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DISEASES OF THE ESOPHAGUS

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**Original Article**

# Endoscopic ultrasound in diagnosis of esophageal tuberculosis: 10-year experience at a tertiary care center

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*SUMMARY.* **Definite diagnosis of esophageal tuberculosis (ET) requires isolation of tubercle bacilli, which is challenging in clinical practice. Difficulty in differentiating ET from other esophageal diseases may well result in a delay in diagnosis. The literature on utility of endoscopic ultrasound (EUS) in diagnosis of ET is insufficient. This study aims to evaluate the role of EUS morphology combined with EUS-guided tissue acquisition in the diagnosis of ET. Data of the 35 patients diagnosed with ET from January 2006 to October 2015 were retrospectively analyzed. After miniprobe and linear echoendoscopic visualization, either linear EUS-guided deep biopsy or EUS-guided fine needle aspiration was performed for tissue acquisition. Histocytopathological results showing caseous necrosis or acid fast bacilli (AFB) or epithelioid granuloma were considered diagnostic. Esophageal wall thickening or mass formation with disruption of the adventitia due to infiltration by adjacent mediastinal lymphadenopathy was typically observed under EUS. Tissue acquisition revealed epithelioid granuloma in 33 patients, caseous necrosis in 13, a positive AFB stain in 14, and nonspecific chronic inflammation in 2. Of the 35 patients, 33 (94.3%) with both characteristic EUS morphology and diagnostic histocytopathology were considered to have an EUS established diagnosis. The remaining two with only nonspecific chronic inflammation received empirical antitubercular chemotherapy based solely on EUS morphology. The two-year follow-up confirmed diagnosis of ET in all patients. While the final diagnosis of ET was based upon two-year follow-up of treatment response to antitubercular medication in addition to caseous necrosis/granuloma/positive-AFB stain revealed by EUS-guided tissue acquisition, an EUS-established diagnosis of ET and medical treatment with long-term follow-up is rational and practical compared with surgery or untreated follow-up.**

*KEY WORDS*: **diagnosis, esophageal tuberculosis, EUS.**

## INTRODUCTION

Esophageal tuberculosis (ET) has nonspecific clinical, laboratory, radiological, and endoscopic features.[1] Its definite diagnosis requires isolation of tubercle bacilli, which is seldom achieved in clinical practice. Difficulty in differentiating it from other diseases such as esophageal cancer may result in unnecessary surgery.[2,3] Endoscopic ultrasound (EUS) provides much more diagnostic information than conventional upper endoscopy since it can visualize and biopsy structures beneath esophageal mucosa and beyond the esophageal wall. To date, there is insufficient literature regarding utility of EUS in diagnosis of ET, perhaps due to the rarity of ET.[3–6] The aim of this study is to evaluate the role of EUS morphology combined with EUS-guided tissue acquisition in the diagnosis of ET.

## MATERIALS AND METHODS

The study consisted of patients diagnosed with ET from January 2006 to October 2015 at our center. Their clinical, laboratory, radiological, gastroscopic, endosonographic, and histocytopathologic data were retrospectively analyzed. The diagnosis was confirmed by long-term follow-up since antitubercular treatment began. The Institution Review Board of The Third People's Hospital of Chengdu approved this study. Informed consent was obtained from each patient.

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*Specific author contributions:* Yu Tang prepared the manuscript and participated in performing EUS examinations; Wei Shi supervised EUS examination and participated in treatment of patients; Xiaobin Sun participated in performing EUS examinations and data collection; Weidong Xi participated in the production of histocytopathological figures and follow-up of patients.

