CLINICAL MANAGEMENT

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The Incidental Upper Gastrointestinal Subepithelial Mass

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Clinical Case

A 50-year-old man undergoes upper endoscopy for the evaluation of dyspepsia. He is found to have a 2-cm mass with normal appearing overlying mucosa in the gastric body. The remainder of the endoscopy is normal. Biopsies taken from the mucosa overlying the mass reveal normal gastric mucosa.

Background

Upper endoscopy is commonly performed for the investigation of symptoms and for the screening and surveillance of neoplasia. A frequent finding is that of a mass, bulge, or impression covered by normal-appearing epithelium. The endoscopist rarely knows the cause or origin of these masses which we term *subepithelial* because they can arise within or outside the gastrointestinal wall and if within the wall, anywhere from the lamina propria to the muscularis propria. We prefer to reserve the commonly used term *submucosal mass* to describe those lesions arising from the histologic submucosa, something that is not known without further characterization of the mass using endosonography or histology.

Although the endoscopist often recognizes that the yield of mucosal biopsy is low when the mucosa overlying a mass appears normal, it is reasonable to obtain mucosal biopsies to exclude epithelial polyps and to detect lesions that may arise in the deep mucosa. The question then arises, what should be the next step in evaluating the lesion?

Every endoscopist has encountered subepithelial lesions during endoscopy and is then faced with the decision of whether to ignore them or to evaluate the patient further. A subepithelial mass is usually suspected at the time of endoscopy if the mass appears to have normal appearing overlying mucosa without ulceration or inflammation; however, histologic confirmation of normal mucosa is generally required. Some subepithelial masses arising in the lamina propria or muscularis mucosae may be defined by mucosal biopsy, in which case further imaging would not be required. If mucosal biopsies are normal, it must be determined whether or not the mass represents a pathologic process and requires further intervention.

Differential Diagnosis

The differential diagnosis of a subepithelial mass depends on whether the lesion is in the esophagus, stomach, or duodenum. The next distinction that should be made is whether the lesion represents compression from a normal or abnormal structure adjacent to the gastrointestinal wall or if it is arising from the wall itself. Even when the endoscopist suspects an intramural lesion is present, the mass may arise from outside the gastrointestinal wall in up to 30% of cases.[1,2] The most common source of extraluminal compression in the stomach is from the spleen and splenic vessels. Other sources of extraluminal compression include normal abdominal structures such as the liver and gallbladder, as well as pathologic lesions such as tumors, abscesses, pancreatic pseudocysts, and enlarged lymph nodes. Potential intramural causes of subepithelial masses according to location are listed in Table 1.

Gastrointestinal Stromal Tumors

It is worth specifically commenting on gastrointestinal stromal tumors (GISTs) since they are the most commonly identified intramural subepithelial mass in the upper GI tract and some controversy exists regarding the diagnosis and management of these tumors. It is believed that there are 5000 to 6000 new cases of GISTs diagnosed each year with 10%–30% being malignant.[3]

Abbreviations used in this paper: CT, computed tomography; ESMR, endoscopic submucosal resection; EUS-FNA, EUS-guided fine needle aspiration; FNA, fine-needle aspiration; GISTs, gastrointestinal stromal tumors; MRI, magnetic resonance imaging; US, ultrasound.

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Table 1. Differential Diagnosis of Intramural Subepithelial Masses Based on EUS Features

Subepithelial lesion	EUS layer[a]	Echogenicity
Upper GI tract		
GIST	4 (rarely 2)	Hypoechoic
Leiomyoma	2 or 4	Hypoechoic
Fibroma	3	Hyperechoic
Neurofibroma	3 or 4	Hyperechoic
Osteochondroma	3	Hyperechoic
Lipoma	3	Intensely hyperechoic
Lymphoma	2, 3 or 4	Hypoechoic
Lymphangioma	3 or 4	Hypoechoic
Fibrovascular polyp	3 or 4	Hyperechoic
Varices	2 or 3	Anechoic
Metastatic carcinoma	Any	Hypoechoic
Esophagus		
Granular cell tumor	2 or 3	Hypoechoic
Bronchogenic cyst	Extramural	Anechoic
Duplication cyst	Any or extramural	Anechoic
Stomach		
Carcinoid	2 or 3	Hypoechoic
Pancreatic rest	2 or 3	Hypoechoic
Glomus tumor	Any	Hypoechoic
Duplication cyst	Any	Anechoic
Duodenum		
Brunner's gland hyperplasia	2 or 3	Hypoechoic
Carcinoid	2 or 3	Hypoechoic
Pancreatic rest	2 or 3	Hypoechoic
Duplication cyst	Any or extramural	Anechoic

