

Clinical Characteristics, Endosonographic Findings and Etiologies of Gastroduodenal Subepithelial Lesions: A Thai Referral Single Center Study

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Objective: The present study was undertaken to evaluate the demographic data, Endoscopic UltraSonography (EUS) characteristics of the sub-epithelial lesions, pathology results, complications and long term follow-up of the patients whom referred for EUS evaluation at Siriraj Hospital.

Material and Method: From January 2008-June 2011, a total of 61 cases was referred for EUS evaluation due to sub-epithelial lesions. The endoscopic reports, pathology results and the patients' medical records were reviewed. The present study was approved by Siriraj Institutional Review Board.

Results: A total of 61 patients were referred for evaluation of subepithelial lesions, 6 of them were excluded. Thus, 55 cases were analyzed. The mean age was 57.7 ± 13.8 years (27-87 years). Sixty seven percent were female. Only one-third of the patients had symptoms. The provisional diagnosis of the sub-epithelial lesions, regarding only clinical and endosonographic characteristics were GIST, neuroendocrine tumor (NET), pancreatic rest, lipoma, granular cell tumor and others (70.9%, 9.1%, 9.1%, 3.6%, 3.6% and 3.6% respectively). All the lesions were diagnosed as GIST originating from either the fourth layer (97.4%) or the second layer (2.6%) of gastric or duodenal wall. Fine needle aspiration (FNA) was performed in 13 patients (23.6%). The positive predictive value, negative predictive value and accuracy of diagnosis of GIST made by endosonographers based on only endosonographic characteristics were 85, 100 and 86% (95% CI: 62.4%-94.4%) respectively.

Conclusion: Most of the subepithelial lesions which were referred for EUS evaluation at Siriraj Hospital were GISTs. The diagnosis of GIST can be accurately made by using the EUS based on only endosonographic characteristics. FNA should be done for the large sized GIST. For small sized GIST (< 3 cm), FNA might not be beneficial but a 1 year interval follow-up with EUS is recommended.

Keywords: Endoscopic UltraSonography, Sub-epithelial, Submucosal, Mass, Lesion, GIST

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Subepithelial lesion has been reported as one of the common incidental findings during routine endoscopy. The common sites of gastrointestinal sub-epithelial lesion were esophagus stomach and proximal portion of duodenum⁽¹⁾. Europe and United states^(2,3) reported that two-third of subepithelial lesions in their countries was Gastrointestinal stromal tumor (GIST) which originated from stem cell precursor to the

interstitial cell of Cajal. This tumor expresses the c-kit proto-oncogene⁽⁴⁾. The presence of this specific receptor is beneficial because it aids in distinguishing GISTs from other sub-mucosal lesions. Endoscopic ultrasonoscope (EUS) is fiber optic endoscope combined with intra-luminal high frequency ultrasonography. This technology provides a better assessment of subepithelial lesions. However, it may still be very difficult to define whether a subepithelial lesion is benign or malignant based on only clinical data and endosonographic findings alone. Some experts recommended performing EUS with Fine Needle Aspiration (FNA) in every subepithelial lesion⁽⁵⁾. Anyway, in the authors opinion, the benefit of EUS

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with FNA in a small lesion, especially a lesion which is smaller than 3 cm, was still doubtful. Given of limited data of subepithelial lesions reported in Thailand, it was very difficult to propose the proper guidelines for management of gastro-duodenal subepithelial lesion. The objective of the present study was to assess the baseline characteristics of subepithelial lesions in Thailand, the utility of EUS and EUS-FNA for diagnosis of submucosal lesions and natural history of small submucosal lesion after long term follow-up. Finally, if the authors are able to gather enough data from the present study, the authors would like to propose the proper clinical practice guideline of management of subepithelial lesions for gastroenterologists in Thailand.

