Gastrointestinal Subepithelial Lesions: A Review

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Abstract

Submucosal lesions, also known as subepithelial lesions, are often encountered during endoscopy of the gastrointestinal tract. Most of the lesions are asymptomatic and can be diagnosed by routine endoscopic ultrasonography. Few lesions like gastrointestinal submucosal tumors (GIST) and leiomyoma require biopsy/fine-needle aspiration cytology (FNAC) for differentiation. Lesions like neuroendocrine tumors can be diagnosed by deep endoscopic biopsy as they originate from the inner mucosal layer. Management depends on the size and layer of origin of the lesion. Smaller lesions can be removed by endoscopic procedures and bigger lesions by surgery. Smaller lesions can be safely surveilled.

Keywords

- endoscopic ultrasonography
- gastrointestinal stromal tumors
- leiomyoma
- neuroendocrine neoplasm
- subepithelial lesions

Introduction

Protuberant lesions inside the lumen of the gastrointestinal (GI) tract with normal overlying mucosa classify as submucosal lesions (►**Fig. 1**). Protuberance may not be there in few lesions due to deeper layer of origin and predominantly exophytic growth. Initially the term "submucosal" was used to describe these lesions. But it has been replaced by the term "subepithelial lesion" (SEL) since these lesions may originate not only from the submucosa but also from the muscularis mucosa and muscularis propria (MP). Sometimes overlying mucosa can be ulcerated. Ulcerations can be due to pressure effect or due to malignant transformation.

SELs are most commonly found in the stomach. SELs are encountered in 1 of 300 endoscopies.[1] However, they can be found throughout the GI tract. In most cases, they are small and incidentally detected. Sometimes they can be symptomatic, in which case the most common symptoms are GI bleeding and abdominal pain.

Rarely they can cause obstruction particularly in the small intestine. Depending upon etiology, they have varying malignant potential. Hence, establishing the diagnosis and determining the malignant potential play a central role in the management of these lesions. Literature regarding management of SELs is still controversial due to the rarity of these lesions, their heterogenous nature, and weak malignant potential.

In follow-up studies of asymptomatic upper GI tract SELs, the lesions increased in size in 3.2 to 13% of patients.[2–5]

The European Society of Gastrointestinal Endoscopy (ESGE) and American Gastroenterological Association (AGA) have published guidelines regarding the management of SELs.

Diagnosis

Endoscopy

It is the initial method of diagnosis. As mentioned earlier, most of the time it is an incidental finding. Endoscopy has limitations in assessing these lesions since the overlying mucosa is normal. Certain maneuvers can help in determining the type of lesion. For example, pillow sign, in which indentation is caused by pushing the closed standard biopsy forceps against the lesion, is 98% specific for diagnosing lipoma, while its sensitivity is only 40%.[6] Certain endoscopic characteristics also help in determining the type of lesion. For example, pancreatic rests are generally found in the antrum along the greater curvature with a central umbilication.

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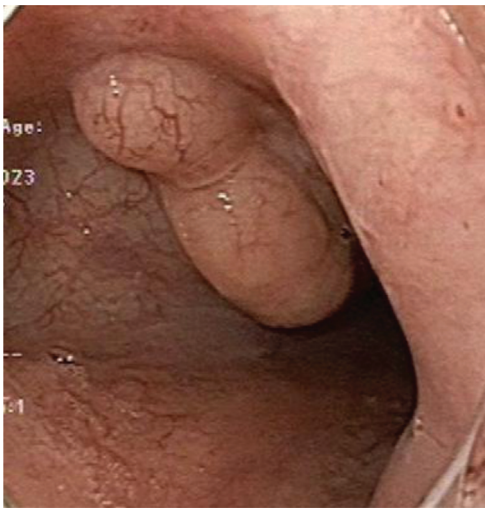

Fig. 1 Endoscopic image of esophageal subepithelial lesion (SEL).