[a]Layer 1 is the interface of luminal fluid and mucosa; layer 2 represents the deep mucosa; layer 3 is largely due to the submucosa; layer 4 represents the muscularis propria; and layer 5 is adventitia or serosa with adjacent fatty or fibrous tissue.

Most patients are in their 5th or 6th decade of life at the time of diagnosis and the most common location of GISTs is the stomach.[3,4] GISTs were once thought to represent smooth muscle tumors (leiomyomas and leiomyosarcomas); however, they are now believed to arise from the interstitial cells of Cajal and can be identified using immunohistochemistry for expression of CD-117, which is also known as c-kit protein (a cell membrane receptor with tyrosine kinase activity). Because of this recent change in classification, the older literature may be confusing and must be considered in light of this new information. A recent study that examined archived tissue of masses previously classified as smooth muscle tumors demonstrated that most were actually GISTs with the exception of masses in the esophagus where true leiomyomas were more common.[5]

GISTs most commonly arise from the muscularis propria and are usually asymptomatic until the tumor becomes large or ulcerates resulting in bleeding. Large (>3 cm) or symptomatic masses should be removed surgically. However, the finding of a smaller sized GIST, (<3 cm), presents a clinical conundrum to the physician. The vast majority of GISTs that are <3 cm in diameter are benign, but all GISTs have a malignant potential; even small GISTs, particularly those in the lower GI tract, have been reported to metastasize.[6–8] Unfortunately, we are currently unable to predict the malignant potential of a small GIST without histologic examination of the resected specimen. There are reports of new techniques using EUS-FNA or core needle biopsies that may be helpful in determining whether a GIST is malignant or has malignant potential.[9–11] However, further prospective studies in larger numbers of patients with adequate follow-up are required to fully evaluate the performance of these techniques.

Potential Management Strategies

Evaluation With Endoscopy

The evaluation of subepithelial masses begins with the initial endoscopy. Features of subepithelial masses that can be assessed during endoscopy include an estimate of the size, shape, mobility, consistency (pillow sign, firm, cystic), pulsation, color, and mucosal appearance. In general, subepithelial masses have normal appearing mucosa overlying the lesion although the presence of erythema or inflammation on histologic examination of mucosal biopsies, unrelated to the underlying mass can be present. Furthermore, subepithelial lesions usually appear smooth with tapered margins along the edge of the lesion. An exception to this is a pancreatic rest, which has a characteristic volcano-like or umbilicated surface.

Intramural mass versus extrinsic compression. Distinguishing whether the lesion is intramural or due to extrinsic compression during endoscopic examination can be facilitated by changing the patient's position to see if the location and appearance of the mass changes. Also, a change in appearance of the mass with either air insufflation or deflation is helpful in determining if the lesion is due to extrinsic compression. However, it can be difficult to differentiate an intramural lesion from extramural compression. A recent multicenter study reported that the sensitivity and specificity of being able to correctly identify an intramural lesion from extramural compression with endoscopy alone was 87% and 29% respectively.[2]

Color. Most subepithelial masses are the same color as the surrounding mucosa. Duplication cysts may have a slight translucent appearance. Lipomas may appear slightly yellow and vascular lesions can be bluish, similar to the appearance of esophageal varices.

