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Review

Fine Needle Aspiration Cytology of the Pancreas: A Guide to the Diagnostic Approach

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A B S T R A C T

Fine needle aspiration (FNA) cytology, together with imaging, has become a primary diagnostic modality for investigation of pancreatic mass lesions, both cystic and solid. Advances in imaging techniques have enhanced our ability to recognize and delineate pancreatic masses and to detect them earlier as smaller mass lesions. However, definitive management often cannot be based on clinical and radiological features alone. Despite the advances in the imaging techniques, management options for patients are limited and a malignant diagnosis of solid lesions still carries a high mortality rate. The importance of a cytopathologist in preoperative diagnosis, as a member of the multidisciplinary team, is exemplified in the management of patients with neoplastic cysts. This is based on the pre-operative distinction of non-mucinous and mucinous cysts in general, and benign and malignant cysts in particular. A cytological diagnosis can be obtained with minimally invasive techniques that utilize CT, US or EUS. Endoscopic Ultrasound guided FNA (EUS FNA) is evolving as the diagnostic method of choice due to its ability to more accurately stage the patient during a single procedure using EUS.

Key words: *pancreas, carcinoma, diagnosis, cytology, FNA, EUS FN*

Introduction

FNA remains the primary means of establishing a pathological diagnosis pre-operatively. A core biopsy (CB) of the pancreas is associated with a significant risk of complications. The accuracy and utility of pre-operative FNA is dependent on the quality of the sample as well as the quality of the interpretation. Cytology interpretation requires experience in pancreatic cytology using a multimodal approach that incorporates the clinical, radiological and ancillary laboratory tests into the overall interpretation of the specimen.

FNA Techniques

It is recognised widely that computerised tomography (CT) is perhaps the most important single test used in preoperative staging of pancreatic cancer and in assessment of tumour resectability, and has been shown to be superior to most other imaging modalities in accurately predicting resectability and staging of pancreatic adenocarcinoma[1,2]. With the advent of endoscopic ultrasound (EUS)[3], transgastric or transduodenal FNA of pancreatic masses has provided a useful investigation for acquiring a sample to confirm the presence of pancreatic cancer. EUS guided FNA, unlike percutaneous FNA, allows biopsy of small (0.5 cm) lesions that are not evident by conventional imaging studies[4]. The short needle path decreases potential complications as well. EUS also simultaneously allows for accurate staging of pancreatic malignancy by sampling suspicious peripancreatic nodes and liver lesions. However, both techniques are robust and the eventual choice is dependent on several factors including availability of EUS and local expertise both in obtaining and interpreting the FNA sample.

The EUS equipment consists of an image guidance system and the echoendoscope that is placed into the stomach or duodenum. Using the guidance of the high frequency ultrasound transducer on the tip of the echoendoscope, a small 19–25 gauge needle is passed through the wall of the gastrointestinal tract and into the pancreatic mass or cyst. Masses in the pancreatic head use a transduodenal approach and those in the pancreatic body and tail use a transgastric approach. Once in the lesion, the stylet is removed, suction is applied using a syringe, and the needle is moved back and forth within the

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lesion. If cystic, the cyst fluid is drained and submitted for routine cytology, biochemical and possibly molecular analysis. Any visible mural nodule or solid component should be separately sampled. Obtaining formalin fixed paraffin embedded tissue from needle rinses or core biopsy (CB) provides additional morphological information about the lesion and readily available tissue for ancillary studies[5].

Rapid on-Site Cytopathology Evaluation

Rapid on-site cytopathology evaluation (ROSE) has been shown to improve the diagnostic yield of EUS--guided FNA[6–8]. Interpretation of selected smears by a cytopathologist provides a sample from which adequate interpretation can be made. In addition to the assessment of the specimen adequacy, on site assessment allows for appropriate triage of the specimen for ancillary studies, such as flow cytometry and immunocytochemistry[9]. Cyst fluids can produce direct smears if the fluid is thick, but thin watery or bloody fluids are collected and processed as cytospins by using routine stains and special stains for mucin. Triage of cyst fluid for biochemical analysis or molecular analysis can be performed either by the sample taker (usually a gastroenterologist) or the pathology lab.

