



# Esophageal Tuberculosis: A Systematic Review

Poras Chaudhary<sup>1</sup> · Ashutosh Nagpal<sup>1</sup> · Sam B. Padala<sup>1</sup> · Mangarai Mukund<sup>1</sup> · Saurabh Borgharia<sup>1</sup> · Romesh Lal<sup>1</sup>

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**Abstract** Involvement of esophagus with tuberculous infection is a rare form of extrapulmonary tuberculosis. Secondary esophageal tuberculosis is much more common than primary TB. The most common source of secondary esophageal involvement is tuberculous mediastinal lymphadenitis. Esophageal tuberculosis mimics carcinoma esophagus. Clinical features are same and it is difficult on imaging studies also to differentiate the two pathologies. Misdiagnosis is common. The disease is medically curable; therefore, it is essential to make all efforts to diagnose the pathology with non-surgical diagnostic modalities in suspected cases so as to save patients from the trauma of major surgical resection. Surgical intervention is indicated for failed medical therapy and complications. A total of 133 cases of esophageal TB have been reported till date. The authors encountered 4 cases of esophageal TB between April 2011 and March 2019. The aim of this article is to present our data and to provide comprehensive review of the available literature on this pathology in order to gain a better understanding of diagnostic methods and provide guidelines for the diagnosis and management of esophageal TB.

**Keywords** Esophagus · Tuberculosis · Misdiagnosis · Medically curable · Surgery for complications

## Introduction

Esophagus lies in the thorax in close proximity to lungs and mediastinal lymph nodes. In spite of close anatomical relationship with lungs, the involvement of esophagus with tuberculous infection is a relatively rare. The first case of esophageal tuberculosis (TB) was reported in the year 1837 on postmortem examination [1], and the first diagnosed case was reported in the year 1907 [1]. In the year 1922, Kragh was the first clinician to report a first case with review of literature on esophageal TB in the English language [2]; while Fahmy et al. was the first clinician to present a detailed review on this pathology [1]. A total of 133 cases of esophageal TB have been reported till date. Primary or isolated esophageal TB is extremely rare; only three cases have been reported [3–5]. This pathology has clinical presentation very similar to esophageal carcinoma, characteristic epidemiological features and a specific and effective medical therapy. Misdiagnosis or delayed diagnosis is common. Earlier clinical recognition and advancement in diagnostic techniques have resulted in decreased complications rate. Most of our knowledge about this pathology comes from individual case reports as there are only a few case series on this disease. The authors encountered 4 cases of esophageal TB between April 2011 and March 2019 (Table 1). The aim of this article is to present our data and to provide comprehensive review of the available literature on this pathology in order to gain a better understanding of diagnostic methods and provide guidelines for the diagnosis and management of esophageal TB.

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✉ Poras Chaudhary  
drporaschaudhary@yahoo.com

<sup>1</sup> General Surgery, Lady Hardinge Medical College,  
New Delhi, India

**Table 1** Description of 4 cases

Case	Age/sex	Clinical presentation/duration of symptoms	History of TB/TB contact	Associated comorbidity	HIV status	Imaging studies	Site of lesion	Endoscopic biopsy/culture/PCR	Follow up and prognosis
1	36/F	Fever of unknown origin, anorexia, weight loss/ 12 weeks	No	No	Negative	USG/CECT- esophageal lesion, no pulmonary or mediastinal focus	Middle third	Biopsy positive, culture negative, PCR positive	Received ATT for 6 months, recovered
2	59/M	Dysphagia, vomiting, anorexia/8 weeks	Active pulmonary TB, history of TB contact	Chronic alcoholic pancreatitis	Negative	USG/CECT- esophageal lesion, pulmonary focus and mediastinal lymph adenopathy	Middle third	Biopsy positive, culture and PCR negative	Received ATT for 12 months, recovered, on follow up
3	52/M	Dysphagia, constitutional features of TB/ 9 weeks	Active pulmonary TB, no history of TB contact	No	Negative	USG/EUS/CECT- esophageal lesion, pulmonary focus and mediastinal lymph adenopathy	Middle third	Biopsy, culture and PCR negative, thoracotomy done— biopsy positive	Received ATT for 12 months, recovered on follow up now
4	45/F	Constitutional features of TB, recent onset dysphagia/8 weeks	Disseminated TB, history of TB contact	History of MRM and chemotherapy for carcinoma breast 4 years back	Negative	USG/EUS/CECT/- esophageal, pulmonary, intestinal, hepatic focus and mediastinal lymphadenopathy	Middle and lower third	Biopsy, culture and PCR positive	ATT starts, patient died of septicemia within 6 days on initiation of ATT

TB tuberculosis, USG ultrasonography, EUS endosonography, CECT contrast enhanced computed tomography, ATT antituberculous treatment, PCR polymerase chain reaction, HIV human immunodeficiency virus

## Methods

The search strategy, inclusion and exclusion criteria, and primary and secondary outcomes were defined before the search. The systematic search of the literature was performed on Pubmed and Medline from 1950 to 2019 according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Fig. 1). Electronic searches were undertaken in PUBMED and MEDLINE using the MeSH terms “esophagus” in combination with “tuberculosis”, “tuberculous”, “tubercular”, “miliary tuberculosis”, “disseminated tuberculosis”, “tuberculosis in immunocompromised patients”, “complications”, “management”.

