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EUS – Fine- Needle Aspiration Biopsy (FNAB) in the Diagnosis of Pancreatic Adenocarcinoma: A Review

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Solid masses of the pancreas represent a variety of benign and malignant neoplasms of the exocrine and endocrine tissues of the pancreas. A tissue diagnosis is often required to direct therapy in the face of uncertain diagnosis or if the patient is not a surgical candidate either due to advanced disease or comorbidities. Endoscopic ultrasound (EUS) is a relatively new technology that employs endoscopy and high-frequency ultrasound (US). EUS involves imaging of the pancreatic head and the uncinate from the duodenum and imaging of the body and tail from the stomach. It has been shown to be a highly sensitive method for the detection of pancreatic masses. It is superior to extracorporeal US and computed tomographic (CT) scans, especially when the pancreatic tumor is smaller than 2–3 cm. Although EUS is highly sensitive in detecting pancreatic solid masses, its ability to differentiate between inflammatory masses and malignant disease is limited. Endoscopic retrograde cholangio-pancreatography (ERCP) brushing, CT-guided biopsies, and transabdominal ultrasound (US) have been the standard nonsurgical methods for obtaining a tissue diagnosis of pancreatic lesions, but a substantial false-negative rate has been reported. Transabdominal US-guided fine-needle aspiration biopsy (US-FNAB) has been used for tissue diagnosis in patients with suspected pancreatic carcinoma. It has been shown to be highly specific, with no false-positive diagnoses. With the advent of curvilinear echoendoscopes, transgastric and transduodenal EUS-FNAB of the pancreas have become a reality EUS with FNAB has revolutionized the ability to diagnose and stage cancers of the gastrointestinal tract and assess the pancreas. Gastrointestinal cancers can be looked at with EUS and their depth of penetration into the intestinal wall can be determined. Any suspicious appearing lymph nodes can be biopsied using EUS/FNAB. The pancreas is another organ that is well visualized with EUS. Abnormalities such as tumors and cysts of the pancreas can be carefully evaluated using EUS and then biopsied with FNAB. There are many new applications of EUS using FNAB. Researchers are looking to deliver chemotherapeutics into small pancreatic cancers and cysts. Nerve blocks using EUS/FNAB to inject numbing medicines into the celiac ganglia, a major nerve cluster, are now routinely performed in patients with pain due to pancreatic cancer. The aim of this study is to perform a review of the literature regarding the usefulness of EUS/FNAB in the diagnosis of pancreatic adenocarcinoma.

Key words: Pancreas, Pancreatic ductal adenocarcinoma, FNAB, cytology, immuno-cytochemistry.

INTRODUCTION

EUS-with FNAB has become an important technique of gastroenterologists for the diagnosis of pancreatic adenocarcinoma before chemotherapy and / or surgery. EUS alone is limited in its ability to discriminate between malignant and benign processes. EUS-FNAB, with its ability to obtain a tissue diagnosis, has increased the accuracy of EUS in the diagnosis of pancreatic adenocarcinoma. The sensitivity, specificity, and accuracy of EUS-FNAB for pancreatic lesions range from 64% to 94%, 71% to 100% and 78% to 95% respectively [1-6] Thirty-three studies published between 1997-2009 with 4984 patients were included, as the pool sensitivity for malignant cytology was 85% and pooled specificity was 98%. If atypical and suspicious cytology results were included to determine true neoplasms, the sensitivity increased to 91%. The diagnostic accuracy of EUS-FNAB was enhanced in prospective, multicenter studies and demonstrates that EUS-FNAB is a highly accurate diagnostic test for solid neoplasms of the pancreas [7]. Pancreatic adenocarcinoma is a significant cause of mortality and represents a major healthcare burden world-wide. Pancreatic adenocarcinomas are the fifth leading cause of cancer related death in the USA [8] and the incidence of these tumors continues to rise. The survival rate of patients with these tumors is extremely poor, with an overall 5- year survival rate of less than 5% [9], making it one of the biggest "cancer killers". This poor survival rate largely reflects the late presentation of patients with pancreatic adenocarcinoma and limited treatment

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modalities for advanced disease, the average survival time after diagnosis is only 6 months [10]. Therefore, early and accurate diagnosis is vital for improving the efficacy of therapeutic intervention. Adenocarcinoma was more likely to be present in the head of the pancreas, have lymph node and vascular involvement, as well as evidence of pancreatic duct and common bile duct obstruction.

