

Patient with a gastric subepithelial lesion

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Received: 05-10-10
Accepted: 25-11-10

Abstract

Although subepithelial lesions are rarely found in the upper gastrointestinal tract, they can cause uncertainty in diagnostic approach and management. Endosonographic findings are described and current recommendations are reviewed in light of one case in order to allow for a rational approach to these lesions.

Keywords

Submucosal tumors, endoscopic ultrasound, GIST.

CLINICAL CASE

A 50 year old man with dyspepsia was sent for an upper endoscopy which found a 9 mm subepithelial lesion in the gastric corpus (Figure 1). Biopsy of the overlying mucosa was normal. The patient had no previous medical history, and his physical examination was normal.

INITIAL APPROACH: WHAT COULD WE DO THEN?

A mass or protrusion in the lumen of an organ covered by normal epithelium is called a subepithelial lesion. They are uncommon lesions which are expected to be present in 1 out of 300 endoscopies (1, 2). Causes can be intrinsic benign or malignant lesions of the gastrointestinal tract wall or extrinsic compression caused by normal or pathological adjacent structures (3).

These lesions are usually found incidentally and often have no relationship with symptoms, as was the case with our patient. This can cause the physician to doubt whether she or he should follow up with more specific investigation and perform additional (4). *In our opinion all of these lesions should be evaluated to clarify their origin.* We should always take a biopsy

of the overlying mucosa (unless we suspect a vascular or cystic origin), because many of these lesions may have an origin in the lamina propria or muscularis mucosa. In these cases they can be reached by forceps and a precise diagnosis can be made. If biopsies are normal, this is where we must define whether we should stop or continue the study.

Once the endoscopy has been performed and a subepithelial lesion has been detected, we can immediately to evaluate it. Initially we must describe its size, shape, color and mobility, and whether or not it is pulsating. Finally we can assess its consistency with closed biopsy forceps, allowing us to detect if it is cystic, solid or soft, depressible and pillow-like (a lesion which is slowly recovering). Pillow-like lesions with yellow halos are highly suggestive of lipomas. If the lesion is a slightly irregularity of the mucosa, and has a central depression, it is suggestive of an ectopic pancreas. Usually cysts or varices have a smooth, symmetrical mucosa. GISTs (gastrointestinal stromal tumors) may be slightly ulcerated, but they are firm and mobile (9). It is also useful to change the position of the patient to rule out the possibility of an extrinsic lesion, the endoscopic appearance of which will change if the patient changes his or her position, inhales, or if the patient's stomach is filled with air (10-12).

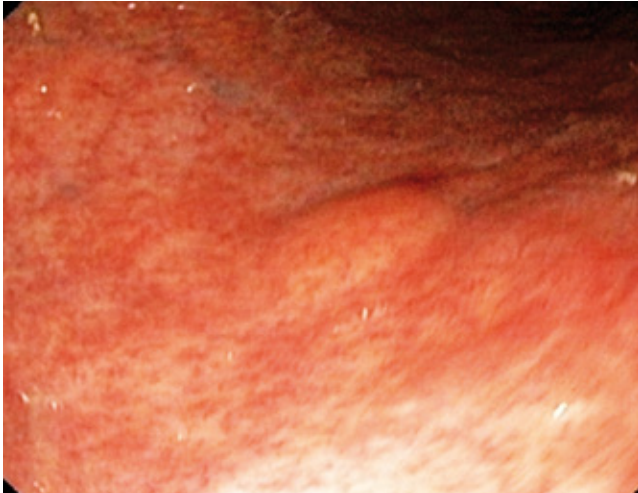


Figure 1. Gastric subepithelial lesion.

WHAT IS THE DIFFERENTIAL DIAGNOSIS?

There are many types of lesions in the gastrointestinal tract that can be categorized as subepithelial. Their causes usually depend on whether the lesion is located in the esophagus, stomach, duodenum or rectum. The next point to consider is whether it is truly a lesion of the wall, or if it is an extrinsic compression since there are structures all around the entire gastrointestinal tract that can lead to compression (Table 1) (5-8).

