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Subepithelial Lesions of GI Tract and Utility of Endoscopic Ultrasound

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Abstract

Subepithelial lesions have increasingly become more common with the advent of increase emphasis on quality of endoscopy and improvement with equipment. There are various types of subepithelial lesions and differentiation utilising endoscopic ultrasound is important which enables reaching a diagnosis. Risk stratification and follow up plans is also possible once a patient has an endoscopic ultrasound examination.

Keywords: *Endoscopic ultrasound; subepithelial lesions; submucosal lesions; gastrointestinaltract*

Introduction

The term submucosal lesion has been used to describe any bulge covered by normal mucosa, usually found incidentally during gastrointestinal (GI) endoscopy. These lesions could either be an intramural mass or an impression caused by extramural structures. More recently, the term 'subepithelial lesions' (SEL) has been used instead because intramural structures may arise from any layer of the GI wall beneath the epithelium.[1]

These lesions are often diagnosed incidentally in approximately 0.36 % of patients. [2]The detection rates have however increased in recent years, which reflect the advance in technology and close attention paid to these lesions. A study more recently quoted an incidence of 0.76 %.[3] Many SEL are benign lesions, such as lipomas, pancreatic rests, leiomyomas, schwannomas or duplications cysts. However, up to 13 % of upper GI tract lesions are malignant and at least 8 % have malignant potential, such as GI stromal tumours. (GIST) and carcinoid tumours.[4] It is therefore important to further characterize and manage these lesions accordingly.

Men and women are equally affected and most patients are more than 50 years old at the time of diagnosis. [5]SEL are most commonly asymptomatic and frequently do not explain the indication for which the patient is undergoing endoscopy. If symptoms are present, chronic anaemia from intermittent GI bleeding is most common. Other non-specific symptoms include abdominal pain, obstruction, haemorrhage and intussuceptions. SEL occluding the papilla can cause jaundice or pancreatitis.[6,7]

Majority of SEL are less than 2 cm therefore computerized tomography (CT) and magnetic resonance imaging (MRI) is often not sensitive enough to detect these lesions. [5]Endoscopic ultrasound (EUS) became a part of clinical practice at the beginning of the eighties and has become the gold standard for evaluation of SEL. It has the ability to differentiate extramural compression and intramural growth, determine layer of origin within the GI tract, size measurements, evaluation of regional lymphadenopathy, tissue acquisition and help determine management pathways. The reported accuracy EUS in predicting the pathologic diagnosis of SEL ranged from 45.5 % to 82.9 %. EUS guided fine-needle aspiration increased this diagnostic accuracy ranging from 63 % to 98 %.[1]

A review of SEL and its EUS utility is provided.

Extramural Lesions

EUS can readily differentiate intramural and extramural lesions due to its ability to examine the gut wall layers in detail. An international multicenter study reported the sensitivity and specificity of extramural compression with endoscopy alone was 87% and 29%, respectively. [8]Oztas et al in their study

reported 66.4 % of patients who had endoscopy for suspected extramural lesion or SEL were found to have extramural lesions. 9Although pathological masses can cause these impressions, it is more likely to represent adjacent normal structures.[1]

A normal spleen makes an impression in the gastric fundus and upper body. Gallbladder tends to compress the gastric antrum. Other causes include splenic hilum vessels, tail of pancreas , colon and left lobe of liver. Normal organs such as trachea, left atrium, spine and liver, can cause extra-oesophageal compression. Abnormal structures to be borne in mind include structures such as pancreatic pseudocyst, splenic artery aneurysm, aortic aneurysm, colonic tumours and enlarged lymph nodes.[1,16]

It is extremely important when assessing extramural masses to observe the hyeperechoic serosal layer to determine wall integrity. This ensures reliable differentiation between gastric wall impression and wall infiltration from an extragastric tumour.[1,16,18]