Surgical resection remains the only potentially curative treatment for pancreatic adenocarcinoma, and yet is still an extremely complex intervention with significant periprocedural morbidity and mortality [11]. Accurate preoperative diagnosis of patients presenting with a pancreatic mass lesion is vital to preventing unnecessary procedures in those with benign disease and to correctly stage individuals with malignant lesions, enabling accurate identification of those who may benefit from surgery [12].

The regional anatomy of the pancreas is complex, making procurement of cytologic samples historically difficult without exploratory laparotomy. Traditionally, computed tomography (CT) or endoscopic ultrasound-guided FNA (EUS-FNA) has been used to obtain biopsies of the pancreas. However, not all lesions are accessible due to surrounding organs and vasculature. Additionally, these techniques are associated with a risk of peritoneal dissemination of cancer cells and have a false-negative rate of up to 20% [13, 14]. Endoscopic retrograde cholangiopancreatography (ERPC) brush cytology has a false-negative rate of at least 30% [15].

EUS was developed in the 1980s to improve the imaging of the pancreas. Traditional transabdominal ultrasound imaging of the pancreas is hampered by intervening bowel gas, bone and fat. By placing a high-frequency transducer directly with the stomach or duodenum lumen, EUS can obtain a detailed image of the pancreas that has a higher resolution than CT scan or magnetic resonance imaging, but with a much narrower field of view. These high-resolution images allow for identification of lesions as 2-3 mm and involvement of adjacent vascular structures [16].

This review specifically addresses the role of EUS-FNAB in the diagnosis and confirmation of pancreatic adenocarcinoma.

REVIEW

Ductal adenocarcinoma of the pancreas (Papanicolaou stain), (Figure 1) and its variants account for more than 90% of pancreatic malignancies. The cytological criteria for the diagnosis of this tumor have been published by Mitchell and Carney in 1985 [17]. They focused on three-dimensional cellular fragments, nuclear enlargement, and nuclear membrane irregularity. Following this publication, several modified cytologic criteria based on those of Mitchell and Carney were reported. Cohen *et al*. [18] identified anisonucleosis, nuclear molding and large nuclei as the significant cytological features for the diagnosis of pancreatic adenocarcinoma.

Robins *et al*. [19] were the first to distinguish major (overlapping nuclei/ crowded groups, nuclear contour irregularity, and chromatic clearing and/or clumping) and minor criteria (single epithelial cells, necrosis, mitosis and nuclear enlargement) for pancreatic adenocarcinoma.

According to Robins *et al*. the sensitivity and specificity for diagnostic pancreatic adenocarcinoma are 100% when two or more major criteria or one major and three minor criteria are identified. Several other authors also considered single epithelial cells, necrosis, mitosis and prominent nucleoli as significant cytologic features [20-22].

Before the published criteria of Mitchell and Carney, Brits and Franz [23] studied a small series of FNAB of pancreas and suggested that pale nodular nuclei were a possible specific marker for pancreatic adenocarcinoma. Pale nodular nuclei were described as homogeneously hypochromatic nuclear chromatin, nuclear membrane irregularity with deep folds, and one or more large eosinophilic nucleoli. Pale nodular nuclei are not diagnostic of pancreatic adenocarcinoma because they are also present in benign pancreatic aspirate specimens as well as in the other types of malignancy, such as melanoma and lung carcinomas.

The cytological diagnosis of poorly differentiated (PDA) or even moderately differentiated adenocarcinoma (MDA) is usually straightforward. The problematic diagnostic cases generally involve well differentiated adenocarcinoma WDA [24].

