ORIGINAL ARTICLE

Endoscopic Ultrasonographic Findings of Benign Mediastinal and Abdominal Lymphadenopathy Confirmed by EUS-guided Fine Needle Aspiration

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Background/Aims: Distinguishing benign and malignant lymph nodes by the findings of endoscopic ultrasonography (EUS) is still controversial. We tried to evaluate EUS findings of benign mediastinal and abdominal lymphadenopathy (BLAP) confirmed by EUS-guided fine needle aspiration (FNA). **Methods:** A total of 37 patients with enlarged mediastinal or abdominal lymph nodes (diameter ≥ 1 cm) were enrolled and EUS-FNA was performed. Final diagnosis was based on FNA cytology and follow up imaging studies (CT scans or EUS). **Results:** Thirteen patients were confirmed to have BLAP by EUS-FNA. Causes of BLAP were as follows; (i) extrapulmonary tuberculosis in six cases including patients with postoperative states due to cervical cancer and advanced gastric cancer, (ii) Kikuchi disease in one case, (iii) hyper-eosinophilic syndrome in one case, (iv) reactive hyperplasia in five cases including patients with postoperative states due to thyroid cancer, lung cancer, and EGC with ESD. EUS findings of BLAP revealed that median lymph node size was 24.7 mm. Lymph nodes were oval or round shaped in 9 cases, sharp borders in 9 cases, hypoechoic echo pattern in 7 cases, heterogenous internal echo pattern in 7 cases. Other findings included internal septation, calcification, multiplicity, attachment to the gastrointestinal tract wall, and conglomeration. **Conclusions:** EUS findings of BLAP were not different from those of malignant lymphadenopathy previously reported in other studies. (Gut and Liver 2007;1:68-73)

Key Words: Lymphadenopathy; Endoscopic ultrasono-

graphy, Fine needle aspiration

INTRODUCTION

Endoscopic ultrasonography (EUS) is an effective procedure for examining lymph nodes in proximity to the gastrointestinal tract such as the celiac axis, and the mediastinum.^{1,2} EUS findings suggesting malignant lymph nodes are lymph nodes with a round shape, a short axis diameter larger than 10 mm, and lymph nodes showing with a hypoechogenic mass with a distinct border in the vicinity.^{1,3} The possibility of lymph nodes satisfying these four conditions, to be malignant is 80-100%, nevertheless, only 25% of malignant lymph nodes satisfy all four conditions.^{1,4} Distinguishing benign and malignant lymph nodes by the findings of EUS is still controversial, as lymph nodes with malignant or benign inflammatory reaction may be enlarged.⁵⁻⁷ In cancer patients with lymph node enlargement prior to surgery, staging depends on establishing its malignant status, thus not only the selection of therapeutic mode but also the future prognosis of patient is influenced by accurate assessment of enlarged lymph nodes. Moreover, lymph node enlargement detected during the postsurgical follow up period, is almost always disconcerting to the clinician. To perform diagnostic tests on all enlarged lymph nodes is not feasible. However, a method that helps differentiate benign from malignant lymph nodes, such as endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA), may be extremely useful in some situations.

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We applied the 4 criteria (size, shape, border, and internal echo) reported previously to suggest malignant lymph nodes^{1,6} to enlarged lymph nodes in the mediastinal and abdominal cavity diagnosed to be benign by EUS-FNA. We examined whether benign and malignant lymph nodes could be distinguished and if there were any characteristic EUS findings of benign lymphadenopathy (BLAP).

MATERIALS AND METHODS

1. Subjects

From March 1999 to August 2006, 13 patients who were diagnosed with BLAP by EUS-FNA were analyzed retrospectively. All patients had lymph nodes enlarged more than 1 cm in the mediastinal and the abdominal cavity.