Gastrointestinal Stromal Tumours

GISTs are rare mesenchymal tumours of the GI tract, representing 0.1 – 3 % of all GI neoplasms. [10]The vast majority of them arise in the stomach (60-70%), small bowel (20-30%) and the remaining elsewhere in the GI tract including oesophagus, colon, rectum, omentum and peritoneum. (11) GISTs usually affect males and females equally with peak incidence in the 6th decade. [12]They rarely occur in children or young adults , unless in association with neurofibromatosis or Carney's triad (gastric stromal tumour , extra-adrenal paraganglioma and pulmonary chordoma).[13]

The most common symptoms are vague abdominal discomfort but most lesions are less than 2 cm and asymptomatic. Lesions more than 2 cm may be ulcerated and these patients can present with bleeding or anaemia. Intestinal obstruction rarely occurs. [1]

GISTs constitute a distinct group of rare GI tract tumours that originate from the interstitial cells of Cajal. Histologically, most GISTs are spindle cell type (70%), followed by epitheloid (20%) and mixed (10%) types. These cells normally express CD 117, a product of the c-kit proto-oncogene that encodes a tyrosine kinase receptor responsible for regulating cellular proliferation in GISTs.[14-15]DOG1 (Discovered on GIST 1) is a new immunohistochemical marker, which can be useful in CD 117 negative cases. It is also useful to differentiate from other lesions such as sarcoma and melanoma, which can also stain for CD 117.[16] Approximately 60-80 % of GISTs are alsoimmunopositive for CD34. [17]

Accurate diagnosis is also reliant on imaging with the main modalities being CT scanning and EUS. It assists with initial diagnosis and staging, assessing operative suitability and post-operative follow-up. [18]CT can show abnormalities in up to 87 % of cases and is able to define the end luminal and exophytic extent of a mass.[19]

These lesions often appear endoscopically as a smooth bulge with normal overlying mucosa.Probing with biopsy forceps may assess firm consistency of the lesion. Endosonography generally demonstrates a hypoechoic, homogenous lesion but can also appear heterogenous with anechoic spaces or calcifications. It can arise from the second hypoechoic layer (muscularis mucosa) or more frequently from the fourth hypoechoic layer (muscularispropria). Assessment for lymphadenopathy and involvement of additional wall layers should be performed at EUS.[1, 35]'Bite-on-bite' pinch biopsies may be attempted, although diagnostic yield is often low. EUS fine-needle aspiration (FNA) improved diagnostic accuracy shown in 2 studies with sensitivities of 86 & and 91 % respectively. [20-21]

Approximately, 10-30 % of GISTs are clinically malignant although it should be borne in mind that all GISTs have malignant potential.[22]They should be stratified by malignant potential, which involves assessment of tumour size, location and mitotic count. Characteristics associated with malignancy include tumour size > 4 cm, irregular borders, cystic spaces and echogenic foci. [23] Sensitivity of these features in detecting malignancy has been reported to be 80-100 % but the absence of these features does not rule out malignancy.[20]Small bowel GISTs behaves more aggressive than the ones in the stomach, approximately 40% to 50 % being malignant.[22]It should be noted that tissue acquisition by FNA does not assess mitotic rate accurately.

Surgical referral should be considered in patients with pain, obstruction and bleeding. Lesions > 2 cm anywhere in the GI tract and lesions in the small bowel should also be referred for a surgical opinion. Surgical resection should be offered for gastric GIST < 2 cm with high risk features, with EUS surveillance at 6 or 12 monthly intervals for lesions without these features.[5]