It is important to recognize that anisonucleosis, nuclear crowding/overlapping, and nuclear membrane irregularity may occur focally in WDA, whereas nuclear enlargement usually involves the entire group of neoplastic ductal epithelial cells. It is also imperative to emphasize that none of those criteria, when present singly, is pathognomonic for WDA. Nuclear enlargement and focal crowding/ overlapping are commonly observed in certain reactive conditions, especially pancreatitis. However, marked anisonucleosis/variation in nuclear size greater than four times in the same epithelial group and nuclear membrane irregularities (deep notch, deep groove, popcorn, or rasinoid) are nearly always absent in reactive conditions. Many tumor-

associated markers have been reported to be useful in the diagnosis of pancreatic adenocarcinoma [25-41]. A recent study [42] investigates the utility of 26 different immunohistochemical markers cytokeratin panel (CAM 5.2, CK7, CK20, CK17, CK19), mucin panel (MUC1, MUC2, MUC4, MUC5AC, MUC6), tumor protein p53, tumor suppressor gene DPC4/SMA D4, CDX2 (a recently cloned homeobox gene that encodes an intestine-specific transcription factor, expressed in the nuclei of epithelial cells throughout the intestine, from duodenum to rectum), the Von Hippel–Lindau tumor suppressor protein (PVHL), the calcium binding protein S100 P, the Insulin-like growth factor II mRNA-binding protein 3 (IMP-3), mapsin, mesothelin, claudin 4, claudin 18, annexin A8, fascin, Prostate stem cell antigen (PSCA), MOC31 antibody, also known as Epithelial Specific Antigen/Ep-CAM, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9, also called cancer antigen 19-9 or sialylated Lewis (a) antigen (CA19-9) (Figures 2, 3) in the diagnosis of ductal adenocarcinoma of the pancreas. The results of that study demonstrate that PVHL, mapsin, S100P and IMP-3 constitute the most effective panel of markers in the distinction of pancreatic adenocarcinoma from benign/reactive pancreatic ducts.

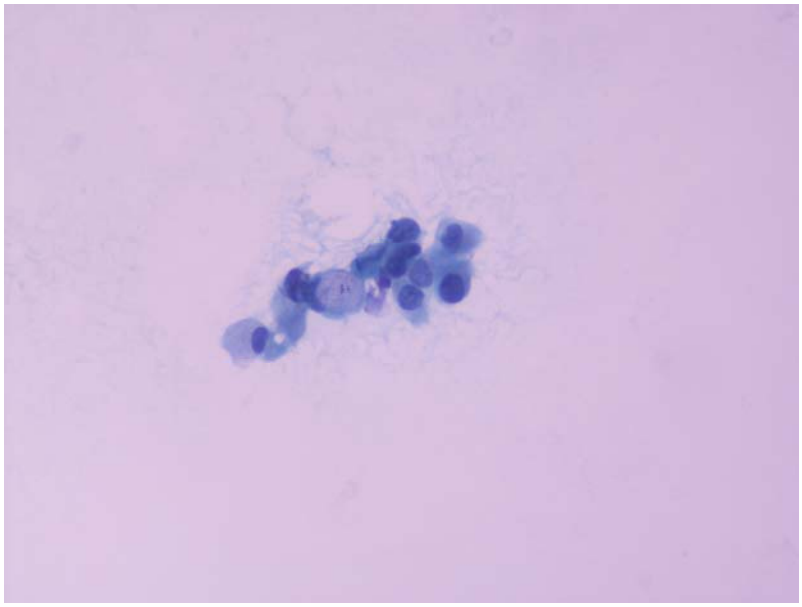

Figure 1. Ductal adenocarcinoma of the pancreas. FNAB. Poorly cohesive group of tumor cells with mild anisonucleosis, pale nuclei. nuclear contour irregularity, and chromatic clearing or clumping Papanicolaou stain X400.