Material and Method

Siriraj Endoscopy Center is a large tertiary referral center of Thailand. In the last few years, more than 350 EUS procedures were performed each year. From January 2008-June 2011, a total of 61 cases was referred for EUS evaluation due to subepithelial lesions. The endoscopic reports, pathology results and the patients' medical records were reviewed. The present study was approved by Siriraj Institutional Review Board. All patients provided written informed consent to undergo the procedure. Patients were placed in the left lateral decubitus position and were given intravenous sedation with full anesthetic monitoring. EUS was performed with a radial echoendoscope (GF UE 160, Olympus, Tokyo, Japan) in order to identify the layer involvement. EUS-FNA was performed with a curvilinear echoendoscope (GF UC 140P, Olympus, Tokyo, Japan) using a 22-gauge FNA needle (Echo tip, Wilson-Cook, Winston Salem, NC, USA) to get tissue sampling. Color Doppler sonography was used to exclude intervening vascular structure along the needle path. 5 ml suction was applied during performing FNA. The aspirated materials were smeared onto the glass slides and then kept in the formalin containing bottle for cell blocks. The authors did not have an on-site cytologist, so the slides and aspirated material containing bottle would be sent for cytological diagnosis within 24 hours. The patients' charts were reviewed. In addition to patient demographics, other details including clinical presentations, endosonographic findings of the lesions, EUS FNA, endoscopic interventions, subsequent surgery, complications and pathology results were recorded. Follow-up was done by means of direct patient contact and endoscopic/EUS re-evaluation; the follow-up period was considered to have been until the last

recorded hospital visit. The authors utilized the final cytology and pathology results (in case of subsequent surgery) in the author's analysis. The provisional diagnosis regarding only clinical and endosonographic characteristics and the final diagnosis based on cytology and pathology results. Complications were defined as any deviation from the normal clinical course after EUS that was associated with the procedure as observed by endosonographers, the recovery room nurses or as reported by the patients.

Statistical analysis

Continuous variable were reported as means (standard deviations) and percent while categorized variables were reported as proportions. The positive predictive value, negative predictive value and accuracy were calculated. The analysis was conducted with SPSS version 13.0.

Results

There were 61 patients referred for EUS evaluation of subepithelial lesions; the endosonographers could not identify any abnormal lesions in both endoscopic and endo-sonographic views in 6 patients, thus they would be excluded from the present study. So, a total of 55 cases of the real sub-epithelial lesions would be analyzed. The mean age of the patients was 57.7 ± 13.8 years. Sixty seven percent were female. Two-third of the sub-epithelial lesions were incidentally identified during routine esophagogastroduodenoscopy. Only one-third of the patients had symptoms. The three most common symptoms of sub-epithelial lesions were abdominal mass, gastrointestinal hemorrhage and anemia, respectively. The clinical presentation of the subepithelial lesion are shown in Table 1. After EUS examinations were performed, the

Table 1. The clinical presentation of the subepithelial lesion

Clinical presentation	EUS n (%)
Asymptomatic cases	37 (67.3)
Symptomatic cases	18 (32.7)
Abdominal mass	7 (12.7)
Hemorrhage	6 (10.9)
Anemia	3 (5.5)
Abdominal pain	1 (1.8)
Fever	1 (1.8)
Total	55 (100)

mean size of the lesions was 3.1 ± 3.4 cm. The provisional diagnosis of the subepithelial lesions, regarding only clinical and endosonographic characteristics, were GIST, neuroendocrine tumor (NET), pancreatic rest, lipoma, granular cell tumor and other (schwannoma)

for 39 (70.9%), 5 (9.1%), 5 (9.1%), 2 (3.6%), 2 (3.6%) and 2 (3.6%) respectively. The endosonographic characteristics of the subepithelial lesions and GIST are shown in Table 2. All the lesions were diagnosed as GIST originating from either the fourth layer (97.4%) or

Table 2. The demographic and endosonographic characteristics of the subepithelial lesions