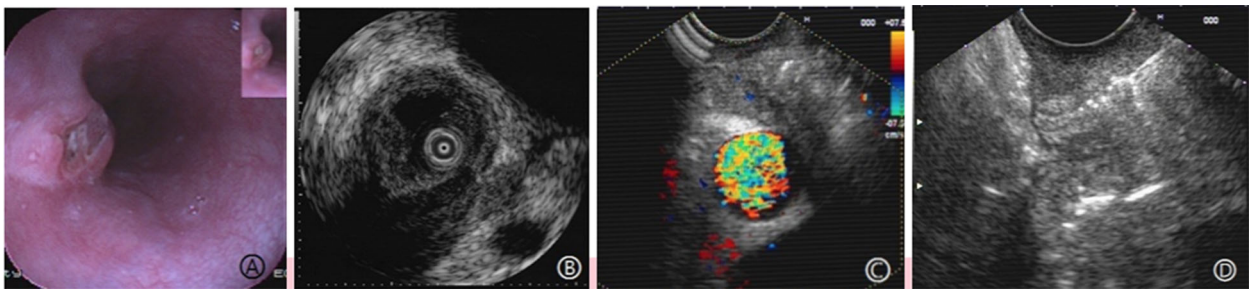

**Fig. 1** (A) Gastroscopy showed an extrinsic bulge protruding into the esophageal lumen with ulcerated mucosa. (B) Miniprobe EUS revealed full-thickness involvement of esophageal wall by a heterogeneous hypoechoic mass, with disruption of the adventitia. (C) Linear array EUS displayed enlarged heterogeneous hypoechoic mediastinal lymph node infiltrating the esophageal wall, with interior hyperechoic strands. (D) Linear array EUS-guided deep biopsy. The opened biopsy forceps was visualized endosonographically.

A miniprobe EUS (UM-DP-25R 15–20 MHz; Olympus Medical Systems, Tokyo, Japan) followed by a linear echoendoscopy (EG3860, Pentax, Tokyo, Japan) were performed to visualize both esophageal wall and adjacent structures such as paraesophageal mediastinal lymph nodes. Then tissue acquisition was carried out by either linear EUS-guided deep biopsy with a standard biopsy forceps (Anrei Medical Holding Company, Hangzhou, China) or endoscopic ultrasound guided fine needle aspiration (EUS-FNA) with a 22-gauge needle (Echo-Tip Ultra, Wilson-Cook Medical Inc., Winston-Salem, USA), depending on endosonographer's discretion as well as patients' choice. We performed 3–6 biopsies and 1–2 passes of the FNA needle during each procedure. The EUS-guided deep biopsy was featured by real-time visualization of biopsy forceps movements both on optical view and ultrasound image, after introduction of the forceps through the working channel of the linear echoendoscope (Fig. 1D). The direction of forceps was altered mainly by elevator to target each bite towards heterogeneous hypoechoic region in the center of lesion. A bite-on-bite strategy was adopted but overly deep excavation was avoided to prevent fistula formation. Color doppler was used to prevent injury of intervening vessels. Histocytopathological results showing at least one of the three following were considered as diagnostic: caseous necrosis, acid fast bacilli (AFB), or epithelioid granuloma. 'Non-specific chronic inflammation' was regarded as nondiagnostic. Patients with both characteristic EUS morphology and diagnostic histocytopathological results were considered to have an EUS-established diagnosis of ET.

## RESULTS

### Clinical and radiologic features

Thirty-five outpatients including 15 men and 20 women, between the ages of 19 and 74, with median age of 37.7, were analyzed. A past history of tuberculosis was found in six patients. Dysphagia was present in 32, odynophagia in 8 and heartburn in 5. Concomitant symptoms, including fatigue, night sweats, and low-grade fever were seen in five, three, and five patients, respectively. None showed signs of weight loss. Thirty-three underwent chest computed tomography (CT), which revealed no sinus tract or fistula. Thirty out of the 33 patients were discovered on CT to have focal thickened esophageal wall and mediastinal lymph node enlargement, which in 29 patients was located in subcarinal region. Precontrast CT scan showed multiregional lymph nodes with clear margins, homogeneous or heterogeneous density with central low attenuation, and peripheral rim enhancement. Inflammation in right upper pulmonary lobe was noted in four while no abnormality on CT was found in three.

### Endoscopic features

Twenty-nine patients had lesions located in the mid esophagus while in six they were present in the lower esophagus. An extrinsic bulge protruding into esophageal lumen was observed in 27 patients. Twenty-two of these patients had ulcerated mucosa overlying the lesion, while five had intact mucosal surfaces. A slight depression with superficial ulceration was seen in five patients, while smooth blue-colored mucosa with sags and crests was presented in the remaining three (Figs 1–4).

