



# Utility of Immunocytochemistry in Differentiating Acinar Cell Carcinoma from Neuroendocrine Tumors of the Pancreas in Small Cytology Specimens. Case Report of Mixed Acinar-Endocrine Carcinoma of the Pancreas and Review of the Literature

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## Abstract

Diagnosis of acinar cell carcinoma (ACC) in small cytology samples can be challenging and can be confused with the diagnosis of pancreatic neuroendocrine tumors (PNET). Both tumors can present with similar cytomorphologic features, and both tumors can be presented with positivity for cytokeratin and for neuroendocrine markers. This case highlights utility of immunocytochemistry in small cytology samples not only to distinguish ACC from PNET, but also to achieve the diagnosis of the rare entity "mixed acinar-neuroendocrine carcinoma of the pancreas" (MANEC). It is our hope that reporting this case will raise awareness of including this rare possible diagnosis in the differential diagnosis of a pancreatic mass, and that continued reporting of such cases will improve efficacious diagnosis and patient outcome.

**Keywords:** Pancreatic mass; Pancreatic neuroendocrine tumors; Mixed acinar-neuroendocrine carcinoma; Differential diagnosis; Immunohistochemistry

## Abbreviations

ACC: Acinar Cell Carcinoma; PNET: Pancreatic Neuroendocrine tumors; MANEC: Mixed Acinar-Neuroendocrine Carcinoma; IHC: Immunohistochemistry

## Introduction

The similarity of cytomorphologic features and some immunohistochemistry profile of both ACC and MANEC is well reported in the literature, and the utility of an expanded panel of immunohistochemistry studies aided in making such differentiation. The diagnostic challenge becomes even more significant when an ACC displays abundant neuroendocrine differentiation. It is reported that the occurrence of pancreatic tumors comprising both acinar cells and neuroendocrine cells,

with neuroendocrine cells making up more than 30% of the tumor, has been referred to as mixed acinar-neuroendocrine carcinoma (MANEC). Mixed endocrine-exocrine tumors of the pancreas have been described and are very rare, with less than 50 cases reported in the English literature [1-3].

Mixed Acinar-Neuroendocrine Carcinoma of the pancreas (MANEC) was first described by Ulich et al in 1982 [1]. MANEC represents only 0.2% of reported cases of pancreatic tumors and is believed to be a subset of Acinar Cell Carcinoma due to the biological and histological similarities [2,3]. Though ACC is rare as well, comprising of only 1-2% of pancreatic tumors [4-6], it has been shown that up to 40% of ACC tissue have scattered neuroendocrine cells. This overlap requires strict adherence to the specific criteria to establish the diagnosis of MANEC. Criteria for diagnosis include: morphology of acinar and endocrine cells, with immunohistochemistry demonstrating both acinar markers (trypsin, chymotrypsin, lipase, and periodic acid-Schiff) of at least 25-30% and endocrine markers (chromogranin A, synaptophysin, CD56, NSE) of at least 25-30% [7-10]. Our case shows the difficulty of diagnosis of this rare tumor, along with the versatility and importance of immunocytochemistry (IHC).

Up to the end of 2018, 46 cases of MANEC had been reported in the English literature, with only five of which were diagnosed solely on cytopathology specimens before surgical resection [4]. Our current report adds one more case diagnosed on cytopathology alone. We report this case, with discussion of the various cytomorphologic features and differential diagnosis with presentation of a brief review of the literature.

## Case Presentation

We report a case of a 71-year old male who presented with

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epigastric pain radiating to the back secondary to a pancreatic mass. Patient reported no family history of pancreatic cancer but reported a history of breast cancer in his older sister, and prostatic cancer in his grandfather. Abdominal Magnetic Resonance Imaging revealed a 2.2 cm pancreatic tail mass, clinically suspected for PNET. Tumor markers were negative including Cancer Antigen 19.9 (CA 19.9), Cancer Antigen 125 (CA 125), and Carcinoembryonic Antigen (CEA). However, Chromogranin A level was markedly elevated.