Characteristics	Total lesions n = 55 (%)	Suspicious Non-GIST n = 16 (%)	Provisional diagnosis of GIST*	
			Suspicious GIST n = 20 (%)	Definite GIST n = 16 (%)
Sex				
Male	18 (32.7)	7 (43.8)	5 (25.0)	5 (31.3)
Female	37 (67.3)	9 (56.2)	15 (75.0)	11 (68.7)
Size				
More than 3 cm	20 (36.4)	1 (6.2)	2 (10.0)	14 (88.0)
Less than 3 cm	35 (63.6)	15 (93.8)	18 (90.0)	2 (12.0)
Location				
Gastric body	22 (40.0)	4 (25.0)	8 (40.0)	7 (43.8)
Gastric fundus	11 (20.0)	0 (0.0)	6 (30.0)	5 (31.2)
Gastric antrum	10 (18.2)	9 (56.3)	1 (5.0)	0 (0.0)
Gastric cardia	5 (9.1)	1 (6.3)	2 (10.0)	2 (12.5)
Duodenum	7 (12.7)	2 (12.6)	3 (15.0)	2 (12.5)
Echogenicity				
Hyperechoic	2 (3.6)	2 (12.5)	0 (0.0)	0 (0.0)
Hypoechoic	50 (90.9)	12 (75.0)	19 (95.0)	16 (100)
Isoechoic	3 (5.5)	2 (12.5)	1 (5.0)	0 (0.0)
Heterogenicity				
Heterogeneous	24 (43.6)	6 (37.5)	4 (20.0)	12 (75.0)
Homogeneous	31 (56.4)	10 (62.5)	16 (80.0)	4 (25.0)
Layer				
Muscularis Mucosae	1 (1.8)	1 (6.2)	0 (0.0)	1 (6.3)
Submucosa	16 (29.1)	15 (93.8)	0 (0.0)	0 (0)
Muscular Propia	38 (69.1)	0 (0.0)	20 (100)	15 (93.7)
Serosa	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cystic change of lesion				
No	48 (87.3)	16 (100)	20 (100)	10 (62.5)
Yes	7 (12.7)	0 (0.0)	0 (0.0)	6 (37.5)
Margin of the lesion				
Irregular/ill defined	10 (18.2)	15 (93.8)	1 (5.0)	7 (43.8)
Smooth/well defined	45 (81.8)	1 (6.2)	19 (95.0)	9 (56.2)
Calcification				
No	54 (98.2)	16 (100)	19 (95.0)	16 (100)
Yes	1 (1.8)	0 (0.0)	1 (5.0)	0 (0.0)
FNA				
Done	13 (23.6)	3 (18.7)	4 (20.0)	6 (37.5)
Not done	42 (76.4)	13 (81.3)	16 (80.0)	10 (62.5)
Complication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

* Another 3 cases which were not shown in this table were the cases which were diagnosed as definite Non-GIST

the second layer (2.6%) of gastric or duodenal wall. None of the non-GIST lesion arose from the fourth layer. Fine needle aspiration (FNA) was performed in only 13 of 55 patients (23.6%). The reasons which the endosonographers did not attempt FNA were; 1) small lesions from which adequate tissue sampling might be not received, thus they decided to have them follow-up by EUS instead (n = 23). 2) the lesions were highly suspicious for GIST and expressed some malignant characteristics and/or were large lesions thus they referred the patients for surgery (n = 11). 3) highly suspicious for benign lesion such as pancreatic rest, lipoma (n = 8). Three patients were excluded from provisional diagnosis of GIST due to other diagnosis confirmed by surgical pathology. The rest of provisional diagnosis of GIST was 36 patients. Finally, a total of 16 patients who were diagnosed of GIST from surgical pathology and FNA were called definite GIST. According to the above reason, 14/16 (88%) of this group were larger than 3 cm in diameter which usually expressed more malignant potential features (heterogenous echo (75%), cystic change of lesion (37%) and irregular or ill defined border (43.8%)) than the lesions suspected of GIST that nearly all (90%) were less than 3 cm in diameter (heterogenous echo only 20%, 0% of cystic change and only 5% of irregular or ill defined border).

The provisional diagnosis regarding only clinical and endosonographic characteristics and the final diagnosis based on cytology and pathology results are shown in Table 3. The accuracy of diagnosis of

GIST made by endosonographers based on only endosonographic characteristics was 86.0% (95% CI: 62.4%-94.4%). Correlation between the endosonographic characteristics and final diagnosis of the patients who underwent FNA or surgery regarding the size of the lesions suspicious of GIST are shown in Table 4.

