Endoscopic ultrasound-guided fine-needle aspiration biopsy for diagnosis of gastric linitis plastica with negative malignant endoscopy biopsies

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Abstract. The value of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) biopsy in the gastric linitis plastica (GLP) with negative malignant endoscopy biopsies was investigated. Forty-six patients with linitis plastica who had undergone EUS-FNA were retrospectively studied, and their clinicopathological data were examined. Among the 46 eligible patients, 38 cases were diagnosed clearly by EUS-FNA. There were 24 cases with lymph node metastasis in the 38 patients. Both the lymph nodes and gastric lesions were punctured by EUS-FNA in the 24 cases. We compared the diagnostic accuracy in different sites, and the results showed that the diagnostic accuracy in lymph nodes was significantly higher than that in gastric lesions ($P<0.05$). Among them, 16 patients underwent surgical resection, and the accuracy of the pathological diagnosis by EUS-FNA was 87.5% (14/16). The preoperative diagnostic accuracy of T and N staging by endoscopic ultrasound (EUS) were both 75%. Neither severe hemorrhage nor perforation occurred in any patient. In conclusion, EUS-FNA is a safe and effective procedure for the diagnosis of indefinite linitis plastica, and puncturing metastatic lymph nodes can improve the diagnostic accuracy.

Introduction

Gastric linitis plastica (GLP), also known as 'leather bottle stomach' or Borrmann type IV gastric cancer, is believed to be a kind of diffuse infiltrative gastric cancer (1,2). In general, since tumor cells migrate throughout the submucosa without severely affecting the mucosal lining of the stomach, it is difficult to detect cancer cells by gastrointestinal series or conventional endoscopic biopsy at an early stage (3-5). On one hand, at the time of detection, these walls of GLP are occasionally accompanied by peritoneal dissemination, considerable lymph node metastasis and direct invasion into the surrounding organs, which results in a poor prognosis (6,7). On the other hand, a number of diseases may present with the same thickened gastric wall as GLP including malignant tumors (lymphoma) as well as benign diseases (Ménétrier's gastritis, amyloidosis, and lymphoid hyperplasia); the therapeutic management of these diseases is clearly different (8). In addition, the incidence of GLP is increasing gradually at present (9). Therefore, it is very important to make a definitive diagnosis promptly and accurately.

Endoscopic ultrasound (EUS) is a reliable non-surgical technique for diagnosis and staging of gastrointestinal malignancies. Although some lesions have distinctive EUS characteristics, using these diagnostic criteria alone to distinguish other diseases from GLP is inadequate (6). Consequently, tissue sampling is necessary to establish a conclusive diagnosis. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) biopsy has evolved to become a leading method to confirm the diagnosis of the pre-therapeutic evaluation in patients suspected of submucosal tumors of the upper gastrointestinal tract (10,11). However, its importance for the diagnosis of GLP has been reported only by description of isolated cases (12), no systematic study has been reported.

In the present study, we retrospectively investigated the safety and efficacy of EUS-FNA for the diagnosis of GLP with negative malignant endoscopy biopsies.

Patients and methods

Patients. Between January 2010 and January 2017, 46 consecutive patients who were suspected of GLP underwent EUS-FNA at the Endoscopy Centers in Renmin Hospital of Wuhan University. All patients had undergone ordinary endoscopic biopsies 2-8 times (4 times on average), and their pathology showed negative results. We extracted and analyzed their medical data. The patient group was composed of 20 males and 26 females, aged 26-72 years old with a mean age of 47±10.3 years.

The study was approved by the Institutional Review Board of Renmin Hospital of Wuhan University (Wuhan, China) and Xiangyang First People's Hospital of Hubei University of Medicine (Xiangyang, China). Written informed consent was obtained from all patients.

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Equipment. EUS was performed to determine the status (size, shape, location, edge and echo intensity, surrounding organs or lymph node metastasis) of the lesion by using a conventional linear array EUS endoscope (Pentax EG-3270UK; Pentax, Tokyo, Japan) and ultrasonic mainframe (Hitachi Preirus; Hitachi, Ltd., Tokyo, Japan). Patients were hospitalized for the procedure and were surveyed for complications till discharge from the Hospital.

EUS-FNA procedure. After the target lesion was detected on an EUS view, EUS-FNA was performed by an endoscopic expert who used a disposable 19-gauge needle (EchoTip Ultra; Cook Medical, Inc., Winston-Salem, NC, USA), as previously reported (13-15). Briefly, color Doppler was used to prevent insertion of the needle into the vessels. To select the appropriate safety path for EUS-FNA 4-8 times, 10 ml tissue was gained by negative pressure suction. The needle was retracted after stopping the negative pressure. The tissue in the needle was extracted.

