Original Article

Endoscopic ultrasound in mediastinal tuberculosis

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ABSTRACT

Background: Tubercular lymphadenitis is the commonest extra pulmonary manifestation in cervical and mediastinal locations. Normal characteristics of lymph nodes (LN) have been described on ultrasonography as well as by Endoscopic Ultrasound. Many ultrasonic features have been described for evaluation of mediastinal lymph nodes. The inter and intraobserver agreement of the endosonographic features have not been uniformly established. **Methods and Results:** A total of 266 patients underwent endoscopic ultrasound guided fine needle aspiration and 134 cases were diagnosed as mediastinal tuberculosis. The endoscopic ultrasound location and features of these lymph nodes are described. **Conclusion:** Our series demonstrates the utility of endoscopic ultrasound guided fine needle aspiration as the investigation of choice for diagnosis of mediastinal tuberculosis and also describes various endoscopic ultrasound features of such nodes.

KEY WORDS: Endoscopic ultrasound, mediastinal lymph node, tuberculosis

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INTRODUCTION

The advent of computer-aided tomography (CT) and magnetic resonance imaging has led to an increased detection of enlarged mediastinal lymph nodes (MLN). Management of patients with MLN depends on the etiology.[1] Bronchoscopy with transbronchial lung biopsy, endoscopic ultrasound-guided aspiration from esophagus (EUS-FNA), endobronchial ultrasound-guided fine needle aspiration from bronchus (EBUS-FNA), and mediastinoscopy are frequently used diagnostic tools for obtaining a tissue sample.[2,3] Transbronchial lung biopsy is considered a relatively blind technique, mediastinoscopy is invasive and most operators choose between EUS-FNA and EBUS-FNA as diagnostic tools.[4] Pulmonologist prefer the route of bronchus for obtaining tissue by EBUS-FNA and gastroenterologists prefer the route of esophagus by EUS-FNA.[5] No standard comparison is available between EUS-FNA and EBUS-FNA and many operators familiar with both techniques prefer the use of esophagus rather than bronchus as the primary route for evaluation.[6] EUS-FNA and EBUS-FNA are nowadays considered complimentary for a comprehensive evaluation of MLN.[7-10] Tubercular lymphadenitis is the most common extra pulmonary manifestation in cervical and mediastinal locations and management requires combined chemotherapy for at least 6 months, or more.[11,12] Normal characteristics of lymph nodes (LN) have been described on ultrasonography.[13,14] Fusion of LN with the presence of hypoechoic center and hyperechoeic foci are characteristic features of tubercular MLN.[15-22]

The study was aimed to define the EUS and EUS-FNA feature of tubercular MLN.

MATERIALS AND METHODS

All patients undergoing EUS-FNA for MLN at the center were reviewed. Patients with confirmed clinical and cytological diagnosis of tuberculosis (TB) with acid-fast bacilli (AFB)/culture positive or polymerase chain reaction (PCR) for mycobacterium TB positive were

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enrolled for the study. The remaining cases had sarcoidosis or malignancy were not included in the study group.

Endoscopic ultrasound-guided examination procedure

All procedures were performed in gastroenterology department by a single experienced endosonographer, using the EG-3870 UTK linear echoendoscope, Pentax Inc., Tokyo, Japan at 5–10 MHz frequency under conscious sedation using intravenous midazolam. Written informed consent was obtained from all the patients. The hospital ethical review board approved the study. EUS examination of the mediastinum was done to describe the location of the node according to the International Association of Study of Lung Cancer classification [Video 1]. When multiple MLN were present in one station, three largest MLN were measured at two stations. The shape was described as oval or round, the border was seen as distinct, coalesced or indistinct with partial/complete disappearance of outline. Echogenicity was identified as focally or diffusely hypoechoeic, isoechoeic, or hyperechoeic.