The results in Table 4 show that the positive predictive value and negative predictive value, using only endosonography characteristics, in the present study was 85% and 100%, respectively. The three cases to which the provisional diagnosis of GIST did not correlate with the final diagnosis were somatostatinoma, gastric carcinoma and schwannoma. All of these cases were large- size lesions of 13, 10 and 4.3 cm respectively. The FNA cytology for the lesions less than 3 cm showed inadequate and non diagnostic results which were 1.0, 1.5, 1.8 and 2.4 cm in diameter.

Discussion

The present study showed that majority of the patients who were referred for EUS evaluation due to subepithelial lesions were female and only one third of them were symptomatic. The most common symptoms were abdominal mass, gastrointestinal bleeding and anemia. After EUS was performed, provisional diagnosis was suspicious for GIST about 70%. The present result was similar to previous reports from Japan and United States^(4,5). According to Table 2, the authors can conclude that more than 90% of GIST in the present study arose from MP layer. Half to three-

Table 3. The provisional diagnosis based on only endosonographic characteristics compared with Final diagnosis based on combined Cytology from FNA and pathology results

Count	Final Diagnosis *					Total
	GIST	Somatostatinoma	Pancreatic rest	Carcinoma	other	
Provisional diagnosis (n = 55)						
GIST (39)	16	1	0	1	1	19
NET (5)	0	0	1	0	1	2
Pancreatic rest (5)	0	0	0	0	0	0
Lipoma (2)	0	0	0	0	0	0
Granularcell tumor (2)	0	0	0	0	0	0
Other (2)	0	0	0	0	0	0
Total	16	1	1	1	2	21

* Another 34 cases which were not shown in this table were those who did not achieve the final diagnosis (No cytology and pathology result)

Table 4. Data revealed correlation of EUS characteristics with final diagnosis from FNA or surgery in regarding to size of the lesions suspicious of GIST

EUS Provisional diagnosis	FNA+/Sx-		FNA+/Sx+		FNA-/Sx+		FNA-/Sx-	
	GIST	Non GIST	GIST	Non GIST	GIST	Non GIST	GIST	NonGIST
	< 3 cm	≥ 3 cm	< 3 cm	≥ 3 cm	< 3 cm	≥ 3 cm	< 3 cm	≥ 3 cm
GIST (n = 39)	2	0	3	0	1	10	0	0
Non GIST (n = 16)	0	1	0	0	0	0	0	12

* Definitions; FNA+ (FNA was done), FNA- (FNA was not done), Sx+ (underwent surgery) and Sx- (No surgery)

fourth of the lesions located at gastric body and fundus compared with non GIST lesions which were found more at antrum. Nearly all the lesions suspicious for GIST arose from the fourth layer and usually showed hypoechogenicity. The non GIST lesions arose mostly from the third layer and could be both iso or hyperechoic lesions. When considering only EUS characteristics in differentiation between GIST and non GIST lesions based on the final diagnosis in Table 3 and 4, the positive predictive value, negative predictive value and accuracy of diagnosis of GIST were 85, 100 and 86%, respectively. In the present study, EUS with FNA was done in only one fifth of the cases. After the authors explored the reasons that the endo-sonographers did not perform the FNA, the authors could conclude that in the present observation for the small sized lesions, less than 3 cm, only 4 (12.3%) of the patient underwent FNA and the result were 3 inadequate samplings and 1 non diagnosis. According to the results mentioned above, EUS FNA might not be a benefit for these patients, even though there had been a recommendation from some experts for doing EUS FNA in every single subepithelial lesion^(5,6). Of the twenty three patients who supposed to be interval followed-up with EUS evaluation, only 11 of them, all with lesions less than 3 cm in diameter, were followed-up after the first EUS examination. Though limitation of the data, the average follow-up time was 12.8 months (3-24 months); most of them showed clinically stability and in 9 of 11 patients it was found that the sub-epithelial lesions were stable in size. Regarding the observations mentioned above, the authors conclude that EUS FNA in small lesions might not be beneficial and the authors recommended them for follow-up endosonography within a year. 2) The endosonographers did not perform FNA for suspicious lesion of GIST larger than 3 cm in diameter but usually referred the patients directly for surgery which is, according to the present study, about the malignant potential features of GIST, which are composed of ill defined and irregular margins, including cystic change and heterogenicity and were found increasingly in the large lesion (> 3 cm) which is the same as the international consensus. But these characters were not common in small sized GIST (< 3 cm). 3) The authors also observed that the lesions which were misdiagnosed as GIST from the EUS evaluation, but that final pathology confirmed was not GIST, were very large lesion (mean size was 9.1 cm; 4.3-13 cm). The reason might be from difficulty in classifying the layer involvement for the large lesions. In the present case, EUS FNA would play a role for definite diagnosis. From