2. EUS-FNA

All patients had either chest or abdominal CT scans performed and lymphadenopathy was defined as lymph nodes with a diameter greater than 1cm. Aloka SSD 5000, Aloka α 5 ultrasound processors and GF-UMQ200, GF-UM2000 radial echoendoscopes (Olympus Co, Tokyo, Japan) were used. Scanning was performed at 7.5 MHz and 12 MHz frequencies. Enlarged lymph nodes were assessed by radial echoendoscope, and EUS-FNA was performed with GF-UCT240P, GF-UC2000 (Olympus Co, Tokyo, Japan) echoendoscopes and 22G needles (NA-10J-1, NA-200H-8022, Olympus Co, Tokyo, Japan, W-EUSN-1, W-EUSN-2, Wilson-Cook, Inc., Winston-Salem, N.C.).

For final diagnosis, pathological diagnosis of FNA cytological tests was used, and the EUS findings of enlarged lymph nodes in 13 patients determined to be benign pathologically were examined. Based on the maximal long axis of enlarged lymph node, the size, shape, border, and internal echo pattern were analyzed, and the differences from already reported findings of malignant lymph nodes were examined.¹

3. Follow up

For 13 patients diagnosed to be benign, the follow up

of the lesion was performed using echoendoscopy and chest or abdominal computed tomography, and the median period of the follow up period was 12 months (1-40 months).

RESULTS

1. Clinical characteristic of benign lymph node enlargement

Thirteen patients were diagnosed with BLAP consisted of 9 mediastinal LAP and 4 abdominal LAP (Table 1). The male to female ratio was 6:7, and the median age was 58.5 years (37-71 years). Five patients had a past medical history of pulmonary tuberculosis and six patients had undergone surgery for various cancers. A total of 15 sessions of EUS-FNA was performed and the mean FNA frequency per session was 4 times (1-7). The median follow up period was 12 months (1-40 months). Among the 13 cases, six cases were diagnosed as extrapulmonary tuberculosis, which was most prevalent (five cases of mediastinal tuberculosis, one case of intra-abdominal tuberculosis). Among five cases diagnosed as mediastinal tuberculosis, two cases were detected during the follow up observation after surgery for cervical and gastric cancer, and EUS-FNA was performed to distinguish lymph node metastasis. In one patient with suspicious esophageal cancer on upper gastrointestinal endoscopy, EUS-FNA was performed on an enlarged LN in the vicinity because repeated endoscopic biopsy results only showed benign findings. EUS-FNA findings were compatible with tuberculosis (Fig. 1). Of remaining seven cases, one case was histiocytic necrotizing lymphadenitis (Kikuchi disease) (Fig. 2), and one revealed hyper-eosinophilic syndrome in which intrahepatic cholangiocarcinoma with suspicious lymph node metastasis was diagnosed previously (Fig. 3). Enlarged reactive lymphadenopathy was observed in 5 cases, these patients were under follow-up observation after surgery for thyroid cancer, lung cancer, and endoscopic sumucosal dissection for early gastric cancer. Enlarged lymph nodes in the subcarinal area were detected in one patient with lung cancer. EUS-FNA of the subcarinal lymph nodes showed reactive lymphadenopathy (Fig. 4) which confirmed to post surgery pathology results. No significant complications were observed in any of the patients following EUS-FNA (Table 2).

2. Endoscopic ultrasonographic findings of enlarged benign lymph nodes

The median value of lymph node size based on the maximal long axis was 24.7 mm (9-49.2 mm), Oval or

Table 1. Pathologic Diagnosis by EUS-FNA for Enlarged Lymph Nodes

	Benign LNs	Malignant LNs
Mediastinum (n)	9	11
Abdomen (n)	4	9

LNs, lymph nodes.

Fig. 1. Mediastinal tuberculous lymphadenitis. (A) A slightly elevated mucosal lesion with ulceration is noticed on esophago-gastroduodenoscopy. (B) A heterogenous hypoechoic mediastinal lymph node with an ellipsoidal form and multiple internal hyperechoic linear stripes is noticed on endoscopic ultrasonography. (C) Cytologic specimens by endoscopic ultrasonography-fine needle aspiration reveal acid-fast bacilli (Ziehl-Neelsen stain, $\times 1,000$).

