Dysphagia (2022) 37:973–987
https://doi.org/10.1007/s00455-021-10360-x

ORIGINAL ARTICLE

Oesophageal Tuberculosis: A Systematic Review Focusing on Clinical Management

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Received: 19 January 2021 / Accepted: 20 August 2021 / Published online: 4 September 2021

Abstract

Oesophageal tuberculosis, an uncommon form of extrapulmonary tuberculosis, has been reported mainly as small case series and the literature is heterogeneous. A systematic review to characterize the clinical presentation, evaluation and management of oesophageal tuberculosis was performed. Electronic databases were searched with keywords: esophagus OR esophageal AND tuberculosis. We included original papers and case series (> 4 patients) with oesophageal tuberculosis. Twenty-two studies reporting 311 patients were included. Mean age in most of the studies was 31–51 years and male gender constituted 50.5% patients. Dysphagia (72.3%), odynophagia (22.4%) and chest pain (31.3%) were predominant symptoms. Mid-oesophagus was the commonest site of involvement (88%). Endoscopic findings included ulcers (59.9%), submucosal bulge (31.7%), extrinsic compression (24.8%) and pseudotumour (5.8%). On endoscopic ultrasound, presence of hypoechoic (69.5%), heteroechoic (47.6%) and matted (86.3%) mediastinal lymph nodes and oesophageal wall involvement (67.3%) were common findings. Computed tomography showed mediastinal lymphadenopathy (76.5%) and oesophageal thickening (52.1%). Diagnosis was confirmed by granuloma (72.3%) and acid fast bacilli positivity (32.5%) in mots patients. Response to antitubercular therapy was excellent; 97.7% patients recovered and 2.3% patients died. Surgery (14.5%) and oesophageal stenting (11.4%) were required infrequently. Oesophageal tuberculosis should be considered in endemic regions as a cause of dysphagia because early treatment is associated with excellent outcomes.

Keywords Dysphagia · Oesophagus · Tuberculosis · Gastrointestinal tuberculosis · Extrapulmonary tuberculosis · Deglutition · Deglutition disorders

Introduction

Extrapulmonary tuberculosis (EPTB) presents enormous clinical challenges related to varied presentations and difficulties in diagnosis [1]. Oesophageal tuberculosis (TB) is an uncommon form of EPTB which usually results from secondary extension from surrounding structures [2]. These patients commonly have concomitant involvement of other structures/organs including mediastinal lymph nodes, lungs and spine [3]. Common presentations include dysphagia, odynophagia, haematemesis and constitutional symptoms. Due to rarity of condition and non-specific presentation, sometimes it is misdiagnosed as malignancy and few of the patients might undergo surgery [4]. Oesophageal tuberculosis is traditionally diagnosed by oesophagoscopy and biopsy of lesions like ulcer, submucosal bulge (due to extrinsic compression by mediastinal lymph nodal mass), growth mimicking oesophageal cancer and occasionally presence of fistula [5]. Characteristic histopathology included caseating granuloma but is infrequent. The presence of acid fast bacilli (AFB) positivity or positivity of other microbiological tests (culture, polymerase chain reaction, i.e. PCR-based test) may provide specificity but the yield is low [6]. Sensitivity of

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endoscopic mucosal biopsy is even lower in cases with submucosal bulge with normal overlying mucosa. Role of endoscopic ultrasound (EUS) is increasing in diagnosis and follow-up of these patients as EUS can characterise paraoesophageal lymph nodal lesion as well as provide tissue for cytological and microbiological evaluation [7]. Response to anti-tubercular drugs is excellent and rarely these patients require endoscopic or surgical intervention [8]. Such interventions are usually warranted for complications like fistula or bleeding and are required infrequently.

In wake of the lack of a standardised approach towards the diagnosis and management of oesophageal tuberculosis, we performed a systematic review to synthesise an evidence-based approach to the diagnosis, treatment and follow-up of patients with oesophageal tuberculosis.

Methodology

This systematic review was conducted as per the available guidelines provided by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) [9].

Literature Search

We searched electronic databases for original research related to tubercular involvement of the oesophagus. We searched the Pubmed and Embase for keywords: esophageal, esophagus with tuberculosis, from 01/01/1971 till 6 January 2021 without any restrictions of region, language and type of articles. The detailed search methodology is shown in Supplementary Table S1.

Study Screening and Study Selection

The citations retrieved by the search were combined and duplicates were removed. The remaining citations were screened for title and abstract by two reviewers (CLB and AK). We excluded studies which were reviews, editorials, letters, case reports or small case series, animal studies or those not relevant to the topic. The studies which were identified as relevant were screened for the full text. Eventually some studies were excluded because of duplication or other reasons. The studies eventually selected for inclusion were those reporting original data on patients with oesophageal tuberculosis reporting on at least 5 patients irrespective of the language of publication. Any disagreement was resolved in consultation with a third reviewer (VS). Also, manual search of the references of the included studies was done to identify any additional eligible studies.

Data Extraction and Synthesis

From the included studies, two reviewers separately extracted data (CLB, AK) with reference to demographic profile, clinical symptoms and signs, laboratory investigations such as Mantoux test, imaging such as Chest X-ray, barium swallow and computed tomography scan, oesophagoscopy and trans-oesophageal endosonography. Note was made on the HIV status, other comorbidities and tuberculous involvement of other organ system(s). Modalities to obtain a sample for the histological/microbiological diagnosis of oesophageal tuberculosis and the findings on such an evaluation were also recorded. The medical and surgical management strategies and response to treatment data were extracted as well.

Results

Study Selection

A total of 3749 citations were identified and after removal of duplicates, 2925 results were screened for title and abstract. After initial screening, 2895 citations were excluded due to various reasons (2208 studies unrelated to topic, 610 case reports/series with sample size < 5, 8 animal studies, 56 reviews, 13 editorials). A third researcher (VS) and the other two resolved the disagreements after coming to a consensus. This yielded 30 studies of which further 8 had to be excluded since 7 had duplicate data and 1 was found unrelated. Finally, 22 studies were selected for extraction of data for systematic review. Of these 22, 3 of them were conference abstracts, whilst 19 were original articles (Fig. 1, PRISMA flow chart). The Table 1 summarises the details of included studies [10–31]. Supplementary Table S2 details the reasons for exclusion of the excluded studies [32–39].