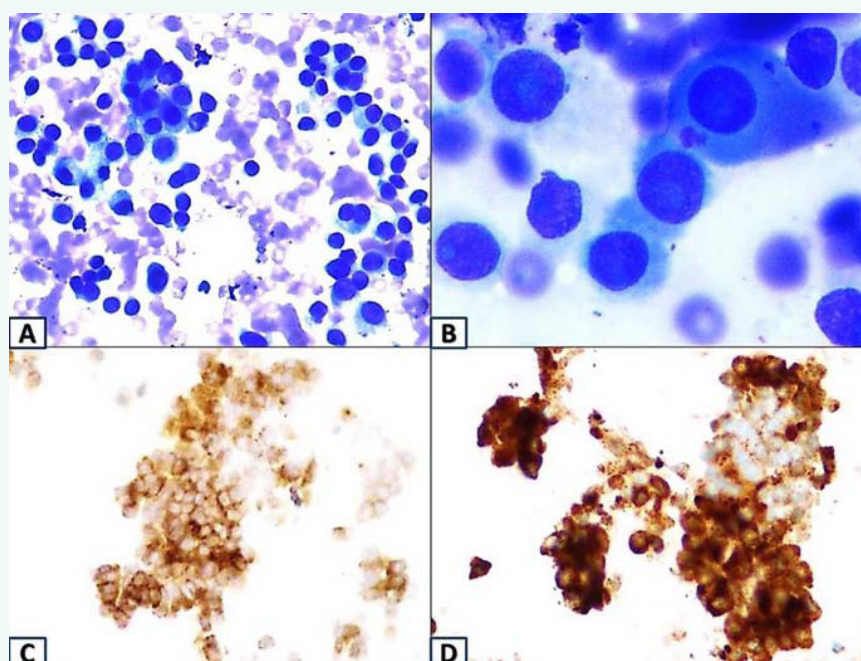
Ultrasound Guided Fine Needle Aspiration (US-FNA) was performed and an adequate sample was obtained and was sufficient to provide a cell block paraffin section preparation. The cytomorphology showed features consistent with PNET including a cellular smear with loosely cohesive cell clusters and abundant single cells. Scattered rosette-like architecture was also noted (Figure 1A). At high power examination, the nuclear chromatin showed areas with the classical salt-and-pepper appearance usually seen in PNET, but also showed many cells with prominent nuclei (Figure 1B). Immunocytochemistry performed on cytology cellblock preparation showed the tumor cells to be positive for Synaptophysin (Figure 1C), Cytokeratin AE1/AE3, and Cytokeratin CAM 5.2. Based on the cytomorphologic features and immunohistochemistry studies, a diagnosis of PNET was rendered. Upon further second opinion review, it was decided to expand the IHC panel to rule out other possible differential diagnosis including the rare entity of MANEC. With additional studies, the tumor cells were negative

for chromogranin and CD56, but positive for Trypsin (Figure 1D). With strong positivity for Trypsin, the diagnosis of ACC was appropriate, but due to presence of expression of endocrine marker (Synaptophysin) in more than half of the tumor cells, the final diagnosis was mixed acinar-endocrine carcinoma of the pancreas (MANEC). Retrospective evaluation showed that, the rosette-like architecture were actually an acinar formation. Due to early diagnosis, the tumor was localized and resectable so the patient underwent Pancreaticoduodenectomy with excision of the tumor. Final diagnosis after surgical excision was the same, confirming the pre-operative cytology diagnosis. Patient received post-operative combination chemotherapy with Cisplatin and Etoposide. No regional lymph node metastasis was identified, and a full body scan showed no evidence of metastatic disease. All surgical margins of resections were free of tumor. Patient was followed up for 4 years with no evidence of recurrence or metastasis, after which he was lost to follow up.

## Discussion

Although it is well established that roughly one-third of acinar cell carcinomas may express neuroendocrine markers, their neuroendocrine component is usually limited to a few scattered cells. When the neuroendocrine cells exceed 30% of the tumor, it is classified as mixed acinar-neuroendocrine carcinoma (MANEC) [9].

Invasion is not a common feature of MANEC so jaundice is typically absent, though can be present due to mass effect [11].



**Figure 1** Fine needle aspiration of the pancreatic mass, cytology smears and cellblock.

A: Cellular smear with loosely cohesive cell clusters and abundant single cells. Scattered rosette-like architecture. Diff Quick stain; X40

B: At high power examination, the nuclear chromatin shows areas with the classical salt-and-pepper appearance, and eccentric nuclei usually seen in PNET, but also shows many cells with prominent nuclei Diff Quick stain X100

C: Tumor cells positive for Synaptophysin

D: Tumor cells strongly positive for Trypsin.



