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EDITORIAL

Opinion: How to manage subepithelial lesions of the upper gastrointestinal tract?

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Abstract

Subepithelial lesions (SELs) in the upper gastrointestinal (GI) tract are relatively frequent findings in patients undergoing an upper GI endoscopy. These tumors, which are located below the epithelium and out of reach of conventional biopsy forceps, may pose a diagnostic challenge for the gastroenterologist, especially when SELs are indeterminate after endoscopy and endoscopic ultrasound (EUS). The decision to proceed with further investigation should take into consideration the size, location in the GI tract, and EUS features of SELs. Gastrointestinal stromal tumor (GIST) is an example of an SEL that has a well-recognized malignant potential. Unfortunately, EUS is not able to absolutely differentiate GISTs from other benign hypoechoic lesions from the fourth layer, such as leiomyomas. Therefore, EUS-guided fine needle aspiration (EUS-FNA) is an important tool for correct diagnosis of SELs. However, small lesions (size < 2 cm) have a poor diagnostic yield with EUS-FNA. Moreover, studies with EUS-core biopsy needles did not report higher rates of histologic and diagnostic yields when compared with EUS-FNA. The limited diagnostic yield of EUS-FNA and EUS-core biopsies of SELs has led to the development of more invasive endoscopic techniques for tissue acquisition. There are initial studies showing good results for tissue biopsy or resection of SELs with endoscopic submucosal dissection, suck-ligate-unroof-biopsy, and submucosal tunneling endoscopic resection.

Key words: Gastrointestinal neoplasm; Gastrointestinal endoscopy; Endoscopic ultrasound-guided fine needle aspiration; Endosonography; Gastrointestinal stromal tumors

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Core tip: Subepithelial lesions (SELs) of the upper gastrointestinal tract include a broader differential diagnosis, which can range from non-malignant tumors to lesions with malignant potential such as gastrointestinal stromal tumors. The possibility of having a potentially malignant lesion may bring anxiety and discomfort to patients and doctors. Further investigation should be carried out for patients with high-risk lesions after risk stratification. This editorial presents the current

evidence about the diagnostic management of SELs.

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TYPES AND DIAGNOSIS OF SUBEPITHELIAL LESIONS

Expansive lesions located below the epithelium of the gastrointestinal (GI) tract pose a diagnostic challenge for the gastroenterologist. In most cases, the endoscopic aspect is not diagnostic and lesions are out of reach for conventional biopsy forceps[1].

The differential diagnosis of subepithelial lesions (SELs) encompasses non-neoplastic lesions such as varices, as well as neoplastic lesions with practically no malignant potential, including leiomyoma or lipoma. However, there are neoplastic lesions with a higher malignancy potential, for example gastrointestinal stromal tumors (GISTs) and neuroendocrine tumors[2]. Dealing with patients with SELs is a real exercise in risk stratification.

In a few circumstances, the endoscopic aspect is sufficient to define a low risk lesion, such as a pancreatic rest located at the greater curvature of the antrum, or a large and ulcerated mass like a high grade gastric GIST. The challenge is the inconspicuous SEL clearly located below the mucosa[3].

Some endoscopic maneuvers should be employed to better characterize SELs: Chromoendoscopy and conventional biopsy are useful to rule out true mucosal neoplasms that rise deep in the epithelium, such as myoblastoma and neuroendocrine tumor. Measuring the lesion is also important. Changing patient decubitus and palpation with the biopsy forceps are usually employed to differentiate a true SEL from an extrinsic compression caused by other organs. Generally, these maneuvers have low sensitivity for defining the true nature of the lesions[4].

Sometimes it is relatively easy to make a differential diagnosis using endoscopic ultrasound (EUS), for example between a small gastric carcinoid limited to the deep mucosa and a compression of the GI tract caused by other extrinsic structures, such as a giant splenic cyst. However, in many circumstances the differential diagnosis is not straightforward, even with EUS. When we are dealing with intramural lesions, the EUS image will define the layer of the GI wall where the lesion lies.

Hypoechoic SELs from the fourth layer include a broader differential diagnosis, for example GIST, leiomyoma, and schwannoma, among other mesenchymal tumors.