Data were extracted by one author independently and then compared. The study author provided additional data if incomplete data were noted. Titles/abstracts considered potentially relevant were retrieved for review of the full manuscript. The list of full manuscript meeting inclusion criteria were compared, and any disagreements were resolved by discussion and consensus.

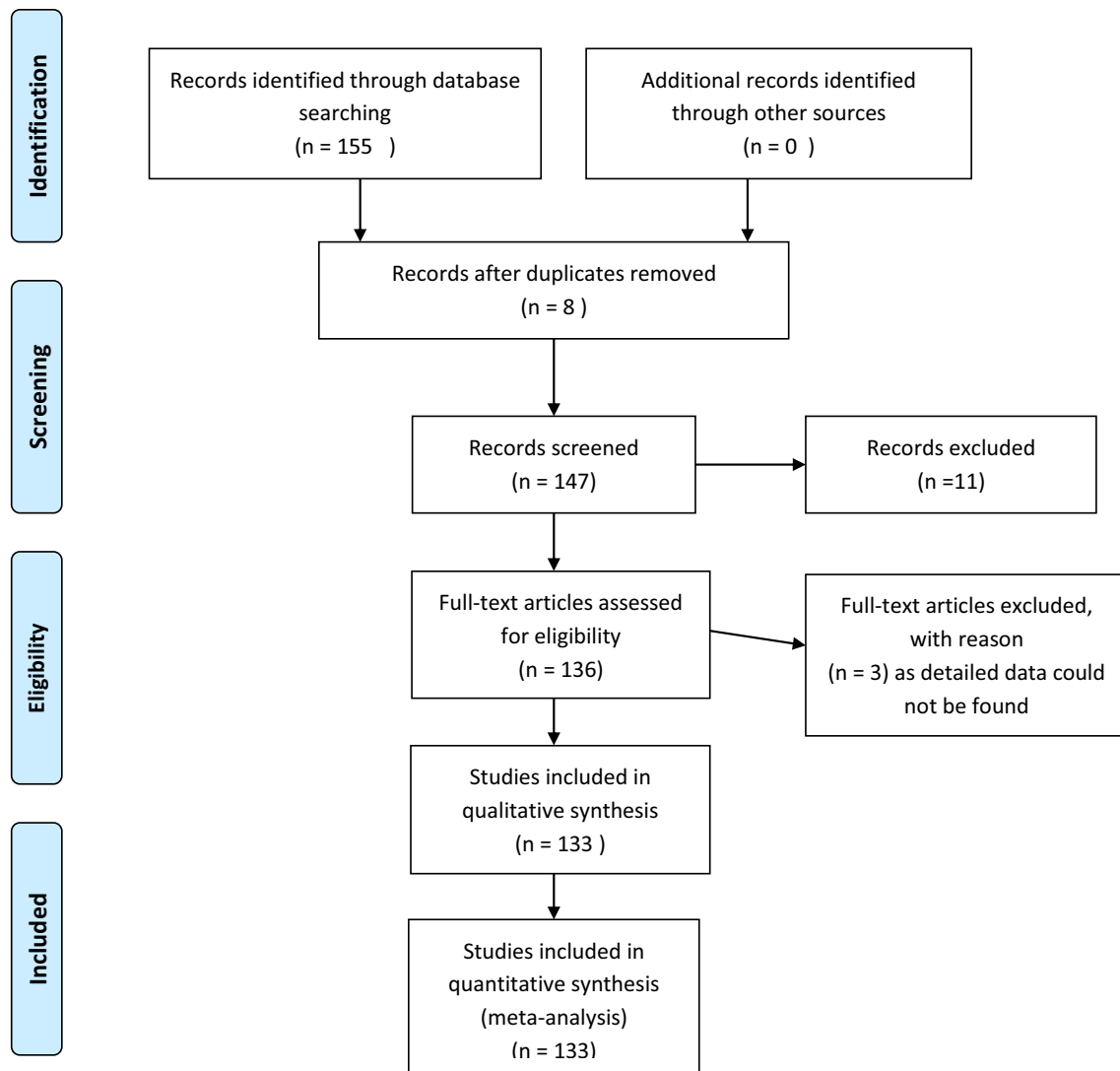
## Results

A total of 133 cases have been identified in various case reports and case series. All resulting titles, abstract, and full text, whenever available, were read and kept for reference, and the findings were summarized. Tables 2 and 3 lists complications and conclusion of various studies.