Size. Knowing the size of a subepithelial lesion is important in its management. However, there is significant error in size estimation by visual inspection with endoscopy, generally leading to an underestimation of

the actual size of the lesion.[12–14] There have been no studies that have compared the visual size estimation of subepithelial lesions by endoscopy to either EUS size measurements or surgical pathology measurements. However, endoscopic estimation of size should still be performed, preferably with the assistance of an open biopsy forceps or other instrument of known size that can be placed adjacent to the mass within the visual field of the endoscope.

Firm data on the clinical significance of small subepithelial masses is not available. In our experience, subepithelial masses <1 cm in diameter are rarely, if ever, of clinical significance. GISTs are the most common subepithelial masses with potential clinical significance, and malignant GISTs in the upper gastrointestinal tract that are <1 cm in diameter have not been reported in several large case series.[6,8] A repeat endoscopy in one year is reasonable for these small masses, and if the mass is unchanged, then further follow-up evaluation may not be required if the patient remains asymptomatic.

Mobility and consistency. With the forceps in the closed position the mass can be probed to determine if it is firm, soft, or exhibits a pillow sign. If there is any concern that the lesion is vascular or cystic, no biopsies should be taken until it has been evaluated with EUS. The consistency of the mass can suggest a diagnosis. For example, a firm, minimally mobile lesion is suggestive of a GIST or leiomyoma. Whereas, a mobile mass that is soft and indents when depressed using biopsy forceps (pillow sign) is highly suggestive of a lipoma. If the mass has a pillow sign and is yellow in appearance, it is probably a lipoma and no further evaluation is necessary. It should be recognized, however, that the specificity of these endoscopic characteristics has not been rigorously evaluated.

Evaluation With Endosonography

Any subepithelial lesion that appears to be larger than 1 cm on endoscopic examination and does not appear to be a lipoma should be referred for evaluation with EUS. EUS examination will differentiate intramural lesions from extrinsic compression. Furthermore, EUS will often result in a specific diagnosis, especially if the lesion is due to extrinsic compression.

If an intramural lesion is identified, EUS can be used to ascertain the exact size, layer of origin, as well as additional morphologic features that can suggest the diagnosis. On EUS the mass can be either homogeneous or heterogeneous and can be hyperechoic, hypoechoic, or anechoic. Anechoic masses can be interrogated with Doppler to assess for blood flow. EUS is also used to evaluate the margins of the mass to determine if they are smooth or irregular and whether the mass disrupts or distorts adjacent layers or organs. Small, well-circumscribed lesions are typically benign, whereas a lesion with irregular margins that invades into other layers or structures is more likely to represent a malignant process.[15,16] The features identified on EUS can then be used to determine if further tests such as FNA or core biopsies are required. Figures 1–4 show examples of EUS images of different types of subepithelial gastrointestinal lesions.

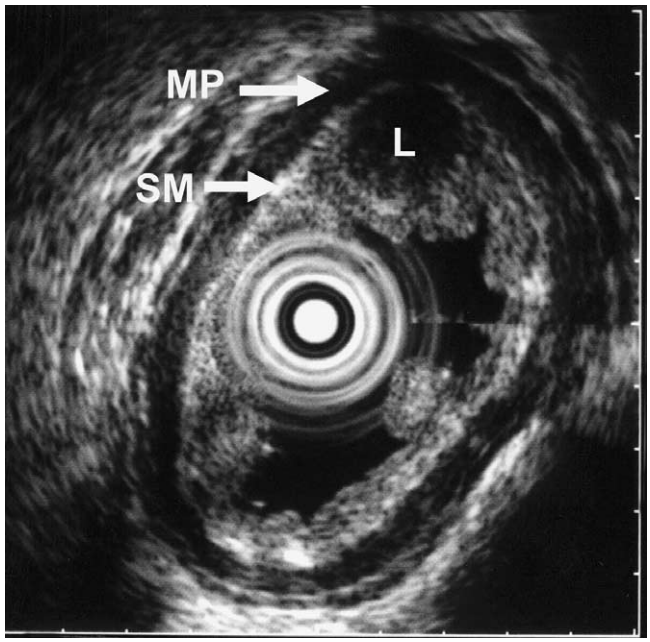

Figure 1. Small esophageal subepithelial mass identified using a 20 MHz catheter probe. The cross-sectional diameter is 5 mm. The lesion (L) is homogeneous, hypoechoic, and confined to the 2nd and 3rd US layer [deep mucosa and submucosa (SM)] without extension into the muscularis propria (MP). The lesion was removed by endoscopic submucosal resection and identified as an esophageal leiomyoma by histology and immunocytochemistry.