Endoscopic ultrasound-guided aspiration from esophagu procedure

The suitability of most appropriate LN for fine needle aspiration cytology (FNAC) was based on size, site, shape, echo texture, and border of the LN. A large MLN was preferred to small, homogenous were preferred to heterogeneous, node with hypoechoeic center was preferred to MLN without hypoechoeic center and in confluent MLN, the MLN with least broken border was preferred to LN with totally broken borders. The puncture was carried out with a 22-gauge needle (Echo Tip, Wilson–Cook, Winston–Salem, North Carolina, USA) into the deepest part of LN, the stylet was completely removed, and a 10 mL syringe was attached to the hub of the needle, followed by application of negative suction and very slow withdrawal of needle. EUS aspirates were expelled from the needle by reinsertion of the stylet and checked by the cytopathologist for adequacy of sample after staining with the Diff-Quik method. A repeat puncture was done if no material was found in the first sample with standard technique of 5–10 to and fro movements. In all cases with suspected TB AFB stain were carried out; aspirates were sent for TB-PCR analysis and conventional culture of Mycobacterium TB. TB-PCR was done for "IS-6110" for identification of Mycobacterium TB complex. A commercially available kit was used in which two primers were used. Patients with clinical and cytological diagnosis of TB with AFB/culture positive or PCR for TB were enrolled for the study. The diagnosis of TB was further confirmed by documenting response to antitubercular therapy on clinical follow-up for at least 6 months. Patients were excluded if there was any doubt in diagnosis or if there was any overlap with other benign or malignant etiology.

Data analysis

Data included the location of the MLN, number, size, shape, border, echo texture, abscess formation, calcification, number of needle passes made, sample adequacy, cytology results, final diagnosis, and procedure related complications.

RESULTS

A total of 266 patients had EUS-FNA for MLN over a period of 5 years. One hundred and thirty four cases were diagnosed as TB. The male to female ratio was 1:1.4. The age of the patient ranged from 8 to 86 years with a mean age of 34.3 years. The clinical presentation was weight loss in 64 cases (47.7%), fever in 83 (61.9%), dysphagia in 12 (8.9%), and abnormal chest X-ray/CT findings in 76 cases (56.7%). Twelve cases (8.9%) had incidental detection of MLN during EUS for abdominal lymphadenopathy. Two patients presented with dysphagia due to ruptured tubercular abscess within the esophageal lumen [Video 2]. Nine cases had a previous history of TB. Two hundred and forty-eight passes were performed in 156 LN with an average of 1.8 passes per patient. Single puncture was required in 72 cases and multiple punctures were required in 62 cases.

Location: All the cases had multiple lymphadenopathies limited to a single station in 19 cases and multiple stations in 105 cases. Twelve cases with abdominal LN where FNA was done from associated MLN were included in 105 cases. In 10 cases, the LN ruptured into mediastinal spaces and were described according to the spaces. The distribution of cases with single and multiple stations is given in Table 1.

Size: A total of 486 LN were measured. The median size of LN based on the maximal long axis was 12 mm (5–25 mm). In conglomerated LN those with preserved outer borders were measured. In 10 cases of abscess, measurement was not possible because of absent outline.

Shape: Oval or rounded LN were observed in 55 cases and elliptical or crescent shaped nodes were detected in 25 cases [Figure 1]. The shape of LN could not be defined in 44 cases of confluent nodes and 10 cases of abscess.

Border: Sixteen cases had LN with an indistinct outer border. LN with a distinct outer border were detected in 108 cases (64 cases of discrete MLN and 44 cases of coalesced MLN) [Figure 1] The border was lost in 10 cases with abscess formation.

Echo texture: Sixteen LN were heterogenous with normal hyperechoeic center, 20 had hypoechoeic areas within discrete LN and 35 had hypoechoeic area within confluent LN [Video 3]. Abnormal hyperechoeic foci were identified in 44 cases of discreet, 9 cases of confluent LN with preserved outer borders [Figure 2], and 10 cases of confluent LN with absent borders [Figures 3 and 4, Table 2].

Table 1: EUS location of tubercular lymph node

Station (IASLC)	7	4L	8	4R	2L	2R	5	6	9	Abdominal LN
Number of single location (*n*=19)	11	3	2	1	1	0	0	1	0	0
Number of multiple locations (*n*=105)	102	46	16	4	16	3	3	6	3	12

Distribution of cases with single and multiple station lymphadenopathies. IASLC: International Association of Study of Lung Cancer, LN: Lymph node