Table 1. Primary causes of upper digestive tract extraluminal compressions.

Esophagus
Vascular: aortic (middle third), subclavian artery (Dysphagia Lusoria) (In upper third)
Vertebrae
Mediastinal tumors (bronchopulmonary or breast)
Chest deformities, sequelae of surgical procedures
Stomach
Back of fundus, splenic vessels, spleen
Back of body: pancreas
Anterior antrum: gallbladder, liver (left lobe)
Duodenum
Anterior side: gallbladder
Pancreas: tumors, pseudocysts
Nodes or metastases in any location

SHOULD ALL LESIONS BE EVALUATED WITH ENDOSCOPIC ULTRASOUND (EUS)?

Actually, all subepithelial lesions (Table 2) must be evaluated with additional imaging techniques, but if the lesion is less than a centimeter across (especially if it is yellow), an evaluation is not necessary because there is a high probability that it is a lipoma.

The endoluminal or endoscopic ultrasound (EUS) is the technique of choice (13, 14). The accuracy of EUS for differentiation of extraluminal compression from a subepithelial tumor is over 95%. This is much better than other imaging techniques such as conventional ultrasound or CAT scans (15-17) (Table 3).

Table 2. Subepithelial tumors of the gastrointestinal tract.

Mesenchymal tumors
GISTs (<i>gastrointestinal stromal tumors</i>)
Muscle tumors
Leiomyoma, leiomyosarcomas
Nerve Tumors
Schwannomas
Neurofibromas
Ganglioneuromas
Granulosa cell tumors: Abrikosov's tumors
Lipoma
Vascular
Lymphangiomas, hemangiomas
Angiosarcoma, Kaposi's sarcoma
Endocrine tumors
Carcinoid Tumor
Cysts
Cystic dilatation of esophageal glands
Bronchogenic cysts
Cysts of the gastric wall
Cystic dystrophy
Aberrant pancreas
Malformations: intestinal duplication
Metastases

Table 3. Accuracy of imaging techniques for differential diagnosis of subepithelial tumors and extrinsic compressions.

Endoscopic ultrasound	95%
Endoscopy	39%
Barium radiography	75%
CAT scans	67%

Once we have determined that the lesion is intrinsic to the wall, and is not an extrinsic compression, we must evaluate to which wall layer it corresponds. Normally, the stomach wall is divided into the mucosa, submucosa, muscularis propria and serosa. The mucous layer is divided into the epithelium, basement membrane, lamina propria and muscular mucosa. With EUS and with the radio equipment the wall can be divided into 5 layers (18):

- The first hyperechoic layer corresponds to the most superficial part of the gastric mucosa.

- The second hypoechoic layer corresponds to the deepest part of the mucosa that can be correlated with the muscular mucosa.
- The third hyperechoic layer corresponds to the submucosal layer.
- The fourth hypoechoic layer corresponds to the muscle itself.
- The fifth hyperechoic layer corresponds to the serosa or adventitia.

Normally there are no lesions in layers one and five (19), so they are limited to three layers. They are usually hypoechoic, anechoic, or hyperechoic.

DIAGNOSIS WITH ENDOSCOPIC ULTRASOUND

We will describe each presentation according to its layer.

Echo layer two

Corresponds to the deepest part of the mucosa or to the lamina propria and to the muscularis mucosa. The lesions that arise in this layer are rare and are usually hypoechoic.

Hypoechoic lesions: Most of the tumors that arise in this layer are muscular, usually leiomyomas. They may have calcifications and large ones can be heterogeneous and show nodules unlike small lesions which are homogeneous. (20).

In this layer, we also find Abrikosov's tumors or granular cells. They are usually small and, unlike leiomyoma, they deform the ball of the endoscope due to their hardness (Figures 2 and 3). Carcinoids can also originate in this layer, usually in the fundus or the rectum (Figure 4).



