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# Laryngeal tuberculosis – case report and systematic review

## *Tuberculoza laringiană – prezentare de caz și review sistematic*

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**Abstract**

*Romania has the highest notification rate of tuberculosis (TB) in the European Union, five times the reported average. Nonetheless, the incidence of laryngeal tuberculosis (LTB) is low, most cases being diagnosed only in the large medical centers of the country. The absence of pathognomonic symptoms of TB and the modification of its clinical pattern often lead to mistaken or late diagnosis, with late treatment, which increases the contagious risk. We report a case of LTB in an HIV-negative female patient, 55 years old, with ulcerative laryngeal injuries and active pulmonary tuberculosis, in the absence of other non-tuberculous conditions.*

***Keywords:*** *laryngeal tuberculosis, dysphonia*

**Rezumat**

*România înregistrează cea mai mare incidență a tuberculozei (TB) din Uniunea Europeană, de cinci ori peste medie. Cu toate acestea, incidența tuberculozei laringiene (LTB) este mică și majoritatea cazurilor ajung să fie diagnosticate doar în centrele medicale mari ale țării. Absența simptomelor patognomonice pentru tuberculoză și modificarea tiparului clinic al bolii conduc frecvent la diagnosticarea greșită și întârziată, cu tratament întârziat, ceea ce determină creșterea riscului de contagiune. Prezentăm un caz de LTB la o pacientă de sex feminin, fără infecție HIV asociată, în vârstă de 55 de ani, cu leziuni laringiene ulcerate și cu tuberculoză pulmonară activă, în absența altor comorbidități non-tuberculoase.*

***Cuvinte-cheie:*** *tuberculoză laringiană, disfonie*

## Introduction

Romania has the highest tuberculosis (TB) notification rate in the European Union (EU), five times over the average, contributing with 20% of the TB cases reported in the EU, while it has only 4% of the EU population[1]. The latest report of the European Centre for Disease Prevention and Control (2017) states that in 2015 there were 16,000 cases of TB, while more than 1000 of these patients die from the disease[2]. Romania also holds the first place in the EU for the number of TB cases resistant to treatment (over 500 cases yearly). However, in the last years, Romania made good progress in the control of TB, the incidence decreasing from 29,000 cases in 2006 to 16,000 in 2015[1,2].

Though the lung is the most frequently affected, TB may set on any organ. In 2015, in Romania, 16% of the TB cases were extrapulmonary[2]. Of these, the ones involving the ear, nose and throat may manifest as cervical lymphadenopathy, otitis media, laryngitis, pharyngitis and nasal TB[3,4]. It is not uncommon that TB located to other organs should mimic other diseases, thus delaying the diagnosis, or, even worse, lead to wrong therapeutic decisions[5].

Literature data indicate that laryngeal tuberculosis (LTB) represents generally less than 2% of extrapulmonary TB cases[6,7]. The correct incidence of LTB for patients with pulmonary TB is difficult to be determined because systematic otorhinolaryngologic evaluation is not usually conducted[8,9].

We report a case of LTB in a human immunodeficiency virus-negative female patient, aged 55 years, with ulcerated laryngeal injuries and active pulmonary TB, without other non-tuberculous diseases.

## Case presentation

A 55-year-old female, non-smoker, of low social-economic status, checks into our clinic for moderate dysphonia suddenly appeared two weeks before, odynophagia, productive cough, lack of appetite, and weight loss of about 16 kg in the past month.

The patient history includes miliary lung tuberculosis diagnosed approximately a year ago and treated with rifampicin (R) 600 mg, isoniazid (H) 300 mg, pyrazinamide (Z) 1500 mg and ethambutol (E) 1600 mg daily for 3 months. The treatment continued for another 5 months in an intermittent mode (3/7 days) with R 600 mg and H 900 mg. The microscopic negativity was noticed after two months from the start of treatment. The patient was followed-up monthly by the pneumologist. After four months from the end of treatment, the patient was referred by her pneumologist to the ENT unit with the suspicion of laryngeal neoplasm.