### Endosonographic features

Esophageal wall thickening or mass formation with disruption of the adventitia due to infiltration by adjacent mediastinal lymphadenopathy was universally observed. EUS showed multiple enlarged homogeneous or heterogeneous, hypoechogenic mediastinal lymph nodes, in close proximity to or fused with each other. Indistinct margins and unevenly scattered interior hyperechogenic strands and foci were noted in all lesions. Endosonographically, the enlarged lymph nodes were between 1.2 and 3.1 cm in diameter. The hyperechogenic foci were not accompanied by

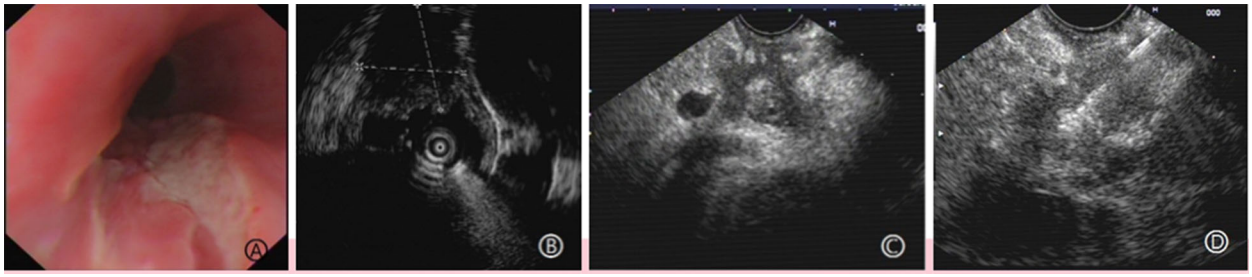

**Fig. 2** (A) Gastroscopy showed slight depression with a superficial broad ulcer in mid esophagus. (B) Miniprobe EUS revealed full-thickness involvement of esophageal wall by a heterogeneous hypoechoic mass, with a mucosal defect. (C) Linear array EUS displayed hypoechoic mediastinal lymphadenopathy with internal hyperechoic patches. (D) EUS-FNA.

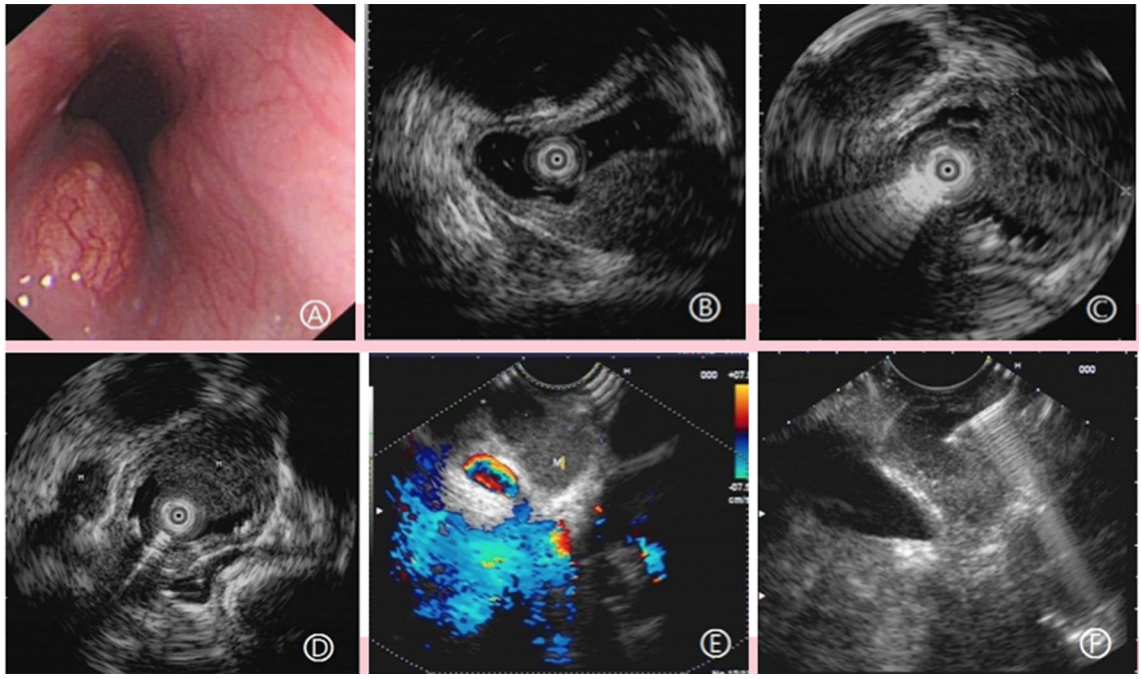

**Fig. 3** (A) Gastroscopy showed extrinsic bulge with smooth surface protruding into esophageal lumen. (B–D) Miniprobe EUS revealed involvement of esophageal wall by a heterogeneous, hypoechoic mass, with intact mucosa and disruption of the adventitia. (E) Linear array EUS displayed homogenous hypoechoic mediastinal lymphadenopathy with internal hyperechoic foci. (F) EUS-FNA.

acoustic shadowing. Endosonographic morphology correlated to some extent with gastroscopic appearances. Five patients with gastroscopically smooth-surfaced extrinsic bulge protruding into esophageal lumen had intact mucosal layer under EUS while the other 30 had full thickness involvement of esophageal wall (Figs 1–4). The EUS characteristics compared to CT imaging are summarized in Table 1.