Some EUS findings are sufficiently diagnostic that further testing, tissue sampling, and follow-up are not required. Intramural anechoic masses without Doppler signals are duplication cysts (Figure 3) and are of no clinical significance unless they are causing luminal obstruction.[17,18] Similarly, densely hyperechoic submucosal masses are always lipomas (Figure 4) which also do not have any clinical importance unless they are causing clinical symptoms such as obstruction or bleeding caused by ulceration.

EUS-guided fine-needle aspiration. EUS-guided fine needle aspiration (EUS-FNA) is commonly used to confirm the presence of malignancy in lymph nodes or organs adjacent to the gastrointestinal tract. EUS-FNA (typically with a 22-gauge needle) can be used to obtain a specimen for cytologic examination, and occasionally core tissue specimens by directing the needle into the area of interest under direct ultrasound guidance (Figure 5).[9,19] Cytology is most useful for distinguishing benign

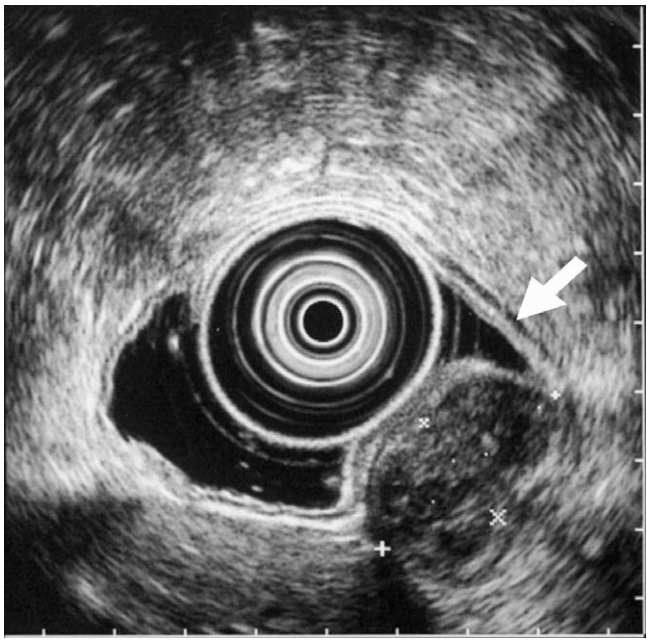

Figure 2. Radial scanning EUS image of a GIST located in the 4th US layer corresponding to the muscularis propria (*arrow*). Marks on image represent size measurements of the tumor (17×33 mm).

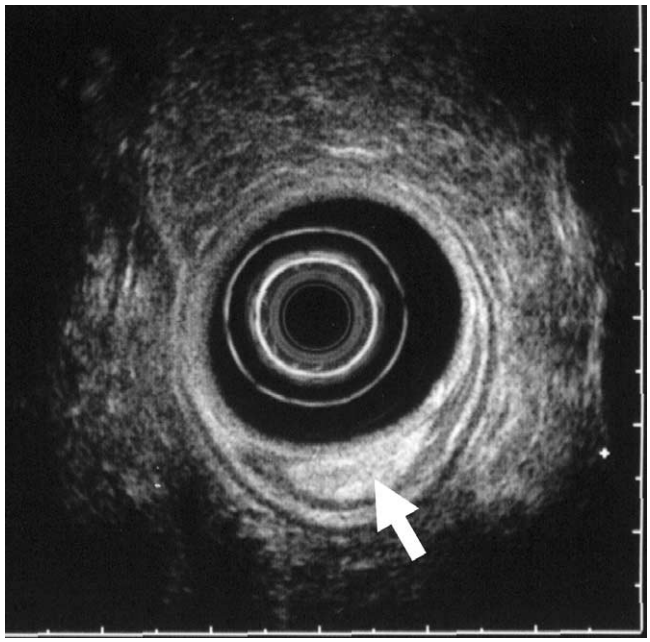

Figure 4. Radial scanning EUS image of a lipoma (*arrow*). The mass is intensely echogenic and located in the 3rd US layer (submucosa).