Laryngoscopy performed with rigid Karl Storz Telelaryngo-pharyngoscope 70° revealed edema and diffuse congestion of the larynx, bilateral ulcerations, and hypomobile vocal cords (Figure 1). There was no evidence of any mass or vocal cord paralysis. No lateral cervical or submandibular adenopathy was found either.

Under sedation and local analgesia with lidocaine spray 10%, an endoscopy-guided laryngeal biopsy sample was collected using the endoscopic tweezers.

Taking into account the history of TB and the suspicion of LTB, the patient was immediately referred back to the pneumophthisiology clinic for further investigation and follow-up until the establishment of a certainty diagnosis. Chest X-ray revealed disseminated micronodular opacities (Figure 2).

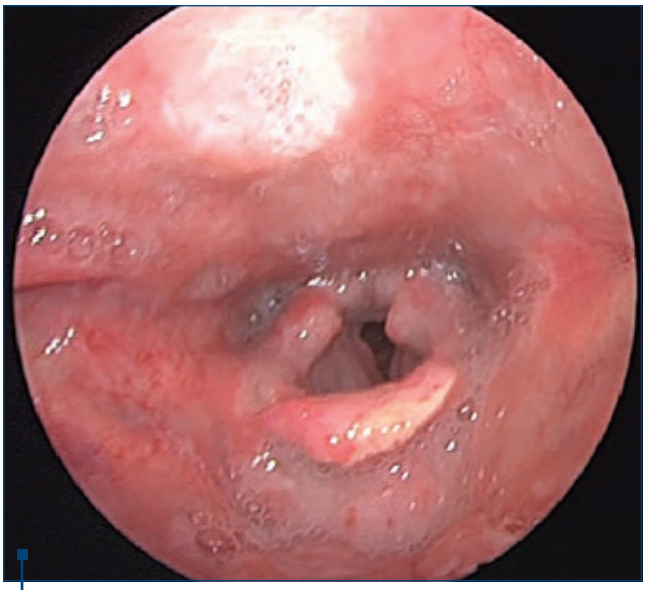

**Figure 1.** *Laryngeal endoscopy: diffuse edema and congestion at the larynx level, bilateral ulcerations*

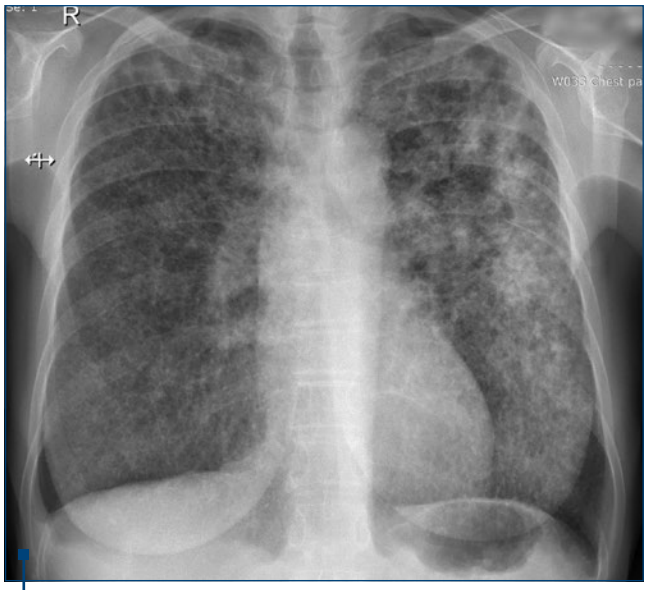


**Figure 2.** *Chest X-ray, AP incidence: disseminated micronodular opacities*

TB was confirmed the same day by auramine-rhodamine stained sputum smear microscopy[10] (Figure 3) and Xpert MTB/Rif assay (Cepheid GeneXpert, Sunnyvale, CA, US), and after eight days by *M. tuberculosis* positive culture in Bactec MGIT 960 system (Becton Dickinson – automated mycobacterial detection system). Xpert MTB/Rif result revealed no resistance to rifampicin; susceptibility to rifampicin and isoniazid was confirmed by phenotypic assay[11].