## Discussion

### Epidemiology

Gastrointestinal TB is the sixth most frequent site of extrapulmonary TB (EPTB) [6]. Involvement of esophagus with tuberculous infection is rare. Most of the reported cases of esophageal TB are of Asian origin. Esophageal TB accounts for less than 0.2% of total TB cases [7]; about 2.8% of gastrointestinal TB cases [8]; and 0.15% of patients who died of TB [9]. In a study by Jain et al. of 2176 patients with persistent dysphagia only 12 patients (0.55%) were found to have esophageal TB [10]. In another study by Buqing et al. 0.3% of patients of dysphagia were found to have esophageal TB [9]. Though, there is an



**Fig. 1** PRISMA flow chart

improvement in chemotherapy for TB, increased awareness, improvement in hygienic conditions and sanitation, and decrease in nutritional deficiencies, still, there is an increase in the number of pulmonary as well as EPTB cases. The possible reasons for this increase in cases are resurge in TB cases in developed nations due to HIV infection, increased frequency of EPTB among immunocompromised patients, and there is no drastic change in the incidence of overall TB cases in developing nations [11].

### Etiopathogenesis

Esophagus is relatively resistant to development of tuberculous infection. The following factors provide immunity to the esophagus:

1. *Enzymatic action of saliva* The saliva has antibacterial properties. The salivary enzymes act as a primary

barrier or natural defense mechanism against development of TB. The salivary enzymes also act as a filter for the clearance of pathogens from the lumen. The fats and waxes are present in a very high percentage in the envelope of tubercle bacillus; thus conferring high resistance. Destruction of this envelope renders the bacillus susceptible. The presence of thiocyanate ions and proteolytic enzymes in saliva results in complete bacteriolysis of tubercular bacillus. The concentration of saliva and its enzymatic action is maximum in upper third of esophagus; thus tuberculous involvement is least common in upper third of esophagus [9, 12].

2. *High motility due to peristalsis of esophagus* Continuous flow of saliva and high motility prevents lodging of Mycobacteria in the esophagus [12].

**Table 2** Complications of esophageal tuberculous

Complications	Number of cases	Mechanism and/or effect
Haematemesis	8	Occurs due to Esophageal ulcer formation which eventually erodes a vessel and bleeds Formation of fistulous communication with an artery or aorta Secondary involvement of aorta which can result in to false aneurysm formation with rupture
Esophageal stricture/ stenosis	7	Fibrous strictures most commonly forms in middle third of esophagus and results from external compression of the esophagus due to mediastinal or cervical lymph nodes. Stenosis results from fibrosis along with adjacent gland infection or with fibrosing mediastinitis. Most commonly forms during healing process at the stage of scar formation
Traction diverticulum	4	Results from deep ulceration of esophageal wall
Fistula formation		Fistula formation is a result of ongoing inflammatory process and tuberculous lymph node erosion which results in pressure necrosis and perforation into the adjacent structure. Site of fistula formation depends on the site of pathology in the esophagus, the group of lymph node involvement, immunological status of the patient and chronicity of the pathological process
Esophagobronchial fistula	4	
Esophagopleural fistula	2	
Esophagomediastinal fistula	1	
Esophagocutaneous fistula	1	
Esophagopulmonary fistula	1	
Esophagoarterial/ aortic fistula	4	
Recurrent laryngeal nerve palsy	1	Direct entrapment of nerve by the involved group of lymph nodes but this is rare
Abscess formation		
Soft tissue abscess	1	Result when a deep esophageal ulcer located on anterior wall of esophagus perforates or forms sinus into surrounding soft tissue, caseous material leaks along the sinus track and eventually forms soft tissue abscess
Mediastinal abscess	1	Results from breakdown of tuberculous mediastinal lymph node
Esophageal perforation	1	Deep ulceration is common with esophageal TB resulting into perforation into mediastinum

*TB tuberculosis*

3. *Anatomical factors* Antireflux effect due to upright posture and intact lower esophageal sphincter. Stratified mucosal lining and presence of submucosal lymphatics provides relative resistance to esophagus [9, 12].

Patients who develop EPTB have been reported to have some risk factors or comorbid conditions [11]. This holds true for esophageal TB also. Congenital or acquired immunodeficiency states are responsible for development of at an unusual site such as esophagus [11]. Therefore, the pathologies resulting in abnormal host-defense mechanism such as acquired immunodeficiency syndrome (AIDS), complement deficiency, malignancies, leukemia are at increased risk of developing esophageal TB [11, 13]. The use of steroids, chemotherapeutic agents and other immunosuppressive medications, prolonged illness,

nutritional deficiencies are also associated with an increasing incidence of esophageal tuberculosis in all age groups [11].