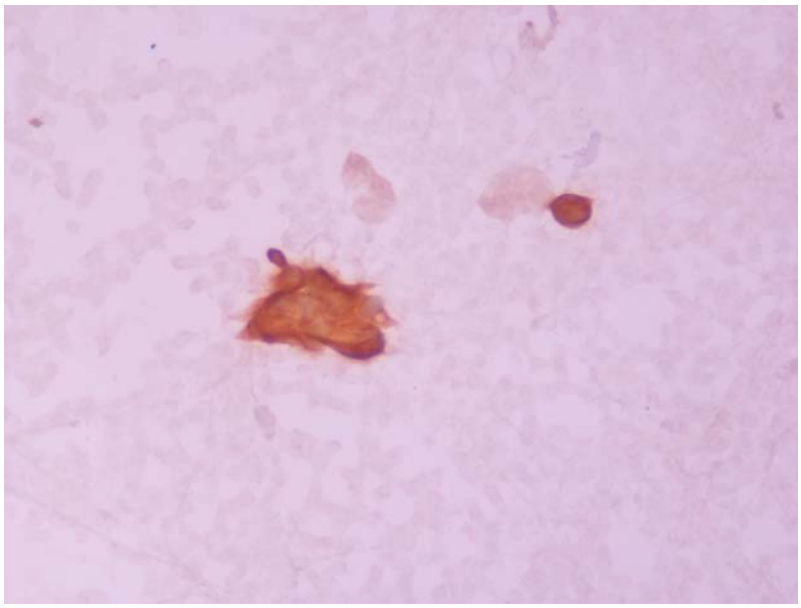

Figure 2. Ductal adenocarcinoma of the pancreas. FNAB. A small cluster of malignant ductal cells CK7 positive. CK7 immunostain X400.

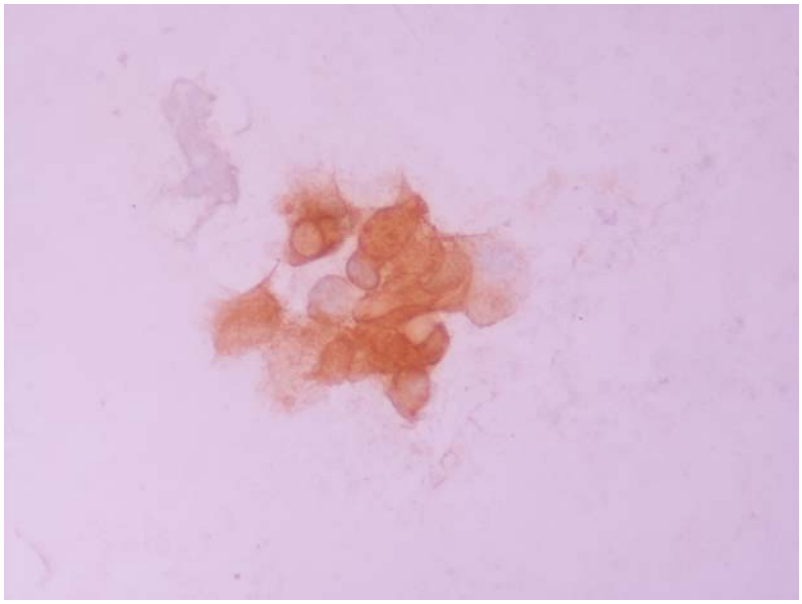

Figure 3. Ductal adenocarcinoma of the pancreas. FNAB. A cohesive cluster of malignant ductal cells CEA positive. CEA immunostain X400.

Another study [43] on EUS-FNAB in cases of pancreatic adenocarcinoma demonstrates that among five antibodies, S100P reveals the best diagnostic characters showing 90% of sensitivity and 67% of specificity. Fascin shows high specificity (92%) but low sensitivity (38%). Mesothelin has a moderate sensitivity (74%) and low specificity (33%), PSCA and 14-3-3 sigma show high sensitivity but zero specificity.

To achieve higher diagnostic efficacy, some investigators have used molecular analysis of EUS-FNA samples. Especially, some reports suggested that the presence of K-*ras* gene mutations in tissue obtained by EUS-FNA improved the accuracy of the diagnosis.

Takahashi *et al*. reported that K-ras point mutations were found in 74% of pancreatic cancers and 0% of focal pancreatitis lesions [44]. They also mentioned that analysis for the K-ras point mutation in specimens obtained by EUS-guided FNA might enhance diagnostic accuracy in indeterminate cases. Hosoda *et al*. suggested they could achieve a diagnosis from EUS-FNA specimens of invasive ductal carcinomas, endocrine tumors and acinar cell tumors by using immunostaining for CK7, CDX2, chromogranin A and synaptophysin with K-ras mutation analysis [45]. Deng *et al*. reported the usefulness of immunostaining of S100P [46] and Giorgadze *et al*. reported a mucin panel comprising all four antibodies (MUC1, MUC2, MUC5AC and MUC6) might be helpful in differentiating normal/reactive duodenal and gastric epithelium from neoplastic pancreatic tissue [47]. Those reports might help to improve the efficacy of EUS-FNA for diagnosis of solid pancreatic masses.

