Original Research Article

Preoperative Diagnosis of Upper Gastrointestinal Leiomyoma by Endoscopic Ultrasound-Guided Fine Needle Aspiration

ABSTRACT

Aims: To evaluate the role of endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) with using immunohistochemical analysis in the preoperative diagnosis of upper gastrointestinal leiomyoma.

Study design: This was 'prospective' observational study.

Place and Duration of Study: Department of surgery №1, Vinnytsia National Pirogov Medical University, Vinnytsia, Ukraine; between September 2016 and February 2019.

Methodology: sixteen prospectively studies have been performed using endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) in patients with submucosal hypoechoic tumors (according to the results of previous gastroduodenoscopy) with continuity to proper muscle layer suspected as leiomyoma of upper gastrointestinal tract. All cases for the final diagnosis underwent surgery (n = 16). Additionally, immunophenotyping of specimens obtained by EUS-FNA and surgical resection specimens have been compared.

Results: The puncture has been performed in all patients without any anatomical problems. The collection rate of adequate specimens from the GI tract subepithelial hypoechoic tumor with continuity to proper muscle layer was 87, 5%. The diagnostic rate for the tumor less than 2 cm, 2 to 4 cm, and 4 cm or more were 77, 8%, 100% and 100% respectively. In 16 surgically resected cases, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of EUS-FNA using immunohistochemical analysis of leiomyoma were 100%; 83,3%; 90,9%; 100% and 93,75% respectively. No major complications were encountered.

Conclusion: EUS-FNA with immunohistochemical analysis is a safe and accurate method in the preoperative diagnosis of gastrointestinal leiomyoma. It should be taken into consideration in decision making, especially in early diagnosis following minimal invasive surgery for gastrointestinal leiomyoma.

Keywords: Gastrointestinal leiomyoma, Endoscopic ultrasound-guided fine needle aspiration, Immunohistochemical analysis, Gastrointestinal stromal tumor.

1. INTRODUCTION

Leiomyomas of the gastrointestinal tract (GI tract) were selected as a separate group of non-epithelial benign tumors in 1983. The tumors of this group have specific histological and immunohistochemical features. Leiomyomas are the most common benign non-epithelial tumors of the GI tract, and according to various literary references, compose up to 75% of them in the esophagus, up to 56% in the stomach, and up to 48% in the duodenum [1-4]. Macroscopically, the tumor grows in the form of a spherical node, originating from the mucosal muscular plate or from the muscularis propria of the wall of the gastrointestinal tube. However, not all tumors of the GI tract, which originate from the muscular layer of the wall, are leiomyomas and have a benign nature of the disease. Among such tumors are a

gastrointestinal stromal tumor (GIST), leiomyosarcomas, neurofibromas, adenocarcinomas, and others. Therefore, it is very important to establish the accurate pathohistological diagnosis for the proper medical treatment and the choice of optimal options of surgical intervention in various diseases. This problem stays especially relevant for the preoperative diagnosis of GIST and leiomyomas [5-9]. Performing an ordinary endoscopic study with using forceps biopsy is often non-informative, because the submucosal tumors (SMT) of the GI tract are usually covered with a normal mucous membrane, and this fact prevent the right selection of informative biological material for the study of deeply placed tissues [10].

The data from previous studies indicate, that endoscopic ultrasonography (EUS) allows intramural imaging of the GI tract, and is useful both for the diagnosis of various SMTs, and for the differential diagnosis of SMT with extraluminal lesions of the gastrointestinal tract [11-16]. However, the diagnosis on the basis of EUS is preliminary and cannot compete in accuracy with the final diagnosis on the basis of histological and immunohistochemical results. Thus, the final differential diagnosis of SMT of the GI tract is not possible without performing surgical intervention. Therefore, the search for a less invasive method for establishment the final diagnosis of SMT of GI tract is relevant.

The Endoscopic Ultraosonography-guided Fine Needle Aspiration biopsy (EUS-FNA) has become the minimal invasive technique that allows the identification and differentiation of various types of submucosal neoplasms of the GI tract [17-26]. In accordance to the current requirements for final diagnosis, the diagnosis of leiomyomas of GI tract should be based on immunohistochemical analysis results. It is the best method that allows establishing the accurate final diagnosis.

We here attempted to determine the diagnostic value of the Endoscopic Ultraosonography-guided Fine Needle Aspiration biopsy (EUS-FNA) with using immunohistochemical analysis for preoperative diagnosis of GI tract leiomyomas.

