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Editorial

Precision in practice: The diagnostic yield of endoscopic ultrasound guided fine needle aspiration/fine needle biopsy cytology in pancreatic mass lesions

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Dear Editor,

The shift to personalized medicine has elevated the role of invasive sampling, making it essential for both cytopathological diagnosis and the development of targeted treatment plans. Diagnostics in pancreatobiliary diseases necessitate a multidisciplinary approach, with pathologists playing a crucial role in cytological diagnosis. The preferred diagnostic modality is endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA).[1] A confirmed pathological diagnosis is a prerequisite for informed decisions regarding either palliative care for unresectable disease or pre-operative chemotherapy aimed at downstaging the tumor for potential surgical resection.[2] While EUS is widely regarded as the optimal modality for identifying pancreatic neoplasms, the results it yields are not always conclusive.[3] For the cytological diagnosis of solid pancreatic masses, EUS-FNA is a highly effective and rapid method with documented high performance. It boasts a sensitivity ranging from 78% to 95%, a specificity of 75% to 100%, and an accuracy rate between 78% and 95%.[4] Despite its long-standing use in diagnosing intra-abdominal and intrathoracic pathologies since the 1990s, EUS-FNA continues to be challenged by a notable incidence of false-negative outcomes. The reported rates range from 4% to 45% for solid pancreatic masses and 21–53% for cystic lesions.[5] False-negative cytological diagnoses frequently arise from sampling errors, which can be attributed to the endosonographer's technique, suboptimal characteristics of the target lesion, or misinterpretation during the on-site cytology review.[5] A study of 554 lesions in 454 patients who underwent EUS-FNA revealed that only five non-fatal complications occurred, including hemorrhage, fever, and perforation. The complication rate was found to be higher in cases involving cystic lesions than in cases involving solid lesions.[6] FNA needles were traditionally used to obtain tissue samples. However, the use of tru-cut biopsy needles (22- and 19-gauge) in EUS-guided fine-needle biopsy (EUS-FNB) enables histological diagnosis rather than cytological diagnosis. This advancement at the cellular level could lead to this diagnostic method being adopted more widely.[7] A study found that an EUS-guided tru-cut biopsy (EUS-TCB) is more effective than an EUS-FNA biopsy. EUS-TCB achieved higher diagnostic accuracy (85% versus 60%) and required fewer needle passes (2.0 vs. 3.3). These results suggest that EUS-TCB is a more efficient method for obtaining diagnostic tissue samples.[7] In a study of EUS-FNA using a standard 22-gauge needle, the length of the core biopsies obtained for histological evaluation was found to be 6.5 ± 5.3 mm. The study also demonstrated that these samples were sufficient for histological diagnosis and more sensitive than cytology.[8] In a study in which a tissue core of at least 550 μm (greatest axis) was considered

positive, the researchers defined "good quality" as one to five core biopsies, and "excellent quality" as more than ten core biopsies.[9] A study of pancreatic and non-pancreatic tissues found that combining FNA and FNB significantly increased the accuracy of pancreatic tissue diagnosis. The respective rates were found to be 77%, 73%, and 91%. The same study showed that, for lesions 2 cm or larger, the combination of the two methods was superior in terms of diagnostic accuracy, sample adequacy, and safety.[10] Percutaneous biopsies have been shown to achieve a diagnostic accuracy rate of between 75.6% and 95.2%. However, they are associated with a higher risk of complications. The utilization of larger needles (20- and 22-gauge) has been demonstrated to elevate the complication rate to 5%, thereby giving rise to concerns regarding bleeding, procedural discomfort, and the potential for tumor seeding throughout the gastrointestinal tract.[11] Pancreatic ductal adenocarcinoma (PDAC) represents the most prevalent form of malignant solid lesion, accounting for approximately 90% of cases [Figure 1a-c]. However, other solid-appearing masses may indicate chronic pancreatitis, pancreatic neuroendocrine tumors, acinar cell carcinoma, pancreatoblastoma, or metastatic tumors. While the majority of cystic lesions are benign, with pseudocysts being the most prevalent, others require meticulous evaluation due to their potential for malignancy.[12] The true value of EUS-FNA/FNB extends beyond traditional diagnosis, as it supplies the material necessary for advanced molecular analysis, which is now essential for personalized medicine. EUS-FNA enables cell blocks (CBs) to be collected, which can be used to establish a cytological diagnosis and increase diagnostic accuracy [Figure 1d-f]. These CBs can also be used to create hematoxylin and eosin sections, as well as for more specialized tests, such as immunohistochemical staining (p53, SMAD4), special histochemical staining, and molecular genetic analyses. The growing acceptance of molecular study results on cytological specimens for clinical use and patient care has significantly increased medical oncologists' interest in EUS-derived materials. These molecular studies are crucial for confirming a diagnosis, guiding prognosis and treatment, and predicting the likelihood of recurrence.[13] Genomic profiling of CBs collected through EUS-FNA is valuable for understanding the molecular basis of a tumor and identifying potential targeted therapies. This is particularly pertinent in the case of PDAC, where next-generation sequencing can reveal a tumor's entire molecular profile using an extensive gene panel. One study found that 55% of PDAC CBs samples contained sufficient nucleic acid for diagnosis, which provided that the CBs contained more than 30% tumor cells. Even samples with low or degraded DNA levels yielded sufficient material for genomic sequencing. The study successfully identified several known pathogenic driver mutations, includingKRAS, TP53, CDKN2A, ATM, PIK3CA,[14] PTPN11, and SMAD4.[15] KRAS (77% to 89%) and TP53 (% 30% to 67%) were the most frequently mutated genes among these.[14,15] Although studies are limited in size and number, they show that molecular