Esophageal TB can be due to primary or secondary infection. In primary infection, there is no evidence of TB elsewhere. Primary and isolated esophageal tuberculosis is a rare occurrence. Esophageal TB is usually secondary to pulmonary infection or it occurs as a part of multifocal gastrointestinal or miliary TB [1, 12, 14].

The possible routes of secondary tuberculous infection of esophagus are [1, 9]:

- (1) *Direct spread through tuberculous lesions in contiguous structure* This is the most common route of esophageal involvement with tuberculous bacilli. This is because of proximity of esophagus to lungs, spine laryngeal and pharyngeal lesions and mediastinal and hilar lymph nodes. Thus, it is relatively

**Table 3** Conclusion of various case series

Author (year) [reference]	Number of cases	Conclusion
Dow [31]	4	It is important to consider esophageal TB in any age group—particularly in those with subcarinal lesions and especially in the immigrant population, as they show an increased incidence of glandular infection
Mokoena et al. [15]	11	Treatment of esophageal TB relies on ATT, with surgery reserved for unresolving complications. Clinicians should be aware of TB of the esophagus as a possible cause of haematemesis in patients with otherwise unexplained upper gastrointestinal haemorrhage
Nagi et al. [4]	23	In all of these patients, more than one group of lymph nodes was involved. The middle third of esophagus was found to be the most frequent site of involvement. CT scan and Barium studies showed characteristic features
Puri et al. [23]	32	Esophageal TB does not appear to be a primary disease and is most likely secondary to mediastinal nodal TB. A conglomerated mass of heterogenous with predominantly hypoechoic lymph nodes on EUS appears to be characteristic feature
Buqing et al. [8]	6	Esophageal TB should be considered as a causative factor for dysphagia. Surgery should be applied in undiagnosed cases. VATS is useful in improving rates of confirmative diagnosis

TB tuberculosis, CT computed tomography, VATS video assisted thoracoscopic surgery, ATT antituberculous treatment

easy for any tuberculous lesion in these regions to reach the esophagus. In spite of this close proximity of esophagus to lungs, the most common site of tuberculous foci, esophageal involvement with TB is a rare occurrence. This is because of presence of submucosal lymphatics and stratified epithelial lining in the esophagus.

- (2) *Retrograde lymphatic spread* Lymphatic dissemination is considered as an important route of spread as lymphatic drainage from the esophagus occurs mainly to the subcarinal, peribronchial and paratracheal lymph nodes and also to the glands found between the esophagus and the aorta near to the inferior pulmonary veins. Buqing et al. reported that all of the 6 cases of esophageal TB were secondary to mediastinal tuberculous lymphadenitis.
- (3) Haematogenous spread from a distant focus such as pulmonary TB is a rare cause of esophageal TB and no such case of transmission has been reported in the literature.
- (4) *Swallowed sputum in patients with extensive pulmonary TB* This mode of involvement is more common in patients with severe nutritional deficiency and immunodeficiency.
- (5) Superinfection of a malignant lesion can occur; though no such case has been reported in the literature.
- (6) Reactivation of a dormant bacillus in an immunosuppressed patient can also occur.

Based on the mode of involvement, esophageal TB can be classified into the following:

- (1) Local, with isolated involvement of esophagus in the form of primary complex with caseation of the associated periesophageal lymph nodes. Dissemination of infection from draining lymph nodes is the most common mode of involvement in patients with AIDS and other immunosuppressive states [1, 14].
- (2) Esophageal TB developing secondary to pulmonary TB either by contiguous spread or swallowed sputum.
- (3) As a part of multifocal involvement of gastrointestinal tract.
- (4) Miliary TB, as a part of generalized TB resulting in involvement of esophagus as well. This is seen in severely immunosuppressed patients and resistant disease.

The most common site of involvement of esophagus in TB is its middle third; because of its proximity to tracheal bifurcation, hilar and mediastinal lymph nodes [10, 14]. Only two cases with involvement of lower third of esophagus has been reported [8, 13], in 1 case both middle and lower third were found to be involved [6], and involvement of upper third has not been reported.

### Clinical Features

The average age at diagnosis is 39 years. The youngest reported patient is 15 [15] while the oldest patient is 85 years old [14]. Majority of patients presented in 3rd decade of life. Males are affected more frequently, with a male to female ratio of 3.2:1. The clinical presentation is slow and insidious. The patients may remain asymptomatic initially. Most patients manifest symptoms ranging from 2 to 8 weeks. A more indolent course is seen in patients with

extrinsic compression of esophagus due to mediastinal lymphadenopathy. Progressive dysphagia is the most common presenting symptom reported in more than 90% of patients [10, 16]. For any esophageal mass lesion, dysphagia is the most common presenting symptom and TB of esophagus is rare; therefore, esophageal TB was not even considered as a possibility in majority of the reported studies. Constitutional features of TB such as weight loss, evening rise of temperature, night sweats, anorexia and weakness are present in up to 65% of cases.

