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Endoscopic ultrasonographic features of gastric linitis plastica in fifty-five Chinese patients*

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Abstract: The objective of this study was to investigate the endosonographic appearance of gastric linitis plastica (GLP) and to study the usefulness of endoscopic ultrasonography (EUS) for the T and N staging of GLP. EUS examinations of 55 patients with histologically proven GLP were retrospectively studied. In all patients, EUS showed that lesions involved at least one-third of the circumference of the stomach. Based on the findings of the EUS, the 55 patients were divided into two groups. There were 32 (58.2%) patients in the first group. EUS of this group showed that the five sonographic layers had disappeared and had been replaced by a hypoechogenic thickening of the gastric wall. There were 23 (41.8%) patients in the second group. EUS of this group showed that the first three sonographic layers were blurred and thickened, and the fourth layer was significantly thickened. The full thickness of the gastric wall was significantly thicker in first than in the second group of patients (P<0.01). The incidence of perigastric lesions was significantly higher in the first than in the second group of patients (P<0.01). Results for the 15 patients following preoperative EUS were compared postoperatively with histopathologic findings for T and N staging. The overall diagnostic accuracy of the T stage was 73.3% and of the N stage was 60.0%. In eight patients, we used EUS to assess a therapeutic response. No response was observed in five patients and a partial response in three. EUS images of GLP are characteristic. EUS is helpful in diagnosing GLP and for assessing the T and N stages.

Key words: Gastric linitis plastica, Endoscopic ultrasonography, Diagnosis, Differentiation, Follow-up
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1 Introduction

Gastric linitis plastica (GLP) is defined as a gastric cancer of the diffuse histotype (Lauren, 1965) that by diffuse infiltration causes thickening and stiffening of the gastric wall and involves at least one-third of the circumference of the stomach (Pedrazzani *et al.*, 2012). There has been a striking increase in the incidence of GLP, which has risen by more than 400% in the USA since the 1970s (Piessen *et al.*, 2009). According to recent Western studies, GLP comprises 32% to 70% of gastric cancer cases (Alberts *et al.*, 2003; Wu *et al.*, 2009). An increasing incidence of GLP has also been observed in China, but no epidemiological data are available for GLP in China. A high frequency of negative endoscopic biopsies makes diagnosis difficult. Endoscopic ultrasonography (EUS) is helpful for diagnosing GLP and for differentiating other diseases (Andriulli *et al.*, 1990; Mendis *et al.*, 1994; Songur *et al.*, 1995; Tio, 1995; Chen *et al.*, 1999; Caletti *et al.*, 2000), but no systematic study has been reported. The objective of this study was to investigate the EUS features of GLP and to assess the usefulness of EUS for T and N staging of patients with this disease.

2 Materials and methods

A total of 55 patients with GLP were included in this study from June 2007 to September 2012 at the

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First Affiliated Hospital, School of Medicine, Zhejiang University, China. All diagnoses were confirmed histologically (gastric mucosa specimens were obtained from endoscopy or surgery). The patient group was composed of 34 males and 21 females, aged from 19 to 84 years with a mean age of 61 years. All patients were undergoing EUS before a clear diagnosis was made.

EUS was performed to determine the status of the lesion. A fluid interface is provided by means of a water-filled balloon around the transducer or by filling the stomach with water. In 12 patients, EUS examinations were performed at 7.5 MHz frequency using a radial scanning echo endoscope (Olympus GF-UM 2000). In 43 patients, EUS was performed with a 12 MHz miniprobe (UM-DP12-25R) passed through the operative channel of an endoscope. Two EUS experts reviewed the ultrasonic images of all lesions, including the location of the lesions, the depth of invasion, the maximum thickness of the gastric wall, the perigastric lymph nodes and ascites. The lesions and the perifocal structures were also investigated.

Results from the 15 patients following preoperative EUS were compared postoperatively with histopathologic findings for T and N staging. Tumors were staged according to the TNM (tumor-node-metastasis) 1997 classification criteria of the Union Internationale Contre le Cancer (UICC).

Lymph nodes with sharp borders and hypoechoic structures, and which were >10 mm in size, were considered as malignant. Stage N0 denotes no sign of metastasis. N+ denotes metastases in perigastric lymph nodes.

Student's *t* test was used to compare statistically the thickness of the gastric wall and the incidence of perigastric lesions between the two groups. A *P* value of less than 0.01 was considered statistically significant.

