Upper Respiratory Tract Tuberculosis

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ABSTRACT Upper respiratory tract involvement in cases of tuberculosis (TB) of the head and neck continues to be described in the most recent reports from several different regions, including some from developed countries. Laryngeal TB is the most common of all forms of upper respiratory tract TB (URT-TB). Pulmonary lesions in URT-TB are present in about 20% of adults and about 50 to 60% of children. Systemic manifestations are uncommon. URT-TB is especially seen in patients with a variety of risk factors, such as the presence of human immunodeficiency virus (HIV) infection, diabetes, smoking, alcoholism, drug abuse, malignancies, and use of immunosuppressive drugs. Nodules or ulcerative lesions are seen on morphological examination. Endoscopic examination is required for mucosal lesions. Diagnosis of TB is suspected on an epidemiological basis in high-prevalence countries or from the failure of a patient to respond to routine treatment. Smear and/or histopathological examinations help in establishing the final etiological diagnosis. Endoscopic examination is required for mucosal lesions. Diagnosis of TB is suspected on an epidemiological basis in high-prevalence countries or from the failure of a patient to respond to routine treatment. Smear and/or histopathological examinations help in establishing the final etiological diagnosis. Treatment includes standard anti-TB chemotherapy for at least 6 months with four primary drugs during the initial intensive phase of 2 months and two or three primary drugs during the remaining maintenance phase of 4 months. Treatment is modified on the basis of culture and sensitivity reports in cases of suspected drug resistance. Surgical intervention may be required for some patients with abscess formation and progressive disease unresponsive to medical therapy. Airway obstruction, although rare, even in fulminant cases may require tracheostomy for relief.

EPIDEMIOLOGY

Almost all parts of the upper respiratory tract from the nose to the vocal cords and the larynx can get involved, although the frequency of involvement may vary to a great degree. Patients with TB of different components of the upper respiratory tract may first report to a general physician, an otorhinolaryngologist, or a pulmonologist. Chest physicians, who also handle TB in developing countries, are frequently confronted with and consulted for URT-TB. Factualy speaking, URT-TB should be considered and handled on par with TB of the lungs.
Tuberculous involvement of the upper respiratory tract was seen in less than 2% of TB admissions in the past (1). In the last two decades, however, there has been an increase in the incidence and a change in the spectrum of URT-TB (2, 3). The upper respiratory tract involvement in cases of TB of the head and neck continues to be described in the most recent reports from several different regions, including some from developed countries (4–8). In different reports, TB is reported to involve a large number of sites in the upper respiratory tract (Table 1). Almost invariably, a majority of cases of URT-TB have cervical lymph node enlargement (2–9). Any enlargement of lymph nodes in the neck calls for careful search for a lesion in the upper respiratory tract and vice versa (Fig. 1). In one series of 17 cases of TB of the nasopharynx from Hong Kong, cervical lymphadenopathy was present in 59% of patients (10). Similarly, in Thailand, the most common site of TB in the head and neck involved the cervical lymph nodes and the nasopharynx (11).

Pulmonary lesions are present in about 20% of adults and about 50 to 60% of children with URT-TB (12–14). Systemic manifestations are, however, uncommon. URT-TB is especially seen in patients with a variety of risk factors (Table 2), especially the presence of human immunodeficiency virus (HIV) infection (15, 16). For example, of the 538 EPTB cases (28.6%) among a total of 1,878 enrollees, the risk for EPTB in HIV-seropositive patients in a multivariate model was high; African American ethnicity was an independent risk factor for EPTB (15). Diabetes, malignancy, and use of immunosuppressive therapies are other important risk factors.

Clinical features of URT-TB depend upon the site of organ involvement (Table 3). Concurrent pulmonary involvement is frequent. Systemic manifestations such as fever and weight loss are uncommon but may occasionally be seen, especially in the presence of involvement of the lungs and/or other organs. Nodules or ulcerative lesions are seen on morphological examination. Endoscopic examination is required for mucosal lesions. Most of these lesions are initially missed as nontuberculous infections or as malignant in nature. Diagnosis of TB is suspected on an epidemiological basis in high-prevalence countries or from the failure of a patient to respond to routine treatment. Smear and/or histopathological examinations help in establishing the final etiological diagnosis.