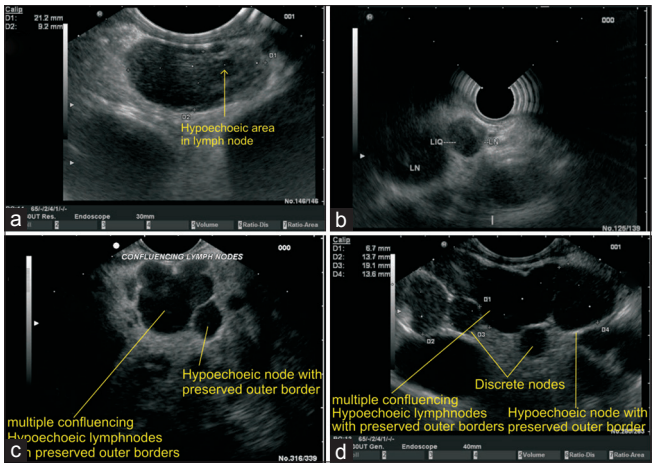

Figure 1: (a) One discrete oval lymph nodes with distinct borders is seen in subcarinal area. This large lymph nodes had a hypoechoic area in the center. (b) Even small lymph nodes can be liquefied and in this case the central hypoechoic area was seen in a 5 mm diameter lymph nodes. (c) Subcarinal 5–15 mm multiple confluent homogeneously hypoechoic lymph nodes with preserved outer borders were seen. (d) Subcarinal 5–20 mm diameter, multiple confluent homogeneously hypoechoic lymph nodes with preserved outer borders were seen

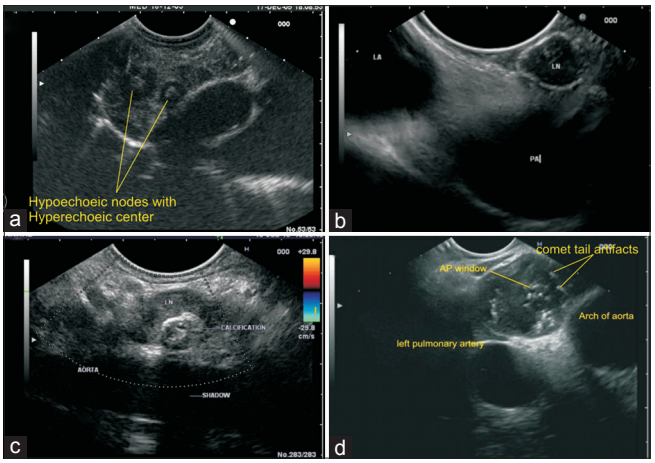

Figure 2: (a) Subcarinal multiple confluent lymph nodes with slight loss of outer borders were seen. Most of the lymph nodes are hypoechoic and homogeneous. Some of the hypoechoic lymph nodes had hyperechoic echoes in central part. (b) Subcarinal calcified lymph nodes with calcification in the margin. The calcified lymph nodes could be punctured. (c) Para aortic confluent lymph nodes with slight loss of outer borders. The lymph nodes had focal calcification causing acoustic shadow. (d) Multiple confluent lymph nodes in aortopulmonary window with presence of calcification producing comet tail artifacts

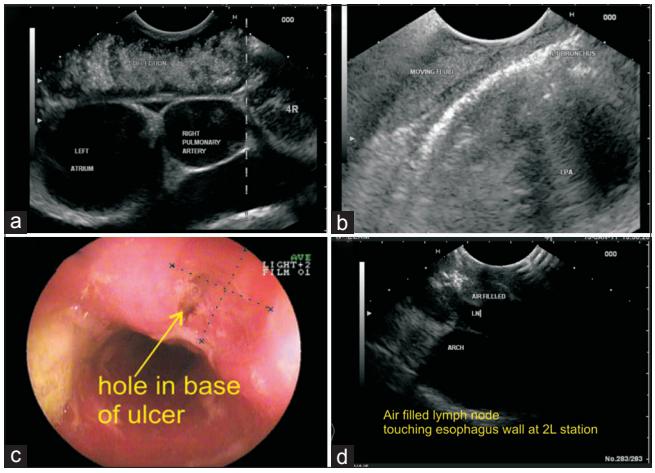

Figure 3: (a) Right paratracheal confluent lymph nodes extending to lymph nodes in station 7. One lymph nodes is seen above the right pulmonary artery belonging to station 4R. (b) The air present in the right bronchus gives sharp contrast with the abscess which extends along the azygoesophageal recess. (c) Endoscopy showed an ulcer at 22 cm distance in esophagus with a hole in the center of the ulcer. (d) Endoscopic ultrasound showed a caseated and ruptured lymph nodes at 22 cm distance just above the arch of aorta and air was seen filled with in the lymph nodes