The overall risk of complications from EUS-FNA is relatively low at approximately 2%, with no severe or fatal incidents reported[10,11]. The most common complications arising from FNA of the pancreas are hemorrhage and pancreatitis[12]. With percutaneous FNA, tumour seeding along the cutaneous needle track is an extremely rare event. Transperitoneal rather than needle track spread may be of greater concern[13]. The biochemical analysis of usually at least 1 mL of fresh, unfixed and undiluted fluid aspirated from cystic lesions of the pancreas is very helpful in distinguishing cystic neoplasms from pseudocysts, serous cysts from mucinous cysts, and benign from malignant mucinous cystic neoplasms. CEA has yielded the best results in discriminating between a mucinous and non-mucinous cyst[14]. Amylase is the second test that is very helpful in the pre-operative interpretation of pancreatic cysts.

Diagnostic Accuracy of Pancreatic FNA

Diagnostic accuracy of pancreatic FNA depends primarily on the nature of the lesion and the quality of the material available but also on the experience of both, the aspirator and the interpreter, and most importantly on the communication between the radiological, surgical and pathology teams. EUS FNA of the pancreas is a technically difficult procedure and yields aspirates that are diagnostically challenging. Thus, the sensitivity is variable, ranging from 60% to 100%[15]. Sensitivity of the procedure can increase overtime, reflecting increasing experience with this technique[15]. The specificity of diagnosis in the setting of a solid pancreatic mass is greater than 90%. The adequacy and sensitivity rates are generally higher when ROSE is available[8]. The inaccuracies of pancreatic FNA appear to be almost entirely due to false negative reports. The sensitivity for cystic neoplasms is lower than that for solid neoplasms primarily due to the sampling problems and low cellularity of most of the cystic lesions[16].

TABLE 1
WHO HISTOLOGICAL CLASSIFICATION OF TUMOURS OF THE EXOCRINE PANCREAS[16]

Benign	Borderline	Malignant
Mature teratoma		
Lymphoepithelial cyst		
Serous cystadenoma		Serous cystadenocarcinoma
Mucinous cystadenoma with mild dysplasia	Mucinous cystic neoplasm with moderate dysplasia	Mucinous cystadenoma with carcinoma in-situ
		Invasive carcinoma arising in mucinous cystadenoma
Intraductal papillary-mucinous neoplasm with mild dysplasia	Intraductal papillary-mucinous neoplasm with moderate dysplasia	Intraductal papillary-mucinous neoplasm with carcinoma in-situ
		Invasive carcinoma arising in Intraductal papilary-mucinous neoplasm
	Solid pseudopapillary neoplasm	
		Ductal adenocarcinoma
		Variants:
		Subtypes-colloid carcinoma, signet ring cell carcinoma, adenosquamous carcinoma, undifferentiated (anaplastic) carcinoma, undifferentiated carcinoma with osteoclastic gint cells
		Pancreatoblastoma
Acinar cell cystadenoma		Acinar cell carcinoma
		Acinar cell cystadenocarcinoma

Contaminants of Pancreatic EUS FNA

Gastrointestinal (GI) contamination can lead to over and under interpretation of pancreatic EUS FNAs. Mistaking benign GI groups as benign ductal cells can lead to interpreting an inadequate sample as adequate contributing to a false negative interpretation. Conversely, reactive atypical GI groups can be mistaken for well-differentiated adenocarcinoma leading to a false positive interpretation. Both contaminating epithelia may appear complex and atypical from folding and dyshesion, or, in the case of duodenum, presenting as intact villi creating a diagnostic pitfall for over-interpretation as carcinoma. These groups of cells are generally distinguishable from ductal adenocarcinomas as they lack the characteristic nuclear features of malignancy, and contain goblet cells and lymphocytes within the epithelium.

Diagnostic Approach to Interpretation of Pancreatic FNA

When interpreting pancreatic FNA, cytopathologists use a WHO classification of pancreatic lesions which broadly divides lesions into solid and cystic[17] (Table 1). Before embarking on interpreting pancreatic FNA cytopathologists should be familiar with the appearances of the normal, reactive (Figure 1 and 2) and neoplastic conditions, the most common of which are described here. For a detailed description of these and some rarer conditions, reader should consult one of the standard textbooks[18].