Tassios et al. [17] reported a case in which patient presented with low-grade fever and no associated esophageal symptom. Other presenting symptoms are nausea, vomiting, belching, heartburn, acid regurgitation, retrosternal pain, hoarseness of voice, cough, epigastric pain, odynophagia, malena, and haematemesis [15, 18]. Table 1 shows the data of 4 of our cases.

Anaemia is the most consistent physical finding. Other less common findings are epigastric tenderness and cervical lymphadenopathy.

## Pathology

### Macroscopy

Esophageal tuberculous lesions are usually solitary. Nodular lesions are small while ulcerative lesions may be large and multiple. Miliary lesions are multiple. The most common gross pathological finding is presence of multiple white caseating nodules in the middle third of esophagus, coalescing to form a large yellowish mass of solid consistency. Pathologically, esophageal TB may have following variations or types [1]:

1. *Ulcerative type* This is most commonly encountered gross pathological finding. They may appear as large solitary or small multiple lesions. These ulcers are deep reaching up to submucosa, have a pale grey purulent floor, rough irregular edge. Initially a nodule appears in the submucosa, followed by caseation within the nodule and then the ulceration occurs. Large lesions may involve a long segment of middle third of esophagus. These ulcers can penetrate deeper into the muscle layer and adventitial layer of esophagus resulting into perforation or fistula formation.
2. *Hyperplastic type* This occurs due to excessive tubercular granulation tissue formation which then eventually gets replaced by fibrous tissue and often results in luminal narrowing and stenosis. This can also involve a long segment of middle third of esophagus.

3. *Granular type* This is the least common type of pathological finding. The mucosal lesion is greyish in colour and appears velvety. This occurs in severe systemic disease.

### Microscopy

The characteristic tubercle caused by *Mycobacterium tuberculosis* bacillus shows central granular caseation surrounded by aggregates of macrophages, epithelioid cells and langhans giant cells with variable degree of central caseous necrosis. This is the usual response in patients who develop cell-mediated immunity to the bacillus. Macrophages are circumscribed by a cuff of both T- and B-lymphocytes contained within the rim of fibroblasts. The lesions vary in size from 1 mm to > 2 cm. Occasionally, tubercular granulomas may not show central caseation. Fibrosis may develop in relation to epithelioid granulomas. Hilar and mediastinal lymph nodes may also show Caseating granulomas [11].

### Diagnosis

A delay in diagnosis is common because the disease is rare, symptoms are non-specific, and there are no specific signs. Up to three-fourth of patients suffer delayed evaluation and management. In up to 20% of cases, diagnosis is made after major surgical resection on histological examination. Clinical presentation, and laboratory features are non-specific; imaging studies also do not support the diagnosis of esophageal TB. The definitive diagnosis requires demonstration of MTB on histopathologic examination. Therefore, it is important to take image/endoscopy guided tissue for histopathological evaluation for timely diagnosis. Isolated or primary TB of esophagus is even rarer and diagnosis is challenging.

### Laboratory Evaluation

A number of laboratory abnormalities may be seen in an esophageal TB patient; however, there is no specific diagnostic laboratory test. These abnormalities reflect the nutritional deficiencies that are associated with chronic inflammatory pathologies, systemic involvement and/or sequelae and complications of the chronic disease process. In an uncomplicated case, total and differential leucocyte counts are usually within the normal range. Decreased haemoglobin and serum albumin level, elevated ESR and C-reactive protein, and positive tuberculin test support the diagnosis of TB. Haematologic and biochemical effects are severe when the esophagus gets involved as a part of disseminated disease. Approximately two-thirds of patients



show strongly positive tuberculin test; however, even a strong tuberculin test in endemic regions is of little or no significance. HIV antibody testing should also be done; though less than 1% of cases of esophageal TB have been found to be HIV positive.

### **Bacteriology and Culture**

Bacteriologic culture followed by use of special stains for acid-fast organisms is indicated when granulomas are present. Specimen for culture and acid-fast bacilli (AFB) staining can be obtained from sputum, esophageal and gastric aspirates, pleural fluid and tissue. The success rate of these modalities for esophageal TB has not been reported in detail. The success rate of tissue obtained through endoscopic biopsy from esophagus or image-guided tissue specimen from enlarged hilar or mediastinal lymph nodes is higher [16]. Seivewright et al. [19] reported that endoscopically obtained tissue specimens demonstrate AFB in less than 25% of cases. In a study by Mokoena et al. [16] of 11 cases, sputum was positive for AFB in one case, lymph node specimen obtained by thoracotomy showed positive AFB staining in one case, and endoscopic biopsy tissue obtained from esophageal lesion showed positive AFB staining in two cases.