### TABLE 1 Various sites of URT-TB described in different reports

<table>
<thead>
<tr>
<th>Nose and nasopharynx</th>
<th>Nose septum, nasal floor and vestibule; rarely, alae nasi</th>
<th>Maxillary sinuses; rarely sphenoid sinus</th>
<th>Nasopharynx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>Tongue: tip, borders, dorsum, and base</td>
<td>Lips, rarely</td>
<td>Floor of mouth, soft palate, tonsils, anterior pillars of fauces, uvula</td>
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<td></td>
<td>Oropharyngeal walls</td>
<td>Salivary glands</td>
<td>Eustachian tubes, middle ear</td>
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<tr>
<td>Larynx</td>
<td>Laryngeal walls: glottic and subglottic areas</td>
<td>Vocal cords</td>
<td></td>
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</table>

### FIGURE 1 Cervical lymph node enlargement, superficial erythema, and sinus formation in an HIV-positive patient with extensive laryngeal TB. (Courtesy of A. K. Janmeja, Government Medical College, Chandigarh, India.)

### NASAL TB

TB of the nose and paranasal sinuses is an uncommonly reported but a well-described entity in otorhinolaryngology practice. In 1997, only 35 cases were identified in a search of the English language medical literature of the last 95 years (17). Several other reports of isolated cases or series of several cases have continued to appear mostly from developing countries, including India, Pakistan, and Hong Kong, many of which showed no evidence of concomitant pulmonary TB (4, 5, 10, 18–21). Its re-emergence as a major health problem in the United States was attributed to HIV infection, homelessness, and deterioration of the social infrastructure (17). Maxillary sinuses are commonly involved in nasal TB. Very rarely, involvement of other sinuses has been described. TB of sphenoid sinuses established on magnetic resonance imaging and endoscopic biopsy was recently reported in two children (22).
TABLE 2 Important risk factors described in cases of URT-TB

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tbody>
<tr>
<td>HIV infection</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Malignancies</td>
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<tr>
<td>Tobacco smoking</td>
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<tr>
<td>Drug abuse, alcoholism</td>
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<tr>
<td>Connective tissue disorders, such as systemic lupus erythematosus</td>
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<tr>
<td>Use of immunosuppressive drugs</td>
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<tr>
<td>Malnutrition</td>
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<td>Poor living conditions, homelessness</td>
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Clinical Features

Patients with nasal TB commonly present with nasal obstruction and purulent rhinorrhea. Blood-stained discharge and/or frank epistaxis is another important manifestation (23, 24). Snoring and nasal twang in the voice can sometimes occur. Lupus vulgaris, a slowly growing, indolent ulcerative lesion caused by Mycobacterium tuberculosis, may affect the nasal vestibule, the septum, and the alae. Occasionally, lupus vulgaris with papulonecrotic TB is reported (25). External deformity may result in about one-third of patients. Physical examination may reveal pallor of the nasal mucosa with multiple minute apple jelly nodules on diascopy. Nasal septal ulceration and perforation of septal cartilage can occur (2, 21). Destructive periodontitis has been described in a rare case (26). TB can also manifest as a polypoidal lesion in the nasal cavity (27). Sinonasal TB can invade the surrounding bones, causing osteomyelitis and abscess formation (28). Intracranial extension can cause neurological manifestations, such as epilepsy and optic neuritis (23, 29). In a series of 18 cases of intrasellar tuberculomas, 6 had involvement of sphenoid sinus (30). Cervical lymph node enlargement is present in about 30% of patients. Nasopharyngeal TB causing isolated hypoglossal nerve paralysis has been rarely described (31).

Most of these clinical manifestations can be seen in other diseases involving the nose, such as fungal infections, leprosy, syphilis, and malignancies. Septal perforations have been reported in a large number of clinical conditions (Table 4), commonly for patients on inhalational corticosteroids, those with allergic bronchopulmonary aspergillosis, and following chronic exposures to metal fumes in welders (32, 33). Granulomatous involvement of the nose and the sinuses can occur in several other conditions (34). Granulomatosis with polyangiitis (Wegener’s granulomatosis), fungal infections, midline granulomatous disease, and leprosy are some examples. Radiotherapy administered for undifferentiated carcinoma can also cause granulomatous inflammation, which in many instances is attributable to TB (35).