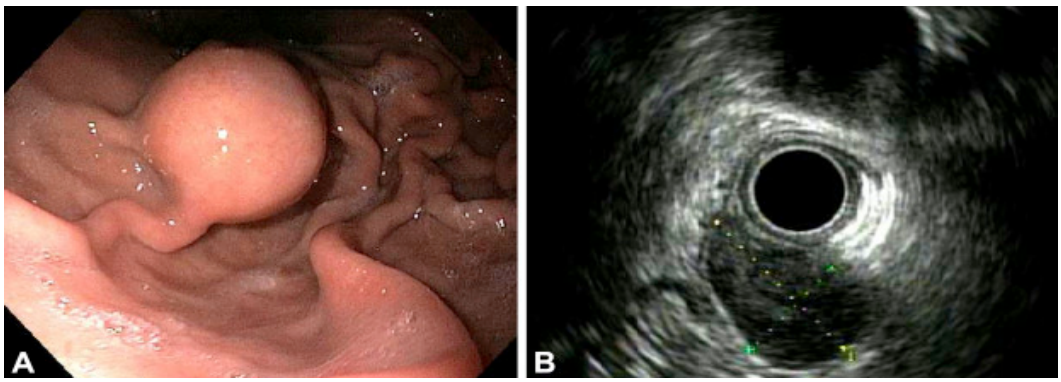

Figure 1. ***(A)*** *Subepithelial lesion seen during OGD* ***(B)*** *EUS image showing GIST arising from 4th layer of GI tract*

Aberrant Pancreas

Aberrant pancreas is a description of ectopic pancreatic tissue lying outside its normal location with no anatomic or vascular connection to the pancreas proper. Other terms include ectopic pancreas, pancreatic rest and heterotropic pancreas, which is used interchangeably. It is quite common and the incidence in autopsy series has been estimated to be between 0.6 % to 13.7 %. [24]Nearly all of them (90%) are located in the stomach and most often in the gastric antrum. [5] Patients are typically asymptomatic but rare complications such as pancreatitis, cyst formation, ulceration, bleeding, gastric outlet obstruction and obstructive jaundice can occur. These lesions are considered benign although there have been rare reported cases of malignant transformation.[25-26]

At endoscopy, an aberrant pancreas appears as a submucosal nodule with a characteristic central umbilication that corresponds to a draining duct. EUS features are that it normally originates from the third layer (submucosa) but can also originate from the second or fourth layer. It is usually hypoechoic or mixed echogenicity. Anechoic structures do exist within the lesion, which corresponds to ductal structures.[1,5]

As malignant transformation is exceedingly rare, these lesions do not require endoscopic surveillance or surgical resection once diagnosis is secured.[5]

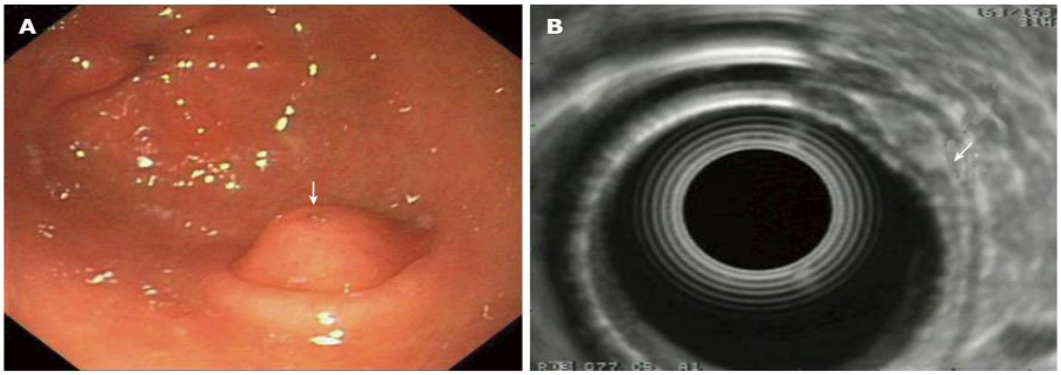

Figure 2. *Endoscopic and EUS image of aberrant pancreas arising from 3rd layer of GI tract*

Lipoma

Lipomas are common and originate from the third (submucosal) layer of the GI tract. They are composed of mature adipose tissue. They can occur anywhere in the GI tract but more commonly in the gastric antrum and colon. [5] They are rarely symptomatic, but may result in haemorrhage, abdominal pain and intestinal obstruction.[27]

At endoscopy, they usually present as soft solitary lesions with a yellowish hue and often exhibit 'pillow sign' when interrogated with biopsy forceps. This feature on a suspected lipoma in the antrum and colon is approximately 98 % specific for a lipoma.[28] At EUS, lipomas characteristically appear intensely hyperechoic , homogenous and has well circumscribed margins.