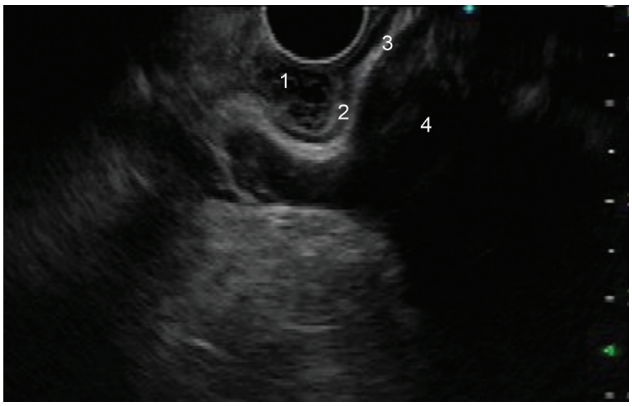

Fig. 2 Endoscopic ultrasound (EUS) image of subepithelial lesion (SEL) arising from the fourth layer in the stomach suggestive of gastrointestinal stromal tumor (GIST). The four layers are the following: (1) mucosa, (2) muscularis mucosa, (3) submucosa, and (4) hypoechoic mass in the muscularis propria.

Standard Mucosal Biopsy

It has a very low pathological yield as the overlying mucosa is normal. Few modified techniques have been described for better yield. Pathological yield is comparatively better in SELs arising from the second to third layer than SELs arising from the fourth layer with these modified techniques. Tunneling /bite on bite technique has been explained where jumbo forceps with jaw volume of 12 to 13 mm are used. This technique has a diagnostic yield of 30 to 40%.[7] The diagnostic yield for the lesions arising from the third layer is 55 to 65%, while the lesions arising from the fourth layer have a diagnostic yield of 40%. Bleeding is seen in up to one-third of cases.[8]

Mucosal Incision Associated Biopsy

The mucosa covering the SEL is lifted with submucosal injection of normal saline or glycerol supplemented with diluted epinephrine. With the help of an endoscopic submucosal dissection (ESD) knife, the overlying mucosa and submucosa are incised to expose the lesion. Tissue samples are then obtained by biopsy forceps. Although the time required to perform mucosal incision–associated biopsy (MIAB) is more than that for endoscopic ultrasound–guided fine-needle biopsy (EUS-FNB), diagnostic yield is better with MIAB than with EUS-FNB for SELs less than 20 mm in size, while diagnostic yield is comparable with EUS-FNB for SELs greater than 20 mm in size.[9]

Endoscopic Ultrasound

EUS is the method of choice in evaluating SELs. It serves two roles: to characterize the lesion and for tissue acquisition. Superiority of EUS over other imaging modalities (computed tomography [CT] and magnetic resonance imaging) in characterizing small (<2 cm) lesions has been established.[10] EUS has 92% sensitivity in distinguishing SELs from extraluminal compression and can evaluate the layer of origin, size, echogenicity, and margins.[11]

The first layer is the mucosa, which is hyperechoic. The second layer is the muscularis mucosa, which is hypoechoic. The third layer is the submucosa, which is hyperechoic. The fourth layer is the MP, which is hypoechoic, and the fifth layer is the serosa, which is hyperechoic (►**Fig. 2**). Sometimes, in the esophagus and duodenum, only three layers are visualized due to balloon inflated with water, which is covering the transducer to improve imaging, where the first hyperechoic layer is representing the balloon–mucosa–submucosa together with the submucosa–MP interface. The accuracy of EUS to determine the originating layer is 63 to 74.6%; it is higher (82.6–100%) for submucosal SELs.[12–15] Determining the layer of origin has therapeutic implications.

Echogenicity is another important feature in evaluating the type of lesion. Anechoic lesions are generally either vascular or cystic fluid-filled lesions. Hypoechoic lesions are GI mesenchymal tumors, granular cell tumors, neuroendocrine tumor (NET), metastasis, lymphoma, infiltrative disease, and inflammatory lesions. Hyperechoic lesions are generally benign, for example, fibrolipoma and lipoma. Mixed echogenicity generally represents pancreatic rest, malignant mesenchymal tumors, and GI tract wall abscess.