Clinical and Demographic Details

Total number of patients included in different studies was 311 (range from 5 to 35). In most of the series, the mean age was between 31 and 51 years except Seo et al. where the mean age was 62 years [26]. The age ranged between 14 and 85 years. Twenty studies described the gender distribution and male constituted of 50.5% (144/285) suggesting an equal gender distribution. Dysphagia was the

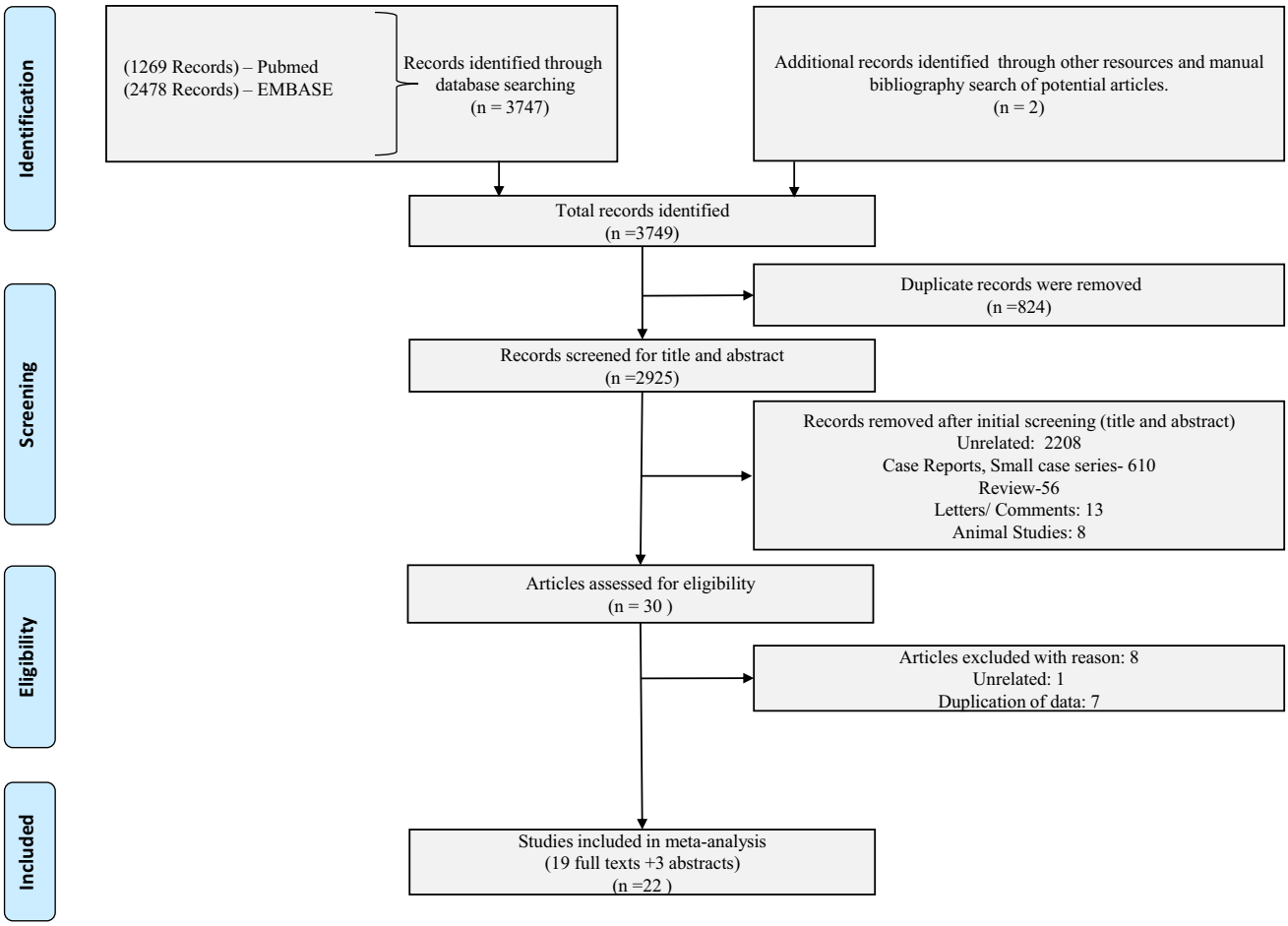

Fig. 1 PRISMA flow chart to show study selection

most common presenting symptom described in all of the studies and was present in 72.3% ($n=225$) patients. Other reported symptoms included odynophagia ($n=30$, 24.4%, 7 studies), chest pain ($n=50$, 31.3%, 11 studies) and cough ($n=34$, 23.1%, 12 studies). In the study done by Nagi et al., 19 (82.6%) patients had dysphagia or odynophagia (not mentioning both the clinical features separately) [24]. Constitutional symptoms such as fever ($n=34$, 24.3%, 12 studies), anorexia ($n=33$, 34%, 6 studies) and loss of weight ($n=34$, 24.2%, 10 studies) were present less commonly in these patients (Table 2). Fatigue and night sweats were present in 5 (14.3%) and 4 (8.7%) patients, respectively; however, only 1 study described these symptoms separately [27, 29]. One study described constitutional symptoms in 14 (46.7%) patients without any clear distinction in the symptom complex [31]. Other occasional symptoms that were reported were haematemesis in 7 (8.14%, 6 studies) and hoarseness of voice due to concomitant laryngeal involvement in 2 (18.2%, 1 study) patients [16]. The presence of an underlying malignancy was reported by only 2 studies: Devarbhavi et al. reported one patient (10%) had malignancy (Myelodysplastic syndrome), whilst Jain et al. reported that 3 patients (25%) had concomitant squamous cell carcinoma of the oesophagus [10, 11]. Other comorbidities in the patients were liver cirrhosis ($n=1$), chronic hepatitis B ($n=2$), coronary artery disease ($n=1$), syphilis ($n=1$) and post-renal transplant status ($n=1$) [15, 22, 23, 28].

