surgery [11-14].

Moreover, it is important to perform laryngostroboscopy to investigate vocal fold motility, mucosal wave and glottic closure [15].

Areas of ambiguity and controversy still exist regarding the efficacy of antituberculous therapy in the recovery of dysphonia. Yelken et al. [27] postulated that TB treatment results in significant improvement in voice quality in all patients. Conversely, Ozudogru et al. [28] stated that an irreversible fibrotic change in the vocal fold caused by LTB results in persistence of dysphonia even after treatment. Currently, specific literature data on post-treatment voice quality are scarce; further studies on this topic should be conducted in the future. In our patient, there was improvement in voice quality after antituberculous treatment, but a mild degree of dysphonia persisted.

Some authors describe speech therapy as a useful approach to improve voice quality after LTB, and we concur [29]. We proposed speech therapy for vocal rehabilitation to our patient, but she refused as she was satisfied with her vocal result.

In our experience, in cases where voice quality does not improve despite speech therapy, the residual scaring (not only as a result of LTB) might be successfully treated with a phonosurgical procedure.

Conclusions

This review is one of the largest in the literature on LTB, which represents the most frequent granulomatous disease in the larynx and usually affects the true vocal folds. Odynophagia or pharyngodynia, hoarseness and dysphonia are the most common presenting symptoms.

The importance of differential diagnosis of this pathology with laryngeal cancer and other benign pathologies of the larynx should be emphasised. Once a suspicion of LTB arises, fibrolaryngoscopic evaluation (possibly with NBI), laryngeal biopsy, sputum test and imaging of the chest should be performed.

LTB results in fibrosis of the lamina propria and therefore complete recovery of voice quality after treatment is not guaranteed. In our experience, a detailed voice analysis should be performed before and after LTB treatment. After complete recovery from the disease, further improvement of the voice may be achieved with speech therapy and a phonosurgical procedure.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

AM and MS: original idea, wrote the paper, conceived and performed the analysis; TM, AB and DB: collected data and performed literature search; MF and FE: contributed to data analysis. All authors read and approved the final version of the manuscript.

Ethical consideration

No Ethical Committee approval was required for this study. The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from each participant/patient for study participation and data publication.

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