3 Results

In this study, EUS results of all the 55 patients showed that lesions involved at least one-third of the circumference of the stomach. Based on the EUS results, the 55 patients were divided into two groups (Table 1). There were 32 (58.2%) patients in the first group. EUS showed that in these patients the five sonographic layers had disappeared and had been replaced by a hypoechogenic thickening of the gastric wall (Fig. 1a). The maximum full thickness of the gastric wall ranged from 8.0 to 27.0 mm, with an average of (15.2±4.3) mm. Perigastric ascites were seen in 8 (25%) and perigastric lymph nodes in 13 (40.6%) patients (Figs. 1b and 1c). Both ascites and lymph nodes were seen in two patients. In total, 59.4% of patients in the first group had perigastric lesions. There were 23 (41.8%) patients in the second group. EUS showed that the first three sonographic layers were blurred and thickened and the fourth layer was significantly thickened (Fig. 2). The maximum full thickness of the gastric wall ranged from 8.2 to 17.3 mm, with an average of (12.2±2.2) mm. No perigastric ascites were seen and perigastric lymph nodes were found in only two (8.7%) patients. In total, 8.7% of patients in the second group had perigastric lesions. The full thickness of the gastric wall was significantly thicker in first group of patients than in the second (P=0.0016). The incidence of perigastric lesions was significantly higher in the first than in the second group of patients (P=0.000136).

For 15 patients, 9 from the second group and 6 from the first, the findings from EUS were compared with histopathologic assessments of T and N staging. The diagnostic accuracy of EUS was 77.8% for T2 staging and 66.7% for T3 staging. Eleven of 15 GLPs were staged correctly and the overall diagnostic accuracy of the T stage was 73.3% (Table 2). Four cases were understaged. The diagnostic accuracy of EUS was 66.7% for N0 staging and 33.3% for N+ staging. The overall diagnostic accuracy of N staging was 60.0% (Table 3).

In our study, 38 patients received chemotherapy. For eight patients, we were able to use EUS to assess a therapeutic response. No response was observed in five patients, and a partial response in three. In two patients, a reduction in the thickening of the gastric wall and in the extent of the lesion was observed. Recovery of a layered structure was observed in one patient (Fig. 3).

Table 1 EUS results of two groups

Group	*n*	Thickness of gastric wall (mm)	Perigastric lesion (%)
First	32	15.2±4.3*	59.7**
Second	23	12.2±2.2*	8.7**

* P=0.0016, ** P=0.000136, comparison between the two groups

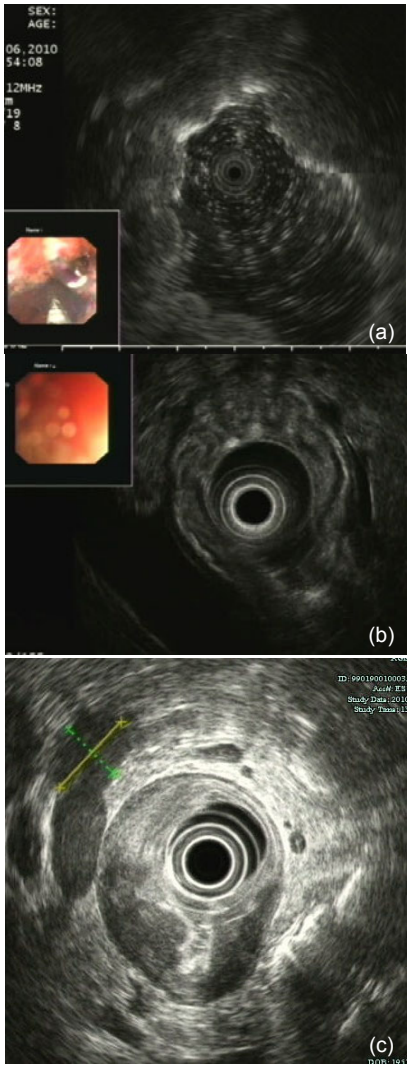

Fig. 1 EUS findings of the first group

(a) EUS showed that the five sonographic layers disappeared and were replaced by a hypoechogenic thickening of the gastric wall; (b) EUS showed ascites around gastric wall; (c) EUS showed three perigastric lymph nodes