Differential diagnosis is achieved on histological and microbiological parameters. Confirmation of diagnosis is made on mycobacterial culture, since the acid-fast bacilli (AFB) on smear examination may occasionally represent Mycobacterium leprae, an important cause of nasal involvement in zones of endemcity. Mycobacteria were detected by PCR of nasal swabs from 6 of 16 smear-positive TB patients and 1 of 10 household contacts (36). However, the sensitivity and specificity of PCR on nasal swabs in clinical diagnosis of nasal TB are not known. Although Mycobacterium tuberculosis is the most common organism, other mycobacteria have, rarely, been implicated. Mycobacterium africanum had been isolated in a case of cutaneous TB with nasal sinus invasion, nasal perforation, and bilateral nodular scle-ritis (37).

Nasal TB responds to standard anti-TB therapy as for pulmonary TB. Surgical interventions may be occasionally required.

ORAL CAVITY AND PHARYNX

The oral cavity is a rare site of TB involvement. Infection of the oral cavity is associated with poor dental hygiene and other conditions which result in mucosal injury. Most patients have concomitant pulmonary TB, and the lesions are believed to result from the infected spu-tum being coughed out (38). Infection can also be acquired by the hematogenous route. The tongue is the most common site of involvement. Almost any part of the tongue, such as the tip, the borders, dorsum, and base, may be involved. Several isolated cases of lingual TB have been reported in the recent past (39–43). Very rarely, TB of the lips has been described (44–46). Similar

TABLE 3 Common symptoms and signs of URT-TB

<table>
<thead>
<tr>
<th>Location</th>
<th>Symptom(s) or sign(s)</th>
</tr>
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<tbody>
<tr>
<td>Nose</td>
<td>Nasal discharge/obstruction</td>
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<tr>
<td></td>
<td>Epistaxis, pain</td>
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<tr>
<td></td>
<td>External nodule, ulcer (lupus vulgaris), or deformity</td>
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<tr>
<td></td>
<td>Mucosal ulcer(s)</td>
</tr>
<tr>
<td></td>
<td>Septal perforation</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>Ulcers—painless/painful on tongue or buccal or pharyngeal mucosa</td>
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<tr>
<td></td>
<td>Localized swelling</td>
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<tr>
<td></td>
<td>Tonsillar infiltration/ulcer</td>
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<tr>
<td></td>
<td>Sore throat, dysphagia, white patches</td>
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<tr>
<td></td>
<td>Secondary otitis media—otorrhea</td>
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<tr>
<td>Larynx</td>
<td>Hoarseness</td>
</tr>
<tr>
<td></td>
<td>Odynophagia, dysphagia</td>
</tr>
<tr>
<td></td>
<td>Upper airway obstruction—rare</td>
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</tbody>
</table>
to TB of the nose, many of these cases are seen in patients with HIV infection (40, 47–49). Other sites in the oral cavity include the floor of the mouth, soft palate, tonsils, anterior pillars of fauces, and uvula.

**Clinical Features**
The lesions in the oral cavity can manifest as ulcers or nodules which can be either single or multiple, anywhere in the mouth. The lesions are usually well circumscribed and painful but can also be irregular, simulating malignant ulcers. Sometimes the lesions are painless and detected on incidental examination, such as during bronchoscopy (Fig. 2). The draining lymph nodes in the neck may also be palpable.

TB of the pharynx can be ulcerative of lupus vulgaris type or secondary to pulmonary involvement (so-called miliary TB of the pharynx). The nasopharynx is the most common site of pharyngeal involvement (50). Symptoms of nasopharyngeal TB include nasal obstruction, rhinorrhea, and nasal twang of the voice, while physical findings may be limited to adenoid hypertrophy without any distinguishing features. Several atypical presentations have been described. Snoring which disappeared after anti-TB therapy was the only complaint reported for a 58-year-old patient (51). Presentation with neck pain and hearing loss is sometimes reported. Two different patterns of nasopharyngeal TB can be identified on magnetic resonance imaging—the pattern of a discrete polypoidal mass in the adenoids and the pattern of a more diffuse soft tissue thickening of one or two walls of the nasopharynx (52). Extension outside the confines of the nasopharynx was not seen (52). Most infections are primary, and less than 20% demonstrate pulmonary involvement. Postradiation granulomatous inflammation in patients with nasopharyngeal carcinoma should be suspected as occult tubercular infection and diligently investigated (35).