Fig. 2. Histiocytic necrotizing lymphadenitis. (A) Chest computed tomography demonstrates mediastinal lymphadenopathy with internal calcifications. (B) Endoscopic ultrasonography shows a 5 cm sized heterogenous hypoechoic mediastinal lymph node ellipsoidal in form with multiple internal hyperechoic spots. (C) Cytologic specimens show multiple lymphoid cells and histiocytes with nuclear debris (H&E stain, $\times 200$).

Fig. 3. Hypereosinophilic syndrome. (A) Computed tomography of the abdomen demonstrates multiple lymph node enlargements around the celiac trunk. (B) Endoscopic ultrasonography image shows an enlarged heterogenous hypoechoic lymph node oval in shape. (C) Cytologic specimens reveal multiple eosinophils (H&E stain, $\times 200$).

round shaped enlarged lymph nodes were observed in 9 cases, and elliptrical shapes were detected in 4 cases. Lymph nodes with a distinct border were detected more often (9 cases). Regarding the internal echo of lymph nodes, 7 were found to be hypoechoic and 6 showed a intermediate echo. A heterogeneous internal echo was observed in 7 cases compared to 6 that showed a homoge-

neous internal echo. In addition 2 patients had internal septa, 2 had concomitant internal calcifications, 7 had with multiple lymph node enlargement and 4 patients had fusion of multiple lymph nodes. Comparing the above findings with the findings of malignant lymph nodes reported previously, we were unable to discover any characteristic EUS findings that allowed benign and malignant

Fig. 4. Mediastinal reactive hyperplasia with lung cancer in the left lower lobe. (A) Chest computed tomography demonstrates a mediastinal lymphadenopathy. (B) Endoscopic ultrasonography image shows an enlarged hypoechoic lymph node with an oval shape. (C) Cytologic specimens show many alveolar macrophages with anthracotic pigment on a lymphoid background (H&E stain, $\times 400$). (D) Operative specimens reveal reactive hyperplasia without tumor metastasis (H&E stain, $\times 200$).

Table 2. Characteristics of Benign Lymphadenopathy

No. of cases	13
M : F (n)	6:7
Median age (yr)	58.5 (37-71)
Past medical history (n)	2
Pulmonary tuberculosis	5
Operations due to cancers*	6
No. of needle passages	4 (1-7)
Median follow up (months)	12 (1-40)
Cytologic diagnosis by EUS-FNA	
Extrapulmonary tuberculosis	6
Mediastinum [†] /Abdomen	5/1
Histiocytic necrotizing lymphadenitis	1
Hypereosinophilic syndrome	1
Reactive hyperplasia [‡]	5
Complications	None

*Thyroid cancer, cervical cancer, advanced gastric cancer, early gastric cancer with endoscopic submucosal dissection, and lung cancer.

[†]Including patients with hysterectomy and gastrectomy due to advanced gastric cancer.

[‡]Postoperative states due to thyroid cancer, lung cancer, and early gastric cancer with endoscopic submucosal dissection.

Table 3. EUS Findings of Benign Lymphadenopathy

EUS findings	n=13
Median L/N size (mm)	24.7 (10-49.2)
Shape	58.5 (37-71)
Oval or round	9 (69.2%)
Ellipsoid	4
Border	
Sharp	9 (69.2%)
Irregular	4
Echogenicity	
Hypoechoic	7 (53.8%)
Intermediate	6
Internal echo-pattern	
Homogenous	6
Heterogenous	7 (53.9%)
Others	
Internal septum	2
Calcification	2
Multiplicity	7
Attachment to gastrointestinal tract wall	3
Conglomerated L/Ns	4

L/N, lymph node.

nodes to be distinguished (Table 3).

DISCUSSION

According to the findings of malignant lymph nodes re-

ported until now, if lymph nodes are detected to be larger than 1 cm, the possibility of malignancy should be suspected.¹ However, some lymph nodes larger than 1 cm show benign findings making it difficult to differentiate these nodes. Therefore, we retrospectively analyzed the EUS findings of lymph nodes larger than 1 cm that were

found to be benign by EUS-FNA. In addition, we tried to reveal characteristic EUS findings that might help discriminate benign from malignant lymphadenopathy.

