EDITORIAL

Cyst wall brushing. Exploring the limits of cytology

With the increasingly widespread use of imaging techniques pancreatic cystic lesions (PCLs) are now commonly identified. Their prevalence among the symptom-free population ranges from 2.4% to 13.5% (1). However, a recent study by our group revealed PCLs in up to 21.5% of patients undergoing endoscopic ultrasound (EUS) for non-pancreas conditions, an incidence that increases with age (2). Identifying PCLs in an otherwise asymptomatic population has become a significant clinical issue.

PCLs represent a heterogeneous group of lesions that includes benign, premalignant and malignant conditions. Premalignant lesions include two primary precursors to pancreatic cancer –intraductal papillary-mucinous tumor (IPMT) and mucinous cystic neoplasm (MCN) (3). Therefore, it is essential that PCLs be correctly diagnosed. On the one hand, this offers an opportunity to reduce mortality from pancreatic cancer, which has remained stable for the last 20 years (4); on the other hand, it may help avoid follow-up for benign cysts, which may flood and overload the health system given the present, notable increase in their diagnosis.

For years EUS has been the most accurate diagnostic method in assessing the pancreas. In a prospective study comparing pancreas protocol computerized tomography (CT), secretin-enhanced magnetic resonance imaging (MRI), and EUS as screening tools for individuals at high risk for pancreatic cancer, pancreatic lesions –mainly cysts– were identified in 11%, 33.3%, and 42.6% of cases, respectively (5).

However, while EUS-FNA achieves a high diagnostic yield in the histological diagnosis of solid pancreatic lesions, its yield is much lower for PCLs, with a sensitivity of 54% and a specificity of 93% for the detection of mucinous lesions (6). This results from low cellularity in the cyst fluid, small aspirate volume regarding most cysts, and contamination with cells from the gastrointestinal tract. In an attempt to improve this low yield of EUS-FNA in the diagnosis of PCLs, in the present issue of *The Spanish Journal of Gastroenterology (Revista Española de Enfermedades Digestivas)* Lariño-Noia et al. (7) report a study on the role of cyst wall brushing by introducing a cytology brush (EchoBrush™, Cook®) through a 19G needle. This was a prospective, randomized, multicenter study to compare the diagnostic yield of cyst wall brushing with EchoBrush™ (EB) versus conventional EUS-FNA. Of 69 patients who were assessed 65 were eventually randomized: 31 in the EB group, 34 in the EUS-FNA group. Most lesions were IPMTs (47.6%), although only 13 (20.6%) cases were confirmed as such on the surgical specimen, which represents a significant bias. Albeit the study specified a minimum follow-up of five years, this period may well be short for the development of symptoms or significant lesions from smaller cysts, particularly for the progression of side-branch IPMT without baseline risk criteria (8). For three patients in the EB group the procedure could not be carried out because of failed cyst puncture using the 19G needle in one case, and inability to advance the brush through the needle in two cases. This amounts to technique failure in 9.7% of cases. Furthermore, diagnostic yield did not differ between groups, neither per protocol nor in the intention to treat analysis (38.4% *vs.* 45.9%, p = 0.55; 44.8% *vs.* 41.1%, p = 0.77, respectively), but samples obtained with the EchoBrush™ had greater cellularity.

Several prior studies assessed the role of EchoBrush™ in the diagnosis of pancreatic cysts, and obtained both positive and negative results (9-12). However, they exhibit methodological and technical differences that may account for discrepancies. In both the study by Sendino (9) and the study by Al-Haddad (11) the authors performed cyst aspiration before introducing the brush, which ensures greater contact of the brush with the cyst wall. Furthermore, in the study by Lozano et al. (10), brush rotation movements were also used, which seems more appropriate to ensure contact between the brush and the cyst wall. In these three studies EchoBrush™ was superior to FNA, particularly for the diagnosis of mucinous lesions. However, in the study by Thomas (12) and the study by Lariño-Noia et al. (7), push and pull maneuvers were used without prior cyst content aspiration, and results were similar to those of FNA. Pushing and pulling a cytology brush on a curved cyst wall is technically challenging, if not impossible, particularly concerning smaller cysts; even more so when brush design, which includes a blunt metal tip 2 mm in length, is taken into account. From a conceptual standpoint, complete aspiration of cyst contents prior to brush introduction with collapsed walls seems clearly superior for ensuring that greater numbers of cells are taken up by the brush. However, complications seem more common with this approach (9), whereas no adverse events occurred in the study by Lariño-Noia.

Another aspect to be considered is the way of recovering the sample obtained by the brush. It seems advisable that, once the cyst wall has been brushed, the brush be tucked away into the needle and, once the needle is withdrawn, advance the brush out of it in order to prepare smears for microscopic study (9). Removing the cytology brush through the needle, rather than withdrawing the needle with the brush inside, may lead to partial sample loss from friction between the brush and the needle wall, which may account for the absence of positive results in the study by Lariño-Noia.

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Other concerns involve the study design. Although this is a randomized study, the groups included are not comparable. The EB group includes significantly larger cysts, with wall nodules, that less commonly involve the head of the pancreas, hence there is a potential selection bias.

The conflicting results of studies dealing with cyst wall brushing, and concerns regarding the safety of this technique, arising from reports of fatal complications (9), have restricted its use. A step beyond the collection of cytology specimens by scraping a cyst wall would be directly obtaining wall biopsy samples by using a through-the-needle microforceps. In this regard, our team demonstrated the feasibility of this technique in a pilot study where a 0.8-mm biopsy forceps was introduced through a 19G needle. Recent studies using a specifically designed microforceps (Moray™ *micro forceps, US endoscopy*) have shown excellent results with a fine safety profile (13-16). The technique also allows histological testing, far superior to cytology for reaching a correct diagnosis. The procedure is simple and reproducible, but puncturing with a 19G needle, and introducing the forceps in cysts located in the head of the pancreas may be challenging. Confocal microscopy has also been assessed in the diagnosis of pancreatic cysts (17). While results are promising, its widespread use in daily practice seems unlikely, mainly because of high equipment costs.

To conclude, PCLs repesent a diagnostic challenge and an opportunity to reduce mortality from pancreatic cancer. However, currently avaiable diagnostic modalities are a long way off perfection. Cyst wall brushing cytology does not seem to be a difference-making technique in this setting. As of today, intracystic biopsy with through-the-needle microforceps is likely the most appropriate approach to the accurate diagnosis of PCLs. However, as-yet-unavailable randomized studies remain necessary.

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