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ORIGINAL PAPER

Primary Laryngeal Tuberculosis: A Series of 15 Cases

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Abstract
Tuberculosis usually involves the lungs, but can also involve various other organs. Extra pulmonary tuberculosis is very rarely confined to the larynx in the absence of an associated pulmonary lesion. In this retrospective study, clinicopathological characteristics of patients with final diagnosis of laryngeal tuberculosis (LTB) were reviewed. The diagnosis of LTB was based on: (1) the existence of chronic granulomatous inflammation with caseous necrosis in the histopathology of laryngeal lesions or (2) the presence of laryngeal lesions with atypical histopathology (chronic granulomatous inflammation) which had a complete response to anti-tuberculosis therapy. Fifteen cases with a diagnosis of LTB were collected. The patients' age ranged between 24 and 75 years with a mean of 49 years. On laryngoscopy, 66.6% of cases (10/15) had an ulceroproliferative lesion while the remaining 33.3% of cases (5/15) had an exophytic growth. The pathology of laryngeal lesions revealed chronic granulomatous inflammation with caseous necrosis in nine cases and chronic granulomatous inflammation without necrosis in six cases. Nine out of 15 cases (60%) showed presence of acid-fast bacilli on Ziehl–Neelsen stain. Any evidence of pulmonary tuberculosis was ruled out by chest X-ray findings. The response to anti-tuberculosis therapy was desirable in all patients. Since the introduction of anti-tuberculous therapy, the incidence of LTB has declined. However, with the incidence of TB increasing, the overall incidence of laryngeal involvement may be on the rise. This study highlights the importance to consider the rare possibility of LTB in the presence of non-specific clinical and laryngoscopic signs and to confirm this by histological examination.

Keywords Laryngeal · Tuberculosis · Extra pulmonary

Introduction

Tuberculosis usually involves the lungs, but can also involve various other organs. Extra pulmonary tuberculosis is very rarely confined to the larynx in the absence of an associated pulmonary lesion [1]. This uncommon site for tuberculosis raises diagnostic difficulties and can be easily confused clinically with laryngeal cancer [2]. In this study, we propose to show the value of considering the possibility of this disease in the presence of varied clinical and laryngoscopy features. In these cases, histopathology serves as an important tool to arrive at a definite diagnosis.

Materials and Methods

In this retrospective study, clinicopathological characteristics of patients with a final histopathological diagnosis of laryngeal tuberculosis (LTB) were reviewed. All patients were admitted to our tertiary referral center for otolaryngology disease, from Sep 2012 to Aug 2017 (5 years). The diagnosis of LTB was based on the presence of well-defined, confluent epithelioid cell granulomas with or without caseous necrosis. Ziehl–Neelsen staining was done in all cases. Demographic data, clinical manifestations, laryngoscopic appearance, and response to anti-tuberculosis therapy were recorded for each patient.

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Results

Fifteen cases with a diagnosis of LTB were found in our records. Clinical, laryngoscopic and histopathological details of these 15 cases are summarised in Table 1. Of these 15 cases, 12 were males and 3 were females with a male to female ratio of 4:1. The patients' ages ranged from 24 to 75 years with a mean of 49 years. One of the patients was immunocompromised and was HIV positive. The duration of illness ranged from 1 to 18 months (mean of 9.5 months). Hoarseness and odynophagia were the most common presenting complaints, seen in six cases each, followed by 'change in voice' in three cases (20%).

Laryngoscopic Findings

On laryngoscopy, 66.6% cases (10/15) demonstrated an ulceroproliferative lesion while the rest (5/15 cases, 33.3%) showed an exophytic growth. In all 15 cases the lesions were single and located in the epiglottis (8 cases), true vocal cord (4 cases), false vocal cord (1 case), anterior commissure (1 case) and the pyriform sinus (1 case) (Fig. 1). The primary clinical diagnosis was malignancy in most of the cases i.e. 66% of cases (10/15), while tuberculosis (3 cases) and nonspecific inflammation (2 cases) being the other clinical diagnoses.

Histopathology Findings

Histopathological examination of the laryngeal lesions revealed chronic granulomatous inflammation with caseous necrosis in nine cases and chronic granulomatous inflammation without necrosis in six cases (Fig. 2). Nine out of 15 cases (60%) showed presence of acid-fast bacilli (AFB) on Ziehl–Neelsen stain (Fig. 3). Of six cases showing confluent, non-caseating epithelioid cell granulomas, two cases showed presence of AFB on Ziehl–Neelsen staining.