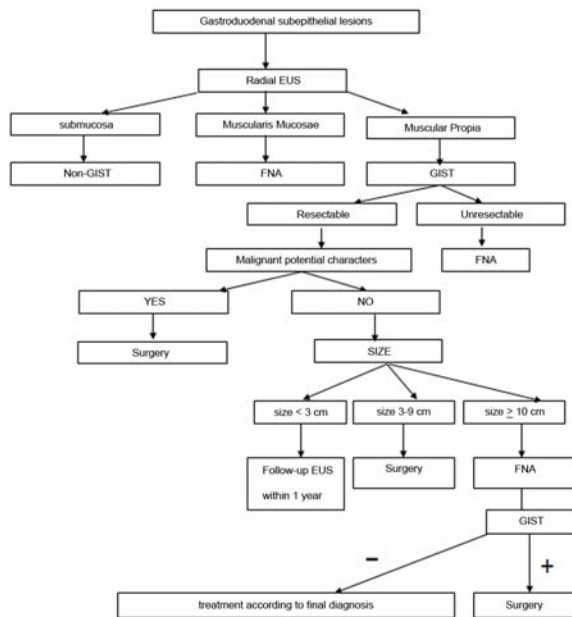


Fig. 1 The proposed algorithm for management of Gastroduodenal sub-epithelial lesions

all the knowledge that the authors learned from the present study, the authors would like to propose the algorithm for management of sub-epithelial lesions detected during the routine upper endoscopy as the chart below (Fig. 1). This algorithm needs to be verified by prospective-long term study in the future.

Conclusion

Subepithelial lesions which were referred for EUS evaluation at Siriraj Hospital were GISTs, neuroendocrine tumor (NET), pancreatic rest, lipoma, granular cell tumor and others at 70.9%, 9.1%, 9.1%, 3.6%, 3.6% and 3.6%, respectively. The most common pathological proved sub-epithelial lesion were GIST. The accuracy, negative predictive value and positive predictive value of 86%, 100% and 85% were good

enough to distinguish the GIST and non GIST lesions by using only EUS characteristics. The role of EUS FNA in every sub-epithelial lesions, especially small lesions, was still questionable according to the data that we acquired from the present study. A prospective long-term study should be conducted.

Potential conflicts of interest

None.

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**ลักษณะทางคลินิก อัลตราซาวนด์และสาเหตุของก้อนนูนใต้เยื่อกระเพาะอาหารและดูโอดิเนียม:
การศึกษาของศูนย์ส่องกล้องทางเดินอาหารโรงพยาบาลศิริราช**

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วัตถุประสงค์: เพื่อศึกษาอาการทางคลินิก ลักษณะตรวจพบทางอัลตราซาวนด์ และสาเหตุของก้อนนูนใต้เยื่อกระเพาะอาหารและดูโอดิเนียมด้วยวิธีส่องกล้องอัลตราซาวนด์ ของผู้ป่วยที่มารับการตรวจที่ศูนย์ส่องกล้องทางเดินอาหารโรงพยาบาลศิริราช

วัสดุและวิธีการ: ทบทวนเวชระเบียนและบันทึกข้อมูลของผู้ป่วยที่มารับการตรวจโดยวิธีส่องกล้องอัลตราซาวนด์ด้วยข้อบ่งชี้คือ ก้อนนูนใต้ชั้นเยื่อกระเพาะอาหารและดูโอดิเนียม ระหว่างเดือนมิถุนายน พ.ศ. 2551 ถึงเดือนมิถุนายน พ.ศ. 2554 เพื่อศึกษาอาการทางคลินิก สาเหตุ ลักษณะทางอัลตราซาวนด์ที่ตรวจพบ ความแม่นยำในการวินิจฉัย ความเพียงพอของเนื้อเยื่อที่ได้จากการใช้เข็มขนาดเล็กเจาะดูดเนื้อเยื่อ ผลทางพยาธิวิทยา ภาวะแทรกซ้อนที่พบ รวมทั้งหาแนวทางในการดูแลและติดตามผู้ป่วยในระยะยาว