RISK STRATIFICATION

Thinking about risk stratification, authors looked for some EUS features predictive of SEL malignancy. Larger, heterogeneous lesions with cystic areas and irregular outer margins were proved to harbor a higher risk for malignancy. The presence of at least two of these features had an 80% sensitivity and 80% specificity for detecting malignancy[4,5].

It is noteworthy that the location of the lesion can also predict its behavior. Esophageal SELs rarely harbor any malignant potential (1%), different from gastric and duodenal lesions which have a higher risk for malignancy, in more than 20% of cases[2].

Indeed, when SELs are located in the esophagus, the risk for a potential malignant lesion, such as a GIST, is low (7%). On the other hand, when the lesion is located in the stomach or duodenum this risk is much higher, as some publications reported that subepithelial neoplasms located in the stomach and duodenum were GISTs in more than 70% and 50% of cases, respectively[6,7].

When we looked at our experience[8], we also noticed that location inside the stomach could be useful for risk stratification. From 11 lesions located in the cardia, none were GISTs, while from 17 lesions located at the gastric body, 11 (70%) were GISTs.

Our numbers were confirmed in a larger trial[9], where 144 patients with SELs were endoscopically resected by endoscopic submucosal dissection (ESD). Only 14% of the lesions located at the cardia proved to be GISTs, while 85% were leiomyomas.

EUS is an important tool for the differential diagnosis of SELs. Its features can be diagnostic of extrinsic compressions, lipomas, cysts and varices, and no further investigation is needed.

GIST: ONCOGENESIS AND HISTOLOGIC ASSESSMENT

The concept of GISTs is relatively recent, and refers to a group of mesenchymal lesions that express a transmembrane protein called KIT. This KIT protein is codified by a proto-oncogene called c-kit. In normal conditions, the stem cell factor activates two kit receptors to signal cell proliferation, by activating tyrosine kinase. In GISTs pathogenesis, oncogenic mutations in KIT result in ligand-independent activation of tyrosine kinase. C-kit mutations located at exons 11 and 9 are the most frequent ones. Around 5% of GISTs do not present c-kit mutations; in those cases mutations of the platelet-derived growth factor are seen[10].

GISTs are rare tumors that affect patients in their fifties. In the United States, the estimated incidence of GIST is 7 to 14 new cases per million in the general population[11]. The most frequent locations of GISTs are the stomach and small bowel. The colorectum and esophagus are much less frequent locations, as well as the omentum, retroperitoneum and mesenterium[11].

Histologically, most GISTs are spindle cell type (70%). In the minority of cases, they present as epithelioid (20%) or mixed (10%) types[12]. It is controversial whether the histologic type has prognostic implications. The spindle cell type is practically identical to the histology of leiomyoma. Only an immunohistochemistry panel can make a differential diagnosis between them.

Immunohistochemistry testing at least for C-kit and CD34 is recommended. It is noteworthy that up to 40% of GISTs express smooth muscle actin[12].

GISTs have been included in the 2010 TNM classification, meaning that they should be regarded as malignant neoplasms. However, not all GISTs present invasive or metastatic behavior. Small bowel GISTs present a more invasive behavior when compared to gastric ones. The overall 5-year mortality rate for small bowel GISTs reaches up to 39%, compared to 17% for gastric GISTs[13,14]. Spindle cell GISTs have a higher 5-year disease-free survival rate[15], but these results have not been replicated. In addition, mutations at exon 11 are associated with a better response to target therapy, such as oral imatinib[16].

However, the most important factors that predict GIST behavior are size and mitotic rate[17]. In fact, these features are used for the 2010 TNM classification[18]. In that classification, gastric GISTs up to 2 cm with a low mitotic rate (< 5 mitoses per 50 high-power field), are staged as Ia.

CAN EUS DIFFERENCIATE GISTS FROM OTHER MESENCHYMAL TUMORS SUCH AS LEIOMYOMAS?

The answer is no. At least up to now.

Hunt *et al*[19] found that gastric hypoechoic lesions measuring more than 4 cm, with cystic spaces and ulceration, are probably GISTs. However, most of incidental SELs do not present these features.