from malignant lesions but is less useful for determining the type of benign lesion present. Thus, the sensitivity, specificity, and accuracy of cytologic evaluation of intramural lesions are low.[19–21] Complications from EUS-FNA are rare and include perforation, infection, and hemorrhage.[9,21–25] An exception may be cyst aspiration, where infection has been reported to occur in up to 15% of cases, justifying the use of pre-procedural antibiotic prophylaxis.[18,26]

The yield of EUS-FNA in the diagnosis of hypoechoic fourth layer masses such as GISTs may be improved with the application of immunohistochemical analysis.[10,19,27,28] Immunohistochemical staining of various cell proteins can be performed on FNA samples to provide diagnostic information. The most important markers used to evaluate hypoechoic intramural masses are CD-117 (c-kit), CD-34, smooth muscle actin, and S-100.[4,28] The c-kit protein is a transmembrane receptor with tyrosine kinase activity that is highly sensitive and specific for GISTs. CD-34 is also expressed in approximately 80% of GISTs. Positive staining for smooth muscle actin suggests the presence of a leiomyoma, and the presence of S-100 suggests a neural origin or Schwannoma (Table 2). A preliminary study by Ando et al.[10] suggested that Ki-67 (a marker of cell proliferation)

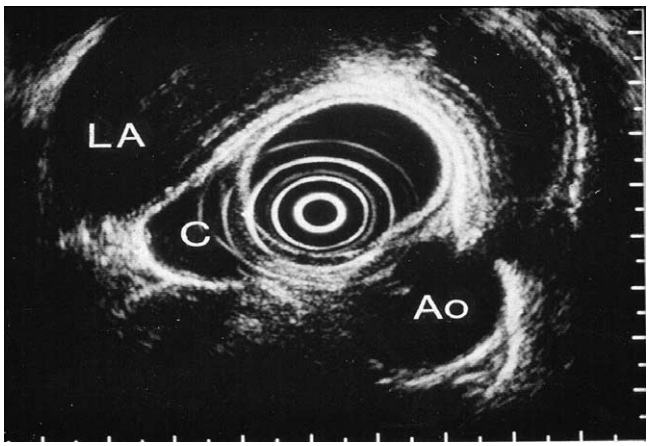

Figure 3. Radial scanning EUS image of an esophageal duplication cyst (C). The lesion is anechoic and located within the esophageal wall at the level of the descending aorta (Ao) and left atrium (LA).

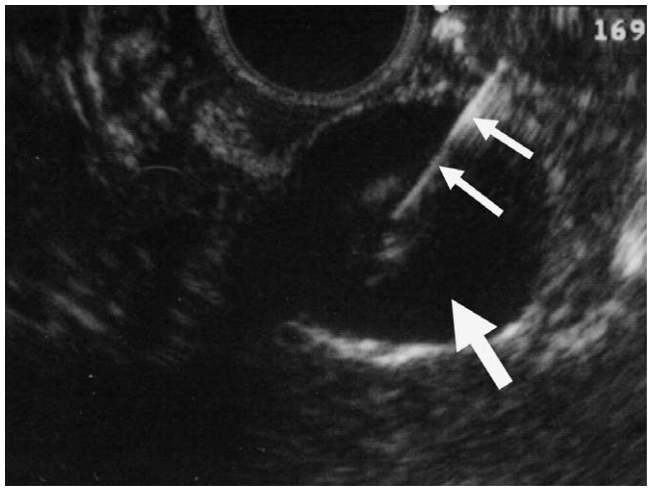

Figure 5. EUS-guided FNA of a hypoechoic mass (*large arrow*) located in the 4th US layer (muscularis propria). *Small arrows* points to the FNA needle which has been inserted into the tumor. Immunocytochemistry was positive for CD-117 staining, diagnostic of a GIST.