Primary pancreatic adenocarcinoma

If the lesion is radiologically solid, differential diagnosis includes in over 90% a primary adenocarcinoma. Pancreatic adenocarcinoma may be well or poorly differentiated. The main features of malignancy are the following: overlapping and crowding, nuclear contour irregularity, gross anisonucleosis and chromatin abnormalities[19]. Well differentiated carcinoma may be overlooked and mistaken for reactive changes such as found in chronic pancreatitis (Figures 3 and 4). Variants of pancreatic adeno-

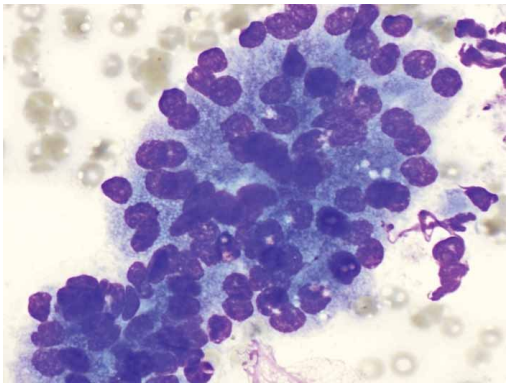

Fig 1. FNA pancreas. Normal pancreatic acini are usually arranged in round, cohesive, complex aggregates with no central lumen, with cell that have a round, eccentrically placed nucleus, anisonucleosis, conspicuous nucleolus coarsely granular chromatin and abundant and granular cytoplasm.

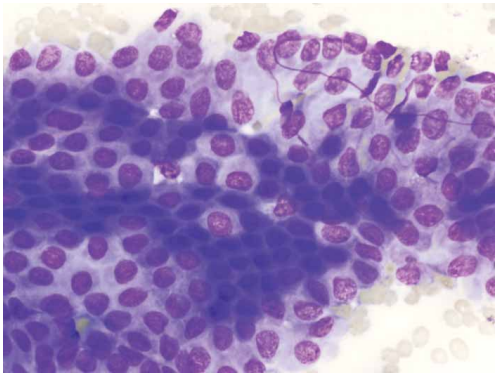

Fig 2. FNA pancreas. Normal ductal epithelium is usually arranged in large monolayered sheets with uniformly spaced oval nuclei, minimal or no overlapping. Cells have small inconspicuous nucleoli, moderate amount of ill-defined cytoplasm and luminal border without visible microvilli.

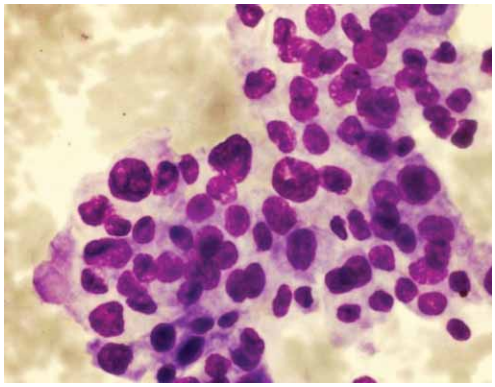

Fig 3. FNA pancreas. Chronic pancreatitis contains mostly ductal cells, few or no acinar cells, in cohesive monolayered sheets with very few single cells. Cells have maintained their polarity, have minimal nucelar overlap, mild anisonucleosis, smooth nuclear membranes, rare/normal mitoses and no coagulative necrosis. Plasma cells can be seen in autoimmune pancreatitis.

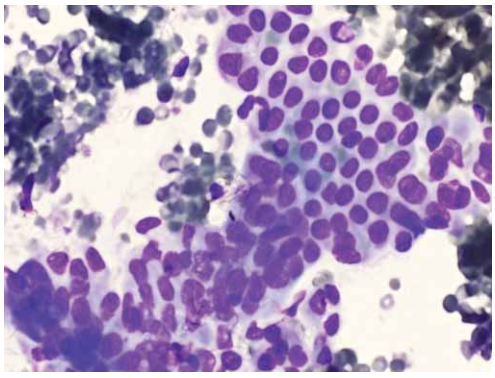

Fig 4. FNA pancreas. Well differentiated adenocarcinoma. Cells show parachromatin clearing, exaggerated honeycomb pattern, loss of nuclear polarity and subtle nuclear membrane irregularities.

carcinoma include undifferentiated carcinoma, osteoclast like giant cell tumour and adenosquamous carcinoma[18].

Other »solid« malignancies include lymphoma, sarcoma, germ cell tumour, metastases, primary endocrine tumour, solid pseudopapillary neoplasm, acinar cell carcinoma and pancreatoblastoma. If the cellular components of the FNA material are insufficient for a confident diagnosis of malignancy, an indeterminate report of »atypical or suspicious« for neoplasm will be issued. In cases of chronic pancreatitis, autoimmune pancreatitis or normal pancreatic tissue, a negative report can be issued. Non-diagnostic material is considered that which, in the presence of radiological abnormality, does not show any pathological features or if it is technically inadequate (blood, polymorphs, crush or drying artefact).