### **Analysis of Pleural Fluid for Adenosine Deaminase (ADA)**

ADA is an important enzyme in T-lymphocytes and its increases concentration may be found in fluids present in the zones of TB serositis. ADA levels of pleural fluid may also be raised. Only one case positive for ADA, suggestive of esophageal TB has been reported in the literature [15].

### **Polymerase Chain Reaction (PCR) Assay and Other Tests**

Specimen for PCR may be obtained from pleural fluid, sputum, and tissue from esophagus and lymph node. Reports have shown that PCR too was positive from tissues obtained for biopsy [15]. Fujiwara et al. [20] concluded that PCR done on tissue is useful in supporting diagnosis in cases where the initial biopsies showed non-specific changes. In another report, bacteriological culture and histology were negative on tissue specimen while mycobacterial DNA was detected by PCR of paraffin-embedded esophageal biopsy specimen [20]. PCR assay was positive in 6 of the reported cases [7, 13, 15, 18, 20, 21]. T-cell spot test was positive in the esophageal lesion biopsy [18]. Interferon gamma release assay facilitated diagnosis in one case [22].

## **Imaging Studies**

### **X-ray Chest**

X-ray chest is an important initial study in patients suspected to have esophageal TB as majority of cases are secondary to either a pulmonary focus or a mediastinal tuberculous lymph nodal mass. Plain X-ray chest is effective in demonstrating both of these foci. X-ray chest shows some abnormality in up to 65% of cases [4]. In a study on 11 patients of esophageal TB, 3 were found to have pulmonary TB and mediastinal mass in 2, and paratracheal mass in 1 patient on chest radiograph [16].

### **Ultrasonography (USG)**

Conventional Ultrasonography (USG): It is the imaging modality of choice for initial evaluation of patients presenting with symptoms related to digestive system. USG of both chest and abdomen should be done. USG is an excellent modality for preliminary screening to confirm the presence of any extraluminal lesion including presence of space occupying in the lungs, any lesion suggestive of tuberculous lymph nodal mass in paratracheal, paraesophageal and presence of pleural fluid. It is difficult to pick up esophageal luminal lesions on conventional USG.

### **Endoscopic Ultrasonography (EUS)**

EUS is an excellent modality for demonstration of esophageal wall lesions, mediastinal lymph nodes and also for evaluation of other anatomical structures in the chest. In a retrospective study of 32 cases of esophageal TB, EUS showed enlarged lymph nodes adjacent to esophageal wall lesions in 18 cases; subcarinal region being the most common site of lymphadenopathy [23]. Lymph nodes were matted, and Puri et al. [23] concluded that a conglomerated mass of heterogenous with predominantly hypoechoic lymph nodes with intervening hyperechoic strands and foci are characteristic features of mediastinal TB. According to Buqing et al. the main features of EUS in esophageal TB are enlarged lymph nodes around the esophagus with hypoechoic center, ambiguous border between the mass and esophagus due to infiltration of the inflammatory mediastinal lymph nodes that resulted in interruption of esophageal adventitial layer [9, 24]. Though, EUS causes some discomfort to the patient but it has the potential to become an excellent and safe alternative to expensive computed tomography and magnetic resonance imaging study.

### Barium Esophagogram (BE)

It is an excellent study as it facilitates direct demonstration of luminal pathologies while extraluminal pathologies are shown as extrinsic compression or bulge into the lumen; but it has largely been replaced by endoscopy and computed tomography (CT) scan. Barium examination shows indentation, thickening of the involved part with or without esophageal narrowing, mucosal irregularity, nodularity [7], kinking, sinus/fistulous tracts, pseudotumor mass, [4] and displacement of esophagus [25]. In a study on 6 patients of esophageal TB, esophagography showed extrinsic compression in 4 cases and filling defect in 2 cases [9]. Extrinsic compression is most commonly seen at the subcarinal level [9].

### Contrast Enhanced Computed Tomography (CECT)

CECT is best imaging study in diagnosing esophageal TB as it typically detects lesions greater than 0.5 cm in diameter, even smaller lesions may be visualized with newer contrast-enhanced spiral techniques. The findings are non-specific as it is difficult to differentiate tubercular lesions from other inflammatory and malignant lesions of esophagus; but other associated findings of lymph node mass and pulmonary focus of TB and its sequelae helps in diagnosis.

CT findings include mural thickening of esophageal wall with luminal dilatation and associated paraesophageal and subcarinal lymphadenopathy showing heterogenous density with mottling calcification, peripheral thin rim enhancement with hypodensity in the central area [7]. In cases with tuberculous lesion involving lower esophagus with or without gastroesophageal junction involvement, CT scan of the upper abdomen should also be done. In a case report by Khan et al. [7] CT scan showed thickening of distal esophagus with infiltration in to lesser omentum and presence of centrally necrotic lymph nodes on gastrohepatic ligament, which were suggestive of malignancy but biopsy clinched the diagnosis. The characteristic finding of hypodense center of lymph node suggestive of TB was seen in 12 out of 23 cases in a study [4].