Evaluation and Routine Investigations

Eleven studies reported HIV status of the patients and only 8 of 132 (6%) were HIV positive. Eight studies reported Mantoux test and 63 (75.9%) patients showed Mantoux test reactive; IGRA was not reported in any of these studies. Ten studies reported chest X-ray findings and 49 (38%) patients reported to have abnormalities on chest X-ray. Most common abnormalities were widening of mediastinum/mediastinal lymphadenopathy ($n=21$, 33.3%, 4 studies) and evidence of pulmonary tuberculosis either healed or active in 21 patients

Table 1 Characteristics of studies included in the systematic review

Study	Study period	Number/male gender	Age years Mean/median (range)	Comorbidity	Clinical features	Other organ system involvement	Oesophagoscopy findings	EUS findings	CT findings	Basis of diagnosis	Final outcome
Devarbhavi et al. [10]	1995–2000	10 4 males	42.2 (18–73)	Malignacy-1 (MDS) HIV-2	Dysphagia 9 Cough 3 Constitutional symptoms 2	Spinal TB 2 Pleural effusion 1 Pericardial eff. 1 Skin 1	Ulcer 10 Sinus/fistula 5 Submucosal bulge 3 Diverticulum 4	–	Mediastinal LN 9 Cervical LN 3 TEF 5 Pneumomediastinum 5	Granuloma 6 Caseous 3 AFB + 2	Recovery 8 Death 1 F/U NA 1
Jain et al. [11]	1995–1999	12 1 male	40 (17–70)	Malignacy-3 (SCC) HIV-0	Dysphagia 12 Chest pain 4 Constitutional symptoms 2	Primary oesophageal TB: 10	Ulcer 7 Stricture 3 Pseudotumour 4 Diverticulum 1 Submucosal bulge 1	–	–	Granuloma 12 Caseous 5 AFB + 7	Recovery 9 Death 3 (SCC) Surgery 2 (SCC)
Rajasekar et al. [12]	1996–2013	21 Gender: NA	NA	–	Dysphagia 18 Cough 7	Other organ system 17	Ulcer 21 Sinus/Fistula 8	–	–	–	Recovery 12 Surgery 6 Stenting 3 Death 0
Puri et al. [13]	2003–2009	32 18 Males	31 (18–46)	No comorbidies	Dysphagia 32 Odynophagia 8 Constitutional symptoms 20		Ulcer 24 Extrinsic compression 26	Hypoechoic 27 Heteroechoic 27 Oesophageal Wall involvement 14 Hyperechoic strands + Subcarinal LN 30 Paraoesophageal LN 2 Matted LN 32	–	AFB + 19 27 patients showed findings suggestive of TB 23/32—FNAC 12/18—Biopsy 27/32—combined	Recovery 32 Death 0 Surgery 0
Park et al. [14]	1997–2006	6 3 males	51 (20–85)	HIV-0	Dysphagia 3 Odynophagia 1 Cough 1 Haematemesis 1 Constitutional symptoms 1	Lungs 1 Cervical LN 1 Supraclavicular LN 1	Ulcer 4 Pseudotumour 2	–	Mediastinal LN 6 Oesophageal Wall involvement 5	Granuloma 6 Caseous 4 AFB + 0	Recovery 6 Death 0 Surgery 0 Intervention 0

Table 1 (continued)

Study	Study period	Number/male gender	Age years Mean/median (range)	Comorbidity	Clinical features	Other organ system involvement	Oesophagoscopy findings	EUS findings	CT findings	Basis of diagnosis	Final outcome
Ni et al. [15]	2006–2011	6 2 males	(28–71)	DM-1 Cirrhosis-1 CAD-1 HIV-0	Dysphagia 6 Cough 1 Chest pain 1 Constitutional symptoms 4	Lungs 1 Pleural effusion 1 Pneumothorax 1	Ulcer 1 Pseudotumour 1 Diverticulum 1 Extrinsic compression 4 TEF 1	LN with hypoechoic centre, interruption of oesophageal adventitia	Mediastinal LN 6 Oesophageal Wall thickening 6	Granuloma 6 Caseous 6 AFB + 6 Culture + 6	Recovery 6 Death 0 Surgery 6 Iatrogenic TEF 1
Mokoena et al. [16]	1972–1990	11 6 males	37.9 ± 14.7	–	Dysphagia 9 Haematemesis 2 Hoarseness of voice 2	Lungs 2 Pleural effusion 1 Mediastinal LAP 3	Ulcer 2 Sinus/fistula 2 Pseudotumour 2 Diverticulum 1	–	–	Granuloma 8 AFB + 3	Recovery 9 Death 2 Surgery 3
Zhu et al. [17]	2011–2018	9 3 males	45 (29–59)	No comorbidies	Dysphagia 5 Chest pain 6	Active PTB 2 Healed PTB 6	Ulcer 7 Sinus/fistula 1 Pseudotumour 5 Diverticulum 1 Submucosal bulge 2	Hypoechoic 4 Oesophageal wall involvement 9 Paraoesophageal LN 8	Active PTB 2 Healed PTB 6	Biopsy at least twice negative—no granuloma, AFB- all	Recovery 9 Death 0 Surgery 0
Hu B et al. [18]	2006–2012	5 Gender: NA	NA	-	Dysphagia 5 Chest pain 3	–	–	–	–	–	–
Dahale et al. [19]	2014–2016	19 9 males	39 (14–45)	HIV-1	Dysphagia 16 Odynophagia 8 Cough 4 Haematemesis 2 Constitutional symptoms 17	Active PTB 3	Ulcer 17 Sinus/fistula 4 Diverticulum 1 Extrinsic compression 8	EUS in 8 patients, all had subcarinal and paraoesophageal LAP, matted LN in 5	Active PTB 3 Mediastinal LN 19 Oesophageal Wall thickening 19	Granuloma 11 Caseous 5 AFB + 4 Gene xpert + 3	Recovery 18 Death 0 Surgery o Clipping 1