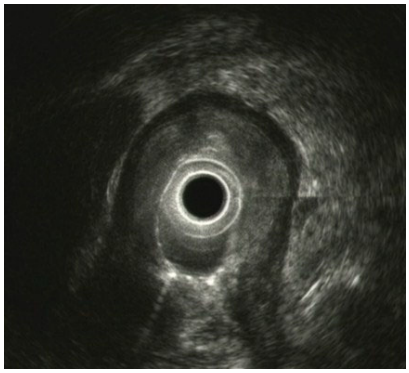

Fig. 2 EUS findings of the second group

EUS showed that the first three sonographic layers were blurred and thickened and the fourth layer was significantly thickened

Table 2 Accuracy of EUS preoperative T staging in 15 patients with GLP

EUS stage	*n*	Pathologic stage			Accuracy of EUS (%)
		T2	T3	T4	
T2	9	7	2	0	77.8
T3	6	0	4	2	66.7
T4	0	0	0	0	
Total	15	7	6	2	73.3

Table 3 Accuracy of EUS preoperative N staging in 15 patients with GLP

EUS stage	*n*	Pathologic stage		Accuracy of EUS (%)
		N0	N+	
N0	12	8	4	66.7
N+	3	2	1	33.3
Total	15	10	5	60.0

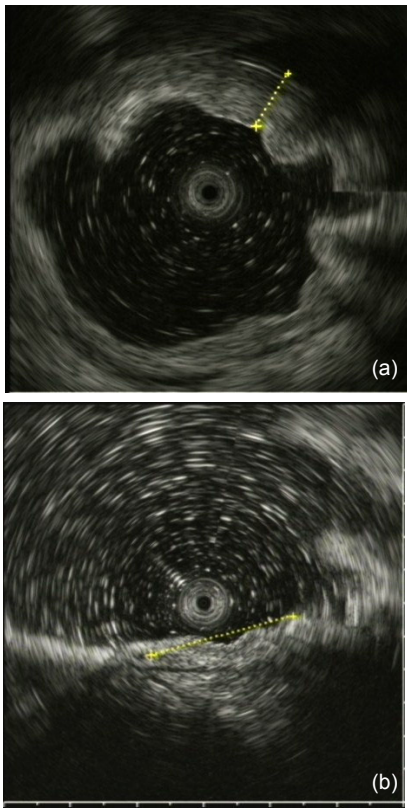

Fig. 3 Recovery of a layered structure observed in one patient

(a) Before receiving chemotherapy, EUS showed that the five sonographic layers disappeared and were replaced by a hypoechogenic thickening of the gastric wall; (b) After the 12th chemotherapy, EUS showed that the first three sonographic layers were thickened and three-layered structure was poorly preserved

4 Discussion

Linitis plastica is a subset of diffuse gastric carcinoma. It is characterized by poorly differentiated tumor cells that diffusely infiltrate the gastric wall, thus provoking reactive fibrosis (Kodera *et al.*, 2004). GLP is usually diagnosed by endoscopy with an endoscopic biopsy. Because of the predominant submucosal or muscular infiltration, the positive rate for superficial biopsies in GLP patients is low. A tissue biopsy can be negative in up to 30% of GLP patients, particularly those without mucosal lesions (Carter *et al.*, 2008). In our study, all patients had negative endoscopic biopsies in the first gastroscopy. Forty-one patients were diagnosed by second and twelve by third endoscopic biopsies. Two patients were diagnosed by surgical biopsy. So, making a diagnosis is difficult because of the high frequency of negative endoscopic biopsies. The typical endoscopic appearance is characterized by thickening and stiffening of the gastric wall. Because of their similar endoscopic appearance, differential diagnosis of GLP includes primary gastric lymphoma (PGL), Ménétrier's disease, anisakiasis and gastritis cystica profunda.

EUS has been shown to be a good tool for the definition of gastric wall involvement and for the detection of perigastric lesions. It has been reported that EUS is helpful for diagnosing GLP. Our study showed that GLP has two characteristic EUS features. The first is that the five sonographic layers disappear and are replaced by a hypoechogenic thickening of the gastric wall. The second is that the first three sonographic layers are blurred and thickened, and the fourth is significantly thickened. In our study, 58.2% of patients showed the first kind of EUS feature and 41.8% showed the second kind. The incidence of perigastric lesions and wall thickening in the first group was significantly higher than that in the second group ($P<0.01$). The second kind of EUS feature may reflect a relatively early stage and the first kind a relatively advanced stage of GLP.