Figure 2. Yellow colored subepithelial lesion in the distal esophagus.

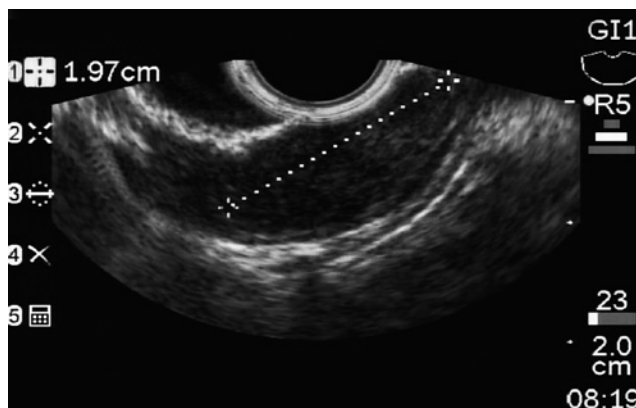


Figure 3. The EUS shows an isoechoic lesion in the third echo layer which deforms the ball, suggesting a 2 cm granular cell tumor

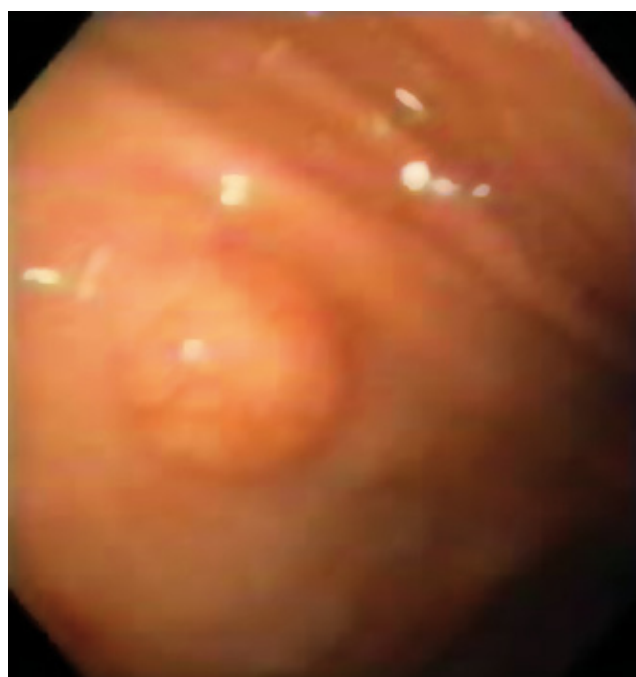


Figure 4. Subepithelial lesion with a reticular pattern in the center suggesting a neuroendocrine tumor.

Anechoic lesions: Usually we can see that inclusion or retention cysts can originate in this layer.

Echo layer three

Is a band of tissue that looks hyperechoic in the EUS. Numerous tumors can originate in this layer.

Hyperechoic lesions: The most frequently found lesions in this layer are lipomas. They are characterized as homogeneous hyperechoic lesions. Usually, they are pillow-like when pushed with endoscopic forceps (Figure 5) (9).

Neurofibromas tend to be hyperechoic. They originate in the submucosa or muscularis propria.

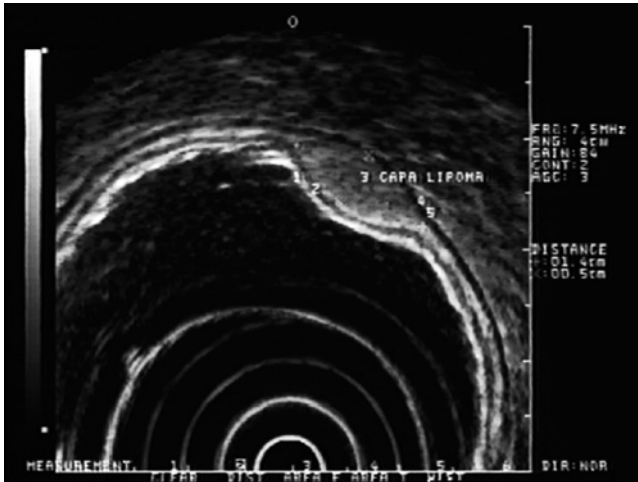


Figure 5. EUS: hyperechoic lesion in submucosal layer 3 compatible with lipoma.