Table 1 (continued)

Study	Study period	Number/male gender	Age years Mean/median (range)	Comorbidity	Clinical features	Other organ system involvement	Oesophagoscopy findings	EUS findings	CT findings	Basis of diagnosis	Final outcome
Jia et al. [20]	1965–1985	10 3 males	(14–45)	No comorbidies	Dysphagia 10	Active PTB 2 Healed PTB 2 Spinal TB 1 Chylous pleural effusion 2	UGIE in 7 patients Submucosal bulge 5 Extrinsic compression 7	–	CT and MRI in 2 patients each Oesophageal wall compression 3 Oeophageal mass 3	–	Recovery 10 Death 0 Surgery 6 (5—pre-op diagnosis of Leiomyoma) Chylothorax 2
Bhatia et al. [21]	2007–2012	9 6 males	36 (18–61)	HIV-3	Dysphagia 5 Haematemesis 2 Constitutional symptoms 5	Other organ system 8-PTB 2 Disseminated 3 Meningitis 1 Bursitis 1 Abscess 1	Sinus/fistula 1	–	–	Granuloma 9	Recovery 7 Death 0 Surgery 0
Baijal et al. [22]	–	5 4 males	43.8 ± 17 (17–59)	HIV-2 Renal transplant 1	Dysphagia 3 Cough 4	PTB 2	Ulcer 3 Sinus/fistula 5	–	–	Biopsy suggestive of TB in all 5 PCR + 2	Recovery 5 Death 0 Surgery 1 Glue + clip 1 PEG 3
Rathinam et al. [23]	1996–2003	14 9 males	(27–79)	DM-3 COAD-1	Dysphagia 14 Cough 4 Constitutional symptoms 14	Old PTB 2	Ulcer 2 Extrinsic compression 10 TEF 4	–	Mediastinal LN 7 Cervical LN 1 Trachea/oesophageal shift 14	Granuloma 14	Recovery 14 Surgery 7 Stenting 1 Iatrogenic TEF 1
Nagi et al. [24]	1985–2001	23 15 males	(18–85)	–	Dysphagia/odynophagia 19 Chest pain 7 Cough 6	Active PTB 8 Spinal TB 1 Pleural effusion 1 Mediastinal LN 9	Done in 23, details not mentioned	–	CT in 15 patients Mediastinal LN 14 Oesophageal wall thickness 5	Tissue diagnosis suggestive in 18 Caseous granuloma 7 AFB + 5	Recovery 22 Death 1 Surgery 1

Table 1 (continued)

Study	Study period	Number/male gender	Age years Mean/median (range)	Comorbidity	Clinical features	Other organ system involvement	Oesophagoscopy findings	EUS findings	CT findings	Basis of diagnosis	Final outcome
Rana et al. [25]	2009–2013	14 10 males	37.7 (26–62)	No comorbidies	Dysphagia 14 Constitutional symptoms 11	No other organ involvement	Ulcer 5 Submucosal bulge 12 Extrinsic compression 7	All had echogenic strands. Focal anechoic/hypoechoic areas in 3, calcification in 1	Subcarinal LN 14 Paratracheal LN 5 Oesophageal wall thickness 5	Granuloma 13 Caseous 9 AFB + 3	Recovery 14 Death 0 Surgery 0
Seo et al. [26]	2007–2014	6 3 males	62 39–79	H/o TB—3	Dysphagia 2 Chest pain 1	Old PTB 4	Submucosal bulge 6	Hypoechoic 6 Heteroechoic 4 Oesophageal wall involvement 6 Hyperechoic strands 4	Healed PTB 4 Mediastinal LN 3	Granuloma 6 Caseous 2 PCR + 2 AFB + 0	Recovery 6 Death 0 Surgery 0
Tang et al. [27]	2006–2015	35 15 males	37.7 (19–74)	H/o TB—6	Dysphagia 32 Odynophagia 8 Chest pain 5 Constitutional symptoms 5	Active PTB 4	Ulcer 27 Submucosal bulge 27	Oesophageal wall Full thickness involvement = 30, Intact mucosa = 5, adventitia disruption in all 35 patients Homogeneous/heterogeneous hypoechoic LN in all 35 patients	Active PTB 4 Mediastinal LN 30 (Subcarinal 29) Oesophageal wall thickening 30	Granuloma 33 Caseous 13 AFB + 14	Recovery 35 Death 0 Surgery 0

Table 1 (continued)

Study	Study period	Number/male gender	Age years Mean/median (range)	Comorbidity	Clinical features	Other organ system involvement	Oesophagoscopy findings	EUS findings	CT findings	Basis of diagnosis	Final outcome
Xiong et al. [28]	1999–2019	14 7 males	44.6 (29–57)	Chronic Hep.B-2 Syphilis-1 HIV-0 DM-0	Dysphagia 7 Odynophagia 1Chest pain 5 Cough	Active PTB 1	Ulcer 6 Sinus/fistula 1 Submucosal bulge 10	Done in 11 patients Hypo/heteroechoic LN 8 Interrupted oesophageal wall 3 Paraoesophageal LN 7 Matted LN 7	Done in 8 patients Mediastinal LN 3 Mediastinal mass 1 Oesophageal wall thickening 3 Oesophageal mass 4	Granuloma 14 Caseous 6	Recovery 14 Death 0 Surgery 3
Wang et al. [29]	2008–2012	11 6 males	49.1 (27–77)	–	Dysphagia 4 Odynophagia 4 Chest pain 3 Constitutional symptoms 1	Active PTB 3 (lung nodules) Old PTB 2	Ulcer 4 Submucosal bulge 7	Hypoechoic 9 Hyperechoic strands 3 Mediastinal LN 6 Oesophageal wall thickening 3 Adventitia disruption 3	Mediastinal LN 5 Lung nodules 3	Noncaseating granuloma 3 Caseating 2 AFB + 0	Recovery 11 Death 0 Surgery 1
Youngguang et al. [30]	1980–2004	9 7 males	47.6 (15–58)	–	Dysphagia 8 Chest pain 5 Cough 3 Constitutional symptoms 4	Lungs 5 (Active + healed) Pleural effusion 1	Ulcer 1 Stricture 3 Pseudotumour 2 Extrinsic compression 5	–	Done in 4 patients Mediastinal LAP 2 Oesophageal wall thickening 2	Noncaseating granuloma 3 Caseating 2 AFB + 0	Recovery 9 Death 0 Surgery 7