The single patient with seropositivity for HIV showed an ulcerative lesion of epiglottis on laryngoscopy. On

Table 1 Clinical, laryngoscopic and histopathological details of the 15 cases

No	Age	Sex	Cl symptom	Duration	Cl suspicion	Laryngoscopy: site	Appearance	Caseous necrosis	ZN stain
1	35	Male	Dysphagia	3 months	Malignancy	Epiglottis	Ulceroproliferative	Present	Positive
2	55	Male	Change in voice	1 month	Malignancy	True vocal cord	Ulceroproliferative	Absent	Negative
3	40	Male	Odynophagia	1 month	Non specific	Left pyriform sinus	Ulceroproliferative	Absent	Positive
4	48	Male	Dysphagia	6 months	Malignancy	Epiglottis	Exophytic	Present	Positive
5	35	Male	Dysphagia	2.5 months	Malignancy	Epiglottis	Ulceroproliferative	present	Positive
6	65	Male	hoarseness	12 months	Non specific	False vocal cord	Ulceroproliferative	Absent	Negative
7	54	Female	Hoarseness	18 months	Non specific	Epiglottis	Exophytic	Absent	Negative
8	38	Male	Hoarseness	1 month	Malignancy	Anterior commissure	Exophytic	Present	Negative
9	30	Female	Hoarseness	2 months	Tuberculosis	True vocal cord	Ulceroproliferative	Present	Positive
10	40	Male	Odynophagia	5 months	Malignancy	Epiglottis	Ulceroproliferative	Present	Positive
11	75	Male	Change in voice	2 months	Tuberculosis	True vocal cord	Ulceroproliferative	Present	Positive
12	35	Male	Dysphagia	2 months	Malignancy	Epiglottis	Exophytic	Present	Positive
13	42	Male	Change in voice	8 months	Tuberculosis	Epiglottis	Ulceroproliferative	Absent	Negative
14	50	Male	Hoarseness	8 months	Tuberculosis	Epiglottis	Exophytic	Absent	Positive
15	24	Female	Hoarseness	1 month	Tuberculosis	True vocal cord	Exophytic	Present	Negative

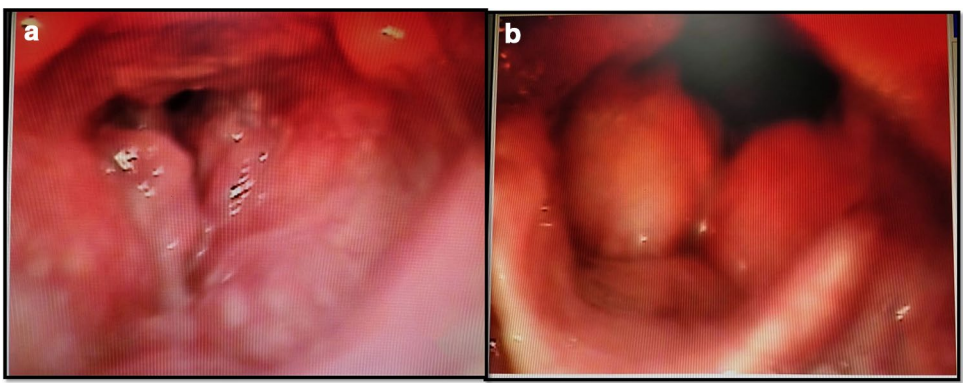

Fig. 1 Direct laryngoscopic findings. **a** Ulceroproliferative growth involving left false and true vocal cords and right true vocal cord. **b** Bilateral edematous false vocal cords