2. MATERIAL AND METHODS

From September 2016 to February 2019, 16 prospectively diagnostic studies using endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) were performed in patients with suspicion of subepithelial gastrointestinal neoplasms (based on previous endoscopy).

These were patients with subepithelial hypoechoic tumors, located in the second or fourth endosonographic layers of the gastrointestinal wall, homogeneous, with well-defined edges, and without signs of malignancy (according to endosonography). There were 9 women (56%) and 7 men (44%). The average age of patients was 56 years (from 31 to 80 years). The informed written consent for the study and treatment was obtained from all the patients.

Diagnostic Endoscopic Ultrasonography-guided Fine Needle Aspiration (EUS-FNA) was performed on an outpatient's basis, in a private diagnostic center. First, with the patient under conscious sedation, a standard endoscopic sonography was performed using conventional radial scanner echoendoscope GF-UM20 (Olympus, Tokyo, Japan). EUS-FNA was performed on a one-day inpatient basis, with conscious sedation, using the GF-UCT160P-OL5 convex array echoendoscope (Fig. 1).

The echoendoscope was connected to a Toshiba ultrasound scanner SSA-550A (Toshiba, Tokyo, Japan). Color flow and Doppler sonography were performed to exclude intervening vascular structures and to select a vessel-free needle track. All FNA procedures were

performed using the Olympus needle (NA-11J-KB) consisting of a 180 cm long steel needle 0.8 mm in diameter (22 G), with a stylet passing through a metal catheter with an outer diameter of 1.6 mm. The needle was inserted into the working channel of the echoendoscope. Once the tip of the catheter was visualized, the needle was advanced from the catheter sheath through the wall of the GI tract and into the target lesion under ultrasonographic guidance (Fig. 2). After that the stylet was removed and continuous suction applied with a 20-mL syringe. The needle was moved back and forth within the lesion under ultrasonographic guidance. When a sufficient amount of biological material was selected, the suction was then released and the needle removed from the biopsy channel. The aspirates were placed on glass slides, and both air-dried and alcohol-fixed smears were prepared. The air dried smears were stained with a modified Giemsa stain and reviewed immediately by a cytopathologist on site to ensure specimen adequacy. All received biological samples were sent to the pathology laboratory for further evaluation using histological and immunohistochemical methods.

Another group of histological specimens obtained later during operative intervention was also sent to the pathology laboratory for their evaluation by the same methods of diagnosis.

Both the EUS-FNA and surgical resection specimens were fixed in 10% formaldehyde, the volume of which was 10-20 folds larger than the volume of the placed material, and left to fix for at least 48 hours. Then, the tissue blocks were embedded in paraffin. The prepared sections thicknesses of 5-7 μm were stained with hematoxylin-eosin and by Van Gieson. The histologic study of leiomyomas was performed using an ocular micrometer by OLYMPUS BX41 light microscope with magnifications of 100, 200 and 400 power.

The polymer method was used for immunohistochemical staining with the following antibodies: c-kit (polyclonal, 1: 200; Dako North America Inc., Carpenteria CA, USA), CD34 (QBend 10, monoclonal, 1: 100; Novocastra, Benton Lane, UK); smooth muscle actin (1A4, monoclonal, 1: 100; Dako A / S, Glostrup, Denmark), S-100 (polyclonal, 1:12; Dako A / S, Glostrup, Denmark). A tumor with a positive response to c-kit and / or CD34 was diagnosed as GIST. A tumor with a negative reaction to c-kit, CD34, S-100, and positive for SMA was diagnosed as leiomyoma. EUS-FNA diagnoses obtained by using immunohistochemical analysis were analyzed for the correlation with final diagnoses, which were based on the results of an immunohistochemical examination of surgically resected pathology materials.