Table 1 (continued)

Study	Study period	Number/male gender	Age years Mean/median (range)	Comorbidity	Clinical features	Other organ system involvement	Oesophagoscopy findings	EUS findings	CT findings	Basis of diagnosis	Final outcome
Song et al. [31]	2008–2012	30 13 males	44.8 (25–68)	–	Dysphagia 11 Odynophagia 7 Chest pain 10 Constitutional symptoms 14	Active PTB 2 Healed PTB 11 Miliary TB 2 Mediastinal LN 4	Ulcer 23 Stricture 4 Sinus/fistula 2 Submucosal bulge 14	Done in 28 patients. Thickened oesophageal wall, adventitia disruption, hypoechoic lesions, punctate hyperechoic shadows, thickening of serosa, LN next to oesophagus, calcification	Done in 19 patients Active PTB 2 Healed PTB 11 Miliary TB 2 Mediastinal LN 4	8 suggestive for TB on biopsy	Recovery 30 Death 0 Surgery 0

Table 2 Clinical features and outcomes of patients with oesophageal tuberculosis

Parameter	Frequency (%)
Clinical presentation	
Dysphagia n (%)	225 (72.3%)
Odynophagia	30 (24.4%)
Chest pain	50 (31.3%)
Cough	34 (23.1%)
Haematemesis	7 (8.1%)
Constitutional symptoms	34 (24.3%)
Other organs involved (Based on CT, $n=179$)	
Active pulmonary TB	18 (11.1%)
Healed pulmonary TB	23 (14.2%)
Other sites	12 (7.4%)
HIV positive	8 (6%)
Mantoux test	63 (75.9%)
Outcomes of treatment	
Recovered	293 (97.7%)
Death	7 (2.3%)
Surgery	43 (14.5%)
Oesophageal stenting	4 (11.4%)
Clip (Haemoclip/OTSC)	2 (8.3%)

(32.3%, 5 studies). Other less frequently reported findings were pleural effusion in 2 patients (5.9%, 2 studies), lung abscess in 1 patient (4.3%, 1 study) and loss of paratracheal stripe in 4 patients (28.6%, 1 study) [16, 23].

Endoscopy and Endoscopic Ultrasound

Oesophagoscopy was done in most of these patients ($n=303$, 21 studies). Fifteen studies reported sites of involvement. Mid-oesophagus was the most common site involved ($n=191$, 88%) followed by lower oesophagus ($n=18$, 8.3%). Upper oesophageal involvement was the least common seen in only 8 patients (3.7%). On oesophagoscopy, presence of ulcer ($n=164$, 59.9%), submucosal bulge ($n=87$, 31.7%) and extrinsic compression ($n=68$, 24.8%) were frequently observed. Other less common findings described were stricture in 10 (3.6%, 3 studies) patients, sinus/fistula in 29 (10.6%, 12 studies) patients, diverticulum in 9 (3.3%, 7 studies) patients and growth mimicking oesophageal cancer in 16 (5.8%, 6 studies) patients.

Ten studies reported endosonographic findings in patients with oesophageal tuberculosis ($n=160$). All have described the presence of mediastinal lymph nodal mass as a frequent finding (Table 3). Lymph nodes appeared either hypoechoic ($n=57$, 69.5%) or heteroechoic ($n=39$, 47.6%). Hyperechoic strands without acoustic shadowing were seen in 21 (67.7%) patients as reported in 3 studies. Two studies which

included 63 patients described lymph nodes as heteroechoic predominantly hypoechoic with hyperechoic strands (did not describe these features separately). Three studies noted that the majority of patients ($n=44/51$, 86.3%) had matted lymph node [13, 19, 28]. Another finding reported on EUS was oesophageal wall involvement ($n=62$, 67.3%). Forty-two patients (40.4%, 6 studies) had oesophageal wall thickening and 45 patients (43.3%, 6 studies) had disruption of adventitia. One study of 28 patients reported lymph nodal mass and oesophageal wall involvement in all of these patients, without describing each of these features separately [31].

Imaging Studies

Seven studies reported the barium oesophagogram of 78 patients. Common findings were presence of extrinsic compression ($n=42$, 53.8%) and fistula ($n=22$, 28.2%). Other less common findings were presence of stricture and irregular mucosa (14 patients each, 17.9%), ulcer ($n=8$, 10.3%), diverticulum ($n=7$, 8.97%), pseudotumour ($n=7$, 8.97%) and kinking of oesophagus ($n=3$, 13%) which was reported only in only one study [24].