Table 2. Immunohistochemical Analysis of GI Mesenchymal Tumors

Tumor	Positive IHC staining
GIST	CD-117 (c-kit), CD-34
Smooth muscle tumor	Smooth muscle actin, Desmin
Schwannoma	S-100
Glomus tumor	Smooth muscle actin, Vimentin

IHC, immunohistochemical.

immunohistochemical staining improved the ability to diagnose malignant GISTs. If this finding is confirmed, it would be a significant advance because the inability of EUS-FNA to accurately diagnose malignant GISTs is a major limitation of this procedure.

EUS-guided Core Needle Biopsy

To overcome some of the limitations of EUS-FNA, EUS-guided core needle biopsy using a 19-gauge Trucut needle (QuickCore, Wilson-Cook, Inc., Winston-Salem, NC) has been proposed.[11,29] The Trucut needle provides a core of tissue that can be examined histologically for changes in tissue architecture in addition to the individual cell morphology scrutinized in the cytologic evaluation of FNA specimens. Initial experience using the Trucut biopsy needle in intramural lesions yielded the correct diagnosis in 4 of 5 cases compared with 1 of 5 cases using EUS-FNA.[11] However, additional prospective studies are required to determine if EUS-guided core needle biopsy results in greater accuracy than EUS-FNA and whether complications are more frequent. The most challenging aspect of diagnosing intramural lesions by any form of needle biopsy is the sampling error in malignant GISTs, which may have only focal areas of increased cellular proliferation. It will have to be determined from prospective studies whether a core needle biopsy will improve the accuracy of diagnosing malignant GISTs.

Endoscopic Submucosal Resection

The use of endoscopic submucosal resection (ESMR) to resect submucosal lesions is another technique to obtain tissue specimens for accurate histologic diagnosis.[30–34] This technique provides greater yield than stacked biopsies but has not been compared with either EUS-FNA or EUS-guided core needle biopsy. ESMR is usually reserved for lesions that are confined to the submucosal or mucosal layers, due to the increased risk of perforation associated with ESMR of lesions from the muscularis propria; however, there are some small case series in the literature of ESMR of lesions arising from the muscularis propria with no associated perforations.[30,34] Given that the perforation rate for ESMR of submucosal lesions is 2%–3%, it is likely that ESMR of lesions from the muscularis propria will be higher.[34] Bleeding, both during the procedure and delayed, are significant complications that can occur with ESMR.

Extracorpeal Imaging Studies

Transabdominal ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) findings in patients with subepithelial masses have been the subject of case reports and small patient series. These imaging studies are most useful for defining the origin and extent of large extramural masses. Large lipomas can be detected on both CT and MRI by the characteristic density and magnetic resonance properties of fatty tissue.[35] CT and MRI can image large GISTs and are especially helpful in the evaluation for metastatic spread of malignant GISTs.[36,37] Unlike EUS, CT and MRI cannot identify the histologic layers of the gut wall and are therefore of limited value in distinguishing between the different causes of intramural masses.

Recommended Management Strategies

At the time of initial endoscopy, the subepithelial lesion should be thoroughly examined with the exact location of the lesion noted and size estimated with the assistance of open biopsy forceps. The lesion should be gently probed with the closed biopsy forceps to further characterize the firmness and mobility of the lesion. If the endoscopist is confident that the lesion is a lipoma, no further work-up is required. If the lesion appears cystic or vascular, no biopsy should be attempted; otherwise, biopsies of the mucosa overlying the lesion should be obtained to confirm that the lesion does not involve the epithelium. In this case, the lesion is >1 cm on endoscopy and therefore the patient should undergo an EUS examination of the lesion.