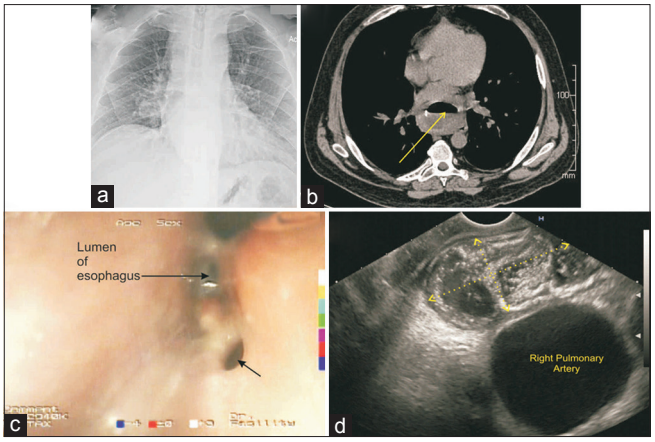

Figure 4: (a) A 36-year-old man presented with complaint of dysphagia after blunt injury of chest (X-ray chest showed widening of mediastinum. (b) Computer-aided tomography scan showed air filled cavity in subcarinal area. (c) Endoscopic examination revealed a communication from which pus was seen flowing into the lumen of esophagus. (d) Endoscopic ultrasound-guided examination showed a large abscess communicating with the esophageal wall. In this case a large abscess had ruptured into the wall of the esophagus

Cytological findings: Granulomatous inflammation without caseous necrosis was seen in 20 cases (14.9%) and caseating granulomas were seen in 97 cases (72.3%). The material was acellular or predominantly composed of necrotic material in 10 (7.4%) and a dense suppurative aspirate was noted in 7 cases (5.2%). AFB could be demonstrated in 61 (45.5%) cases. AFB positivity was 10.0% in cases associated with granulomatous reaction without necrosis, 45.3% with caseating granulomas, 90%

Table 2: EUS features of tubercular lymph nodes

EUS classification of MLN	Echotexture of MLN
Discrete MLN=80	Heterogeneous hyperechoic=16
	Hypoechoic areas=20
	Hypoechoic with hyperechoic foci=44
Confluent MLN=54	Hypoechoic areas=35
Confluent LN with preserved outer borders (44) and with absent borders (10)	Hypoechoic with hyperechoic foci=19

On the basis of EUS features the LN could be classified into two groups: Discrete MLN and confluent MLN. MLN: Mediastinal lymph node, EUS: Endoscopic ultrasound, LN: Lymph node

in cases with acellular necrotic material, and 85.7% in cases with suppurative inflammation. Culture was positive in 44 cases (32.8%) and PCR in 46 cases (34.3%). One case was diagnosed as atypical mycobacterium TB.

DISCUSSION

The present study shows the location, EUS features, EUS-FNA features, and the finding of cytopathology in cases of tubercular MLN. MLN were located mainly at station 7 followed by station 4L and only 5 cases had presence at 4R station. The usual location of MLN in normal persons and TB is at station 7 followed by station 4L and 4R.[23-25] The lower reporting of presence of MLN at 4R station in this series is due to difficult detection of MLN present on the right side of trachea (2R and 4R station) by EUS. In one case, the FNAC was done by transaortic route for obtaining sample from station 6 node [Video 4]. The diameter of discrete MLN ranged from 5 mm to 25 mm and average diameter was 12 mm, which is similar to the diameter of MLN in a normal person and in patients with TB.[15,23]