Hypoechoic lesions in this layer may correspond to ectopic or aberrant pancreata. These lesions are usually heterogeneous and occasionally anechoic ductal structures which may correspond to ducts can be seen in the center. In an endoscopy a lesion with a depressed center is seen (21).

Hypoechoic lesions can also correspond to carcinoid tumors. Although they are not subepithelial tumors because they are neuroendocrine rather than mesenchymal, they may be located in the digestive wall and give rise to the same type of nodules. Usually they are small (less than one cm), hypoechoic (but more echogenic than muscular) and settle in the mucosa. Histological study is usually possible from a biopsy (22, 23).

Gastric lymphomas may also be present as hypoechoic or hyperechoic lesions of the submucosa (24).

Anechoic lesions observed in this layer are likely to be vascular structures or cysts (25).

Echo layer four

Corresponds to the muscular layer. Hence the majority of tumors in this layer are of muscular origin.

Hyperechoic lesions are very rare, but may be linked to lymphomas, neurogenic tumors or metastases (26).

Most of tumors of this layer are hypoechoic, mostly stromal tumors (GIST) when they are situated in the stomach. However, if they are located in the esophagus they are usually called leiomyomas. Other lesions that may have this appearance are metastases originating in the lungs or breasts and glomus tumor (27). Lymphomas can also compromise this layer but are generally accompanied by commitment of the upper layers.

GIST (gastrointestinal stromal tumor) is the name of lesion about which our knowledge has greatly improved in

recent years (28-30). These tumors appear to originate in totipotential cells which are also the points of origin of the so-called interstitial cells of Cajal. They can be differentiated into groups: predominantly muscular, predominantly neural, or a combination of the two. The diagnosis is made by the immunohistochemical identification of CD-117 protein (also known as c-kit protein) which is a membrane receptor with tyrosine kinase activity (31).

The importance of these lesions is that 30% may have malignant behavior and give rise to metastases. In the United States alone, 5,000 to 6,000 cases are reported each year (32). Their distribution in the gastrointestinal tract is: stomach (40-70%), small intestine (20-40%), colon and rectum (5-15%) and esophagus (<5%) (33). This means that if we have a fourth layer hypoechoic lesion in the esophagus, it is probably a leiomyoma, but if it is in the stomach, it is usually a GIST (Figure 6-8). Most patients are in their fifth or sixth decade of life. Usually they have a lesion located in the fourth layer or muscularis propria, although it could also be located in the muscularis mucosa (34). Most patients are asymptomatic until the tumor becomes large enough to ulcerate, bleed or metastasize.

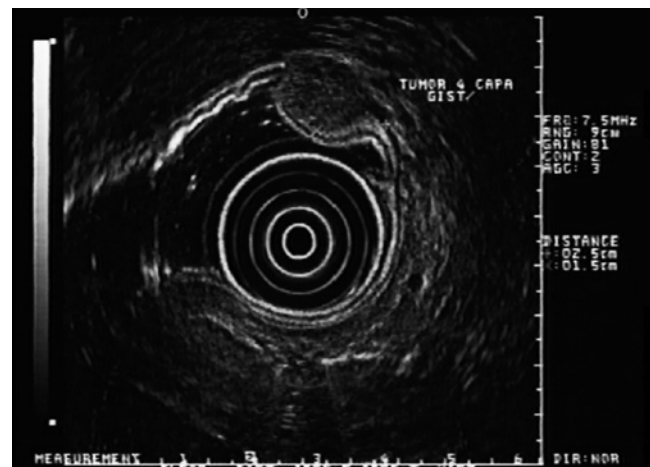


Figure 6. EUS shows hypoechoic lesion of the fourth layer compatible with GIST.