### EUS-guided tissue acquisition and diagnosis

It was presumed that lesions with intact mucosal layer were more suitable to receive FNA than deep biopsy, whose tissue acquisition capability would be reduced by intact mucosa. To the contrary, for lesions with full thickness involvement of esophageal wall, deep biopsy would be a promising method and a better choice than FNA considering cost saving. According to this presumption, our initial tissue acquisition strategy was to perform EUS-FNA for the five lesions with intact mucosal layer and linear EUS guided deep excavation for the 30 with full thickness involvement of esophageal wall. However, of the former five patients, three refused FNA for financial concern, and one was not considered a good candidate for FNA because of suboptimal needle movement inside the lesion of only 1.2 cm size. One patient of the latter 30 underwent EUS-FNA because of a broad ulcerous surface that was likely to have a high risk of massive bleeding during excavation. Eventually, 33 patients underwent linear array EUS-guided deep biopsy, which revealed epithelioid granuloma in 31 patients, caseous necrosis in 11, a positive AFB stain in 13, and nonspecific chronic inflammation in 2. EUS-FNA was performed in two patients with adequate tissue acquisition. In both, epithelioid granuloma and caseous necrosis were found. One of them had positive AFB stain.

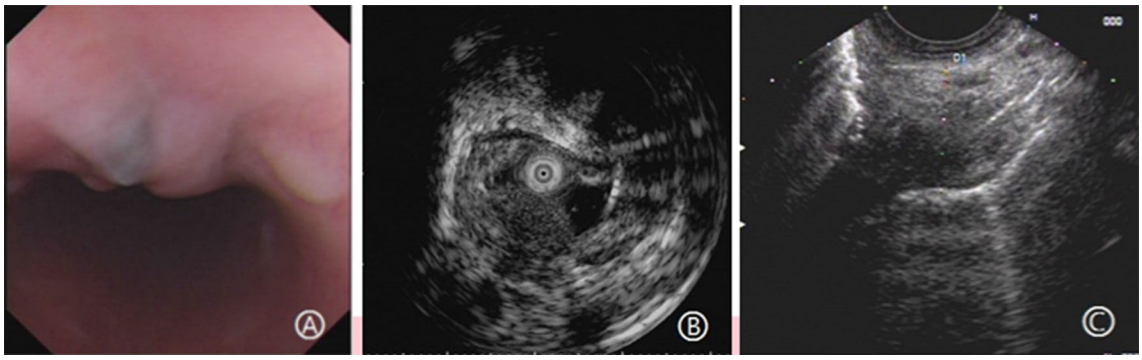

**Fig. 4** (A) Gastroscopy showed smooth blue-colored mucosa with sags and crests. (B) Miniprobe EUS revealed heterogeneous hypoechoic thickening of all layers of the esophageal wall with adventitial disruption. (C) Linear array EUS displayed mediastinal lymph node enlargement with outer membrane breakage.

**Table 1** EUS characteristics compared to CT imaging

| | EUS | CT |
|---|---|---|
| Esophageal wall | | |
| | Thickened esophageal wall<br>Mass formation<br>Adventitia disruption<br>Full-thickness involvement or with intact mucosa | Focal esophageal wall thickening |
| Mediastinal lymphadenopathy | | |
| | Conglomeration of multiple lymph nodes with indistinct margins | Multiregional lymph nodes with clear margins |
| | Homogeneous or heterogeneous hypoechogenic echotexture | Homogeneous or heterogeneous density with central low attenuation |
| | Unevenly scattered interior hyperchoic strands or foci | Peripheral rim enhancement |

Overall, epithelioid granuloma with neither caseous necrosis nor positive AFB stain was discovered in 18 patients. The two lesions of mere nonspecific chronic inflammation were with intact mucosa. According to the histocytopathological results, a diagnosis of tuberculosis was achieved in 33 patients with at least epithelioid granuloma, thus making the overall diagnostic yield of EUS-guided tissue acquisition 94.3% (33/35). Four patients had postbiopsy blood oozing that was stopped by endoscopic spray of 1:10000 concentration of adrenalin–saline solution. The remainder of the patients exhibited self-limited minor bleeding. No perforation, mediastinal emphysema, or fistulae were observed.