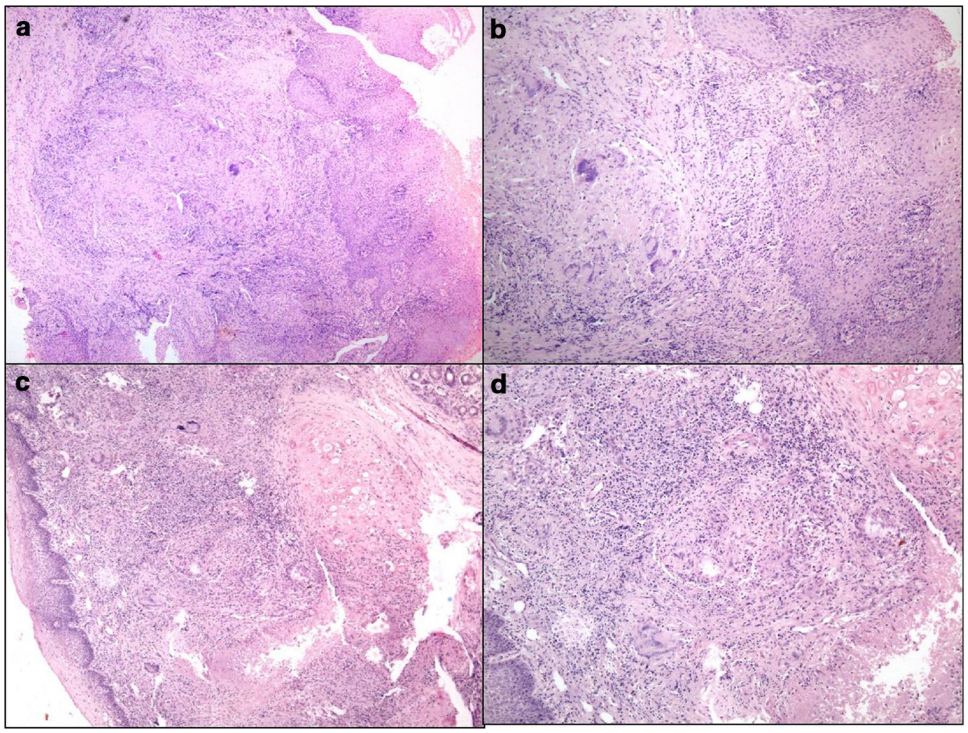

Fig. 2 Microphotographs showing **a** and **b** non-caseating epithelioid cell granulomas along with multiple Langhans type of giant cells in a laryngeal biopsy (H&E, ×40 and H&E, ×100 respectively), **c, d** caseating epithelioid cell granulomas in a biopsy from epiglottis (H&E, ×40 and H&E, ×100 respectively)

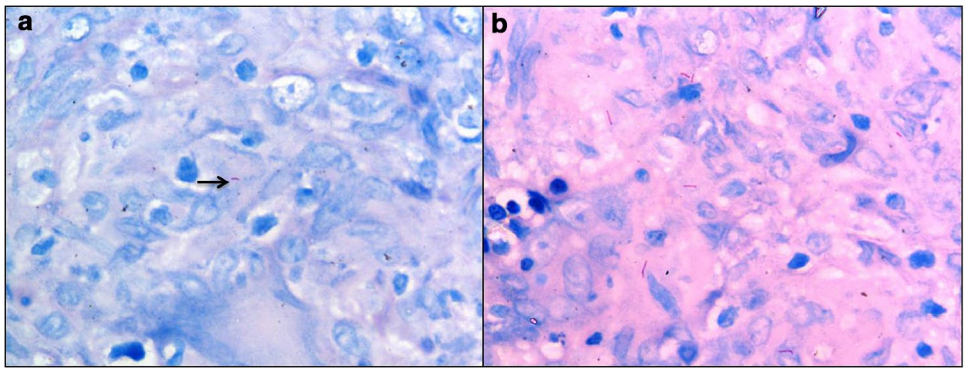

Fig. 3 **a** Single acid-fast bacillus (marked by arrow), **b** multiple acid-fast bacilli (Ziehl–Neelsen stain, ×1000)

histopathology the biopsy showed abundant caseous necrosis and numerous AFB on Ziehl–Neelsen staining with multiple bacilli being seen in one oil immersion field.

Evidence of pulmonary tuberculosis was ruled out by chest X-ray findings. The response to anti-tuberculosis therapy was desirable in all patients.

Discussion

Primary LTB is very uncommon [1]. It often mimics malignancy on laryngoscopy and imaging and the final diagnosis is based on biopsy [3]. In spite of the high prevalence of tuberculosis in India, we could gather only 15 patients with LTB. In this study males were involved four times more than females. This is compatible with results of most other studies that show a male predominance [4, 5], incidence in males being greater owing to higher exposure. The mean age of patients in our series was 49 years. This mean age is observed in developing countries like India where tuberculosis is endemic. In developed countries, the age of onset of LTB is around 60 years [5].

The primary clinical diagnosis was tuberculosis in only 20% of the cases which is consistence with a study done by Hasibil et al. [6]. Overall the most common primary clinical diagnosis was malignancy in 66.66% of cases which is not unusual due to the similarity in presenting complaints and laryngoscopic features of LTB and laryngeal malignancy [7].