### Image Guided Fine Needle Aspiration Cytology (FNAC)/Trucut Biopsy

The best way to diagnose TB is direct histopathological examination. USG or CT or EUS guided FNAC/trucut can be done to obtain tissue from subcarinal, paratracheal and mediastinal lymph nodes. Obtaining tissue samples for biopsy from surrounding lymph nodes are important in esophageal TB as majority of cases are secondary with

primary focus of TB is found either in the lungs or lymph nodes. The success rate for this modality is not reported in the literature. EUS-guided FNA is preferred over conventional USG or CT guide FNA/biopsy [8]. In a study by Puri et al. [23] of 32, 27 cases were diagnosed by EUS-FNA of lymph nodes.

### Endoscopy

Endoscopy is the best modality as it facilitates not only direct visualization of the esophageal lesion but also aids in obtaining tissue for histopathological examination. Abid et al. [26] reported that esophageal ulcer is the most common esophagosopic finding. The most common endoscopic finding in esophageal TB patients are extrinsic bulge (62.5%) followed by ulcer formation (56.25%) [23]. Based on endoscopic findings, esophageal tuberculous lesions can be classified as:

1. Ulcerative lesion
2. Submucosal nodule
3. Nodule with central ulceration
4. Multiple aphthous ulcers
5. Polyps
6. Diverticulum
7. Stricture formation
8. Extraneous extrinsic compression
9. Sinus or fistula formation

In a study on 11 cases of esophageal TB, 4 cases were diagnosed by histopathological examination of tissue obtained by endoscopic biopsy [16]. Classical granulomas are seen in 50% of cases on endoscopically obtained tissue [19]. The sensitivity of endoscopic mucosal biopsy is 22% [16]. Welzel et al. [27] reported that sensitivity of endoscopy samples is low, ranging from 25 to 60.8%. This is because of low density of granulomas in the affected tissue. Efficacy of endoscopy samples can be increased by taking deeper biopsy bits reaching up to submucosal layer in suspected cases of esophageal TB.

### Role of Mediastinoscopy, Thoracoscopy and Exploratory Thoracotomy

Mediastinoscopy is indicated in presence of enlarged mediastinal lymph nodes and other imaging modalities fail to differentiate them from mediastinal tumors and/or cysts [15]. EUS-FNA and endoscopic biopsy in successful in diagnosing majority of ETB cases; but if they fail, mediastinoscopy should be considered before diagnostic thoracoscopy or thoracotomy [15]. In a study, out of 11 cases of esophageal TB, diagnosis was made by thoracotomy and biopsy in 3 cases [16].



## Positron Emission Tomography (PET) Scan

The role of PET scan in diagnosing esophageal TB has not been clearly specified and studied. In a study, out of 6 cases PET scan was done in 1 case but could not diagnose the nature of pathology as it shows increased metabolic activity in both inflammatory and malignant lesions [9].

## Criteria/Definition for Diagnosis of Esophageal TB

Based on the abovementioned epidemiological, clinical features and diagnostic modalities, the criteria for diagnosing esophageal TB in a suspected patient are- a relatively young patient with dysphagia from a region having a high incidence of active pulmonary TB cases, with exposure and/or history of pulmonary TB, with presence of active pulmonary TB and/or presence of tuberculous mediastinal lymph nodal mass on imaging study, elevated ESR, strongly positive tuberculin test, any of the microbiological test on fluid, pus or tissue obtained with the help of EUS or esophagoscopy with associated congenital or acquired immunodeficiency state, biopsy demonstrating caseating granuloma and last but not least, responds well to standard ATT started empirically.

In clinical scenarios with a high index of suspicion for the disease, treatment should not be withheld until the diagnosis is confirmed. This is crucial to prevent complication and avoid major surgical intervention. Table 2 describes conclusion of previously reported case series.

## Complications

Complications of esophageal TB are described in Table 3.

## Differential Diagnosis

Esophageal TB mimics carcinoma esophagus. Clinical features are same and it is difficult on imaging studies also to differentiate the two pathologies. Relatively younger age group at presentation, long history and history of pulmonary TB or active tuberculous lesion and/or presence of necrotic subcarinal, paraesophageal and mediastinal lymph nodes help in differentiating the two pathologies. Other differential diagnosis includes Crohn's disease and behcet's disease.

## Treatment

There are no specific or established guidelines for the management of esophageal TB. The management depends on the clinical presentation, its pathological stage at which diagnosis is made, the level at which the lesion is present,

extent of disease, immunological status of the patient, type of disease—whether reactive or occurring as a new pathology, site of associated primary focus, whether pulmonary or mediastinal lymph nodal mass, presence of disseminated disease and any associated sequelae and/or complication.