Primary endocrine tumour

Primary endocrine tumours (PET) are uncommon (0.4/100,000), they have a much better prognosis than non endocrine tumours. With the advent of EUS FNA which can target small lesions, the incidence of primary endocrine tumours (PET) in the FNA is growing. EUS and EUS-FNA have become the preferred modalities for localizing and diagnosing PETs, sensitivity and accuracy rates are between 80–90%[20,21].

PETs are usually very vascular tumours and consequently, FNA samples are usually full of blood and inadequate for assessment. If adequate, they are hypercellular, cell monotony/absence of pleomorphism being a notable feature. Cells are usually arranged as single or in small clusters with a tendency towards acinar formations. Branching blood vessels may be present. The individual cells are round or polygonal, finely granular with a well defined cytoplasm, eccentrically located round to oval nuclei (plasmacytoid) and one or two nucleoli. If immunocytochemistry can be performed, this is usually confirmatory, particularly chromogranin and synaptophysin. The latter is more sensitive if less specific and tends to stain a greater proportion of PETs (Figure 5 and 6). According to WHO classification, different endocrine tumour types differ in clinical behaviour and prognosis[22] (Table 2). EUS-FNA findings can predict 5-year survival in patients with PETs[21].

Cystic lesions

Until recently, cysts of the pancreas were thought to be relatively rare, but with the advances in imaging, there has been a dramatic increase in the detection of often asymptomatic cysts[23–25]. In the past, it has been advocated that all pancreatic cysts be resected due to the uncertainty in pre-operative diagnosis and the fear of malignant degeneration of a mucinous cyst. However, as we gain knowledge about the biological behaviour of these neoplasms and improve our ability to accurately diag-

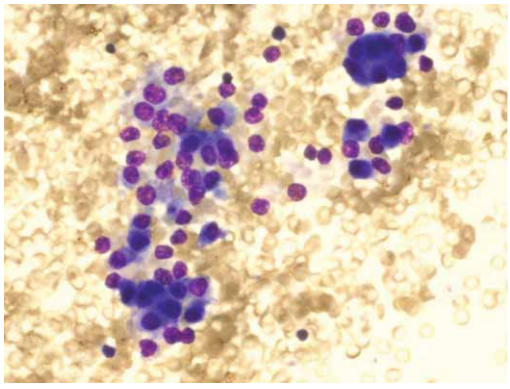

Fig 5. FNA pancreas. Pancreatic endocrine tumour. Smears are hypercellular, arranged singly and in small clusters giving a monotonous appearance with absence of pleomorphism. There is a tendency towards acinar formations. Branching blood vessels may be present.

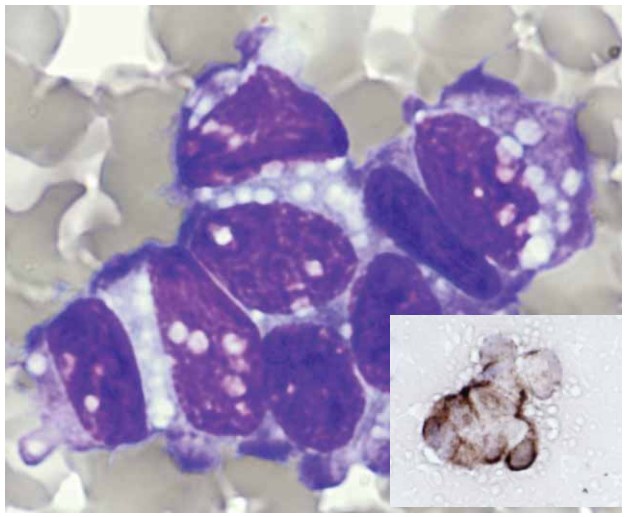

Fig 6. FNA pancreas. Pancreatic endocrine tumour. Individual cells are round or polygonal with fnely granular, well defined cytoplasm and eccentrically located round to oval nuclei (plasmacytoid).They have one or two nucleoli. Inset: Tumour cells are synaptophysin positive with immunoperoxidase.