Fig. 1. Echoendoscope GF-UCT160P-OL5

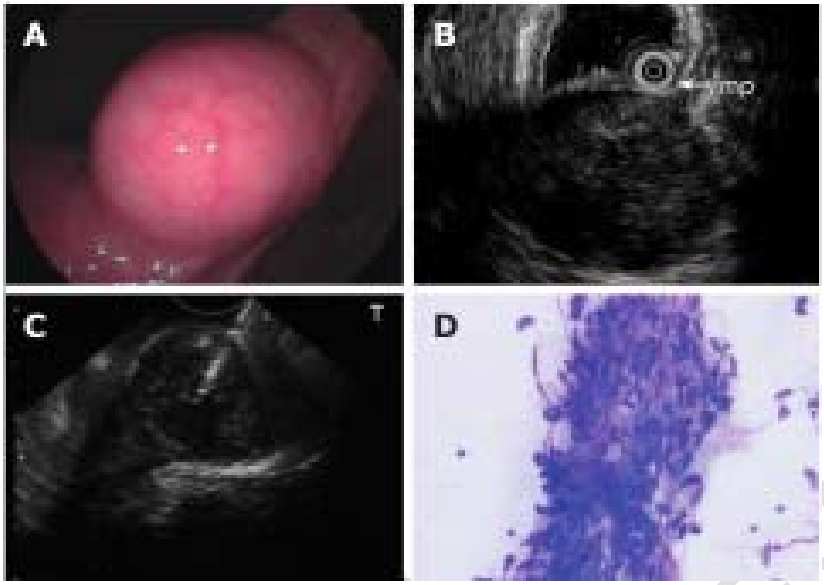

Fig. 2. Steps of the EUS-FNA study: A: Submucosal lesion in the angulus of the stomach shown on endoscopy; B: EUS using ultrasound catheter probe reveals 3 cm subepithelial hypoechoic tumor with continuity to proper muscle layer (arrow-mp); C: Puncture of submucosal lesion under direct endosonographic visualization. The needle can be visualized; D: EUS-FNA smear, showing a small tissue fragment composed of ovoid to spindle-shaped nuclei without signs of atypia (modified Giemsa stain).

3. RESULTS

All the patients in our study group have been diagnosed with SMT of the GI tract according to the results of previous gastroduodenoscopy, that had prompted their referral for EUS-FNA for tissue diagnosis. The anatomical localization of subepithelial tumors of the GI tract of 16 patientsare is summarized in Table 1. The puncture was performed in all 16 patients; there were no anatomical impediments to its execution. The collection rate of adequate specimens was 87.5% (14/16). When the selected specimen was recognized as non-informative, the puncture was repeated. We encountered no complications associated with this procedure. The diagnostic rate of EUS-FNA, according to the tumor size is shown in Table 2. When the size of the tumors was classified into three grades, depending on their size (the interval between the grades sizes was 2-cm), a clear statistical trend was observed: the larger the size of the tumor, the higher the rate of diagnosis. For tumors, with size less than 2 cm, the diagnostic rate was 77.8% (the number of informative specimens, that were obtained at the first attempt of a puncture in one patient). When the size of the tumor was greater than 2cm, the diagnostic rate for them was 100%. After performing EUS-FNA, all the patients in the study group had undergone surgical interventions. Table 3 shows all types of surgical interventions performed in patients of our study group. The results of the immunohistochemical analysis of specimens, obtained by EUS-FNA compared with the results of immunohistochemical analysis of specimens, obtained after surgical resections are shown in Table 4. According to the obtained results, the effectiveness value of using a research method such as EUS-FNA in the diagnosis of leiomyoma of the GI tract was

determined. The distribution of the results of the study is reflected in the table 5. Calculated the rates of diagnostic sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of this method of study. The overall diagnostic accuracy of EUS-FNA using immunohistochemical analysis of leiomyoma of the GI tract was 93.75%, diagnostic sensitivity was 100%, diagnostic specificity was 83.3%, positive predictive value was 90.9%, negative predictive value was 100 %.

Table 1. Anatomical localization of subepithelial tumors of the gastrointestinal tract in patients our study group according to endosonography

Anatomical localization of tumors	Number (Total = 16)	Percentage ratio
Esophagus	8	50%
stomach	7	43.75%
duodenum	1	6.25%

Table 2. Diagnostic rate according to tumor size

Tumor size	Diagnostic rate, n (%)
0-2 см	5/7 (77,8%)
2-4 см	6/6 (100%)
> 4 см	3/3 (100%)
Total diagnostic rate (%)	14/16 (87,5%)

Table 3. Types of surgical interventions performed in patients study group (n = 16)

Type of surgical interventions	Number of performed surgical interventions
Submucosal endoscopic dissection of esophageal leiomyomas	5
Thoracoscopic enucleation of esophageal leiomyomas	2
Laparoscopic proximal resection of the stomach	1

Laparoscopic enucleation of leiomyomas of the stomach	2
Laparoscopic sectoral resection of the stomach	3
Resection of the stomach by Billroth II	2
Resection of the duodenum with Roux-en-Y gastro-entero anastomosis	1

Table 4. The results of immunohistochemical analysis of biological specimens

Biological specimens, obtained via EUS-FNA		Biological specimens, obtained by surgical resection	
Leiomyoma	11	Leiomyoma	10
GIST	4	GIST	5
schwannoma	1	schwannoma	1