The principles of treatment are-

1. timely diagnosis of esophageal lesion and associated primary focus with non-invasive diagnostic modalities or with optimum use of invasive diagnostic modalities,
2. recognition of any associated sequelae,
3. medical management with optimum doses and duration of standard combination antituberculous therapy (ATT),
4. timely surgical intervention whenever indicated with pre- and post-operative ATT,
5. prevention of complications, and optimum management medically and/or surgically should they arise, and
6. regular assessment of disease burden and follow up.

Once a correct diagnosis has been made, the disease is curable with standard ATT; consisting of a combination of four drugs: isoniazid (5 mg/kg BW/day), rifampicin (10 mg/kg BW/day), pyrazinamide (30 mg/kg BW/day), ethambutol (20 mg/kg Bw/day) PAN [28]. Isolated disease with no past history of TB should be considered as a new case of EPTB and ATT should be given for 6 months [11, 29, 30]; treatment regimen consists of 2 months of intensive phase with four drugs followed by 4 months continuation phase with two drugs [7]. The best results of ATT are seen in patients with isolated or primary esophageal TB without complications. Isolated EPTB is associated with lower bacillary burden than pulmonary disease. Therefore, isolated EPTB such as esophageal TB can be treated with standard short-course regimens that are effective for pulmonary disease. However, primary or isolated esophageal TB is extremely rare and the most common form of disease is secondary to mediastinal lymph adenopathy. Secondary esophageal TB and disseminated disease with tuberculous esophageal involvement needs to be treated with 12 months chemotherapy [31].

Indications of surgical intervention [7, 14, 31]

- (1) Imaging studies and image guided FNAC, endoscopic biopsy and microbiological cultures and assay fail to diagnose esophageal TB.
- (2) Malignancies such as esophageal squamous and adenocarcinoma cannot be ruled out; mediastinal lymph nodal mass cannot be differentiated from mediastinal cyst or tumor.

- (3) The disease fails to show complete clinical response with ATT.
- (4) No radiological improvement even after standard ATT, the diseased segment needs to be resected for histopathological confirmation.
- (5) In presence of complications. The complications are rare and can be avoided. There is a report where esophagobronchial fistula healed completely with medical management [32].

#### Role of surgical intervention

1. *Endoscopic or surgical intervention to relieve esophageal stricture/stenosis* In case of esophageal stricture or stenosis causing esophageal obstruction, endoscopic dilatation with stenting is a preferred technique to relieve obstruction and ATT should be continued [33]. This is curative and any major surgical intervention is not required. When dilatation fails to relieve obstruction, resection of diseased segment and reconstruction. In a clinical scenario, when diagnosis is not confirmed, exploratory thoracotomy may be done, frozen section confirms the diagnosis and in such a case resection and reconstruction would be required depending on clinical scenario. Thoracotomy is also done for complications such as massive haematemesis and fistula formation and rarely for diagnostic purpose to provide tissue for histopathological examination [16].
2. Video-assisted thoracoscopic surgery (VATS)—it is done for patients with extraneous compression with intact mucosa. In a reported study, 5 out of 6 patients underwent VATS [9].

## Conclusion and Recommendations

TB of esophagus is a rare form of EPTB. Secondary esophageal TB is much more common than primary TB. The most common source of secondary esophageal involvement is tuberculous mediastinal lymphadenitis. Misdiagnosis is common as the clinical presentation closely resembles the more common esophageal pathology, esophageal carcinoma. The disease is medically curable with standard ATT if the correct diagnosis is made timely. The authors recommend.

1. Consider the possibility of esophageal TB in a patient presenting with dysphagia who is relatively young, in 3rd or 4th decade of life, comes from areas with high incidence of active pulmonary TB cases, with a past history or presence of active pulmonary TB. Laboratory evaluation shows raised ESR and strongly positive tuberculin test. Imaging studies suggestive

- of mediastinal mass with endoscopy showing ulcerative or nodular lesion, or a bulge in the esophagus.
2. As the disease is medically curable, try and make all efforts to diagnose the pathology with non-surgical diagnostic modalities in suspected cases so as to save patients from the trauma of major surgical resection.
3. Surgical intervention is indicated for medical treatment failure and complications. For undiagnosed cases, frozen section should be utilized before making any radical resection.

**Author Contribution** Study design, concept, drafting, data analysis: PC. Data collection, drafting: AN. Data collection: MM. Drafting: SBP. Drafting: SB. Critical analysis: RL.

#### Declarations

**Conflict of interest** Author declared that they have no conflict of interest.

**Ethical Approval** All the authors are in agreement with the final version of the manuscript.

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