Oropharyngeal TB is likely to manifest with symptoms of sore throat (53, 54). Commonly, there is simultaneous involvement of the larynx, causing severe dysphagia and odynophagia (54). Dysphagia may sometimes result from retropharyngeal abscess caused by TB (55). Local hyperemia and irregularity of mucosa, erythematous papules, and swelling of the cheek have been described in different case reports (17). Cervical lymphadenopathy is frequently present. Similarly, cutaneous lupus vulgaris and scrofuloderma may also be seen.

**FIGURE 2** Pale nodule in the oropharynx noticed incidentally during fiber optic bronchoscopy for mediastinal lymphadenopathy. Needle aspiration from the nodule revealed necrotizing granulomatous inflammation and multiple, pink-stained AFB.

**TABLE 4** Differential diagnosis of lesions of nasopharyngeal TB

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Fungal infections, especially allergic aspergillosis/nasal aspergillomas</td>
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<tr>
<td>Malignancies</td>
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<tr>
<td>Following radiation therapy</td>
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<tr>
<td>Prolonged use of nasal sprays, especially of corticosteroids</td>
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<tr>
<td>Granulomatosis with polyangiitis (Wegener’s)</td>
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<tr>
<td>Midline granulomatous disease</td>
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<tr>
<td>Rarely, leprosy and syphilis</td>
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</table>

Tonsils constitute another important site of involvement with TB. Again, involvement may occur in isolation or along with TB of the larynx and the lungs. Tonsillar TB was common in the era of unpasteurized milk and was acquired by drinking milk contaminated with *Mycobacterium bovis*. It may manifest with features of sore throat, lymphadenopathy, dysphagia, ulceration, masses, and white patches (56–58). Pharyngeal TB can also spread to the middle ear through the eustachian tube (59). Tympanic membrane perforations (especially multiple), painless otorrhea, and hearing loss may result. Preauricular lymph node enlargement and postauricular fistula are considered pathognomonic of tubercular otitis media. Occasionally, TB might complicate a malignant lesion in this region. Physical examination includes unilateral tonsillar enlargement, ulcerations, and fibrosis of the tonsils. Incisional biopsy confirms the diagnosis based on histopathological findings and the identification of AFB. Patients tend to re-
spond quickly to anti-TB chemotherapy; if no response is seen in 2 weeks, the diagnosis should be questioned.

TB of the salivary glands occurs as a result of infection of the oral cavity or secondary to pulmonary TB. Primary sialitis may occur but is rare. Although parotid involvement is the most common, submandibular glands may also be involved (60). The clinical presentation can be either acute or chronic. Most patients present with only parotidomegaly and no other systemic manifestations. In a few case reports, diagnosis was not suspected until histopathological evidence was obtained (61). When suspected, diagnosis can be made by fine-needle aspiration cytology (60). The diagnosis can also be suggested preoperatively by contrast-enhanced computed tomography (CT) appearance. The presence of thick-walled rim-enhancing lesions with a central lucency on contrast-enhanced CT should suggest the diagnosis. Filling defects with or without thin walls are nonspecific findings and are seen in tumors and other inflammatory processes. In an appropriate clinical setting, thick-walled round rim-enhancing lesions with a central lucency are characteristic of TB.

Diagnosis of most forms of extralaryngeal URT-TB is difficult and requires biopsy procedures. In a series of 16 cases of TB with involvement of the oral cavity and/or pharynx, the average duration of symptoms was 11.5 months and biopsy was required in all; the purified protein derivative skin test was also positive for 15 of 16 patients (62). Treatment for all patients with pharyngeal and oral-cavity TB consists of anti-TB chemotherapy. The treatment response is generally favorable, and the prognosis is good (62). Surgical intervention should be avoided (63).