Certain features in EUS can predict malignant potential. Size and vascular involvement help in predicting the malignant potential. Presence of two of the following features, that is, diameter greater than 4 cm, irregular extraluminal border, echogenic foci, and cystic space, has sensitivity ranging from 80 to 100% in predicting the malignant potential.[16] EUS has an overall sensitivity of 64% and specificity of 80% in predicting the malignant potential of SELs.[2] Contrast-enhanced EUS may help in differentiating benign gastrointestinal stromal tumors (GISTs) from leiomyoma where there will be hyperenhancement in case of GISTs and hypoenhancement of leiomyoma lesions. It has an accuracy of more than 95%.[17]

EUS imaging is operator dependent. Diagnostic accuracy of EUS imaging alone is as low as 43% in SELs originating from the third and fourth layers.[6] Hence, there is the need for tissue acquisition to improve the diagnostic yield. Diagnostic yield of EUS-FNA depends on site, size, and characteristics of the tumor and also technical and procedural factors like type of needle, biopsy technique used, and material processing method.

The accuracy of FNA in lesions of 2, 2 to 4, and greater than 4 cm is 71, 86, and 95 to 100%, respectively.[18] On the other hand, the diagnostic accuracy of EUS-FNB histology is 83 to 100% when surgical pathology findings are considered as a reference.[19] It is not that high with cytology.[20] A meta-analysis showed a pooled diagnostic rate of endoscopic ultrasound–guided tissue acquisition (EUS-TA) procedures for upper GI SELs as 59.9% (95% confidence interval [CI]: 54.8–64.7%). These studies involved mostly FNA needles or the Quick Core Tru-Cut needle. Only two of these studies involved FNB needles.[21]

In another meta-analysis where EUS-FNB was compared with FNA, FNB outperformed FNA in all diagnostic outcomes.[22,31] Mitotic index values in EUS-FNA samples are lower than that in surgical specimens of the same tumors.[23] Also the Ki67 levels in EUS-FNA samples are lower than that in surgical specimens.[24] However, the Ki67 protein assessment requires less tissue than mitotic index calculation.[25]

Endoscopic Resection Techniques

Endoscopic resection techniques are divided into two types, exposed and nonexposed, depending upon whether there is breach of MP and whether there is exposure to the extraluminal space. The choice of technique depends upon the layer of origin, size, extent of lesion, and location. Although as per the AGA updates the ultimate goal of resection is R0, that is, complete microscopic resection, as per the ESGE guidelines R1 resection is not associated with recurrence if en bloc resection is achieved.[26]

Endoscopic Submucosal Resection

It can be done for a lesion up to 20 mm in size originating from the mucosa or the submucosa. It is performed with the help of a snare via cap assistance or a ligation device. It carries risk of bleeding of around 4 to 13% and of perforation of around 5%.[27,28]

Endoscopic Submucosal Dissection

It is used for SELs confined to the muscularis mucosa or the submucosa, for example, gastric carcinoids and granular cell tumors. Lesions should be accessible for knife manipulation as well as closure techniques. It involves technical difficulty in certain positions where it should be performed only by expert hands.[29,30]

Submucosal Tunnel Endoscopic Resection

It is a nonexposed type of resection technique. It is used for deeper lesions in which risk of MP involvement and consequent perforation is high, or in lesions in which ESD techniques may be difficult. It is difficult in lesions greater than 3 to 4 cm in size. In this technique, mucosal incision is given after submucosal injection. Then the submucosal tunnel is made by dissecting the submucosal tissue and, finally, dissection around and beneath the SEL is done. SEL is removed through the tunnel, following which the mucosal defect is closed.