Molecular analysis has widened the role of EUS-FNA of solid pancreatic masses into treatment fields. Referring to the correlation between deoxycytidine kinase (dCK) activity and gemcitabine sensitivity [48], Ashida *et al*. reported dCK mRNA expression in EUS-FNA biopsy specimens might be a predictor for response to gemcitabine in patients with unresectable cancer [49]. Although there was no correlation between the expression levels of human equilibrative nucleoside transporter-1 (hENT-1) and gemcitabine efficacy in Ashida *et al*.'s study, Giovannetti *et al*. suggested hENT-1 expression might be a possible prognostic factor for chemosensitivity of pancreatic cancer to gemcitabine [50]. In addition, Fujita *et al*. reported that quantitative analysis of not only dCK and hENT-1, but also RRM1 and RRM2 mRNA levels in microdissected neoplastic cells from EUS-FNA specimens might be useful in predicting the gemcitabine sensitivity of patients with pancreatic ductal adenocarcinoma [51]. Through these further investigations, EUS-FNA might lead the way to 'tailor made therapies'.

EUS-FNAB shows the highest sensitivity (95%) and specificity (91%). In different studies retrieved from PUBMED database since 2003, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of EUS-FNA for pancreatic solid masses were reported to be 78-95%, 75-100%, 98-100%, 46-80% and 78-95%, respectively. There was no improvement of the efficacy of EUS-FNA even though new equipment and procedures have been developed. Of course,

one of the reasons is that EUS-FNA has been carried out in many different hospitals and institutes all over the world, at times by relatively inexperienced operators. But the results have been excellent, that is to say, EUS-FNA for diagnosis of solid pancreatic masses is 'a nearly perfected procedure' [52].

CONCLUSION

We reviewed the role of EUS-FNA for the diagnosis of pancreatic adenocarcinoma and EUS-FNA should be carried out with an on-site pathological evaluation. EUS-FNAB cytomorphology is superior to any one of the immunohistochemical markers used. In the diagnosis of pancreatic adenocarcinoma if there is enough cytomorphological evidence for the diagnosis of malignancy, immunohistochemical markers are not required.

To reach a higher level of accuracy, it might be necessary to explore different diagnostic dimensions. Because on-site cytopathologic evaluation improves the diagnostic yields of EUS-FNA, more effort should be made to include this assessment during EUS-FNA procedures.

Masele solide pancreatice reprezintă o varietate de tumori maligne şi benigne ale ţesutului enodcrin şi exocrin pancreatic. Un diagnostic bioptic este de multe ori necesar în faţa unui diagnostic incert sau dacă pacientul nu poate fi operat datorită comorbidităţilor sau a bolii avansate. Ecografia endoscopică (EUS) este o metodă dezvoltată relativ recent. EUS presupune evaluarea capului de pancreas şi a lobului uncincat atunci când sonda este plasată duodenal şi a cozii şi corpului pancreatic atunci când sonda este plasată gastric. EUS s-a demonstrat a fi o metodă foarte sensibilă pentru detecţia maselor pancreatice, fiind superioară ecografiei abdominale şi a CT-ului mai ales când masele pancreatice au mai puţin de 2-3 cm. Totuşi capacitatea de diferenţiere dintre inflamaţie şi tumori este scăzută. Colangiografia pancreatică retrogradă endoscopică (ERCP) însoţită de periaj, biopsiile ghidate prin CT sau ecografie sunt tehnicile standard utilizate pentru obţinerea de ţesut pancreatic în vederea diagnosticului maselor pancreatice. Aspiraţia pe ac fin ghidată ecografic (US-FNAB) s-a dovedit a fi înalt specifică, fiind o tehnică care a îmbunătăţit capacitatea de a diagnostica şi a evalua malignităţile tractului digestiv şi ale pancreasului. În plus, orice ganglion limfatic suspect poate fi biopsiat. Această metodă pare să deschidă noi orizonturi întrucât se evaluează posibilitatea de a administra ţintit chimioterapeutice direct în masele tumorale. Tehnica este deja utilă pentru blocarea selectivă a nervilor ganglionilor celiaci folosită în tratamentul paleativ al durerii la pacienţii cu cancer pancreatic. Obiectivul acestui articol a fost de a evalua literatura de specialitate privind diagnosticul adenocarcinomului pancreatic.

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