Computed tomography was the most frequent cross-sectional imaging used ($n=179$, 16 studies). Most common findings were presence of lymphadenopathy (130 patients (76.5%) had mediastinal lymphadenopathy, 5 patients (2.9%) had cervical lymphadenopathy) and oesophageal wall thickening ($n=73$, 52.1%, 14 studies) (Table 3). Other less common findings were oesophageal mass ($n=9$, 50%, 2 studies), pneumomediastinum ($n=5$, 50%, 1 study) and pneumothorax ($n=1$, 17%, 1 study) [15, 20, 28]. Pneumomediastinum has been reported in only one study and was present in 50% of the patients [10]. Concomitant tubercular involvement elsewhere was also seen on CT. Eighteen (11.1%) patients had active pulmonary tuberculosis, 23 (14.2%) patients had evidence of old pulmonary tuberculosis, 2 (6.1%, 2 studies) patients had miliary tuberculosis, 5 (3.1%) patients had pleural effusion, 1 patient had pericardial effusion and 4 (9.3%, 3 studies) patients had spinal tuberculosis [10, 20, 24, 31]. Interestingly, none of the studies reported the presence of GITB.

Histology and Microbiology

Tissue diagnosis either by histopathology of endoscopic biopsy/surgical specimen or by cytology was the basis of confirmation of diagnosis in 20 studies ($n=249$). Granulomatous inflammation was present in 144 (72.3%, 15 studies) patients and 64 (32.2%) patients had caseous granuloma. Microbiological evidence in form of AFB positivity on Ziehl Neelsen staining was present in 63 (32.5%) patients; other methods like Gene Xpert Mtb/Rif ($n=3$, 16.7%, 1 study) and PCR ($n=4$, 23.5% 2 studies) were less commonly reported [14, 19, 22, 26]. Out of these 20 studies in which description of tissue diagnosis was provided, 3 studies reported diagnosis of tuberculosis confirmed on either the presence of granuloma or AFB; however, details of either of the findings are not provided separately [20, 22, 31]. A total of 105 patients (9 studies) of oesophageal tuberculosis underwent EUS-guided FNAC. Two studies reported that aspirated material was caseous in character ($n=7$, 33%) [25, 29]. Presence of chronic granulomatous inflammation (80.2%, $n=61$, 8 studies) and caseous necrosis (43.4%, $n=33$, 8 studies)

Table 3 Endoscopic, endoscopic ultrasound and imaging features of oesophageal tuberculosis

Oesophagoscopy findings	Frequency (percentage)
Site	
Upper oesophagus	8 (3.7%)
Mid-oesophagus	191 (88%)
Lower oesophagus	18 (8.3%)
Morphology	
Ulcer	164 (59.9%)
Submucosal bulge	87 (31.7%)
Extrinsic compression	68 (24.8%)
Pseudotumour	16 (5.8%)
Sinus/fistula	36 (20.3%)
Stricture	10 (3.6%)
Diverticulum	9 (3.3%)
Endosonographic findings	
Hypoechoic lymph nodes	57 (69.5%)
Heteroechoic	39 (47.6%)
Hyperechoic strands	21 (67.7%)
Oesophageal wall involvement	62 (67.3%)
Oesophageal wall thickening	42 (40.4%)
Adventitia disruption	45 (43.3%)
Matted lymph nodes	44 (86.3%)
Chest X-ray ($n=129$)	
Abnormal chest X-ray	49 (38%)
Mediastinal mass/widening	21 (33.3%)
Barium swallow ($n=78$)	
Extrinsic compression	42 (53.8%)
Fistula/sinus	22 (28.2%)
Stricture	14 (17.9%)
Irregular mucosa	14 (17.9%)
Ulcer	8 (10.3%)
Diverticulum	7 (9%)
Pseudotumour	7 (9%)
CT chest ($n=179$)	
Mediastinal Lymphadenopathy	130 (76.5%)
Oesophageal wall thickening	73 (52.1%)

were the most common histologic features identified. The yield of acid fast bacilli on ZN staining (38.1%, $n=40$, 9 studies) and Xpert MTB/RIF & PCR positivity ($n=3$, 2 studies reported) were also reported in some studies. One study reported EUS FNAC to be diagnostic in 72% ($n=23$) of the patients amongst whom 19 (59.3%) had AFB on ZN staining. However, the presence of granulomatous inflammation and caseous necrosis were not reported separately [13]. None of the studies reported use of mycobacterial culture from EUS-FNA material for the diagnosis of oesophageal tuberculosis. The diagnostic superiority of EUS FNAC compared to standard endoscopic biopsy was reflected in some studies. Puri et al. reported that the yield of EUS-guided FNAC was better (23/32, 71.9%) compared to endoscopic biopsy (12/18, 66.7%) [13]. Likewise, Dahle et al. reported that 61.1% (11/18) of the patients were diagnosed by endoscopic biopsy; however, EUS FNAC was diagnostic in 100% (8/8) of the patients including seven patients with inconclusive endoscopic biopsy [19]. Rana et al. reported 92.9% (13/14) sensitivity of EUS-guided FNAC in patients with prior inconclusive endoscopic biopsy in patients with oesophageal tuberculosis [25]. Tang et al. reported 94.3% (33/35) sensitivity of EUS-guided biopsy/FNAC [27].

Treatment and Outcomes

Two studies reported use of standard treatment, i.e. HRZE (Isoniazid, Rifampicin, Ethambutol and Pyrazinamide) for induction and HR/HRE for maintenance. Anti-tubercular therapy (ATT) was prescribed for duration ranging from 3 to 12 months in various studies. Most of the authors used either 6 ($n=154$, 10 studies) or 9 months ($n=50$, 3 studies) of ATT. Six months of ATT showed complete response in 92.9% ($n=143$), need of surgery in 4.5% ($n=7$) and death in 2.6% ($n=4$) patients. All the patients who received ATT for 9 months improved. Two studies (both in abstract form) reported 6–12 months of ATT, but the outcomes were not reported in both [12, 18]. One study each reported duration of ATT for 3–10 months ($n=9$), 6–18 months ($n=9$) and for 12 months ($n=5$) [17, 22, 31]. All three studies reported complete response or improvement in 100% of the patients and there was no difference in patients who received treatment for 3 months or 10 months. The treatment with four drugs for three months is unusual but the study reporting it mentions its use a diagnostic strategy with confirmation of endoscopic healing with treatment [17].