Lipomas have no malignant potential and once confirmed, follow up EUS is not recommended.

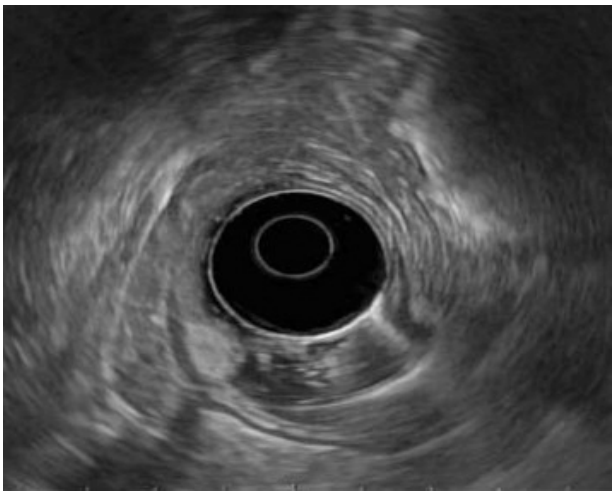

Figure 3. *EUS image of gastric lipoma*

Leiomyoma

Leiomyomas are benign tumours that most commonly arise from the muscularis propria but can be seen within the muscularis mucosa. It is most commonly seen in the mid or distal oesophagus and rarely in the stomach. Immunohistochemistry staining is negative for CD117, CD34 and s100, but positive for desmin and smooth muscle actin protein. [5]Malignant transformation to leiomyosarcoma is rare.[29]

In EUS, these lesions present as hypoechoic, homogenous, well circumscribed lesions in the second or fourth layer.[1]

Suspected leiomyomas should have an EUS assessment. For lesions less than 2 cm, annual surveillance OGD and/or EUS may be performed in the asymptomatic patient.[30] Surgical resection is adviced for symptomatic patients or when there is interval changes or enlargement on surveillance EUS.[5]

Varices

Gastric varices may be misdiagnosed endoscopically as submucosal lesions or thickened gastric folds. When found incidentally during endoscopy without adequate patient information, biopsies may be hazardous. [1]EUS in these circumstances is appropriate. On EUS, fundic varices appear as small round to oval, anechoic structures within the submucosa. Its easy compressibility differentiates it from submucosal cysts. Demonstration of flow with Doppler examination is a definite clue for diagnosis. EUS can also be used fortreatment of varices with sclerosant agent injections.[1,31]

Granular Cell Tumour

Granular cell tumours (GCTs) are subpeithelial lesions of Schwann cell origin. Most GCTs accur within the oesophagusand rarely in the stomach, colon or rectum.(1) Risk of malignant transformation is low and has been quoted to be 2-4 % in one study. All the malignant lesions were > 4 cm.[32]

Endoscopically, GCTs are usually < 2 cm in diameter, sessile nodules or polyps with a yellowish-white colour resembling a molar tooth.[35]

At EUS, GCTs appear as hypoechoic, homogenous lesions with smooth margins originating from the second or third layer of the GI tract.[1]

For asymptomatic GCTs that are not excised, surveillance EUS 1-2 yearly is recommended to monitor for interval changes. Lesions > 2 cm should be considered for surgical resection.[1,5]

Cysts

Cystic subepithelial lesions may appear as simple cysts, multicystic or solid cystic lesions. Cysts in the GI tract are a rare clinical entity and usually are the result of a resolved inflammatory process or they can derive from embryological development, including foregut and duplication cysts. Foregut cysts are usually located in the mediastinum and categorized as bronchogenic or neuroenteric, according to their embryonic origin. EUS and EUS-FNA plays a pivotal role in their diagnosis.[22] FNA of bronchogenic cyst can be associated with cyst infection and mediastinitis therefore antibiotic prophylaxis is needed.[1]