For this reason, if we identify a GIST greater than 3 cm it is an indication for surgery even if it is asymptomatic (other authors suggest a limit of 4 cm). (35). However, lesions of less than 3cm represent challenges for management because the majority are benign. Nonetheless, it should be clarified that all GISTs are potentially malignant, and small GISTs that have metastasized have been reported, especially in the lower gastrointestinal tract. Currently we are unable to predict with endoscopic ultrasound the malignant potential of a GIST. Nevertheless, we know that lesions which are larger than 4 cm, have irregular borders and/or cystic spaces

within them, or have echogenic foci have high probabilities of being malignant (36).



Figure 7. Ulcerated lesion suggestive of GIST.

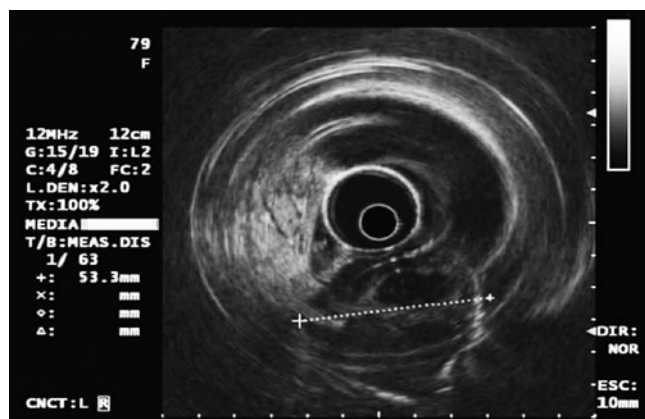


Figure 8. EUS of Figure 7 shows hypoechoic lesion of the fourth echo layer highly suggestive of a GIST, more than 5cm.

On the other hand endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) can not only diagnose GIST by identifying CD-117, but can also the presence of the Ki-67 protein which indicates proliferation and suggests malignant behavior (37). It is very important to emphasize that GIST lesions are very dangerous. We must follow them continuously, assessing tumor size and proliferation rate according to the established risks. Even after complete resection, these lesions may recur, especially at the site of origin, but also in the peritoneum or liver. 40% to 90% of lesions recur despite complete resection. 50% of recurrences involve the liver. GISTs have 4 times greater risk of recurrence when the primary site is the gut than they do when it is in the stomach (38).

WHAT IS THE ACCURACY OF ENDOSCOPIC ULTRASOUND?

Multiple studies have shown that EUS is very accurate for determining whether or not a lesion is on the wall, and for establishing which wall layer the lesion is from. This allows us to choose the best diagnostic approach. One study determined that the source layer in 48 of 50 patients (96%) with surgical confirmation (39). Interobserver agreement is very good, especially when identifying lesions such as leiomyomas and vascular lesions. It is important to note that the sonographic appearance of lesions does not allow us to determine their causes with 100% certainty. A study by Karaca et al. (40) of 22 patients undergoing EUS followed by mucosectomy showed that the accuracy of EUS was only 45%. However, the lesions were mostly smaller than 20mm, and Ultrasound precision increased to 66% for differentiating malignant from benign tumors. As the sonographic criteria can be imprecise, it seems reasonable that we should, if possible, try to obtain a specific diagnosis. This can be achieved with EUS-FNA or mucosal resection of the lesion as demonstrated in this work. Mekky et al. studied 141 patients undergoing EUS-FNA checked surgically. They found an accuracy of 95.6% for their final results (41).

MONITORING, PUNCTURE BIOPSY OR RESECTION?

The decision to monitor, use or perform a resection depends on several factors including the size of the lesion, its endoscopic appearance, the layer of origin and its echogenic characteristics. If we face a subepithelial lesion of less than 1 cm, more tests are not justified, but a follow-up endoscopy should be performed. If the lesion is greater than 1cm, EUS is mandatory. If the lesion is small and depends on the first, second, or third echo layer, diagnostic mucosal resection, which is also therapeutic, can be performed. However, if the lesion is in the fourth layer and is less than 2cm, monitoring with endoscopy alone is recommended. If it measures between 2cm and 5cm, EUS-FNA is ideal. If it is established that it is a benign lesion, a follow-up examination can be performed after 6 months. If it has not grown, no further monitoring is required. If it is malignant, has malignant potential, or is larger than 5cm, treatment is recommended (42).