The needle was advanced and moved back and forth 10-20 times while suction was applied. The lock of the syringe was then closed and the needle removed.

If the collected specimen was a shaped tissue strip, it was immediately placed in 10% formalin for histologic examination, and the remaining extract was injected onto a dried glass for cytological examination by an on-site cytopathologist. Cell smear was obtained from all of the 46 patients and complete tissue strips were obtained in 10 cases. The number of needle passages depended on the cytological diagnosis of the expert. If a certain amount of eligible cells was found, the puncture was completed. After the operation, all patients were fasted and given treatment of fluid replacement and acid suppression.

Statistical analysis. SPSS 17.0 (SPSS, Inc., Chicago, IL, USA) software was applied for data analysis. Measurement data are presented as mean ± standard deviation; Chi-square (χ^2) test was applied to compare the enumeration data and rate between the two groups. $P<0.05$ was considered to indicate a statistically significant difference.

Results

In the 46 cases, 40 cases were diagnosed as GLP by EUS-FNA or operation. The lesions of 12 cases were situated in total stomach, 16 cases in gastric body, 8 cases in gastric antrum, 4 cases in cardia and fundus of stomach. The lesion site had been replaced by a thick gastric wall. The maximum full thickness of the stomach wall ranged from 7.4 to 22 mm, with an average thickness of 15.7±5.8 mm (Fig. 1). Thirty cases had homogeneous hypoechoic changes, 8 cases had inhomogeneous hypoechoic changes, and 2 cases had medium echo. Elastography is a type of virtual biopsy that attempts to assess differences in elasticity between normal and tumor tissue. In the present study blue dominated in all the lesions. On elastographic images, soft tissues are shown in red and hard tissues in blue. The elastic strain rate (SR) ranged from 44 to 81, with an average value of 61±18.7. There were 24 cases with lymph node metastasis among the 40 patients (Fig. 2). Three cases had ascites, and 4 cases had both lymph node metastasis and ascites.

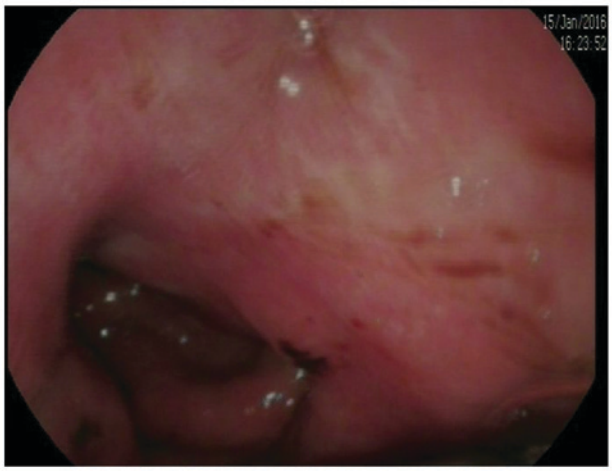

Figure 1. The gastric mucosa is thick, the gastric wall is stiff, and the surface is covered with shallow ulcer.

Of the 26 patients who underwent EUS in the lower stomach wall whose 1-5 layer structure disappeared, the average stomach wall thickness was 16.6±2.1 mm. Among these, 24 patients were with gastric lesions, such as ascites or lymph nodes. Of the 13 patients with merged 1st-to-3rd layer structure and thickened 4th layer, the average thickness of gastric wall was 13.1±2.9 mm, and in patients with gastric lesions (6/14), the gastric wall thickness and the incidence of gastric lesions in the former (6 patients) were significantly higher.

In the 46 patients, there were 38 cases who were diagnosed clearly by EUS-FNA, and the positive rate of aspiration diagnosis was 82.6%. Pathological findings showed that among the 38 lesions, 26 were adenocarcinoma, 8 were signet-ring cell carcinoma, and 4 were lymphoma. The final operations were performed in 16 patients, and the postoperative pathological findings were consistent with EUS-FNA in 14 cases. The diagnostic accuracy of EUS-FNA was 87.5% (14/16). However, another 2 cases had indeterminate diagnoses by EUS-FNA, while the pathological findings after operation were poorly differentiated adenocarcinoma and undifferentiated adenocarcinoma, respectively. In 16 cases, the findings of EUS were compared with postoperative assessments of T and N staging. The diagnostic accuracy of EUS was 80% for T2 staging and 66.7% for T3 staging. Twelve of 16 GLPs were staged correctly and the overall diagnostic accuracy of the T stage was 75% (Table I). The diagnostic accuracy of EUS was 66.7% for N0 staging and 80% for N^+ staging. The overall diagnostic accuracy of N staging was 75% (Table II). Lymph nodes with sharp borders and hypoechoic structures, and >10 mm in size, were considered as malignant. Stage N0 denotes no sign of metastasis. N^+ denotes metastases in perigastric lymph nodes (15). According to the clinical and imaging follow-up, the diagnoses of patients without surgical resection were consistent with the EUS-FNA findings.