EUS showed 59% discrete and 41% confluent MLN. Among the confluent MLN 82% had preserved outer borders and 18% had absent borders. Hypoechoic areas were noted in 88% cases and the smallest LN with hypoechoic area measured 5 mm. The finding of hypoechoic area in TB is consistent with the presence of necrotic process, loss of central vascularity, and a tendency toward fusion near their adjacent borders.[15,21,22,26] In general small, triangular, or crescentric MLN with indistinct borders and central hyperechoeic hilum containing nodal vessels are likely to be benign in nature whereas round or oval, sharply demarcated, homogenous, and hypoechoic LN with loss of central vascularity are likely to be pathological.[14] On CT scan of the chest, tuberculous MLN show a characteristic central low attenuation area representing caseous necrosis and peripheral enhancement, representing active disease: Analogous to EUS features.[24] Other reported ultrasound features of tubercular LN apart from hypoechoic center include abnormal hyperechoeic foci due to necrotic debris that is, caseation, calcification, or air.[15-18,20,27] A significant number of cases in this series (no = 63), showed the presence of abnormal hyperechoeic foci due to necrotic debris (no = 56), calcification (no = 10), and air (no = 6). Three cases of calcification and all cases of air coexisted with necrotic debris. The calcification was of three types: Micro calcification with reverberating artifacts (no = 5), larger size calcification (no = 3), and peripheral eggshell calcification (no = 2) [Figure 2]. Nodal calcification has been infrequently reported on CT in tubercular lymphadenopathy, but the presence of peripheral calcification has not been reported.[28] Presence of air was seen within discrete MLN communicating with esophagus in 1 case, secondary infection in matted LN in 3 cases, and in 2 cases of abscess. In 2 cases, there was rupture of MLN into esophagus and both of them presented with acute onset of dysphagia. In 1 case of dysphagia, a discrete MLN located at station 4L was seen ulcerating into the wall of esophagus on EUS [Figure 3] while in another case a roadside accident resulted in rupture of asymptomatic preexisting subcarinal abscess into esophagus [Figure 4]. Spontaneous fistulization of mediastinal LN into the esophagus has been reported as a case report.[29]

The present case series demonstrates unique EUS appearance of coalescent nodes with absent borders and moving necrotic material forming cold abscesses in 10 cases. The cold abscesses were located in subcarinal area in all cases and extended beyond subcarinal area in 6 cases. In one case, there was coexistence of cold abscess at station 4L. The most common site of extension was around the right intermediate and right main bronchus ($n = 4$). The other areas of extension were azygoesophageal recess, preaortic recess, and right paratracheal space [Figure 5]. The presence of cold abscess has been shown to cause compression of bronchus but in this series no symptoms were noted.[29,30]

A number of ultrasonic features have been described for evaluation of LN. In a recent series, a total of 390 LN (207 malignant and 183 benign) were analyzed.[31] The authors measured the length of short axis, shape, margin, echogenicity, homogenicity, coagulation necrosis, calcification, coalescence, and posterior acoustic enhancement.[31] However, the inter and intraobserver agreement of the endosonographic features for mediastinal or hilar LN was good for shape or size but was not good enough for the other ultrasonographic features like coagulation necrosis, heterogenicity, margins, etc.[32] One of the main features that has been emphasized in recent studies is coagulation necrosis of LN where the authors have taken into consideration a standard endobronchial ultrasound image classification system.[33,34] The definition of

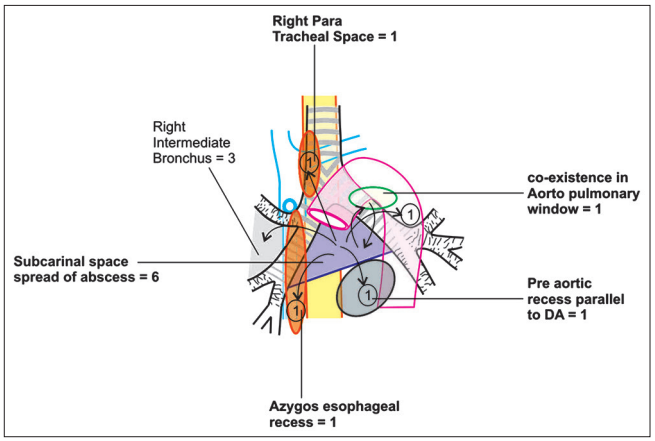

Figure 5: The pattern of localization and spread of mediastinal abscesses in tuberculosis in 10 cases. All the abscesses were located in subcarinal area and in one case there was coexistence of abscess in aortopulmonary window. The subcarinal area is a pyramidal space the tip of which lies at the tracheal bifuracation. In one case, the abscess spreaded into azygos esophageal recess, in one case into preaortic recess parallel to descending aorta and in one into right paratracheal space. The spread along the right intermediate bronchus was seen in 3 cases

coagulation necrosis is, however, not uniform and there is an apparent paradox of definition in literature.[33,35] Coagulation necrosis has been defined as ill-defined, nonshadowing echogenic areas within malignant LN on neck ultrasound but many authors have included hypoechoeic area within LN as a feature of coagulation necrosis.[36] We have avoided the controversial discussion along this line and we feel that coagulation and caseous necrosis are different pathologies and more studies are required to standardize the description of caseous LN.

