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Pancreatic Mixed Neuroendocrine Non Neuroendocrine Neoplasm, a rare malignancy, co-existing with Prostatic Carcinoma: A Case Report.

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Abstract

Mixed neuroendocrine non neuroendocrine neoplasms present a diagnostic challenge. They are heterogenous malignancies that occur primarily in the GI tract and are characterized as having at least 30% each of exocrine and endocrine component occurring at the same site. Mixed neuroendocrine non neuroendocrine neoplasms are difficult to recognize due to their specific diagnostic criteria; occur rarely, and are infrequently described in literature. Only 30 cases of this tumor occurring in the pancreas have been previously reported. Men with prostatic carcinoma have occasionally been found to develop a secondary primary tumor. However, Pancreatic mixed neuroendocrine non neuroendocrine neoplasm has not been previously reported in conjunction with prostate cancer. Herein, we report a case of an elderly male with preexisting advanced prostatic malignancy, found to have a pancreatic mixed neuroendocrine non neuroendocrine neoplasm, on an endoscopic biopsy sample.

Introduction

Mixed neuroendocrine non neuroendocrine neoplasm (MiNEN) is an aggressive, heterogenous group of malignancies, thought to arise almost exclusively in the digestive tract. They comprise of both neuroendocrine and exocrine components, each accounting for at least 30% of the tumor. It is a rare malignancy with a reported incidence of 0.01/100,000 cases per year. (1)

In previous studies, the occurrence of prostate carcinoma with other primary cancers in non-contiguous sites has been reported. Multiple primary cancers (MPCs), although uncommon, occur as both synchronous and metachronous malignancies. GI cancers accounted for 3.6% of these cases. (2) Pancreatic carcinoma was rarely found in concordance with preexisting prostate carcinoma.

Herein, we report a rare case of an elderly male with preexisting advanced prostatic malignancy, found to have a pancreatic MiNEN.

Comment [1]: Pancreatic Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm, a Rare Malignancy, Co-existing with Prostatic Carcinoma: A Case Report.

Comment [2]: 30% of each of the exocrine and endocrine components

Comment [3]: Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm ….. correct this where-ever it has been mentioned

Comment [4]: In the literature.

Comment [5]: The line "Only 30 cases of this tumor occurring in the pancreas have been previously reported" can be more assertively framed, perhaps as "Only approximately 30 cases of pancreatic MiNEN have been reported in the literature."

Comment [6]: The claim that the incidence is about 0.01/100,000 cases per year is generally supported by available literature but may vary in specific regions or studies.

Comment [7]: Consider adding a brief mention of the patient's age in the first sentence to highlight the demographic aspect.

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Clinical Case

A 65-year-old male presented to the Gastroenterology department with new onset abdominal pain, fever and jaundice. He characterized the pain as sharp, moderate in intensity and localized to the right hypochondrium. He complained of low-grade fever which was undocumented. His past history was significant for chronic kidney disease, ischemic heart disease (post PCI) and prostatic carcinoma with bony metastases. He was on Goserelin (LHRH analogue) therapy for prostatic carcinoma. On examination, he was hemodynamically stable, afebrile and well oriented but deeply jaundiced. His right upper quadrant was mildly tender, no mass or viscera were palpable. Standard baseline laboratory tests revealed a raised Total Bilirubin 136 umol/L, Alanine Transaminase 88 U/L, and Alkaline Phosphatase 1564 U/L; consistent with an obstructive pattern. Total leucocyte count was 11 x 10^9, Hb 11.4 g/dL and Serum creatinine 219 umol/L. He underwent a magnetic resonance cholangiopancreatography (MRCP) which showed a poorly circumscribed mass lesion in the pancreatic head and body measuring 4.8 x 5.6 x 5.4 cm, encasing the terminal CBD and Pancreatic duct (**Figure 1**).