TABLE 2
THE WHO CLASSIFICATION OF PANCREATIC ENDOCRINE TUMOURS[19A]

WHO category	Defining feature	Clinical behaviour
Well-differentiated endocrine tumour	Confined to the pancreas	Only rarely show aggressive behavior
Well-differentiated endocrine carcinoma	Lymph node or liver metastasis	Variable but generally aggressive tumours
Poorly differentiated endocrine carcinoma	>10mitosis/10HPF	Extremely aggressive tumour
	Small cell carcinoma-like morphology	

nose pancreatic cysts, alternative treatment options to surgery become available.

Cystic lesions can be non epithelial or epithelial, benign or malignant, of low or high grade malignancy (Table 1).

Pseudocyst is the most common non-epithelial cyst. It is unilocular, contains inflammatory cyst debris, patients have usually a history of pancreatitis. Cytologically, the characteristic features include degenerative cyst debris without thick extracellular mucin, but with acute and chronic inflammatory cells, histiocytes, and hemosiderin-laden macrophages. No cyst lining epithelial cells should be present, however, contaminating gastric or duodenal epithelium and even extracellular mucin may be present presenting a diagnostic pitfall for the misinterpretation of a mucinous cyst (Figure 7). Pseudocysts invariably have an elevated amylase level, usually in the thousands[26]. An amylase level of <250 U/L virtually excludes the diagnosis of a pseudocyst. They contain low CEA, no K-ras or LOH mutations. These are benign cysts and the management depends on patient's condition.

Serous cystadenoma (microcystic or glycogen-rich cystadenoma) has characteristic radiological appearances, is usually poorly cellular, most of the slides being empty apart from a few flat sheets of bland cuboidal epithelium with round central to slightly eccentric nuclei and scant but visible cytoplasm that is homogenous to clear (non mucin secreting) (Figure 8). They often contain haemosiderin laden macrophages. Mucin stains are negative, fluid has low amylase and CEA levels. A CEA of >200 ng/mL would for all practical purposes exclude a serous cystadenoma[27]. Serous cysts are almost always benign.

Mucinous cysts are neoplastic and can be subdivided into Intraductal papillary mucinous neoplasm (IPMN) and Mucinous Cystic Neoplasm *(MCN).* Both lesions have elevated CEA >200 ng/mL (at MGH) and positive mucin stains. K-ras mutation or ≥3 LOH mutations are supportive of this diagnosis.

Intraductal papillary mucinous neoplasm (IPMN) is a mucin producing neoplastic cyst that arises from and is directly connected with the pancreatic ductal system, either the main duct and/or side branch duct, and is lined by typically papillary and variably atypical mucinous epithelium. Most IPMN occur in elderly men and women with a peak age of close to 65 years and a slight male predominance. The epithelial lining of IPMN includes gastric-foveolar type, intestinal type, pancreatobiliary type and oncocytic type. FNA of IPMN produce variable amounts of mucin and cyst lining epithelium, and, as such, may not accurately reflect the histological grade of the cyst[28–34]. A specific diagnosis of IPMN, therefore, is a less common cytological interpretation than a more general diagnosis of a neoplastic mucinous cyst that includes MCN. Air dried smears of thin mucin may produce »ferning«, an indication of its mucinous nature. Mucin stains

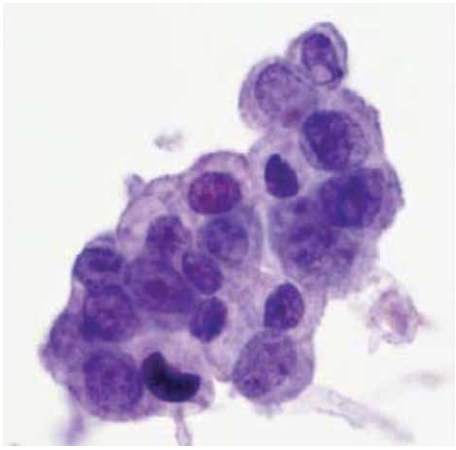

Fig 8. FNA pancreas. Serous cystadenoma. Small cuboidal epithelial cells rich in cytoplasmic glycogen on a clean background, often in monolayered sheets of small flat clusters. Cells have bland round nuclei, usually central and scant non mucinous cytoplasm.