ผลการศึกษา: จากผู้ป่วยที่เข้ารับการตรวจจำนวน 61 ราย แพทย์ผู้เชี่ยวชาญตรวจไม่พบรอยโรค 6 ราย ดังนั้นจึงมีผู้ป่วยเข้ามารับการตรวจด้วยวิธีส่องกล้องอัลตราซาวนด์ในการศึกษานี้จำนวนทั้งสิ้น 55 ราย (ผู้ป่วยชาย 18 ราย ผู้ป่วยหญิง 37 ราย) อายุมัธยฐาน 57.7 ปี (พิสัยระหว่าง 27-87 ปี) โดยมีข้อบ่งชี้คือ ก้อนนูนใต้เยื่อกระเพาะอาหารและดูโอดิเนียมพบว่าเป็นการตรวจพบโดยบังเอิญระหว่างส่องกล้องทางเดินอาหารส่วนต้น ร้อยละ 69 โดยผู้ป่วยมีอาการแสดงเพียงร้อยละ 31 และอาการที่นำผู้ป่วยมาพบแพทย์มากที่สุดคือ ก้อนในช่องท้อง และภาวะเลือดออกในทางเดินอาหาร (ร้อยละ 13 และ 11 ตามลำดับ) ตำแหน่งที่พบรอยโรคบ่อยที่สุดคือ กระเพาะอาหารส่วนบอดี้ (ร้อยละ 40) ส่วนดูโอดิเนียมพบเพียงร้อยละ 13 เท่านั้น อาศัยผลการตรวจลักษณะทางอัลตราซาวนด์ แพทย์ผู้เชี่ยวชาญให้การวินิจฉัยเป็นเนื้องอก GIST, เนื้องอก neuroendocrine (NET), เนื้อตับอ่อนอยู่ผิดตำแหน่ง (Pancreatic rest), เนื้องอกไขมัน, เนื้องอก granular cell และอื่นๆ ร้อยละ 70.9, 9.1, 9.1, 3.6, 3.6 และ 3.6 ตามลำดับ ในจำนวนผู้ป่วยที่มารับการตรวจส่องกล้องอัลตราซาวนด์ทั้งหมด แพทย์ได้ตรวจเพิ่มเติมด้วยการใช้เข็มขนาดเล็กเจาะดูดเนื้อเยื่อส่งตรวจทางเซลล์วิทยา ร้อยละ 24 โดยพบความแม่นยำในการวินิจฉัย ที่พิจารณาจากลักษณะทางอัลตราซาวนด์ถึงร้อยละ 86 การศึกษารุ่นนี้ไม่พบว่ามีภาวะแทรกซ้อนทั้งที่เกิดจากการส่องกล้องอัลตราซาวนด์ และการใช้เข็มขนาดเล็กเจาะดูดเนื้อเยื่อส่งตรวจทางเซลล์วิทยา

สรุป: ผู้ป่วยที่มารับการตรวจด้วยเรื่องก้อนนูนใต้เยื่อกระเพาะอาหารและดูโอดิเนียมส่วนใหญ่ไม่มีอาการ มักเป็นการตรวจพบโดยบังเอิญสาเหตุส่วนใหญ่คือเนื้องอก GIST ซึ่งสามารถให้การวินิจฉัยโรคนี้ โดยพิจารณาจากลักษณะทางอัลตราซาวนด์สูงถึงร้อยละ 86 การใช้เข็มเจาะดูดเนื้อเยื่อเพื่อส่งตรวจทางเซลล์วิทยา เหมาะสมสำหรับเนื้องอก GIST ที่มีขนาดใหญ่เท่านั้น ส่วนเนื้องอก GIST ที่มีขนาดเล็กกว่า 3 เซนติเมตร แนะนำให้ตรวจติดตามใน 1 ปี