Until now, EUS findings of BLAP have not been reported in abundance. BLAP has been detected in chronic pancreatitis, liver cirrhosis, sardoidosis, pulmonary tuberculosis, histoplasmosis, autoimmune hepatitis, cholecystitis, etc. Even in the absence of cancer as age increases, enlarged lymph nodes are increasingly detected.^{3,8-11} In a study on mediastinal lymph nodes in 100 patients without cancer, the maximal lymph node width was less than 10 mm in 95% of cases. However, the maximal lymph node length was less than 10 mm in only 40% of cases. In addition, such lymph nodes were in triangular or crescent shaped on EUS, and the internal echo was homogeneous or accompanied by an echogenic lesion in the center.³ In another study the size (>1 cm), shape (spheroid, oval, triangular), border, and echo (low echo with a amorphous and scattered internal echogenic center) did not differ between benign and malignant lymph nodes. Rather 31% of malignant lymph nodes showed a very low echo and amorphous and scattered internal echogenic areas compared to 0% in benign lymph nodes.⁴ Therefore, the absence of findings that facilitate the differentiation of benign and malignancy was suggested.⁴

Opinions on lymph nodes with a low echo and amorphous scattered internal echogenic areas are diverse. Some investigators reported that the possibility of this finding to suggest malignancy is high,^{6,12} others have claimed otherwise.¹³ In addition, the evaluation of the echogenicity and borders of lymph nodes depends on the frequency and gain of EUS, as well as the experience of the endoscopist.¹⁴ It has been reported that examining the difference of benign and malignant lymph node by classifying the findings suggesting malignant lymph nodes on endoscopic ultrasound more in detail, malignant lymph nodes were shown to be bigger, more round, and homogeneous hypoechogenicity.⁵

In our study, all tests were performed by a single investigator to minimize differences in interpretation. The 13 cases of BLAP in our study were mostly round or ovoid in shape, and had distinct borders which did not differ from EUS findings malignant lymph nodes. In addition, although most lymph nodes showed a heterogeneous internal echo most had an overall low echogenicity and could not be differentiated with the criteria suggesting malignant lymph nodes. In our study, the shape of enlarged lymph nodes assessed was diverse, and regarding the size of benign lymph nodes, the mean maximal long axis, was measured to be 24.7 mm, which was thought to be more suitable to the malignant lymph node criteria re-

ported until now. Previous study reported that 60% of these nodes had a length greater than 1 cm, even though the width of benign lymph nodes was less than 1 cm in 95%.³ This indicates that enlarged benign lymph nodes may have a tendency to be either ovoid or elliptical in shape. Most of the lymph nodes in our study were also oval or elliptical in shape. Additionally, some EUS findings such as lymph nodes with a moderate heterogeneous internal echo, the presence of an internal septum or calcification, simultaneous enlargement of several conglomerated lymph nodes, and nodes close to the gastrointestinal wall as if attached were helpful to differentiate benign from malignant lymph nodes. According to in-vitro studies using high resolution ultrasound on lymph nodes resected from surgical tissues, lymph nodes with a long axis short axis ratio (L/S) larger than 2 were more likely to be benign.¹⁵ In our study, only four cases showed an elliptical shape.

The effectiveness of EUS in evaluation and differentiation of enlarged lymph nodes is still an area of uncertainty. It has been reported that false positive or false negative results were obtained in 27% of patients in the evaluation of enlarged lymph nodes by EUS alone.¹ Therefore, to perform diagnostic histological tests in parallel to EUS may be extremely useful. Clinical situations that EUS-FNA may be useful are enlarged lymph nodes detected during follow up observation after surgery in cancer patients, accurate staging in patients diagnosed with cancer, and pathological diagnosis of diseases suspicious to be benign.

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