In conclusion, since our patient had a lesion smaller than 1 cm, we believe his lesion merited only follow-up endoscopy (see algorithm, Figure 9). A new follow-up examination was proposed in one year. If the lesion has not grown, additional follow-ups will be scheduled every 2 or 3 years, but if it grows we will propose EUS-FNA and an immunohistochemical study.

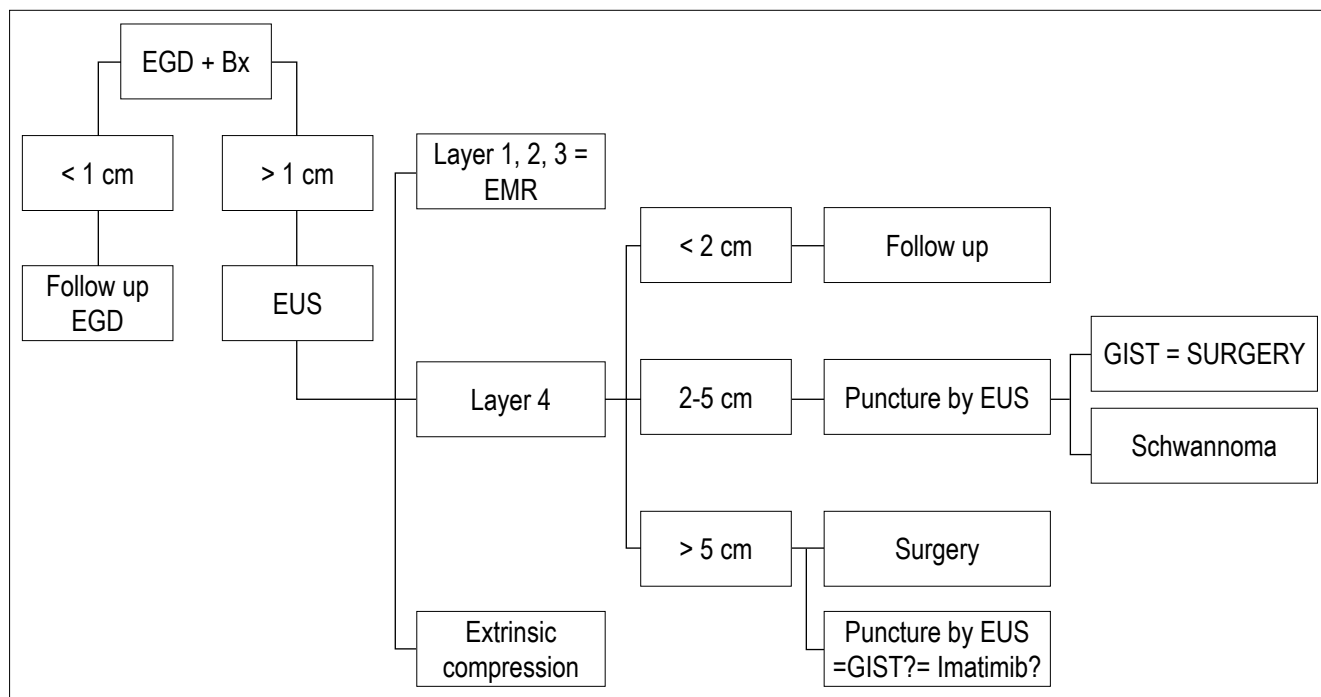


Figure 9. Treatment algorithm in subepithelial lesions. EGD: upper endoscopy. Bx: Biopsy. EUS: endoscopic ultrasound. EMR: endoscopic mucosal resection.

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