Another publication[20] looked at the correlation between EUS and the final histology of small (< 2 cm) resected gastric SELs. It is noteworthy that none of the 22 patients had a GIST, probably because the authors did not resect lesions from the fourth layer, where GISTs usually lie. Most lesions were pancreatic rests, and the presumptive EUS diagnosis was correct in ten of the 22 cases, less than 50%.

In our experience using EUS[8], the presence of flow detected by power Doppler and irregular outer borders had a positive likelihood ratio of 10 for GIST diagnosis. But, from 21 patients with gastric GISTs, power Doppler was positive in only five cases (25%), and irregular outer borders in seven (35%). Therefore, the absence of these features does not rule out the diagnosis of GIST, or in other words, these features have a low negative predictive value for the diagnosis of GIST.

Recently, contrast-enhanced harmonic EUS (CEH-EUS) has been employed for differential diagnosis of gastric SELs. The results were positively convincing in the study by Kannengiesser *et al*[21], but with a limited cohort (fewer than 20 patients). CEH-EUS showed hyperenhancement of gastric lesions from the fourth layer that proved to be a GIST, and no enhancement of gastric leiomyoma.

Computed tomography (CT) and magnetic resonance imaging (MRI) may also be valid tools for GIST diagnosis, especially when a cytological diagnosis is unnecessary. In fact, a meta-analysis[22] that evaluated 4534 patients with GISTs, from 46 studies, showed that CT and MRI had a pooled diagnostic yield of 73% and 91% respectively.

CAN WE PREDICT GIST BEHAVIOR BY ENDOSCOPY OR EUS?

It has been observed that high grade GISTs double in size in 9 mo, while those with benign behavior do it in 18 mo.

Onishi *et al*[23] reported that hypoechoic spots were present in 84% of gastric GISTs which grew in size, and in 52% of gastric GISTs that remained stable in size (84.2% *vs* 51.9%, $P = 0.023$). Again, this is another interesting piece of information but useful only when it is present.

A previous study[24] looked at the use of CEH-EUS to predict GIST grade. Based on enhancement of features immediately after contrast administration (the vessel phase), and a few minutes after (the perfusion phase), gastric GISTs were classified as types Ⅰ and Ⅱ. All type Ⅰ lesions revealed low grade GISTs after resection. On the other hand, all type Ⅱ lesions were high grade GISTs. Once more, this is very interesting data that needs validation in a large cohort of patients.

TISSUE IS THE ISSUE

The bite-on-bite biopsy technique has been described for tissue acquisition of hypoechoic lesions of the fourth layer. However, some reports demonstrated low diagnostic yield of around 17%[25].

EUS-guided fine needle aspiration (EUS-FNA) is the logical procedure for tissue acquisition. A study by Hoda *et al*[26] performed EUS-FNA on gastric lesions with a mean size of 28 mm. They employed a standard 22 G needle, and the diagnostic yield was 62%.

When we remember that during EUS-FNA the GI wall, including the proper muscle layer, is sampled, the first question that comes to our minds is: Is EUS-FNA diagnosis correct? Apparently, the answer is yes. Stelow *et al*[6] reported, in a study of EUS-FNA with sufficient material from 29 patients with SELs and follow-up information, that EUS-FNA diagnosis was correct in 93% of patients, and in almost all cases of mesenchymal tumors.

EUS-FNA diagnosis of SELs may be correct, but the diagnostic yield is not so high for lesions smaller than 30 mm. EUS-FNA had an overall diagnostic yield of 40% to 50% for lesions measuring up to 10 mm, and of 60%

to 70% for lesions measuring from 11 to 30 mm[26]. In conclusion, EUS-FNA has a diagnostic yield of 60% to 70%, with a lower diagnostic yield for small lesions.

The next logical development would be to employ needles that make core biopsy possible. In a prospective study[27], the authors did not find any difference between EUS-FNA and EUS-trucut core biopsy of SELs. They employed the trucut biopsy needle model that was a rigid, 19 G needle. Needle malfunction was relatively common when the scope was in a bent position.

Now, there are new models of core biopsy needle available, such as the 19 G flexible nitinol needle, and the ingenious core trap, which come in different sizes. The first results with these new needles were presented a couple of years ago. In a limited cohort of patients, the diagnostic yield reached impressive figures.