The follow-up was on clinical grounds and only 5 studies reported follow-up endoscopy in these patients ($n=63$) and all showed endoscopic healing [14, 17, 25, 26, 31]. Most common method of assessment of response was improvement of local (dysphagia, odynophagia, cough) and systemic (constitutional) symptoms and mucosal healing on endoscopy. Clinical response to ATT was present in 94.6% ($n=245$, 20 studies reported). Death (1.1%, $n=3$) and need of additional treatment (4.2%, $n=11$) were uncommon. Studies by Puri et al. and Xiong et al. reported resolution of oesophageal wall thickness and mediastinal lymphadenopathy on EUS [13, 28]. Ni et al. reported radiological healing using repeat CT scan after completion of ATT [15].

Complications

Most common complications of oesophageal tuberculosis observed in the patients were oesophago-tracheal/oesophago-mediastinal fistula ($n=36$, 20.3%, 13 studies) and haematemesis ($n=7$, 15.6%, 4 studies reported). Mediastinal abscess ($n=1$) and oesophagocutaneous fistula ($n=2$) were reported less frequently [12, 16, 20]. Those who had developed oesophago-tracheal/oesophago-mediastinal fistula usually presented with coughing on swallowing in 29.5% ($n=19$, 6 studies), hematemesis in 10% ($n=3$, 2 studies) and aspiration with chest infection ($n=5$, 2 studies) [10, 12, 15, 16, 19, 22, 23]. Tracheo-oesophageal fistula was diagnosed in the patients using contrast oesophagogram (8 studies) and/or oesophagoscopy (7 studies). Some of the patients were diagnosed with TEF on CT thorax (3 studies) and PET CT (1 study) [10, 12, 18, 28]. Bronchoscopy was not used in any of the studies to identify TEF.

Management of Fistula and Indications of Surgery

Most of the patients of oesophageal tuberculosis complicated with oesophago-tracheal/mediastinal fistula required interventions other than ATT. Short-term placement of naso-gastric tube ($n=10$, two studies) and percutaneous endoscopic gastrostomy tube ($n=3$, one study) was reported to bypass diseased oesophagus and subsequent healing of fistula [10, 22]. Devarbhavi et al. reported that all the fistulae were healed and the NG tube was removed after 2–4 weeks [10]. Baijal et al. reported that the NG tube was placed for 1 month in all 5 patients with TEF, and complete healing of fistula was reported only in 1 patient. Out of remaining 4 patients, three underwent the PEG tube placement (for 3 months in 2 patients, and for 6 months in 1 patient). Another patient with large fistula underwent glue and haemoclip application but later required surgery in view of failed endotherapy [22]. Four patients underwent a retrievable stent placement [12, 23]. In the study done by Rajasekar et al., all of the three placed stents were removed after 6 weeks [12]. The only

patient who underwent an oesophageal SEMS placement for TEF resolution in Rathinam et al. study did not improve and the patient later was managed with surgery [23]. One patient underwent OTSC placement for TEF [19]. Some form of surgery was done in 43 patients. The indications for surgery were repair of TEF ($n=12$), excision of lymph nodes/biopsy ($n=16$), drainage of abscess or lymph node suppuration ($n=5$), malignancy ($n=6$) and misdiagnosis of leiomyoma ($n=7$). The indications of surgery were not reported in 2 studies [24, 28]. Complications of surgery were reported in 2 studies [20, 23]. Jia et al. reported chylothorax as complication of surgery in two of their patients [20]. Rathinam et al. reported TEF as complication of suppurating mediastinal lymph node drainage in one patient [23]. All of these patients required repeat reparative surgeries. Only one death was reported in patients who underwent surgery. Mokoena et al. reported death due to massive haematemesis in one patient despite gastroduodenal exploration, vagotomy and pyleroplasy. An aorto-oesophageal fistula was diagnosed on autopsy which was missed premortem [16]. None of the patients required endoscopic dilatations for stricture.

Discussion

The present systematic review summarises clinical features, diagnosis and management of oesophageal tuberculosis. The review had identified that the dominant presentation would include symptoms of dysphagia, odynophagia, chest pain in addition to constitutional symptoms. However, the review also identified that a subset of patients present with complicated disease like fistulae with adjacent structures like mediastinum or trachea and present therapeutic challenges. The diagnostic strategy clearly depends on the morphological pattern of the lesions; whilst patients with mucosal lesions like ulcers benefit from endoscopic biopsies, those with submucosal lesions should be evaluated using endoscopic ultrasound. In fact, EUS provides an opportunity to clearly identify the site of involvement and also obtain tissue for microbiological and cytological analysis. Thickening of oesophageal wall and disruption of adventitia on EUS may also suggest its diagnostic possibility. EUS-guided FNAC from mediastinal lymph nodes and submucosal lesions additionally helps to diagnose it as the literature suggests an increased sensitivity of EUS FNAC when submucosal bulge/extrinsic compression due to lymph nodal mass with overlying normal mucosa are present (Supplementary Table S3). Needless to say, a cross-sectional imaging in form of computed tomography may help direct the endoscopic ultrasound and may also identify any associated pulmonary lesions [10, 11, 16, 19, 24, 30]. Therefore, the present review clearly points to the need for a systematic approach to achieve the diagnosis. The condition must be considered in patients with oesophageal lesions but negative for malignancy.