The result of the histopathological test (Figure 4 A, B, C) confirmed the granulomatous nature of the lesions: mucosa with ulceration areas and reactive alterations, containing in the lamina propria multiple granulomatous lesions formed of lymphocytes, epithelioid cells and multinucleated Langhans-type giant cells.

The diagnosis of LTB was confirmed one week after the first visit and the patient was referred to the special healthcare unit for antituberculous treatment. The patient was treated with a relapse regimen with H 300 mg, R 600 mg, Z 2000 mg, E 1600 mg, and amikacin 1000 mg daily for two months. The treatment continued for another 10 months whitout amikacin (one month with H 300 mg, R 600 mg, Z 2000 mg, E 1600 mg, 7/7 and 9 months with H 900 mg, R 600 mg, E 2000 mg, 3/7).

The microscopic negativity was noticed after two months from the beginning of treatment. The patient was followed-up by the ENT and lung specialists for 6 months. Four months after the initiation of therapy the clinical and endoscopic findings documented disease remission.

## Discussion

In the pre-antibiotic era, LTB was perceived as a fatal disease: "all were doomed to die; the occurrence of the disease in the larynx was the warrant of death"[12]. The typical patient was 20-40 years old, with ulcerations in the larynx and advanced cavitary lung TB, fever, weight loss, night sweat, fatigue, hemoptysis and dyspnea[13-16]. In the 1920s, in England, LTB was considered to be the most common disease of the larynx[12]. With the emergence of antituberculous drugs, the incidence of all forms of TB decreased. Toward the end of the 20th century, LTB was brought back to attention by reports indicating a change in the clinical picture, especially in developed countries[16].

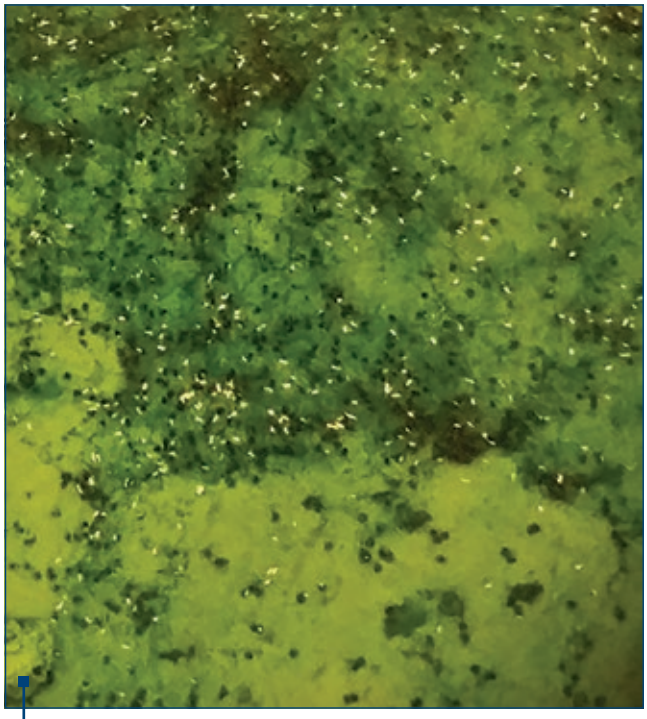

**Figure 3.** *Aspect of acid fast bacilli in UV microscopy (magnification 200x)*

**Pathophysiology**. LTB may result from direct bronchogenic, hematogenic or lymphogenic spread[17]. According to the majority of studies, LTB occurs mostly by a direct bacilli spread, from a bronchial site through bronchial secretion to the larynx (bronchogenic theory)[18,19]. In our patient, the relapse of pulmonary TB with secondary involvement of the larynx was the most probable mechanism of onset.

The true vocal folds are directly related to voice because they are the oscillatory component in voice production[20].

Because the true vocal folds are mainly affected in LTB, dysphonia is usually the main symptom[21]. Odynophagia was reported in case of the involvement of the epiglottis, aryepiglottic folds and arytenoid regions[8]. These laryngeal sites have stronger movements during deglutition, therefore a higher potential of generating painful stimuli[22]. Considering the extensive laryngeal injuries in these structures, our patient presented both dysphonia and odynophagia.