Songur *et al.* (1995) also reported that there were two kinds of EUS features in 15 GLP patients. In their study, 66.7% of patients had a thickened gastric wall and a well-preserved five-layered gastric wall structure, and in 33.3% of patients the five-layered structure had disappeared and the wall had thickened. According to our study and previous studies, there are three kinds of EUS features reported in GLP patients (Songur *et al.*, 1995).

Although GLP and several other diseases have a similar endoscopic appearance, the EUS images of these diseases are different. When the second layer alone is thickened, Ménétrier's disease may be one of the possible pathologic entities, while when the third layer alone is abnormally enlarged, anisakiasis might be suspected (Maunoury *et al.*, 1994; Okada *et al.*, 1994; Songur *et al.*, 1995). The typical EUS appearance of gastritis cystica profunda is an echo-poor, multilocular cystic mass in the thickened submucosal layer (Béchade *et al.*, 2006). So, from the different images we can differentiate GLP from Ménétrier's disease, anisakiasis and gastritis cystica profunda.

A differential diagnosis between GLP and PGL is not easy. Both usually have a low frequency of positive endoscopic biopsies. However, the distinction between GLP and PGL is very important because of their different prognoses. Previous studies showed that GLP and PGL could have similar EUS images (Songur *et al.*, 1995). Differential diagnosis by EUS is difficult, especially at an advanced stage. At an advanced stage, both GLP and PGL show the disappearance of the five layers and their replacement by a hypoechogenic thickening of the gastric wall. Songur *et al.* (1995) noted that the echogenicity of PGL was markedly lower than that of GLP. We also noticed this phenomenon. We suppose that the reason is that PGL and GLP originate from different tissues. Lymphoid tissue has a lower echogenicity than epithelial tissue. In our center, we usually compare the echogenicity of lesions with that of lymph nodes. When the echogenicity of lesions is lower than that of lymph nodes, PGL is considered first. When the echogenicity of lesions is higher, GLP is considered first. In this way, no patients in our study were misdiagnosed as having PGL by EUS. However, the differentiation between GLP and other diseases on the basis of the echo pattern alone is not always possible and the final diagnosis depends on histological study.

EUS was helpful in assessing the T and N stages of gastric cancer in previous studies. The accuracy of EUS for staging gastric cancer from different studies ranges from 64.8% to 92.0% for T staging and from 50% to 90% for N staging (Tsendsuren *et al.*, 2006). In the present study, EUS had a diagnostic accuracy of 73.3% for T staging and 60.0% for N staging. These accuracies are similar to those from previous studies (Tsendsuren *et al.*, 2006). Catalano *et al.* (1994)

suggested that a sharp border and hypoechoic lymph nodes indicate malignancy, and some authors have suggested that a node greater than 10 mm in diameter is considered malignant (Grimm *et al.*, 1993). In our study, the diagnostic criteria for a malignant lymph node included: a sharp border, hypoechoic structures, and a size of >10 mm. Only one (33.3%) malignant node in three patients with N+ staging and metastases in perigastric lymph nodes in 4 (33.3%) patients with N0 staging were confirmed by pathohistological findings. Therefore, the differential diagnosis between benign and malignant lymph nodes according to EUS features can be problematic. For these reasons, the only safe way to assess the real N stage is to perform an EUS-guided fine-needle aspiration biopsy, if suspicious lymph nodes are detected.

In conclusion, EUS images of GLP are characteristic and three kinds of EUS features are found in GLP patients. EUS is useful for the diagnosis of GLP and for distinguishing between the T and N stages.

Compliance with ethics guidelines

Guo-dong SHAN, Guo-qiang XU, and You-ming LI declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000(5). Informed consent was obtained from all patients for being included in the study.

References

Alberts, S.R., Cervantes, A., van de Velde, C.J.H., 2003. Gastric cancer: epidemiology, pathology and treatment. *Ann. Oncol.*, **14**(S2):31-36.

Andriulli, A., Recchia, S., de Angelis, C., Mazzucco, D., Berti, E., Arrigoni, A., Verme, G., 1990. Endoscopic ultrasonographic evaluation of patients with biopsy negative gastric linitis plastica. *Gastrointest. Endosc.*, **36**(6):611-615. [doi:10.1016/S0016-5107(90)71180-7]

Béchade, D., Desramé, J., Algayres, J.P., 2006. Gastritis cystica profunda in a patient with no history of gastric surgery. *Endoscopy*, **39**(S1):E80-E81. [doi:10.1055/s-2006-945070]