Tumor location preference seems to be up for debate. A recent study found that 60% of its reviewed cases of MANEC showed preference for the head of the pancreas [11]. This was not the case in our patient who had his tumor located at the tail of the pancreas. Another paper stated that the tumors showed no preferential localization [10]. The age range for developing MANEC has been noted to be middle aged individuals [2,11,12]. Several articles debated the preferred gender of this tumor, but reached no conclusive decision [2,8-10]. ACC seems to have a higher prevalence in males as compared to females [2,8,10], though it must be noted that a case study of 25 high-grade transformation ACC did find a nearly two-fold increased incidence in females [13]. PNET tumors have shown no gender selection bias, and appears equally likely for both [14]. It appears that tumor location and gender do not represent a significant contribution to the differential diagnosis of these tumors.

MANEC may represent a collision tumor, in which two histologically distinct acinar and endocrine components are relatively separated, or may represent intermingled tumors consisting of cancer cells with both acinar and endocrine phenotypes [15]. Due to these possible histo/cytomorphologic features, the utility of IHC is essential for making definitive diagnosis of one of these entities.

Studies also reported that MANEC and ACC patients have been shown to display similar median overall survival rates [11,16], which is different from that of patients with pancreatic neuroendocrine tumors [17]. Survival rates of PNET has shown to have a much better prognosis depending on if they had surgical removal of the tumor or not based on slow growing rates of the tumor [17]. Though a good prognosis has been deemed for PNET patients, it has been suggested that only 65% of PNET are resectable [18], making other treatment options of vital importance. The smaller size of our tumor at 2.2 cm was not supportive of the diagnostic of an ACC tumor, which has been-reported to have an average size of greater than 10 cm [13]. Studies describing metastasis of MANEC are lacking, and additional reports are encouraged for further understanding of the metastatic nature of these tumors. Due to the small number of cases of MANEC reported, no standardized management protocol has been established. However, it is generally agreed that surgery is the first line of treatment for all cases with resectable tumor [19].

MANEC is still considered to be a tumor with a poor prognosis with surgery and chemotherapy as main treatment options [11]. Some benefit to patients has been shown from debulking surgery of the tumor [11,19]. It has been suggested that MANEC containing greater component of PNET in ACC may be correlated with a more favorable outcome [20]. Recent reports have been shown that S-1 as a chemotherapy option can have a beneficial effect [12,21,22]. The chemotherapy agent S-1, an orally administered prodrug of 5-FU, works most effectively on the ACC component of the tumor versus the PNET component, and has shown to be beneficial to patients with ACC tumors even when the tumor has been deemed unresectable [23-25]. One study reported response to the active Sunitinib and PRRT treatment, and suggested that the treatment of the PNET component of the

tumor, in addition to surgery may be beneficial [26]. This shows that using chemotherapy on either component of the MANEC prior to surgery could benefit the patient. Despite the advances of treatment options, the survival rate of patients with MANEC has been approximately 10-12 months [11,27]. In our patient, there was no evidence of recurrence or metastasis in four years before being lost to follow up. We suggest that the favorable outcome in our case may be due to the small size, negative surgical margins, and the use of combined chemotherapy.

The combination of cytology and radiology has allowed for minimally invasive, safe, accurate, and cost-effective diagnosis of suspicious masses, previously accessible only by surgical biopsy techniques. As a result, cytologists are increasingly called upon to diagnose disease in a specimen procured under image guidance for different organs. Rather than causing delay, cytology facilitates timely diagnosis and management is an integral part of a multimodal approach to various tumor diagnoses. On site cytology interpretation increases the diagnostic yield of the procedure by allowing for additional needle passes as necessary. The process culminates in a multidisciplinary conference such as tumor board where the results of clinical, radiologic, cytologic, and laboratory evaluations are discussed, and a treatment is planned. Several reports have already concluded the efficacy of cytology specimens alone, including cellblock preparation, in establishing definitive diagnosis of tumors in different organs before surgical resection [28,29]. The definitive diagnosis of MANEC in our case was solely established utilizing cytology sampling including cellblock preparations.

Given the rarity of the cases of MANEC, continuous reporting of these cases when identified should be encouraged to raise the awareness of pathologists and clinicians to this entity. It is our hope that this report raises awareness of what remains an unmet need in management of uncommon types of pancreatic cancer, and that continued investigation drives further development of efficacious diagnosis and safe treatments for improving patient outcomes.

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