The glosso-epiglottic folds, adjacent to the epiglottis, present a higher potential for the accumulation of the secretions from the lower airways, which can remain for a long time restrained there, contributing to the development of infection and illness[8]. On the other hand, by classical acceptance, the posterior part of the larynx is more frequently affected due to the accumulation of infected secretions in patients who spend more time lying in bed[16]. However, this injury pattern is rarely seen nowadays, recent studies showing that the anterior half of the larynx is affected twice more often than the posterior half[7].

**Clinical presentation**. The disease occurs predominantly around the age of 50, mainly in men[23-25]. Studies in the last years have indicated a less strong association between LTB and active pulmonary TB[26,27].

Dysphonia is the common symptom in laryngeal TB, with some discomfort and even pain in swallowing[12,28-30]. The grade of dysphonia varies from moderate to severe[21]. The patient may also present a negative body weight curve, lack of appetite, borderline fever, and asthenic hypodynamic syndrome. Dyspnea on exertion was associated with the extent of the laryngeal lesions[8].

The examination of the larynx may reveal multiple or unique injuries, bilateral or one-sided[31]. The lesions of the larynx are variable and may appear as ulcerative, granulomatous, polypoid or non-specific inflammatory[32]. It seems that patients with active pulmonary TB present mostly multiple granulomatous, ulcerative lesions, while those with a normal pulmonary status have non-specific, unique lesions[19,32]. Thus, LTB may mimic laryngeal carcinoma, chronic laryngitis or laryngeal candidiasis, as well as other infectious or autoimmune granulomatous diseases[33,34]. Particularly in countries with low TB incidence, the diagnosis of carcinoma of the larynx is initially made[5]. LTB is an extremely rare condition in childhood, but it may take various clinical forms: palato-pharyngo-tonsillar membrane, painful edematous pharynx and larynx, or membrano-ulcerative lesions[35,36].

**Laboratory**. As a rule, the first test performed is the laryngeal biopsy. We did the same in this case, taking into account the history of TB and the somewhat suggestive clinical presentation. After the biopsy, we directed the patient to the pneumophthisiology clinic in order to continue investigations and remain in isolation till the certainty diagnosis.

Chest X-ray is a very useful complementary test as the images that indicate a pulmonary TB in a patient with laryngeal injury will reinforce the suspicion of LTB till histopathological confirmation[25], which is very important from an epidemiological viewpoint.