Two hundred and forty-eight passes were performed in 156 LN to obtain adequate sample from inside a node or abscess. On the basis of EUS-FNA features, the MLN were categorized into two groups: MLN with significant aspirate on single puncture (54%), and MLN with aspirate after standard puncture (46%). Slow withdrawal of needle from the node/abscess after a single puncture was adequate in 72 cases while 62 cases required 2.4 punctures/LN to obtain the sample. In this series, overall less punctures were done as compared to others due to rapid on site cytology and adoption of slow aspiration after puncture technique in patient having hypoechoeic areas. EUS FNA in tubercular MLN has a rare complication of a mediastinal esophageal fistula.[37] In this series, slow aspiration was successful as the initial procedure of aspiration in 61% cases with hypoechoeic areas. The reason to avoid to and fro movement by the EUS-FNA in LN with hypoechoeic area was firstly to avoid complication of mediastinal-esophageal fistula and secondly with a logic that continuous aspiration and slow movement of the needle withdraws needle from one part of LN containing semisolid content to another part of LN (liquid fluid, as in a cyst, requires only negative suction, whereas solid tissue requires to and fro movement for aspiration). In our series, there was no complication. In one case, transaortic puncture was required to obtain a diagnosis. Theoretically, it can lead to mycobacteremia and increase the risk of dissemination of TB bacilli but it was important to establish the diagnosis and no such complication was clinically noted.

Granulomatous inflammation with caseous necrosis was the most common finding, AFB could be demonstrated in 45.5% cases and the highest positivity of AFB was noted in cases with acellular necrotic material (90%). This is in accordance with previous findings. Culture was sent in all cases and was found positive in 32.8%. PCR was positive in 34.3% cases.

In the present series, there were four HIV-positive patients. The smallest isolated liquefied LN was found in a HIV positive case. Earlier reports have suggested the HIV positive patients had more multifocal lesions and fewer tendencies for fusion and multiple-station lymphadenitis with extensive lung parenchymal, extra thoracic LN, and extra thoracic organ involvement.[38] Though the number of HIV positive cases was small, lung parenchymal lesions and extra thoracic LN and extensive organ involvement was not found in our series.

Our study has some limitations. First, it was retrospective and patients were selected on reviewing the files of all EUS in which TB was the final diagnosis. Unfortunately, there is no information on how the patients were selected beforehand. There were potentially many patients with tuberculous MLN who were not sent for EUS. The pathology grades are grouped as compatible with TB due to the presence of epithelioid granulomas with caseation and necrosis, which can be seen in cases with sarcoidosis and cancer also. A more conservative analysis combining strict pathological and microbiological criteria may have been more informative. However, we had good clinical follow-up and, therefore, were able to follow the natural history of the patient over at least 6 months.

This series describes the EUS features in detail in a large number of cases of TB from an endemic area. It also shows that slow aspiration from a necrotic LN may be beneficial in aspirating the semisoild material of a necrotic LN and can achieve the diagnosis in 61% of cases. A point worth commenting upon is the role of TBNA and EBUS-FNA for the cases referred for EUS. TBNA and EBUS-FNA are also useful for evaluation of MLN. Comparative studies can establish the first line investigation of choice but till further studies are available it may be reasonable to say that EUS may be considered the first test for evaluation of benign MLN for FNA.[39]

CONCLUSION

In a tropical country like India, TB is an important differential diagnosis of mediastinal lymphadenopathy. Endosonography is an important tool for diagnosis of mediastinal TB. EUS features may be helpful in selecting the site of EUS-FNA and for establishing a diagnosis. Slow aspiration from a hypoechoeic node may provide satisfactory sample for evaluation in a large number of cases. Experienced cytologists and rapid on-site pathologic examination may increase the sensitivity. The EUS features described can be helpful in evaluation and understanding the nature of disease, site of selection of EUS-FNA, progression of disease, and follow-up of the patients.

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Conflicts of interest

There are no conflicts of interest.

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