Caletti, G., Fusaroli, P., Togliani, T., Bocus, P., Roda, E., 2000. Endosonography in gastric lymphoma and gastric folds. *Eur. J. Ultrasound*, **11**(1):31-40. [doi:10.1016/S0929-8266(99)00080-4]

Carter, J.E., Nelson, J.J., Eves, M., Boudreaux, C., 2008. Diagnosis of linitis plastica-type gastric adenocarcinoma by endoscopic ultrasound-guided fine needle aspiration: a case report. *Acta Cytol.*, **52**(6):725-728. [doi:10.1159/000325630]

Catalano, M.F., Sivak, M.V., Rice, T., Gragg, L.A., van Dam, J., 1994. Endosonographic features predictive of lymph node metastasis. *Gastrointest. Endosc.*, **40**(4):442-446. [doi:10.1016/S0016-5107(94)70206-3]

Chen, T.K., Wu, C.H., Lee, C.L., Lai, Y.C., Yang, S.S., 1999. Endoscopic ultrasonography in the differential diagnosis of giant gastric folds. *J. Formos. Med. Assoc.*, **98**:261-264.

Grimm, H., Binmoeller, K.F., Hamper, K., Koch, J., Henne-Bruns, D., Soehendra, N., 1993. Endosonography for preoperative locoregional staging of esophageal and gastric cancer. *Endoscopy*, **25**(3):224-230. [doi:10.1055/s-2007-1010297]

Kodera, Y., Nakanishi, H., Ito, S., Mochizuki, Y., Yamamura, Y., Fujiwara, M., Hibi, K., Ito, K., Akiyama, S., Tatematsu, M., *et al*., 2004. Detection of disseminated cancer cells in linitis plastica-type gastric carcinoma. *Jpn. J. Clin. Oncol.*, **34**(9):525-531. [doi:10.1093/jjco/hyh097]

Lauren, P., 1965. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol. Microbiol. Scand.*, **64**:31-49.

Maunoury, V., Klein, O., Houcke, M.L., Colombel, J.F., 1994. Endoscopic ultrasonography in the diagnosis of hypertrophic gastropathy. *Gastroenterology*, **106**:820.

Mendis, R.E., Gerdes, H., Lightdale, C.J., Botet, J.F., 1994. Large gastric folds: a diagnostic approach using endoscopic ultrasonography. *Gastrointest. Endosc.*, **40**(4):437-441. [doi:10.1016/S0016-5107(94)70246-2]

Okada, M., Lizuka, Y., Oh, K., Murayama, H., Maekawa, T., 1994. Gastritis cystica profunda presenting as giant gastric mucosal folds: the role of endoscopic ultrasonography and mucosectomy in the diagnostic work-up. *Gastrointest. Endosc.*, **40**(5):640-644. [doi:10.1016/S0016-5107(94)70272-1]

Pedrazzani, C., Marrelli, D., Pacelli, F., di Cosmo, M., Mura, G., Bettarini, F., Rosa, F., de Manzoni, G., Roviello, F., 2012. Gastric linitis plastica: which role for surgical resection? *Gastric. Cancer*, **15**(1):56-60. [doi:10.1007/s10120-011-0063-z]

Piessen, G., Messager, M., Leteurtre, E., Jean-Pierre, T., Mariette, C., 2009. Signet ring cell histology is an independent predictor of poor prognosis in gastric adenocarcinoma regardless of tumoral clinical presentation. *Ann. Surg.*, **250**(6):878-887. [doi:10.1097/SLA.0b013e3181b21c7b]

Songur, Y., Okai, T., Watanabe, H., Motoo, Y., Sawabu, N., 1995. Endosonographic evaluation of giant gastric folds. *Gastrointest. Endosc.*, **41**(5):468-474. [doi:10.1016/S0016-5107(05)80005-7]

Tio, T.L., 1995. Large gastric folds evaluated by endoscopic ultrasonography. *Gastrointest. Endosc. Clin. N. Am.*, **5**(3):683-691.

Tsendsuren, T., Jun, S.M., Mian, X.H., 2006. Usefulness of endoscopic ultrasonography in preoperative TNM staging of gastric cancer. *World J. Gastroenterol.*, **12**(1):43-47.

Wu, H., Rusiecki, J.A., Zhu, K., Potter, J., Devesa, S.S., 2009. Stomach carcinoma incidence patterns in the United States by histologic type and anatomic site. *Cancer Epidemiol. Biomarkers Prev.*, **18**(7):1945-1952. [doi:10.1158/1055-9965.EPI-09-0250]