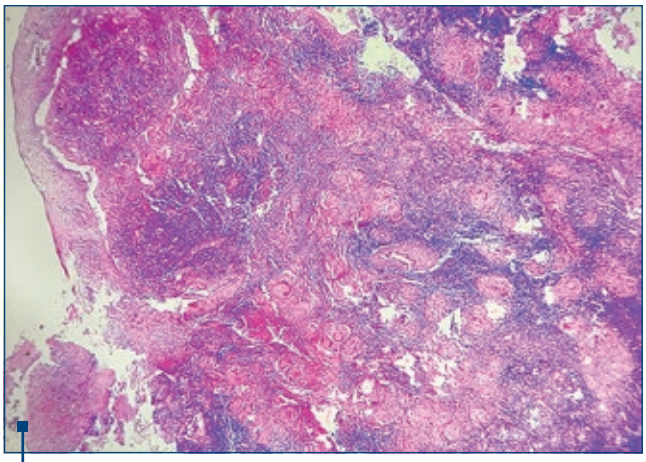

***Figure 4A.*** *Hematoxylin-eosin (HE) stain, magnification 4x: granulomatous inflammation in the larynx wall*

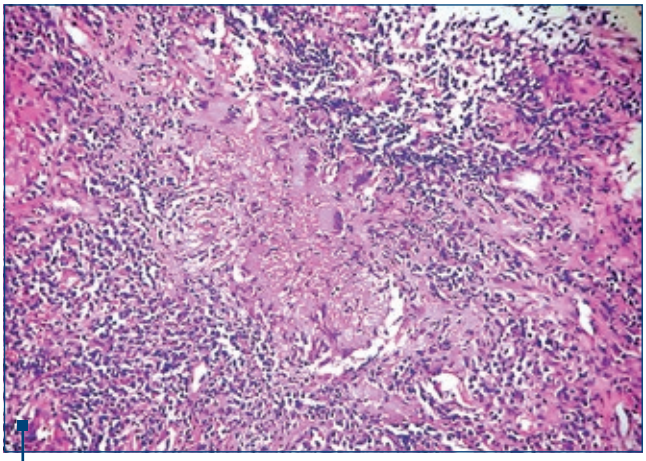

***Figure 4B.*** *HE stain, magnification 10x: granuloma with central necrosis, multinucleated giant cells and lymphocytes around*

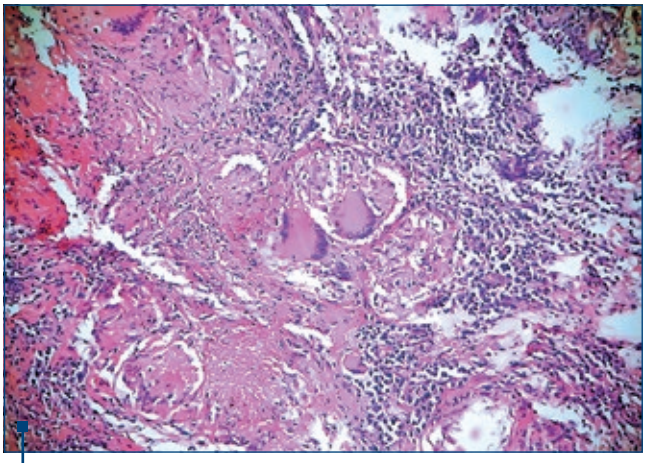

***Figure 4C.*** *HE stain, magnification 20x: granuloma with central necrosis*

Sputum microscopy is the non-invasive procedure for a rapid confirmation of the presence of acid-fast bacilli in the specimen and a molecular biology method, GeneXpert in our case[37].

**Diagnosis**. Certainty diagnosis is obtained by correlating clinical and paraclinical findings. Negative results of the bacteriological tests in some LTB cases without lung involvement demonstrate the importance of laryngeal biopsy[8]. The

presence of a granuloma with caseous necrosis suggests TB. Moreover, the coexistence of laryngeal malignant neoplasms with pulmonary TB has also been described[18,38], which makes pathological diagnosis even more important. On the other hand, histopathological diagnosis may be flawed by pseudoepithelial hyperplasia that mimics squamous cell carcinoma[28]. It is mandatory to correlate all the data in order to establish an accurate diagnosis.

There is no evidence that delayed diagnosis worsens laryngeal injuries[8,25], but early diagnosis is crucial in disease transmission control.

**Treatment**. The treatment of LTB is initiated and conducted by the pneumologist. Surgery is reserved only for cases of airway compromise.

The majority of studies show that the response of LTB to antituberculous medication is good[32]. The larynx aspect is restored to normal in about 18 weeks by antituberculous medication[9]. In our case, remission was obtained, clinically and endoscopically, 16 weeks after the treatment was started.

**Otorhinolaryngological follow-up**. The follow-up shows, in most cases, complete healing – *restitutio ad integrum*[24]. Long-term follow-up is recommended because laryngeal complications can occur[28]. The fibrotic healing of the tuberculous lesions may lead to long-term compromise of voice[5]. The surgery may be required in the chronic complications cases (posterior glottic stenosis, vocal cord paralysis when cricoarytenoid joint, affected recurrent laryngeal nerve)[17].

## Conclusions

At present, the aspect of a TB-injured larynx varies widely, being different from the classical descriptions. Injuries have unspecific features, and laryngeal TB may or may not be accompanied by active pulmonary TB.

Also, in our country the diagnosis of LTB is often delayed because of little clinical suspicion, therefore these patients present a considerable epidemiological risk. They are often correctly diagnosed only in large medical centers, weeks after the onset of symptoms.

On the other hand, given the very high TB incidence in Romania and the high emigration rates of Romanians to Europe, LTB should be considered in the differential diagnosis of any laryngeal injuries in Romanian patients. ■

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