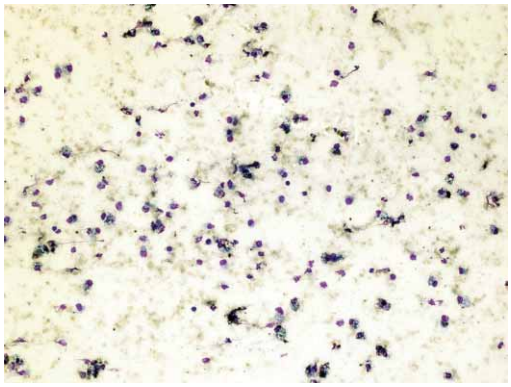

Fig 7. FNA pancreas. Pseudocyst. Numerous macrophages, often contain aemosiderin as well as cyst debris with blood, proteinaceous material and sometimes bile. Variable inflammation and no cyst lining epithelium present.

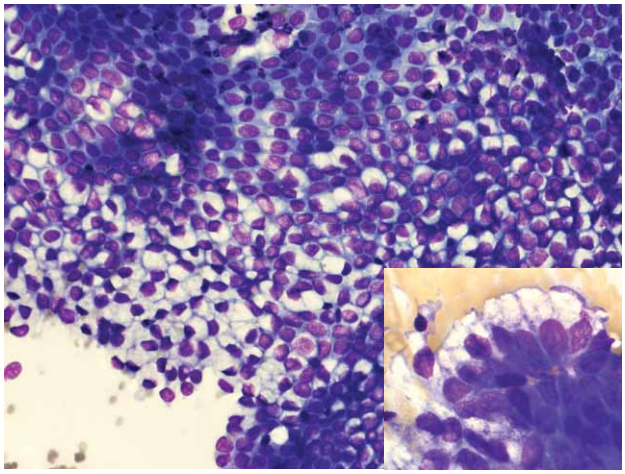

Fig 9. FNA pancreas. Intraductal papillary mucinous neoplasm. Background-Abundant thick mucin, mucinous glandular epithelium in sheets, clusters, papillary groups and single. Inset: Mucus secretion in every cell. Cellular atypia can be variable; none-adenoma, moderate-borderline and malignant, at least in situ carcinoma.

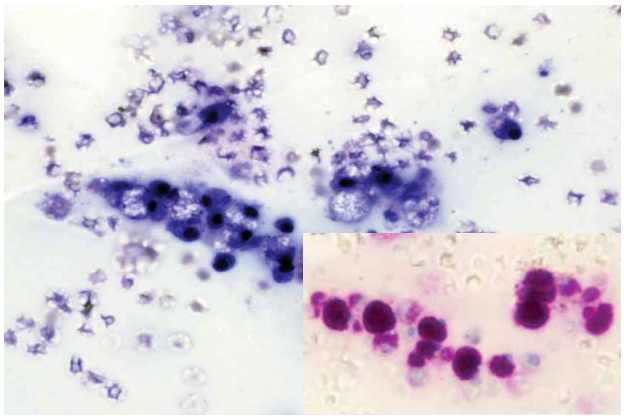

Fig 10. FNA pancreas. Mucinous Cytic Neoplasm, cytologically impossible to distinguish from IPMN. There is copious mucin background and necrotic debris. apillary clusters and sheets of uniform, columnar cells embedded in mucin with distinct cell borders, occasional signet ring forms and rarely frankly malignant features. Inset: Tumour cells are Pas diastase positive.

(mucicarmine and/or Alcian blue pH 2.5) can help to identify and distinguish proteinaceous fluid from mucin. Cytological findings of IPMN with low-grade dysplasia (adenoma) include variable amounts of mucin, thick, colloid-like mucin with or without mucinous epithelium, thin, watery mucin, low cellularity, papillary fragments, mucinous glandular epithelium with mucin occupying >1/3rd filling the columnar cytoplasmic compartment, absence of nuclear atypia and no background necrosis (Figure 9)[18].

IPMN-moderate dysplasia and IPMN-carcinoma are lined by atypical to malignant appearing glandular epithelium with variable amounts of cytoplasmic mucin. Although malignant IPMN typically have increased overall cellularity with respect to low-grade neoplasms, not all carcinomas produce cellular aspirates[18]. Open chromatin, irregular nuclear membranes and nucleoli, significant background inflammation and necrosis supports the interpretation of an in situ or invasive carcinoma. Complete surgical resection is currently the treatment of choice, although treatment options are evolving for branch duct IPMN due to the more often low grade nature of these neoplasms. Prognosis is directly related to the presence or absence of an invasive carcinoma[35,36].