### Treatment and follow-up

Thirty-three patients with both characteristic EUS morphology and diagnostic histocytopathological results were considered to have an EUS established diagnosis of ET. Standard 2HRZE/4HR antitubercular chemotherapy was administered. As to the remaining two patients whose biopsy specimen merely revealed nonspecific chronic inflammation, empirical antitubercular chemotherapy was administered based on EUS morphology. Follow-up was carried out every two month since initiation of treatment. Neither liver function impairment nor intolerance to antitubercular drugs was observed. All patients had symptom resolution at the end of treatment. Follow-up gastroscopy showed bluish-colored smooth mucosal surface with slight elevation while EUS follow-up displayed resolution of the esophageal mass, a reduction in esophageal wall thickness and a decrease in size of the mediastinal lymph nodes with remnant hyperechoic patches (Fig. 5). No signs of recurrence were discovered during the two-year follow-up period in any of the patients.

## DISCUSSION

ET is a rare disease, which has nonspecific clinical, laboratory, radiological, and endoscopic features.[1] Isolation of tubercle bacilli from esophageal lesion remains the gold standard for diagnosis, but is frequently unachievable in routine clinical work. Difficulty in differentiating ET from other esophageal diseases such as cancer may result in unnecessary surgery.[2,3] With prompt and accurate diagnosis on the other hand, ET is typically curable with appropriate antitubercular chemotherapy.

With standard endoscopy, ET may have multiple manifestations such as a mucosal ulcer, a submucosal bulge and flat nodules, all of which are nonspecific and

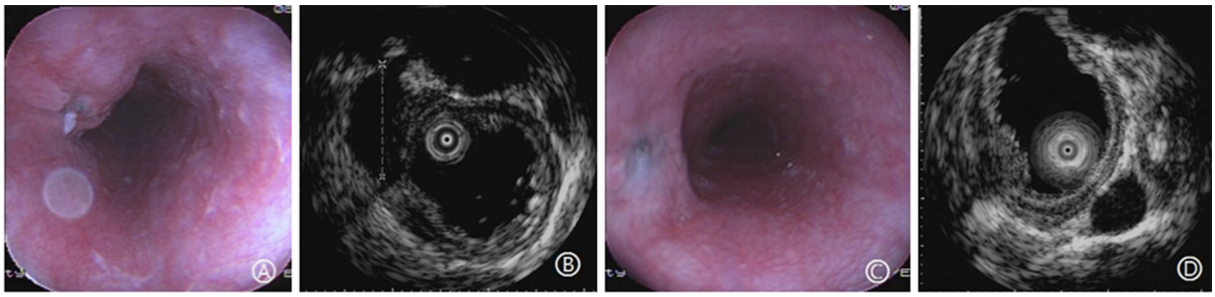


**Fig. 5** Post-treatment gatroscopy and EUS of the patient in Figure 1. (A,B) 3 months after initiation of antitubercular treatment gastroscopy showed a reduction in size of the extrinsic bulge with ulcer healing, covered by smooth blue-colored mucosa. EUS revealed a reduction in size of the lymph node, an intact mucosal surface and muscularis mucosa, and partially recovered submucosa. C,D) At the end of treatment, gastroscopy demonstrated disappearance of the extrinsic bulge, leaving flat smooth blue-colored mucosa. EUS showed disappearance of the lymph node and a much recovered esophageal wall which, however, had not completely regained its well-defined five-layer structure. The Adventitia was still not intact.

do not provide a definitive diagnosis. In contrast, characteristic EUS morphological features highly suggestive of ET are reported in this study. Initially, infiltration of the esophageal wall by adjacent mediastinal lymphadenopathy gives rise to adventitial disruption accompanied by wall thickening or formation of an intramural mass. The typical five-layer esophageal wall structure is destroyed, resulting in full-thickness involvement or leaving only the mucosal layer intact. Later, different EUS morphological appearances may result depending upon which pathological stage of tuberculosis is ongoing at the time.[4] Multiple pathological changes may be found simultaneously in one lesion. Homogenous, hypoechoic EUS areas correspond to proliferative lymphadenitis characterized by lymphocyte infiltration and capillary proliferation in early stages of the disease. Heterogeneous, iso-hypoechoic EUS regions correlate with caseous necrosis and enlarged lymph nodes fused with each other because of membrane disruption on the other hand are seen in mid stage of tubercular pathology. Unevenly distributed hyperechogenic strands and foci on EUS images represent fibrosis and calcification.