Endoscopic Full-thickness Resection

It is done when lesions involve the MP and/or extend into the extraluminal space. It involves mainly two steps: resection and closure. It is done with the FTRD (Ovesco Endoscopy AG, Tübingen, Germany). Following are the contraindications of nonexposed endoscopic full-thickness resection (EFTR) for SELs: size greater than 35 mm, large extramural component, systemic metastasis, stenosis impeding insertion of EFTR device.[31] A study showing comparison between transanal endoscopic microsurgery and EFTR concluded that EFTR was equally effective for small rectal NETs.[32] A similar study comparing EFTR with laparoscopy in case of GIST less than 2 cm has shown similar operating times and R0 resection rates.[33,34]

Management

Management of SELs mainly includes surveillance strategy, resection, and follow-up.

Surveillance

Surveillance mainly depends on whether the diagnosis is known or not.

Known Diagnosis

Leiomyoma, lipoma, heterotopic pancreas, granular cell tumor, schwannoma, and glomus tumor are benign lesions, so there is no need for surveillance and there is no evidence to suggest the benefits of surveillance. However, lesions with malignant potential should have individualized strategies.

Unknown Diagnosis

It mainly depends on the location of SEL. For example, in the stomach, GIST is more likely. As in the case of neuroendocrine neoplasms (NENs), tissue biopsies are diagnostic since the lesion is superficial. Asymptomatic hypoechoic esophageal or gastric lesions of less than 20 mm lesions with no high-risk features on EUS has very low risk of malignancy, and surveillance can be considered.[35] A retrospective study of 954 patients of such lesions showed that less than 4% of the lesions increased in size during surveillance with no clinical consequences[36] There is no single standard recommendation for surveillance strategy due to lack of comparative studies between different strategies. Most of the studies suggest EUS and/or esophagogastroduodenoscopy (EGD) in 3 to 6 months (to look for stability of the lesion in terms of size and high-risk features) followed by EUS or EGD at 6 to 12 months.[35] Nevertheless, since these lesions might be lesions that carry inherent malignant potential, for example, GIST, repeated attempts should be made to establish a diagnosis or diagnostic resection. Decision should be considered after consultation with the patient considering the age of the patient, risk of losing to follow-up, and possible morbidity after diagnostic resection.

Management of Individual Lesions

Lipoma

As already stated, since lipoma has distinct endoscopic and EUS features, tissue diagnosis is not required to establish

diagnosis. Being benign in nature, surveillance is not required in these lesions. Endoscopic or surgical resection is recommended in case of larger lesions causing bleeding, obstruction, or intussusception.[37]

Pancreatic Rest

These are typical endoscopic appearance comprising SEL with central umbilication and commonly located in the antrum. Sometimes EUS is required to establish diagnosis. They are benign lesions, so no surveillance or resection is warranted. Removal is only recommended in larger lesions causing pain or bleeding.[38]

Duplication Cysts

These are rare congenital GI malformations that can be asymptomatic or can present with abdominal pain and bleeding. Accurate diagnosis can be done by EUS. EUS-FNA of duplication cysts should be avoided due to increased risk of complication. Surgical resection is often the choice in case of symptomatic patients. Surgical resection is controversial for asymptomatic cases as few authors recommend resection due to risk of malignant transformation, while others recommend observation.[39]

Gastrointestinal Submucosal Tumor

A GIST always has some inherent malignant potential depending upon its size and location. Gastric GIST of less than 2 cm has very low risk of metastasis irrespective of their mitotic index.[40] For a lesion measuring 3 to 5 cm with low mitotic index, risk of metastasis is 3% and the risk of metastasis in a lesion with high mitotic index is 16%.[41] In case of small intestinal GISTs, the risk of metastasis is up to 50% even in lesions less than 2 cm in size with high mitotic index[42] (►**Fig. 3**). AGA recommends EUS surveillance for gastric GIST less than 2 cm. But no recommendations were made regarding optimal surveillance interval. AGA suggests surgical management for small intestinal GISTs, symptomatic gastric GISTs, and those with high-risk EUS features. Irregular borders, cystic spaces, ulceration, and echogenic foci are high-risk EUS features. AGA also suggests gastric GISTs of 2 to 4 cm with low mitotic index with no metastasis on cross-sectional imaging and with no high-risk EUS features can undergo advanced endoscopic resection. Surgical management should be considered for an unfavorable disease.[43]