Table 5. Leiomyoma diagnosis using EUS-FNA with immunohistochemical analysis among other subepithelial tumors of gastrointestinal tract (n = 16)

Surgical resection with immunohistochemical analysis	EUS-FNA with immunohistochemical analysis	
	Leiomyoma	Other subepithelial tumors
Leiomyoma	10	0
Other subepithelial tumors	1	5

4. DISCUSSION

Gastrointestinal Leiomyomas remain among the least studied benign non-epithelial neoplasms. The rarity of this pathology does not allow us to accumulate enough information to determine the precise tactics of diagnosis and treatment of this type of tumors [1-3]. In addition, leiomyomas should be differentiated with other submucosal lesions of the gastrointestinal tract, especially with GIST, because, despite of similarity in these two types of tumors, GIST is a potentially malignant tumor, and the management for these two diseases will be different [4-5]. The problem of the final identification of GISTs and their differential diagnosis with leiomyoma was finally facilitated with the onset of using the immunohistochemical method. This method identifies the c-kit proto-oncogene product, which is overexpressed in nearly all GISTs and distinguishes these neoplasms from leiomyomas, leiomyosarcomas, lipomas, schwannomas, or other GI tumors [6-9].

Since all these tumors have submucosal location in the gastrointestinal wall, accurate diagnosis with using of a conventional endoscopic study is not possible. Since the endosonography has begun to be used as a diagnostic method in clinical practice, the diagnostic situation with SMTs of the GI tract, in particular leiomyomas, has changed significantly [10]. By performing endosonography, the five-layer structure of the GI tract wall is clearly visualized. According to various endosonographic imaging, we can predict the nature of submucosal neoplasm; determine its size and level of its origin [11-12]. At the endosonographic study, leiomyoma looks like a homogeneous hypoechoic lesion, with well-defined edges, which derives from the second or fourth endosonographic layers (Fig. 3). According to literature data [10-16], the diagnostic specificity of the endosonography for the gastrointestinal tract exceeds other noninvasive imaging methods, such as transabdominal ultrasound, radiography and computed tomography of the GI tract.

However, the above mentioned submucosal tumors of the GI tract may have similar echogenic signs and cannot be accurately diagnosed without histological and immunohistochemical examination. Accurate preoperative histological and immunohistochemistry diagnosis [5-9] can directly influence the choice of treatment for these diseases. All non-invasive diagnostic methods do not allow establishing the precise pathohistological diagnosis and differentiating GIST from gastrointestinal leiomyoma. Even those non-invasive diagnostic methods, criteria of which demonstrate the best correlation help only to predict the nature of the submucosal neoplasm and the degree of its malignancy. For example, endoscopy alone has suboptimal accuracy of as low as 40% for identifying the cause of submucosal bulges [11-13]. Usually the mucosal surface is normal, and conventional forceps biopsy results are frequently negative. Other noninvasive imaging methods such as transabdominal ultrasound and computed tomography are also suboptimal for evaluating submucosal indentations [14].

EUS combines the endoscopic view with ultrasonographic images generated by a high-frequency intraluminal probe. This allows clear imaging of the gastrointestinal wall layers and precise evaluation of the submucosal tumor whether from extrinsic compression or the layer in which the intramural lesion originates. Although EUS provides important morphologic information from submucosal lesions, including some features suggestive of malignancy (size > 3-4 cm, irregular margins, internal echogenic foci or cystic spaces, and rapid growth rate at follow-up EUS) [11-16], this method cannot establish a final pathologic diagnosis.

One of the alternative diagnostic methods in this situation is EUS-FNA, and according to recent studies, this method has been used increasingly for the evaluation of various tumors located in the GI tract [17-20]. Observations to date indicate that EUS-FNA is a safe and accurate diagnostic procedure. However, most of the results of previous studies were related to the diagnosis of pancreatic lesions and lymphadenopathy. In addition, the diagnostic value of EUS-FNA for the diagnosis of leiomyoma of the GIT was not determined in previous studies [21-26]. The ability to determine the level of origination of gastrointestinal leiomyomas using endosonography will directly affect the surgical treatment options, which

will be different at various localization of this type of tumors. Typically, leiomyoma, which originates from the muscular plate of the mucosal membrane, can be treated by endoscopic resection, while such a method of treatment is contraindicated for leiomyomas, which originate from the muscularis propria of the hollow organ's wall. Incorrectly chosen surgery can lead to perforation of the GI tract [27-32].

