EDITORIAL

Diagnosis of subepithelial lesions: Should we rest on pieces?

Often unexpectedly detected during a routine endoscopy, subepithelial lesions (SELs) are protruding lesions arising from the muscularis mucosa, submucosa, or muscularis propria covered with a normal mucosal surface. The differential diagnosis of such protruding lesions includes a broad range of entities, including stromal tumors, duplication cyst, lipoma, varix, pancreatic rest, and extrinsic compression from normal and abnormal structures.[1] Most commonly found in the stomach, SELs, for a long time, seemed to be innocent and harmless findings.[2] However, occasionally evolving with bleeding, obstruction, or metastases, among other features, they uncover their bad side, imposing further investigation and invasive management. Although some endoscopic features such as size, location, shape, firmness, and color may suggest a possible tumor as the cause, an accurate but sometimes burdensome histopathologic diagnosis is frequently necessary to enable the choice of the best strategy among ignorance, resection, or surveillance. Although most of these tumors have a benign behavior, the unsuspected appearance of some may mislead our clinical judgment and guard potentially malignant SELs against being appropriately treated. The risky SELs are GI stromal tumors, neuroendocrine tumors, and lymphomas, among others.[3] In the past, endoscopists struggled with distinct diagnostic limitations for the elucidation of SELs, given the few options of endoscopic sampling techniques, the absence of well-defined pathologic diagnostic criteria, and the lack of a specific code in the International Classification of Diseases system, hindering earlier tumor characterization and epidemiologic profiling.[3] In small lesions (<2 cm in diameter), this task might be more challenging, promoting innovation of technologies on one side (which is good!) and predisposing patients to unnecessary surgery on the other (which is not good!). By revisiting the diagnostic problem of GI SELs in this issue of *Gastrointestinal Endoscopy*, Facciorusso et al[4] prompted us to ask this question: With which procedure/method should we proceed for a further investigation?

EUS can elegantly investigate lesions through the GI wall and may identify the already-described worrisome endosonographic characteristics (eg, >3 cm hypoechoic masses arising from the fourth hypoechoic layer with inhomogeneous echogenicity, cystic spaces, and irregular margins).[5] Contrast-harmonic EUS may add promising advanced imaging to the differential diagnosis of SELs. Nevertheless, the still-limited experience and availability of contrast-harmonic EUS restrict its use as a reliable replacement for tissue diagnosis. Therefore, the need to predict the clinical behavior of SELs paves the way to tumor risk group stratification for malignancy, matching tumor size and mitotic rate.[6] Beyond defining the origin of tumor cells and grade differentiation, in the targeted drug therapy era, enriching our knowledge with protein expression and molecular profile is becoming imperative.[7] Thus, for SELs with nondiagnostic endoscopic and EUS appearance, tissue sampling and adequacy are crucial. EUS-guided fine-needle tissue acquisition techniques, either standard EUS-FNA or the more recent EUS fine-needle biopsy (EUS-FNB), aim to promote a broader understanding of the clinical characteristics and biologic aggressiveness of these tumors.

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Is there any difference in choosing between biopsy and aspiration when dealing with SELs? Because SELs are usually rooted in the GI wall, tissue acquisition may be challenging. Many variables play a role in biopsy diagnostic yield (type of lesion, needle characteristics, different techniques to choose, tissue quantity and conservation, on-site interpretation, histopathologic analysis, professional expertise, and sometimes just good luck). Concerning endosonography, whereas FNA counts on its ability to collect fluid and cells for analysis, core needle biopsy trusts fundamentally in its cutting tip capacity to induce columns of tissue to come inside the needle from a suspicious area. After a comprehensive search and a predefined data extraction strategy, Facciorusso et al[4] systematically compared the performance of EUS-FNB with that of EUS-FNA, enrolling 10 recent studies. The authors took appropriate meta-analysis cautions, including directly contacting the authors of the primary studies and requalifying them. By focusing primarily on sample adequacy, they looked for the optimal

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EUS-guided sampling technique for SELs. Going through optimal histologic core sample, diagnostic accuracy, number of needle passes needed to obtain an adequate sample, and procedure safety investigations, the take-home message of the study is to use preferably EUS-FNB or EUS-FNA with an onsite pathologist for rapid on-site evaluation to define the cause of SELs.