In our study, we did not observe under EUS extensive anechoic regions, which would reflect massive liquefied necrosis. Neither did we discover any fistulae or sinus tracts. The underlying reason may be that symptoms such as dysphagia and odynophagia occurred early because of esophageal neuromuscular dysfunction together with luminal compression prompting patients to seek medical attention. The fact that few patients exhibited general tubercular consumptive symptoms such as weight loss supports this assumption.

Primary ET was not observed even in a single case in our study, though it has been mentioned in earlier reports.[7,8] All the 35 patients were shown to have esophageal wall infiltrated by adjacent mediastinal lymph nodes. Therefore, we believe that ET is exclusively secondary to mediastinal tubercular lymphadenopathy. A recent study by Puri *et al*. reached a similar conclusion,[5] which could also explain why ET occurs most frequently in the mid esophagus in close proximity to the lymph-rich subcarinal region.

ET should be distinguished from esophageal carcinoma and submucosal tumors (SMTs). Both ET and esophageal carcinoma can have the endosonographic appearance of a heterogeneous hypoechoic mass with mediastinal lymphadenopathy. Based on EUS morphology, there are two differentiating diagnostic points. First, malignant lymph nodes do not fuse with the esophageal wall leading to disruption of the adventitia. Second, hyperechogenic foci or strips are neither found in esophageal carcinoma nor in metastatic lymph nodes. Benign SMTs are unlikely to be mistaken as ET under EUS since they are homogeneous hypoechoic masses with well-defined margins without associated mediastinal lymphadenopathy. It may, however, be difficult to distinguish ET from some malignant SMTs such as leiomyosarcomas and neurofibrosarcomas, which may also present with unclear margins and full-thickness invasion. Therefore, EUS-guided tissue acquisition plays an important role in establishing a definitive diagnosis.

Park *et al*. reported that the diagnostic yield of one-session gastroscopic biopsy is as low as 50%.[9] We performed linear EUS-guided deep excavation biopsy, which enabled real-time guidance of biopsy forceps movements both on optical view and ultrasound image. This novel tissue acquisition method, a derivative of EUS-FNA, was proved to be safe and have a high diagnostic yield (93.9%, 31/33). Rana *et al*. reported that the diagnostic yield of EUS-FNA in 14 cases of ET was 100%.[6] Nonetheless, application of EUS-FNA in all patients would result in a significant increase in expense. Our complementary use of the two EUS guide tissue acquisition modalities resulted in a fairly high overall diagnostic yield of 94.3% (33/35) at a significantly reduced cost.

There are two limitations in our study. First, it is a retrospective case analysis from a single institution. Second, we did not perform polymerase chain reaction(PCR) or culture of tubercle bacillus to pursue a definitive microbiologic diagnosis. Our diagnosis

was based primarily on EUS morphology and EUS-guided tissue acquisition, which revealed epithelioid granuloma in 94.3% (33/35), caseous necrosis in 37.1% (13/35), and a positive AFB stain in 40% (14/35) of patients. Eighteen patients were found to have only epithelioid granuloma without caseous necrosis or positive AFB stain. Epithelioid granuloma may be found in other granulomatous diseases such as sarcoidosis, syphilis, Crohn's disease, and histoplasmosis, all of which can involve the esophagus.[3,9,10] Sarcoidosis, which is characterized by clustered, well-margined mediastinal lymph nodes with an isoechoic texture under EUS, can readily be differentiated from ET.[11] Since the remaining three granulomatous diseases mentioned have never had their endosonographic features detailed in published reports, the possibility of misdiagnosis existed in the 18 patients.

These 18 patients received empirical antitubercular therapy identical to the two patients whose tissue sampling only revealed nonspecific inflammation. A convincing clinical response to therapy confirmed the diagnosis of ET and supported the feasibility of establishing the diagnosis of ET based on presence of epithelioid granuloma combined with characteristic EUS morphology. Although the above-mentioned granulomatous diseases are difficult to distinguish from tuberculosis, since their esophageal involvement is extremely rare, they are unlikely to significantly reduce the diagnostic accuracy of endosonography with tissue acquisition for the diagnosis of ET in routine clinical practice. Therefore, an EUS-established diagnosis of ET and medical treatment with follow-up is rational and practical compared with surgery or untreated follow-up.

In conclusion, EUS morphology combined with EUS-guided tissue acquisition is feasible and reliable to establish the diagnosis of ET. Application of this combinative diagnostic strategy in routine clinic work leads to prompt proper management of ET. Large-scale prospective comparative study is needed for further research.

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