**LARYNGEAL TB**

TB is an important and perhaps the most common cause of granulomatous disease of the larynx. Though the clinical presentation of tubercular laryngitis has changed significantly from what it was before the advent of chemotherapy, it continues to be reported in small series from different countries the world over (6, 7, 64–71). Some recent reports from developed countries, including the United States, Japan, and Spain, continue to point to the importance of the problem (5, 67, 72). Presently, laryngeal TB is reported in 1 to 2% of cases (1, 73). Laryngeal involvement is especially common in patients with immunodeficiency, such as HIV infection (74). In a series of 45 patients with upper aerodigestive tract TB, 16 had laryngeal and 23 nasopharyngeal TB; 4 of 26 patients had positive serological tests for HIV infection (11). Similarly, laryngeal TB has been described in other diseases. In a review of 283 patients with systemic lupus erythematosus in Korea, TB was documented for 15 patients, 1 of whom had laryngeal involvement (75). Two cases of laryngeal TB were reported in renal transplant patients; both responded promptly to anti-TB therapy (76). Occasionally, patients on glucocorticoids can develop laryngeal TB. For example, a patient with Addison’s disease on glucocorticoids and another on inhaled steroid therapy are reported to have developed tubercular infection (77, 78).

Laryngeal TB more closely resembles a laryngeal carcinoma than any other laryngeal illness (79–81). The primary infection can involve any part of the larynx, while the previously described direct mode of spread from the lungs predominantly involved the posterior larynx. In most reports published in the recent past, laryngeal TB, especially in the low-prevalence countries, generally occurred as an isolated manifestation (70, 82).

**Clinical Features and Diagnosis**

There has been a shift in the age and sex distributions of laryngeal TB in the last three or four decades (1, 82). It is now more common in the older age groups and in males than females. Above 50 years of age, the male predominance is even more marked. Besides patients with immunosuppressive states, such as HIV infection, it is also more frequent in individuals of poor constitution and health, especially those who are alcoholics and undernourished (11, 74–76). Use of tobacco is also identified as a risk factor (83). Smoking was reported to be associated with more extensive lesions in an analysis of 36 patients in Brazil (69).

The presence of laryngeal symptoms is generally quite bothersome and brings the patient to the physician early in the course of disease. The most common symptom is hoarseness of voice and other dysphonias, present in more than 90% of patients (66, 72, 82). Voice disorders in a recent study were reported to be similar to those seen after clinical healing (83). The authors suggested that process of recovery of vocal quality may be affected during the active stage itself (83). In another study, the incidence of dysphonia was found to be high after TB treatment but was shown to recover following speech therapy (84).

Cough, dysphagia, odynophagia, pain in the throat, and referred pain in the ear are also common (65, 67, 73). Laryngeal involvement can also present with edema and granulomatous involvement of the laryngeal mucosa (Fig. 3). Such a presentation with stridor and severe upper airway obstruction may land the patient in
an emergency situation. Upper airway obstruction may be present because of the presence of granulation tissue at the level of the glottis, subglottic stenosis, and vocal cord paralysis secondary to mediastinal lymphadenopathy (85). Involvement of the posterior larynx was thought to result from pooling of infected saliva in the recumbent position, although not all reports have shown this predilection for posterior laryngeal involvement, and some experience has emphasized anterior vocal cord involvement; hypertrophic lesions are seen more commonly than ulcerative lesions. A variety of endoscopic appearances have been described (Table 5): perichondritic, ulcerative, granulomatous, polypoid, and nonspecific inflammatory (67, 68). Occasionally, there is isolated involvement of the epiglottic, supraglottic, or subglottic region (85–87). Solitary lesions are four times more frequent than multiple lesions. In a recent study, a variant of Mycobacterium tuberculosis complex or a closely related novel mycobacterium was shown on molecular analysis of tracheal microbiota in cases of idiopathic subglottic stenosis (88). The clinical picture in patients with underlying HIV infection and AIDS is somewhat different, posing greater difficulties in diagnosis. Systemic features such as fever, night sweats, and weight loss are common. Multispecies infections are also more frequent. Laryngeal TB, especially the nodular presentation, sometimes with abscess formation, may be difficult to differentiate from cancer on physical examination (85, 89). A good lateral X ray of the neck and CT can help (90). In an occasional case, F-18 fluorodeoxyglucose positron emission tomography/CT is employed to detect systemic TB presenting as an epiglottic mass (91). Although appearances of laryngeal TB are not specific on CT appearances, the possibility should be raised when there is bilateral involvement, thickening of the free margin of the epiglottis, and preservation of the pre-epiglottic and paralaryngeal spaces even in the presence of extensive mucosal involvement (90). Any nonspecific chronic laryngitis of poor evolution should lead to a suspicion of laryngeal TB (83). Cartilage destruction is more common in malignancies but may occasionally result from TB (92). Bacterial and fungal infections, granulomatosis with polyangiitis (Wegener’s granulomatosis), sarcoidosis, and malignancies need to be considered in the differential diagnosis.