There were 24 cases with lymph node metastasis, the abnormal stomach walls (gastric lesions) and lymph nodes of these patients were punctured, respectively, by EUS-FNA. The diagnostic accuracy in different puncture sites was compared. The results showed that there were 18 cases with accurate diagnoses by puncturing lymph nodes (the positive rate of

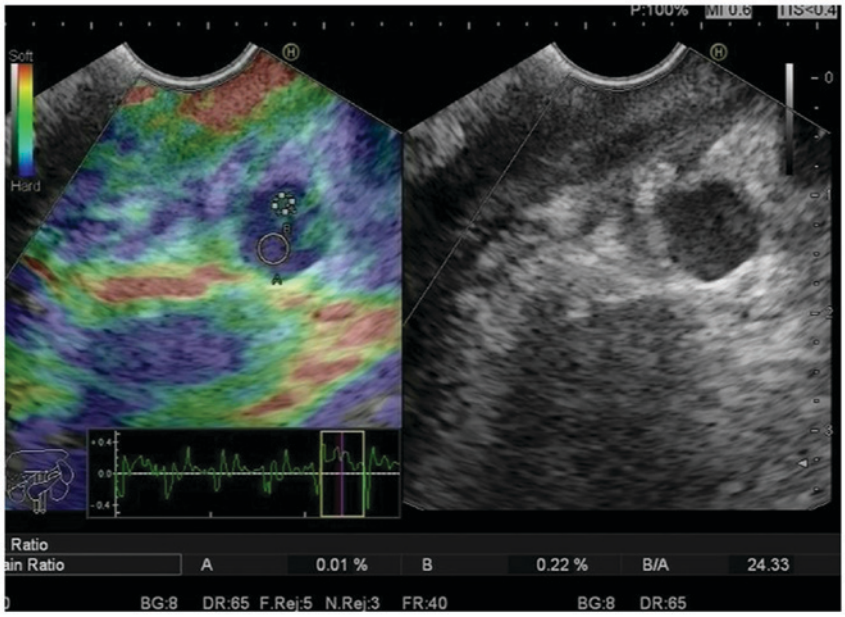

Figure 2. Endoscopic ultrasonography of peripheral metastatic lymph nodes.

Table I. Accuracy of EUS preoperative T staging in 16 patients with linitis plastica.

		Pathologic stage			
EUS stage	n	T2	T3	T4	Accuracy of EUS (%)
T2	10	8	2	0	80
T3	6	0	4	2	66.7
T4	0	0	0	0	
Total	16	8	6	2	75

EUS, endoscopic ultrasound.

Table II. Accuracy of EUS preoperative N staging in 16 patients with linitis plastica.

		Pathologic stage		
EUS stage	n	N0	N^+	Accuracy of EUS (%)
N0	6	4	2	66.7
N^+	10	2	8	80
Total	16	6	10	75

EUS, endoscopic ultrasound.

diagnosis was 75%). However, of the 24 patients, only 13 cases had positive and accurate diagnoses by puncturing gastric walls (the diagnostic accuracy was only 54.2%). Accordingly, the diagnostic accuracy by puncturing lymph nodes was higher than the thick stomach walls (Figs. 3 and 4), and this difference was statistically significant (P=0.033, <0.05) (Table III).

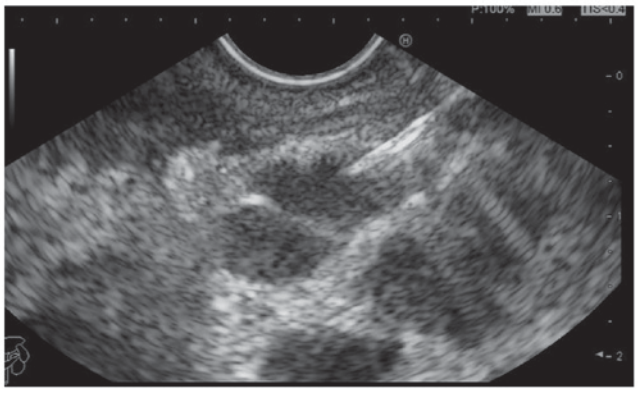

Figure 3. Metastatic lymph node puncture guided by EUS-FNA. EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration.