While European Society for Medical Oncology, Japanese GIST guideline, and Chinese Society for Clinical Oncology suggest surgical resection for SEL immunohistologically diagnosed as GIST even when it is less than 20 mm,[44–46] National Comprehensive Cancer Network (NCCN) recommends surveillance for less than 20 mm GISTs. However, accordingly to ESGE guidelines, resection can be considered as an alternative to surveillance in a young patients of GIST < 20 mm.[47] Endoscopic resection should be avoided in case of duodenal GISTs due to higher risk of malignant degeneration and metastasis.[48]

Leiomyoma

Leiomyomas are commonly found in the esophagus and are most often benign (►**Fig. 4**). The closest differential for a leiomyoma is a GIST. Histological workup is necessary to differentiate it from a GIST.[49] Hence, tissue sampling is required by EUS-FNA/EUS-FNB. Asymptomatic leiomyomas do not require surveillance or resection.[47]

Carcinoids

Gastric carcinoids/gastric neuroendocrine neoplasms (gNENs) are of mainly three types.

- *Type 1 gNENs:* These commonly develop in the setting of chronic autoimmune gastritis and are associated with hypergastrinemia and are associated with high gastric pH. They are generally well differentiated with low mitotic indices. Risk of metastasis is very low.

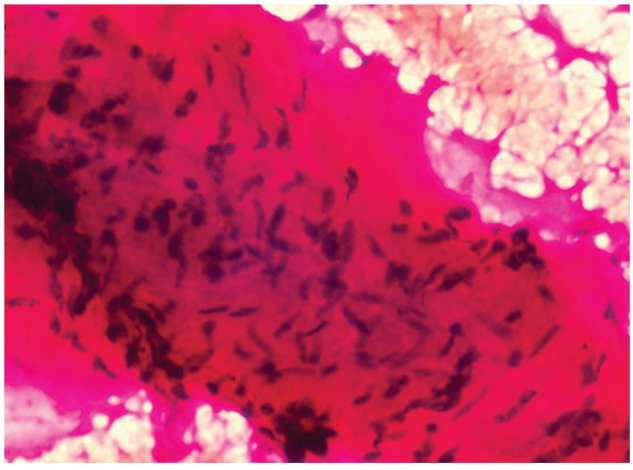

Fig. 3 Histology of the above subepithelial lesion (SEL) showing a cluster of spindle-shaped cells, positive for CD117 and DOG1 suggestive of gastrointestinal stromal tumor (GIST).

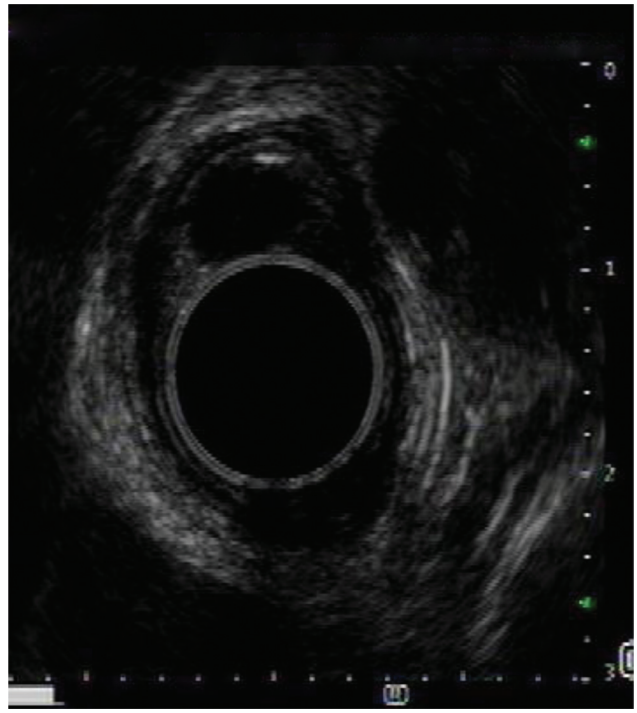

Fig. 4 Radial endoscopic ultrasound (EUS) image of the esophageal subepithelial lesion (SEL) in the second layer, which is a leiomyoma.