Before EUS, the patient should be consented for any potential additional procedures that may be attempted to evaluate the lesion such as FNA, core needle biopsy, or ESMR. If the lesion is small, as in the case presented previously, it can be imaged with a through-the-scope catheter probe (typically 12 or 20 MHz). The catheter probe is used with a standard forward viewing endoscope and allows easier localization of smaller lesions. If an ultrasound (US) probe is available at the time of the index endoscopy, imaging can be performed at that time, without waiting for the results of mucosal biopsies.

Larger lesions should be examined with a combined US endoscope. This can be either a radial scanning or curvilinear array echoendoscope, depending on availability and operator preference. An accurate measurement of the size of the mass on the US image should be made, as this could guide further management. The layer of origin must be identified and the morphologic features on

ultrasound, such as echogenicity, homogeneity, and margins assessed. Table 1 lists the layer of involvement identified on ultrasound of various subepithelial lesions, as well as the typical echogenicity of the lesion.

Patients with an intramural cyst or vessel or a hyperechoic submucosal mass (lipoma) found on EUS require no further follow-up. Other patients should have an attempt at tissue diagnosis made since the performance of EUS alone is poor in distinguishing between a benign and malignant process.[2]

EUS-FNA or EUS-core Needle Biopsy

Hypoechoic fourth layer masses that are over 3 cm in diameter with irregular borders and those which are ulcerated should be referred for surgical resection due to the risk of malignancy.[15,16] Other fourth layer masses that do not have these EUS features should undergo EUS-FNA for further evaluation. If a GIST is confirmed with immunocytochemistry, the risks of malignant transformation need to be discussed with the patient and serious consideration for surgical referral to remove this risk is advisable. Leiomyomas and schwannomas do not require surgical removal or follow-up if the patient is asymptomatic.

Endoscopic Submucosal Resection

ESMR should be considered for hypoechoic masses in the deep mucosa or submucosa to both diagnose the cause of the mass and in many cases provide a curative resection. Masses with these characteristics may be due to GISTs arising from the muscularis mucosae, gastric or duodenal carcinoid tumors, granular cell tumors and metastatic tumors, the presence of which justify the small risk of complications with ESMR.

Evolution of the Case

The patient was referred for EUS evaluation of the subepithelial lesion. EUS revealed a 2-cm, hypoechoic mass arising from the 4th layer (muscularis propria) with regular margins. FNA of the lesion was performed. Cytology and immunohistochemistry (CD-117 staining) was diagnostic of a GIST. No increased numbers of mitotic figures were noted on cytology.

Subsequent Management

Lesions, which are indeterminate for malignancy such as the 2-cm diameter GIST in this case, are the most problematic. Guidelines for determining the malignant risk of GISTs were recently outlined by a GIST workshop at the U.S. National Institutes of Health.[4] Unfortunately, the proposed stratification is based on both size of the tumor and mitotic count from a *resected* specimen. Therefore, FNA or a core needle biopsy does not appear to have utility in determining the malignant potential of a GIST, and we cannot confidently tell the patient that there is a low risk of malignancy being present or occurring sometime in the future. At this point, the physician and patient should discuss the risks and benefits of all potential management strategies including periodic endoscopic evaluation, periodic EUS evaluation with or without repeated needle biopsy, or surgical resection. In a young, otherwise healthy patient, as in the case described previously, we would recommend surgical resection.

Subepithelial masses without a clear diagnosis based on EUS and tissue sampling should undergo periodic follow-up examination by endoscopy or EUS. The duration of the follow-up interval depends on the index of suspicion of the examiner that the lesion has malignant potential, as well as the age and health status of the patient. The most common interval selected in our practice is 1 year and if the lesion is unchanged for 2 consecutive follow-up examinations with EUS, to extend the length between surveillance examinations.

Conclusions

Identifying a subepithelial mass during endoscopy is common. Fortunately, the increasing availability of EUS allows for improved evaluation of subepithelial lesions, although the specificity of EUS imaging findings alone has been disappointing. Obtaining a tissue diagnosis using EUS-FNA or endoscopic submucosal resection is very helpful in directing further patient management. Further research is needed to better define the optimal management of patients with GISTs and those with indeterminate lesions.

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