The mean duration of the disease until diagnosis was 9.5 months. Our patients were referred late compared with patients in other reports [7]. This could possibly be

explained by delayed referral to a center equipped with laryngoscopy. As found in other reports, hoarseness and odynophagia were the commonest presenting symptoms. Tuberculosis of the epiglottis can obstruct the upper airway causing these symptoms. In most studies, hoarseness is described as the most common laryngeal symptom, followed by odynophagia and dyspnea [7, 8]. In our study, 20% cases had a change in voice corresponding to the involvement of true and false vocal cords [8].

On laryngoscopy, laryngeal lesions in tuberculosis have an inconsistent appearance and simulate other diseases such as contact ulcer, leukoplakia, reflux disorders, polyp and malignancy [2]. In the present study, a majority of the lesions were ulceroproliferative and hence mimicked malignancy. LTB was not considered in the clinical differential diagnosis owing to its rarity. Lin et al. compared the site of involvement of LTB before and after 1998 and concluded that epiglottis was more frequently involved in the past when compared to recent trends [9]. However, in the indexed series, epiglottis was involved in a majority of the cases. Laryngoscopy is useful to perform biopsies, which are mandatory for a definitive diagnosis. Histological examination classically reveals granulomas composed of a central zone of caseation surrounded by epithelioid cells and lymphocytes along with Langhans giant cells [10]. Microscopy in the present study revealed chronic granulomatous inflammation with caseous necrosis in 60% of cases while the remaining 40% of cases showed confluent, non-caseating epithelioid cell granulomas.

With this microscopic picture (especially the presence of caseating granulomas), tuberculosis is the primary diagnosis to be considered in a country like India, where tuberculosis is endemic, other causes of granulomatous pathology being much more rare. The other exceptional diagnoses to be considered in the presence of granulomatous lesions of the larynx are syphilis, amyloid, actinomycosis, blastomycosis and granulomatosis with polyangiitis [11].

In sarcoidosis, granulomas are usually discrete, non-caseating with occasional presence of asteroid and Schaumann bodies. In granulomatosis with polyangiitis, vasculitis with necrotizing granulomas is seen along with systemic manifestations. Laryngeal involvement by fungal infections is more common in immunocompromised states and fungal profiles can usually be appreciated on H&E stains.

Demonstration of AFB on Ziehl–Neelsen staining is confirmatory for tuberculosis. In the study conducted by Ayoubi et al., Ziehl–Neelsen staining was negative in 100% of cases. In the present series, AFB were detected in 60% of cases (including 33.3% of the cases that had non-caseating epithelioid granulomas), confirming the diagnosis of tuberculosis.

This indicates the importance of making a diligent search for AFB in the presence of confluent epithelioid cell granulomas with or without caseous necrosis. This not only confirms the diagnosis but provides results much faster and is cheaper than culture and other molecular based techniques like PCR [11].

Chest X Ray was performed in all our cases and no evidence of pulmonary involvement was found in any of these cases. This ruled out secondary involvement of the larynx from pulmonary tuberculosis. Association of HIV and tuberculosis is well known, however in the present series only one case was seropositive for HIV and the biopsy from the same patient showed numerous AFB on Ziehl–Neelsen staining [12]. All patients responded well to anti-tuberculous therapy corroborating the diagnosis of LTB, particularly in cases where ZN staining was negative for AFB.

The main differential diagnosis for LTB is carcinoma of the larynx, which may have a deceptive clinical, laryngoscopic and even histological presentation [13]. Uncertainty persists even after microscopic examination of biopsies, especially when the biopsies are comprised of superficial layers only. Deeper and repeated biopsies must be performed when histological examination is inconclusive. Clinicians must also bear in mind that carcinoma and tuberculosis can coexist in the same patient. Several cases of concomitant carcinoma and tuberculosis have been reported in the literature [9].

Conclusion

Laryngeal TB is a rare differential diagnosis to be considered in cases presenting with clinical and laryngoscopic findings of malignancy. Histopathological examination and examination of Ziehl–Neelsen stained slides play a significant role in diagnosis. Once the diagnosis is confirmed, treatment is curative. Treatment is primarily medical with surgery required only for those cases with compromised airway. Despite excellent treatment results, long-term follow-up is advised in these cases as laryngeal complications can occur occasionally.

Compliance with Ethical Standards

Conflict of interest All authors declare that there were no conflicts of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Since this was a retrospective study, reviewing the case records and pathology materials of the patient, no informed consent was needed.

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