Commonly they are less than 1 to 2 cm in size and multiple in number. AGA suggests type 1 gNENs of less than 1 cm can undergo surveillance without resection. While few studies quoted in *Sleisenger and Fordtran's Gastrointestinal and Liver Disease* suggest endoscopic resection for type 1 gNEN of less than 1 cm, ESGE recommends type 1 gNENs that grow larger than 1 cm should undergo endoscopic resection as they carry risk of metastasis.[47,50] On the other hand, NCCN recommends surveillance in type 1 gNENs of less than 1 cm only in case of aged patients or patients with comorbidities. Otherwise, endoscopic resection is recommended in such lesions. For type 1 gNENs measuring 1 to 2 cm, there is no clarity to recommend endoscopic resection or surgical resection. Hence, treatment should be individualized in such lesions. For larger lesions, resection is recommended.[51] NCCN suggests that type 1 gNENs be surveyed every 2 to 3 years.[52]

- *Type 2 gNENs:* These lesions develop in the setting of gastrinomas with hypergastrinemia and low gastric pH. These are commonly associated with Multiple Endocrine Neoplasia (MEN1). Type 2 gNENs are well differentiated with low mitotic indices. Like type 1 gNENs, these lesions rarely metastasize. NCCN recommends resection of primary gastrinoma; however, if the primary gastrinoma is not resected, surveillance and endoscopic resection of small (<2 cm) gastric lesions are recommended.[52]
- *Type 3 gNENs:* These are not derived from any underlying gastric pathology. Generally, they are solitary and well differentiated, but occasionally these can be less differentiated. A subset of type 3 gNENs are aggressive, large tumors. Often surgical resection is recommended. But ESGE suggests only submucosal invasion if they are less than 20 mm. In case of a negative gallium-68 DOTATOC scan suggestive of no extraintestinal spread, then endoscopic resection can be considered.[53–55]

Duodenal NENs

Most commonly duodenal NENs (dNENs) are nonfunctional. Due to technical difficulty, endoscopic resection is difficult for duodenal NENs. There is high risk of bleeding and perforations in case of endoscopic resection. ESGE recommends endoscopic resections for nonampullary, nonfunctional, dNENs of less than 20 mm in size[47]

Rectal NENs

Management of rectal NENs mainly depends upon size. According to NCCN, rectal NENs less than 1 cm in size can undergo endoscopic mucosal resection (EMR), and no surveillance is required thereafter. ESD or transanal surgery can be considered for a lesion of size 1 to 2 cm and T1 without lymph node (LN) involvement. Surveillance after resection should be considered and done by endoscopy and EUS or MR at 6 and 12 months.[52]

Granular Cell Tumors

These are most commonly found in the esophagus and originate from the submucosal layer. A tumor less than 1 cm in size is generally benign, and should be under surveillance by endoscopy and/or EUS. However, tumors larger than 4 cm have the potential to be malignant. Hence, resection is must in such cases. Lesions up to 2.6 cm in size can undergo ESD or EMR.[56]

Conclusion

SELs are generally incidental findings. So dilemma regarding approach is always there as guidelines are ambiguous. Although most of the SELs are detected during routine endoscopy, endoscopy has a limited role in management. EUS plays an important role in management as it helps in determining the size, layer of origin, and echogenicity. Lesions originating from the second and fourth layers should be approached cautiously. Further prospective studies are required to assess whether tissue acquisition is necessary in all SELs or only for SELs with high-risk features. The endoscopic technique of resection should always be preferred to avoid surgical morbidity.

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Conflict of Interest
None declared.

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