In our study, 5 patients with leiomyomas of the esophagus, which derived from the mucosal muscular plate, were operated. Complications, such as bleeding or perforation of the wall did not occur. This indicates that endosonography is very useful for the choice of technique and options of surgical intervention for patients with gastrointestinal leiomyomas. This method makes the treatment of gastrointestinal leiomyomas more safe, rational and economic.

In our study, the collection rate of adequate specimens from a GI tract subepithelial hypoechoic tumor using EUS-FNA was 87.5%. The diagnostic rate of this method of study, depending on the size of the tumor, was 77.8% for tumors less than 2 cm and 100% for neoplasms with size greater than 2 cm. The overall diagnostic accuracy of EUS-FNA using immunohistochemical analysis of leiomyoma of the GI tract was 93.75%, compared with the immunohistochemical results of surgically resected specimens. According to previous studies, accuracy of preoperative diagnosis of EUS-FNA using immunohistochemical analysis ranged from 91% to 100% [17-26], which coincides with the data of our study. This method allows precise preoperative and differential diagnosis of submucosal tumors of the GI tract, which facilitates the choice of the optimal treatment and surgical option management.

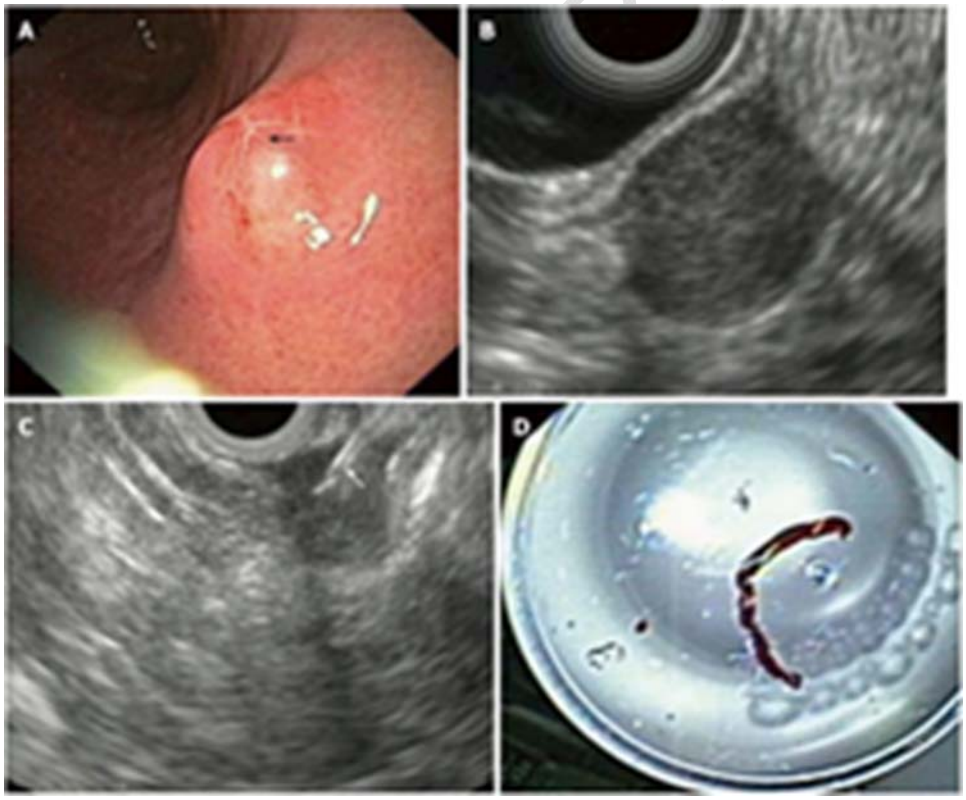

Fig. 3. EUS-FNA leiomyoma of the stomach. A- appearance of leiomyomas in the stomach during endoscopic examination; B- EUS- visualization of the lesion, which is located in the fourth endosonographic layer of the stomach wall; C- EUS-FNA of lesion, needle marked with arrow; D- histological specimen of EUS-FNA.

5. CONCLUSION

Our study confirms the important role of EUS-FNA using immunohistochemical assays to evaluate submucosal lesions of the gastrointestinal tract. This technique is absolutely safe and according to its results, the treatment tactics and the planned surgical management options can be considerably altered. Also, according to EUS-FNA results using immunohistochemical analysis, it is possible to establish a final pathologic diagnosis without performing surgical resection, which is important for oncologists before any chemotherapy, radiation therapy, and palliative treatment.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

CONSENT

Informed consents have been sought and obtained from all the patients.

ETHICAL APPROVAL

Ethical approval has been obtained from institutional and university ethical research cell committee.

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