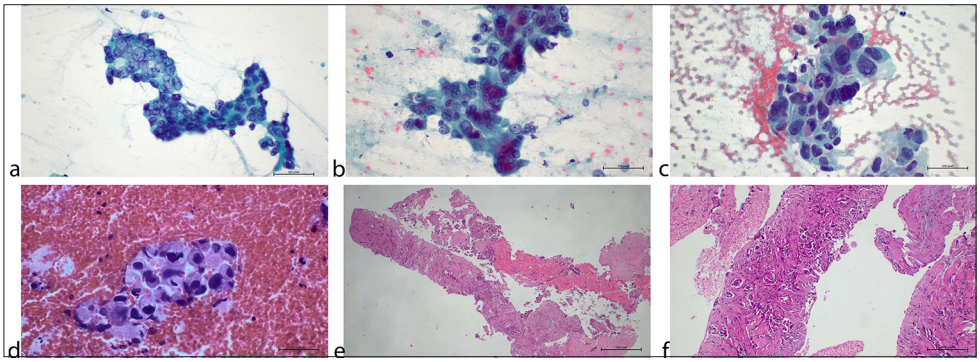

Figure 1: The following are examples of pancreatic EUS-FNA/FNB materials from six different cases. (a-c) This EUS-FNA cytology sample shows characteristic features of pancreatic ductal adenocarcinoma. The direct smear, stained with the Papanicolaou method, reveals markedly pleomorphic and irregular nuclei, as well as significant differences in size (anisokaryosis, 4:1) and irregular nuclear membranes with clefts and notches, chromatin clearing, and clumping (original magnification ×40, objective). (d) Pancreatic ductal adenocarcinoma, cell block. Processing FNA washes and aspirates for a cell block may provide tissue fragments that can support the diagnosis, thus avoiding the need for a repeat biopsy (cell block, hematoxylin and eosin [H&E], ×40, objective. (e) The EUS-FNB sample from pancreatic ductal adenocarcinoma shows clear malignant histology. The core biopsy, measuring 6 micrometers along its greatest axis, provides a sufficient specimen for definitive histological evaluation (H&E stain, ×4, objective). (f) The EUS-FNB sample from pancreatic ductal adenocarcinoma (H&E stain, ×10, objective). EUS-FNA/FNB: endoscopic ultrasound-guided fine-needle aspiration/fine-needle biopsy.

profiling is possible as long as the extracted DNA is of sufficient quality. This suggests that tissue obtained from EUS can be used for diagnosis and the future testing of new biomarkers.[15] Although the use of comprehensive genomic profiling (CGP) analyses for pancreatic cancers using EUS-FNA/FNB samples has increased in recent years, the success rate remains unsatisfactory from a clinical perspective. Clearly, there is still a long way to go to improve these results. CGP analyses using EUS-FNA/FNB samples are also valuable for low-grade neoplasms such as solid-pseudopapillary neoplasms or pancreatic neuroendocrine tumors, not just pancreatic cancer. This allows for personalized, genome-guided treatment options for these less aggressive tumors as well. This means that the importance of CGP analysis will increase even further in the future. To improve the success rate of CGP analysis using EUS-FNA/FNB samples, further research is required into various factors, including the needle thickness used by clinicians, the number of punctures performed, the aspiration method, and the specimen.[16] Although precision medicine for treating PDAC is still in its early stages, genetic analysis of EUS-FNB samples is a key area of focus. This approach is already being used to predict how patients will respond to chemotherapy drugs such as gemcitabine, and to help determine prognosis. With new treatments on the horizon, such as poly(ADP-ribose) polymerase (PARP) inhibitors and immune checkpoint inhibitors, the prognosis for PDAC patients is expected to improve. This makes EUS-FNB an even more critical tool in the age of precision medicine. Endosonographers must now not only collect samples for diagnosis but also actively consider genetic analysis during the procedure.[17-19]

In conclusion, EUS-guided sampling has significantly advanced the diagnosis of pancreatic cancer, providing a valuable resource for cytology, histopathology, and molecular genetic analyses. Combining FNA and FNB to obtain tissue and generate genetic profiles has reduced the workload of clinicians, oncologists, and healthcare providers. This evolution shows that, in the era of personalized medicine, pathologists play a critical role in guiding treatment as well as providing diagnosis. Thus, we are moving toward a future where each sample provides a comprehensive molecular profile, treatments are personalized, and patient success is maximized.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

ABBREVIATIONS

CB: Cell block
EUS: Endoscopic ultrasonography
EUS-FNA: Endoscopic ultrasound-guided-fine-needle aspiration
EUS-FNB: Endoscopic ultrasound-guided fine-needle biopsy
GEM: Gemcitabine
H&E: Hematoxylin and eosin
ICIs: Immune checkpoint inhibitors
NGS: Next-generation sequencing
PARP: Poly(ADP-ribose) polymerase
PARPi: PARP inhibitors
PDAC: Pancreatic ductal adenocarcinoma
SPN: Solid-pseudopapillary neoplasm

AUTHOR CONTRIBUTIONS

AK: Designed and supervised the study. AK, HA, EK, and KÖ: Contributed to preparing the manuscript draft. All authors (AK, HA, EK, and KÖ) conducted the study and contributed to the critical revision of the manuscript for important intellectual content. All authors read, approved, and agreed to be accountable for all aspects of the final version to be published and met the ICMJE authorship requirements.

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The authors declare no conflicts of interest.

EDITORIAL/PEER REVIEW

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