There were certain lacunae and gaps in knowledge which were identified by the present review. It is clear, like in other forms of EPTB, the microbiological diagnosis is

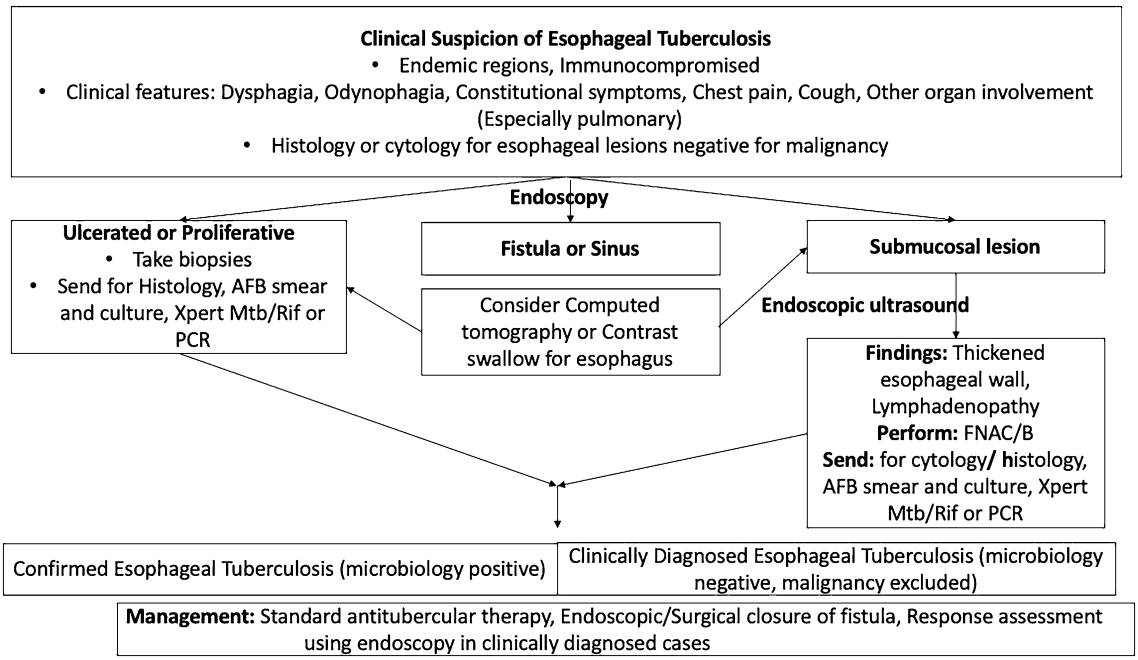

Fig. 2 Suggested management algorithm for oesophageal tuberculosis

possible only in a small subset of patients. Indeed, one series described cases which could not be diagnosed microbiologically and pathologically. Herein, the authors embarked on a trial of ATT to demonstrate healing of lesions as early as after 3 months of therapy [17]. Whilst response to ATT is often used to discriminate intestinal tuberculosis from Crohn's disease, this strategy has its risks [40, 41]. Whilst it exposes patients to risks and adverse effects of ATT, it also may result in progression of malignancy which is a much more common diagnosis in oesophageal lesions. Therefore, we suggest that all efforts should be made to achieve a confirmed diagnosis of oesophageal tuberculosis. It is unclear if novel molecular modalities could improve the diagnostic yield in oesophageal tuberculosis. Whilst Xpert Mtb/Rif has been rolled out by tuberculosis programmes in many countries, the yield in EPTB including abdominal TB is modest [42]. There are only occasional reports of use of Xpert Mtb/Rif for diagnosis of oesophageal TB and therefore future studies must address its role [43]. Polymerase chain reaction-based tests have been recognised to increase the yield of microbiological diagnosis in oesophageal ulcers [44]. A positive diagnosis would require high index of suspicion. On most occasions, samples for microbiological diagnosis are not sent as oesophageal tuberculosis is not considered in the differential diagnosis. In endemic countries and especially in patients where an initial endoscopic/endosonographic biopsy is negative, the diagnosis of oesophageal TB must be considered [13] (Fig. 2).

Another issue of concern is the lack of clarity regarding the appropriate duration of treatment. Whilst the standard anti-tubercular therapy (Isoniazid, Rifampicin, Ethambutol and Pyrazinamide) is recognised to be sufficient for abdominal tuberculosis (intestinal and peritoneal), there is a lack of clarity about appropriate duration of treatment in oesophageal TB. Our review identified a lot of variability in the duration of ATT but most studies indicated range between 6 and 12 months. On follow-up, clinical symptoms usually resolve after 6–8 weeks. Studies have reported complete endoscopic healing after 6 months of ATT in intestinal TB but none of the studies has documented usefulness of an early endoscopy for mucosal healing. One report suggests endoscopic improvement after 3 months of ATT. Whether an analogy can be made from findings in intestinal TB and an early endoscopy can benefit in monitoring treatment response is a question of future research. Response to ATT is excellent and endoscopic or surgical interventions have been rarely needed especially to manage the associated complications such as stricture, tracheo/broncho-oesophageal fistula, bleeding or when instead of malignancy, a misdiagnosis was made. We suggest endoscopy after 8–12 weeks to document mucosal healing especially if initial diagnosis was not microbiologically confirmed. A follow-up endoscopic ultrasound may be considered if initial diagnosis was made using EUS-guided aspiration/biopsy. ATT should be continued for at least 6 months. An alternate diagnosis should be considered in patients without mucosal healing/persistent symptoms or lesions. Unless complicated by fistulisation, the treatment is conservative and the response is excellent. In patients with fistulisation, imaging to identify the complete fistula tract is necessary. Occasionally, fistulae may improve with ATT alone, but additional measures like fully covered self-expanding metallic stent, clips (including over the scope clips) or surgery may be warranted [45–47]. During the treatment with ATT, placement of percutaneous endoscopic gastrostomy may be done to maintain nutrition and aid in spontaneous healing [46].

Conclusion

Oesophageal tuberculosis should be considered in a patient presenting with dysphagia residing in endemic areas and having concomitant involvement of other organ systems, constitutional symptoms and after an initial evaluation for malignancy was inconclusive. Diagnosis is established by endoscopy or endoscopic ultrasound-guided cytological/histological analysis supported by microbiological assessment of diseased tissue. Treatment is standard anti-tubercular therapy and response to treatment is excellent. Endoscopic and surgical interventions are needed to manage complications like fistulising disease.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00455-021-10360-x.

Declarations

Conflict of interest The authors declare that they have no conflict of interests.

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