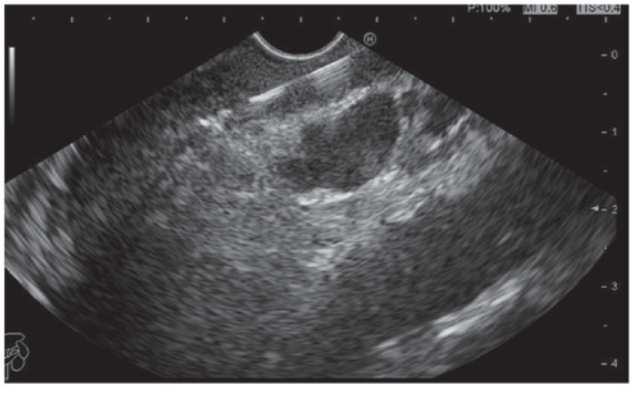

Figure 4. Puncture of pathological gastric wall guided by EUS-FNA. EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration.

According to the follow-up (the follow-up interval after EUS-FNA ranged from 1 week to 1 month), none of the 46 patients required any procedures related to adverse events.

Table III. The positive rates of diagnosis in different puncture sites.

Puncture sites	Pathological findings of aspiration		Diagnostic accuracy of aspiration (%)
	Positive	Negative	
Metastatic lymph node	18	6	75
Stomach walls (gastric lesions)	13	11	54.2

P=0.033, <0.05.

Discussion

GLP has a unique pathological growth pattern. The tumor tissue originates from the submucosa and infiltrates around the gastric wall, resulting in reactive fibrosis (16). The positive rate for superficial biopsies in GLP patients is low. Kim *et al* (17) showed that the missed rate of ordinary biopsies in diagnosing Borrmann type IV gastric cancer was as high as 55.9%. Therefore, misdiagnosed and missed diagnosis are common in conventional endoscopic biopsy and that not only affects the treatment and prognosis of the disease, but also increases the patient's pain and psychological, and financial burden.

Endoscopic ultrasonography has developed rapidly and has dual functions of endoscope and ultrasound. It can clearly display the structure of gastric wall and its relation with tumors (18). Therefore, EUS greatly improves the diagnostic rate of GLP (8). EUS has special sonographic signs for gastric cancer, and correct diagnosis and staging can be achieved in most patients. EUS can be used to observe the gastric wall and extramural lesions. At the same time, according to the characteristics of the EUS sonogram, it is possible to distinguish whether the thickened gastric wall has a destructive lesion and infer its properties. Therefore, there is an advantage in diagnosing the leather stomach. By conventional endoscopy it is difficult to distinguish primary gastric lymphoma, Ménétrier's disease, and hypertrophic gastritis from leather stomach. Caletti *et al* reported that the hypertrophic gastritis EUS showed diffuse thickening of the 2nd and 3rd layers of the stomach wall, but thickened lesions usually show hyperechoic changes (19). Some studies have found that the lesions of primary gastric lymphoma under EUS are multifocal, and the diffuse thickened layer 2 and 3 hypoechoic lesions pass through the pylorus to the duodenum. Further comparison of the difference between primary gastric lymphoma and leather stomach under EUS revealed that the former tends to grow along the longitudinal axis of the stomach, whereas the leather stomach grows along the transverse axis of the stomach (20). In this study, we summarized the characteristics of EUS sonograms of 40 cases of leather stomach: i) the lesions were widely distributed, with continuous diffuse infiltration around the stomach wall as the main type, lesion area is beyond the abnormal area under endoscopy, and the lesions were mainly located in the stomach; ii) all layers of the stomach wall at the lesion were thickened, 1st-3rd layers were most commonly thickened and sometimes the 4th layer was also thickened. The mean thickness of the stomach wall measured by ultrasound was 15.7±5.8 mm. The thicker the stomach wall, the higher the incidence of gastric lesions; iii) the lesions were mainly hypoechoic; iv) lesions tend to grow along the transverse axis of the stomach; v) lesions are hard tissue, elasticity ultrasound shows mainly blue signal, average SR value was 61±18.7. The characteristics of these ultrasound images are basically consistent with those reported by Shan *et al* (21), and they are consistent with the special biological characteristics of leather stomach, which is helpful for the diagnosis of leather stomach.