Cysts in the stomach are rare and they are predominantly asymptomatic or present with obstructive symptoms, pain and bleeding. At endoscopy, cysts appear as compressible nodular structures which protrusions. In EUS, they present as well-demarcated, round or oval anechoic lesions, located in the 3rd GI layer. Inflammatory cysts have a single hyperechoic layer.[1,22]

Duplication cysts are rare congenital abnormalities and may involve the entire GI tract, with ileum being the commonest site. The stomach is the least common site representing only 2%-8% of all duplication cysts. Diagnosis in adulthood is uncommon.[33] At EUS, they appear as anechoic, homogenous lesions with regular margins. The walls appear as a 3 or 5 layer structure due to presence of a submucosa and a muscularis layer.[22,34]

Duplication cysts have low malignant potential, although rare reports of malignant transformation exist.[1,22]

Carcinoid Tumour

Carcinoid tumours are slow growing neuroendocrine tumours with malignant potential. They most commonly affect the GI tract and lung. It is the commonest neoplasm of the small bowel and at least 25 % of all carcinoid tumours occur within the small bowel predominantly in the ileum. It has a slight female predominance with a male: female ratio of 1: 1.6. They are usually asymptomatic but rare complications include abdominal pain, bleeding, obstruction and carcinoid syndrome from secretion of functionally active hormones. These lesions tend to originate from the mucosal layer and penetrate into submucosal layer. As a result, it is often diagnosed on mucosal biopsy at index OGD or colonoscopy.[1,5]

Endoscopically, carcinoid tumours are small, round, sessile or polypoidal lesions with a smooth surface and yellow hue. They usually have normal overlying mucosa. Gastric and ileal carcinoids are commonly multiple and usually solitary elsewhere. At EUS, carcinoids usually appear homogenous, well demarcated and mildly hypoechoic originating from the first, second and/or third layer.[1,5,35]

Carcinoids less than 2 cm are rarely malignant and when it is of this size with no invasion beyond the third layer and no local lymphadenopathy, endoscopic resection is possible.[1]

Conclusion

SEL are difficult to diagnose definitively by conventional imaging such as CT and MRI scans. Endoscopic views are limited and standard biopsy techniques have a low yield.

EUS imaging is essential for the evaluation of SELs because EUS performs better than other modalities. It can be used to determine size, layer of origin, margins, echogenicity and detailed morphology of these lesions. These features can then identify benign lesions that do not require management or follow up. In addition, EUS can guide additional work up such as FNA and biopsies, which guides differentiation from benign and malignant lesions via cytological and histological analysis.

EUS can also serve as both a diagnostic and therapeutic approach for endoscopic resection of small lesions originating from the muscularis mucosa or submucosal layer.

Table 1. *Summary of types of subepithelial lesions (SELs)*

Lesion	EUS layer	EUS appearance	Malignant potential
GIST	Fourth (rarely second)	Hypoechoic(heterogenous echogenicity, irregular margins, cystic space & lymphadenopathy suggest malignancy	10-30 % clinically malignant
Aberrant pancreas	Second, third and/or fourth	Hypoechoic or mixed echogenic, anechoic ductal structure may be present	Extremely rare
Lipoma	Third	Intensely hyperechoic, homogenous	None
Leiomyoma	Second,fourth	Hypoechoic, well circumscribed	None (primary leiomyosarcoma extremely rare)
Varices	Third	Anechoic, tubular, serpiginous	None
Granular cell tumour	Second or third	Hypoechoic, homogenous	Low risk
Duplication cyst		Anechoic, homogenous	Low risk
Carcinoid tumour	First, second and/or third	Hypoechoic, homogenous, well demarcated	Rare < 2 cm

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