Meta-analysis of 21 studies[28] comparing standard EUS-FNA and the ProCore needle for tissue acquisition of solid masses, including pancreatic masses, lymph nodes and SELs, showed no significant difference in the rates of diagnostic yield, diagnostic accuracy or histologic yield, between the two techniques.

Another meta-analysis[29] focused on diagnostic yield, and on the complication rate of EUS-FNA and EUS-guided core needle biopsy (EUS-CNB), for patients with GIST. The authors reached the same conclusion, *i.e.*, the diagnostic yield of EUS-FNA and EUS-CNB are the same, 65%. The EUS-FNA complication rate was 0.4%, and for EUS-CNB it was 1.1%. Death is rare but may occur after EUS-FNA of GIST, so one must beware of that.

Core biopsy is necessary for GIST diagnosis, and EUS-FNA provides core biopsy in 70% of cases, especially for lesions larger than 2 cm. EUS-core biopsy needles did not prove to be better; therefore, their higher cost is not justifiable. Severe complications and mortality are rare, but may occur after EUS-FNA and EUS-core needle biopsy of SELs.

ENDOSCOPIC TECHNIQUES FOR SEL DIAGNOSIS AND RESECTION

The limited diagnostic yield of EUS-FNA and EUS-core biopsy of SELs prompted the development of more aggressive endoscopic techniques for tissue acquisition. One of them [suck-ligate-unroof-biopsy (SLUB)] consists of placing an endoloop at the base of the lesion with the aid of a cap. After unroofing, biopsies are taken. A few months later, endoscopic and EUS control confirms the complete disappearance of the tumor. Not all fourth layer SELs can be treated by SLUB. The authors suggest that the dimension should not surpass 2 cm and, very importantly, the tumor should have no exophytic growth[30].

ESD is another option for tissue acquisition and treatment of SELs located at the cardia. In a large series[31] of 143 patients, the authors obtained a 95% complete resection rate of leiomyomas and GISTs, with a 4% perforation rate, and no recurrence in 2-year follow-up.

Submucosal tunneling endoscopic resection (STER)[32] involves the creation of a submucosal tunnel in the same fashion as the peroral endoscopic myotomy procedure. The tumor is then resected, and the mucosal incision site is closed, which guarantees the safety of the procedure, even in cases of perforation.

The first published series[32] includes fewer than 20 patients. The majority of them had SELs in the esophagus and cardia. In this paper, only three cases with gastric lesions were treated by STER. It should be remembered that most esophageal SELs are benign leiomyomas.

A word of caution is advised for those interested in these innovative procedures such as SLUB and STER. EUS is absolutely necessary to select lesions suitable for these techniques. In this scenario, a CT scan often demonstrates a smooth outer contour of gastric SELs. However, in the operative field, it is clear that the lesion may project to the serosal surface, making SLUB and STER very dangerous.

CONCLUSION

In conclusion, SELs that are indeterminate after endoscopy and EUS examinations may have a challenging diagnosis. Otherwise, as mentioned before, if the aspect is typical of a neuroendocrine tumor, a pancreatic rest, lipoma, cyst, or varices, management poses no major problems. If EUS demonstrates small hypoechoic tumors of the second and third layers, endoscopic resection is possible and quite safe. For small hyperechoic lesions of the second and third layers, endoscopic resection is a valid alternative. For larger lesions, a tissue diagnosis is necessary. For larger lesions of the fourth hypoechoic layer, EUS-FNA and core biopsy are safe and have a good diagnostic yield. Some authors advocate referring the patient directly for surgery, if the lesion is located in the stomach or in the duodenum. SLUB, STER, and ESD are techniques under investigation for SELs.

Small hypoechoic lesions of the fourth layer should be simply followed (every six months for one year, and then yearly or biannually), especially if EUS features indicate a benign lesion. Oh the other hand, if EUS features are worrisome, EUS-FNA or core biopsy should be tried, but they have a very low diagnostic yield in small lesions. Surgery is a reasonable option especially if the lesion is located in the stomach or duodenum. Again, ESD, SLUB, and STER are under investigation.

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