Histopathological examination is required for a definite diagnosis. Sputum microscopy is positive for 20% of patients with laryngeal TB. A laryngeal swab smear positive for mycobacteria should not be considered diagnostic of laryngeal TB, because such swabs are frequently positive for patients with pulmonary TB, especially in children. In a study of 116 children with suspected pulmonary TB, mycobacteria were seen on either smear examination or culture for one-third of 51 patients for whom laryngeal swabs were examined (93). Direct laryngoscopic examination with biopsy provides the most conclusive evidence for diagnosis. The sample should be sent for both histopathological examination and culture. It is the presence of mycobacteria on culture of a biopsy specimen which provides the conclusive etiological evidence of TB. PCR-based analysis has been found to be helpful to demonstrate the presence of mycobacterial DNA and to differentiate between different species of mycobacteria (36, 88). However, in clinical practice, histological demonstration of epithelioid cell caseating granulomas is considered enough to initiate anti-TB therapy.

**Treatment and Outcome**

The laryngeal lesions of TB respond quickly to standard anti-TB regimens, within weeks. The larynx is reported

<table>
<thead>
<tr>
<th>TABLE 5</th>
<th>Endoscopic appearances of lesions of laryngeal TB</th>
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<tr>
<td>Mucosal inflammation: hyperemia, mucosal edema</td>
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<tr>
<td>Granulomatous mucosa</td>
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<td>Mucosal ulcers</td>
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<tr>
<td>Localized swelling, abscess</td>
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<tr>
<td>Restricted movements of vocal cords</td>
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<tr>
<td>Epiglottic swelling/mass</td>
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<tr>
<td>Polypoidal growth simulating malignancy</td>
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to return to its normal appearance in 18 weeks on average (73). Voice outcomes improve after anti-TB treatment in most patients (94). Vocal cord immobility due to fibrosis and adhesion may produce permanent hoarseness in a minority of patients (95). Such an eventuality happens when the disease remains undiagnosed and untreated for long periods, which results in significant damage. While laryngeal TB can mimic carcinoma, coexistence of laryngeal TB and carcinoma is reported in 1 to 2% of cases (96). For such patients, anti-TB drugs should be given for at least 3 to 6 weeks before treatment for laryngeal carcinoma is initiated.

Treatment includes anti-TB chemotherapy for at least 6 months, modified on the basis of culture and sensitivity reports in cases of suspected drug resistance. Laryngeal TB generally responds well to multiple-drug anti-TB chemotherapy. The standard treatment consists of four primary drugs (rifampin, isoniazid, pyrazinamide, and ethambutol) given together during an intensive phase of 2 months, followed by a maintenance phase of 2 or 3 drugs for 4 months. Surgical intervention such as tracheostomy, partial or complete laryngectomy, or laryngotracheoplasty may be required for some patients with abscess formation and progressive disease unresponsive to medical therapy. Airway obstruction, although atypical, even in fulminant cases may require tracheostomy for relief (97). Speech therapy is useful to improve the vocal quality following anti-TB treatment.

In conclusion, TB should be kept in the differential diagnosis of upper airway diseases and/or cervical lymphadenopathy whenever a patient presents with insidious onset of symptoms, ulcerative or granulomatous lesions, and failure of response to therapy for more common lesions. Classic clinical features may not always be present. Early diagnosis and treatment are essential to prevent long-term complications.

REFERENCES


Upper Respiratory Tract Tuberculosis