Furthermore, because meta-analysis combines studies considered to have similar characteristics so as to reveal an estimate of effect that has clinical relevance (eg, EUS-FNB diagnostic yield), the findings of a high inconsistency rate (high I2 value) from their fewer EUS-FNB needle passes needed to obtain adequate samples analysis probably reveals the "invisible" differences between the included studies. Although the calculation of heterogeneity is crucial for assessing the confidence of their results found, this high inconsistency rate advises us to question the methodology applied to this issue in the study by Facciorusso et al.[4]

Despite the very interesting conclusions, the authors adequately acknowledged the low number of included studies and enrolled patients, and the lack of individual patient's data supporting subgroup analysis (eg, location of the sampled lesion, and specific technical characteristics such as use of stylet, fanning, or slow-pull technique) among the limitations. Besides concerning peculiar study methods, we may consider whether their results, based on the comparison of 1 predominant type of beveled-tip needle against the fewer amount of the more recently developed needles, are reproducible in future studies. So, with the seemingly inexorable trend of endosonographic tissue acquisition moving from FNA to FNB, given that technologic developments have gone so far, concerning the diagnosis of SELs, should we rest in peace with the conclusions of Facciorusso et al,[4] or are there still any other diagnostic scenarios to be considered?

Keeping an eye on advanced endoscopic procedures, which may enable complete removal of such lesions instead of grasping a piece of them, we may add endoscopic submucosal resection (ESMR), endoscopic submucosal dissection (ESD), and submucosal tunneling with endoscopic resection (STER) techniques, particularly the last because it may represent a promising treatment for SELs.

Derived from the technique of EMR, and with the use of a standard snare, a transparent cap, or a ligation device method, ESMR may promote the excision and treatment of small SELs (<20 mm) arising in the muscularis mucosa or submucosa layers. Reported to have a significantly higher diagnostic yield compared with the bite-on-bite technique, although manageable endoscopic adverse events may occur, its application requires special attention for lesions developing in the muscularis propria because of the risk of perforation, tumor spillage, and incomplete resection.[8] Having in common with ESMR the rupture of the mucosal layer, ESD (also known as endoscopic enucleation, endoscopic submucosal excavation, or endoscopic muscularis dissection) is applied for either diagnostic or therapeutic removal of deeper SELs (eg, gastric muscularis propria). With higher complete resection rates, the technique is challenging, is time-consuming, requires adequate selection of cases (not suitable for lesions >5 cm), and has a particular risk of perforation (19%), among other inherent adverse events. Therefore, its indication remains debated.[8]

Addressing the exciting role of third-space endoscopy in the management of SELs, STER, a fundamentally different technique from the above-mentioned minimally invasive procedures, is a novel method that permits submucosal access to the removal of GI SELs. Based on the per-oral endoscopic myotomy technique, its principal advantage consists in maintenance of the overlying mucosal layer, the integrity of which may reduce the risk of postoperative adverse events. Other benefits may include shorter operative times and lengths of postsurgery hospital stay.[9] Although a recent review registered an en bloc resection rate of 94.6% for upper GI lesions arising from the muscularis propria layer and no tumor recurrence during the follow-up period,[10] similar to ESD learning, it is wiser to be aware of the difficulty and time required to learn STER and of the technical limitations of the staff. Give that the technique is evolving, it is advisable to conduct more extensive and long-term comparative studies in highly specialized endoscopic centers to properly elucidate the clinical indications for STER and acquire more experience with it.

So finally, even though EUS-FNB seems to be the present best choice for establishing a definitive histopathologic diagnosis for SELs, and STER seems to offer definitive resection, the most important question remains: How can we really determine which lesion, especially a small and asymptomatic one, requires resection and should not be followed up clinically?

DISCLOSURE

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Abbreviations: ESD, endoscopic submucosal dissection; ESMR, endoscopic submucosal resection; EUS-FNB, EUS fine-needle biopsy; SEL, subepithelial lesion; STER, submucosal tunneling with endoscopic resection.

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