Mucinous cystic neoplasm (MCN) is a neoplastic mucin producing cyst that, in almost all cases, occurs in a female, does not communicate with the pancreatic ductal system, is lined by mucinous epithelial cells with varying degrees of atypia, and by definition contains subepithelial ovarian type stroma[35]. On a pure cytological level, FNA of MCNs for all practical purposes are identical to those described for IPMN. The subepithelial ovarian-type stroma typically is not appreciated on cytology smears. Unlike IPMN that can have different types of epithelium lining the cyst, the mucinous lining epithelium of MCN is generally a single layer of uniform appearing columnar mucinous epithelium that increases in nuclear atypia with increasing grade of the neoplasm[18]. The cyst lining cells may become attenuated from pressure decreasing the mucinous appearance of the cells. Sometimes only cyst debris and foamy histiocytes are seen and, as such, aspirates may be devoid of identifiable mucin or epithelial cells causing misdiagnosis as a pseudocyst or serous cyst (Figure 10). Biochemical analysis of the cyst fluid showing CEA levels above 200 ng/mL support the interpretation of a mucinous cyst and very high levels of CEA correlate with (but are not diagnostic of malignancy).

Ancillary Techniques

Although cyst cytology alone is often non-diagnostic, when evaluated in the context of the clinical history, radiological features and gross cyst fluid observations and ancillary tests such as special stains for mucin, biochemical testing for CEA and amylase and increasingly molecular analysis, accuracy can be greatly improved.[37–42] An educated and experienced cytopathologist is critical for accurate interpretation[24,25,33,36–42]. The purpose of these pre-operative investigations is primarily to distinguish mucinous neoplasms from pseudocysts and serous cystadenomas, distinctions that directly affect patient management decisions[43–45].

Molecular analysis of cyst fluid can be carried out with commercially available kits but it is controversial as there have been few published reports[46–51]. As currently reported malignant cysts require either k-ras gene point mutation, two or more LOH or high quantity/quality of DNA with k-ras or LOH mutation present at a high amplitude (>75%) suggesting a significant clonal expansion. Mucinous cysts show either k-ras gene point mutation, two or more LOH or high quantity/quality of DNA, and non-mucinous cysts do not show any of these molecular changes and little, poor quality DNA. A recent study comparing the molecular classification of cysts into general categories of non-mucinous, benign mucinous and malignant mucinous cysts with the current practice using clinical, radiological and cyst fluid parameters shows good concordance[52].

In conclusion, FNA pancreas is an evolving discipline, currently in the forefront of the pre-operative patient management. A definitive morphological diagnosis can be made, provided we improve the skills of collection, preparation and interpretation of pancreatic FNA samples. In order to maintain and enhance our position in the management pathway, cytopathologists cannot underestimate the use of ancillary techniques and the value of the multidisciplinary team approach.

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CITOLOŠKA PUNKCIJA GUŠTERAČE: DIJAGNOSTIČKI PRISTUP

SAŽETAK

Citološka punkcija (fine needle aspiration, FNA) je zajedno s tehnikama slikovnog prikaza postala primarnim dijagnostičkim sredstvom ispitivanja cističnih i solidnih tvorba gušterače. Napredak u tehnikama slikovnog prikaza povećao je mogućnost raspoznavanja i ocrtavanja tvorba gušterače, te njihovog ranijeg otkrivanja. Međutim, konačno liječenje često se ne može temeljiti samo na kliničkim i radiološkim obilježjima. Usprkos napretku u tehnikama slikovnog prikaza, mogućnosti liječenja ovih bolesnika su ograničene, dok je zloćudna dijagnoza solidnih tvorba još uvijek udružena s visokom stopom smrtnosti. Važna uloga citopatologa kao člana multidisciplinskog tima u prijeoperacijskoj dijagnostici

ilustrira se na primjeru liječenja bolesnika s neoplastičnim cistama. Ovo liječenje se temelji na prijeoperacijskom razlikovanju nemucinoznih i mucinoznih cista općenito, te osobito dobroćudnih i zloćudnih cista. Citološka dijagnoza dobiva se minimalno invazivnom tehnikom, vođenom kompjutoriziranom tomografijom, ultrazvukom ili endoskopskim ultrazvukom. Citološka punkcija pod kontrolom endoskopskog ultrazvuka (EUS FNA) razvija se u dijagnostičku metodu izbora zahvaljujući mogućnosti da se točnije utvrdi stadij bolesnika u samo jednom postupku pomoću EUS.