In addition, the peripheral lymph node metastasis rate of GLP is slightly higher. These sonographic features which are consistent with the findings of Shan *et al* (21) and the special biological characteristics of GLP (22) are beneficial for the diagnosis of GLP. In addition, EUS can accurately judge the TNM staging of GLP, and is of great value for the resectability and prognosis (23). In the present study, compared with postoperative staging of the 16 patients who underwent surgical resection, EUS had a diagnostic accuracy of 75% for T staging and 75% for N staging. The accuracies are similar to those from the previous studies of Cardoso *et al* (24). However, Park *et al* considered that the level of experience and proficiency of an operating doctor could directly affect the accuracy of staging (25). Therefore, with the increasing diagnostic experience of endoscopic doctors, the accuracy of EUS for T and N staging of GLP will be further improved.

Although EUS is a reliable imaging method for the diagnosis of GLP, a clear diagnosis based only on the sonographic features is inadequate (20). More importantly, we need definitive diagnosis to guide the treatment and prognosis of GLP. In recent years, with the improvement of endoscopic diagnosis and treatment technology, a number of new endoscopic biopsy techniques have emerged, such as jumbo biopsy, endoscopic submucosal resection, endoscopic submucosal dissection and the bite-on-bite technique (26-28). Although jumbo biopsy and endoscopic submucosal resection may increase the surface area of the tissue sample, they do not significantly increase the depth (29), and there are procedural risks and complications such as perforation and hemorrhage (30). In contrast to EUS-FNA, endoscopic submucosal resection is more costly and GLP usually has a thickened epithelium which may limit the use of bite-on-bite technique (10,31). EUS-FNA biopsy can accept partial submucosal lesions and surrounding metastatic tissue purposely, which significantly improves the biopsy positive rate of GLP (32). In this study, we assessed the diagnostic yield of EUS-FNA for GLP that had received negative results for malignancy via endoscopy biopsies. EUS-FNA provided a definitive and confirmative diagnosis in 38 (82.6%) of the 46 patients. Pathology of these patients was mainly adenocarcinoma. Based on the systemic assessment, patients were given a definite diagnosis and underwent individualized treatment. Finally, of the 16 patients who received surgery, the pathological results of 14 cases were the same by operation and EUS-FNA. The diagnostic accuracy of EUS-FNA was 87.5%. Carter *et al* obtained similar results (12). Futhermore, we compared the positive rates of diagnosis in different puncture sites, and the result showed that the positive rate of diagnosis in lymph node was significantly higher than that

of gastric lesions ($P<0.05$). Nevertheless, some studies have shown that positive rate of diagnosis is low by EUS-FNA, because the cytological tissues obtained by EUS-FAN are small (31). In our study, the positive rate of diagnosis for GLP by EUS-FNA is high, and we obtained ideal tissue samples. The main reasons are: first and foremost, the thick wall of GLP is fibrotic, while the lymph nodes around the stomach have more cancerous tissues (1), so we punctured the metastatic lymph nodes. Secondly, we had rapid on-site evaluation by a cytopathologist during EUS-FNA, which assisted us to judge whether the adequate samples were obtained or not (33). Accordingly, on-site pathology contributes to improved diagnostic accuracy and reduced complications (34). Last but not least, EUS-FNA has less risk of bleeding and perforation, thus, it can be repeated several times (35). Therefore, if we select the metastatic lymph nodes as far as possible and have cytology experts present, the positive rate and accuracy of GLP by EUS-FNA can be improved greatly.

As a limitation, this study was performed with a small number of patients. Further studies on this method are needed to clarify the indications and clinical outcomes.

In conclusion, EUS-FNA biopsies provided extremely accurate pathological diagnoses and were associated with no major complications or disease recurrence. The results of this small sample size study suggested that EUS-FNA could obtain submucosal lesions and puncturing lymph node tissue significantly improving the diagnostic accuracy of GLP with negative endoscopy biopsies. Moreover, EUS-FNA is an effective and safe diagnostic method for GLP.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YY collected and analyzed the data. ST was responsible for the EUS-FNA procedure. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Renmin Hospital of Wuhan University (Wuhan, China) and Xiangyang First People's Hospital of Hubei University of Medicine (Xiangyang, China). Informed consents were signed by the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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