Comment [8]: Add a comma before and

Comment [9]: post-PCI

Comment [10]: .and well-oriented

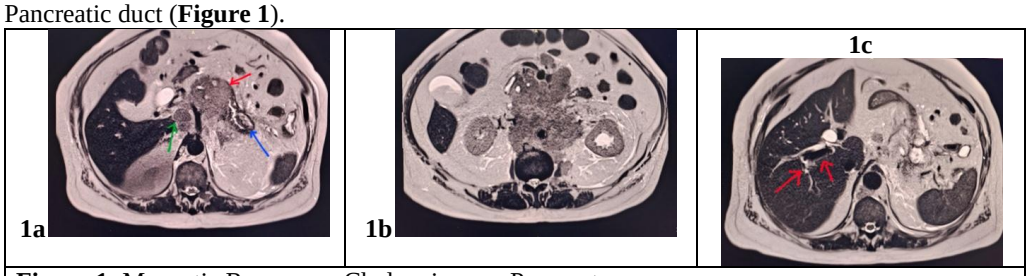

Figure 1: Magnetic Resonance Cholangiogram Pancreatogram.
1a) Ill-defined mass in pancreatic head (green arrow), body (red arrow) and remnant pancreas (blue arrow)
1b) Discrete and conglomerate mass of paraaortic lymph nodes at renal level in T2 weighted image.
1c) Dilated intrahepatic biliary channels (red arrow)

A staging CT scan could not be done due to a deranged renal profile. Therefore, an ERCP and biliary stenting was attempted to relieve the jaundice. Biliary cannulation failed due to a large infiltrated and friable ampulla, which was identified endoscopically. (**Figure 2**)

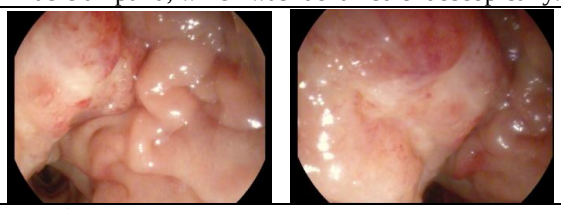

Figure 2: Infiltrated, ulcerated ampullary region. CBD cannulation not possible.

Multiple biopsies were obtained from the ampullary region. Histopathology showed a malignant neoplasm comprising of dual population of neoplastic cells. (**Figure 3**) There were a few haphazardly arranged glands showing nuclear stratification and crowding suggesting adenocarcinoma.

Comment [11]: • The description of the biopsy sample with H&E staining could be slightly more concise. For example, "Histopathology showed a malignant neoplasm with dual populations of neoplastic cells: one resembling adenocarcinoma (left) and the other a neuroendocrine tumor (right)."
· A more thorough explanation of the Ki67 index (>20%) in the context of neuroendocrine tumors (NETs) would be helpful. While it's understood as a proliferation marker, some readers might not fully grasp its prognostic value for NETs.

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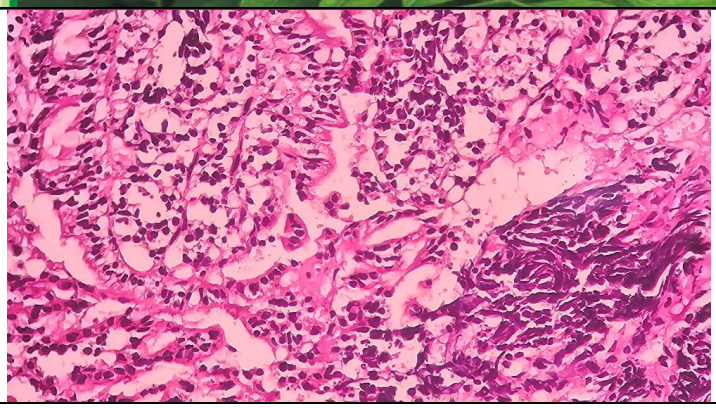

Figure 3: Complete biopsy sample stained with Hematoxylin and Eosin (H&E), showing dual population of cells: adenocarcinoma on the left and neuroendocrine on the right half of the slide.

Comment [12]: the dual.....

Other areas showed monotonous population of small hyperchromatic cells with apoptosis and frequent mitosis, indicating a neuroendocrine tumor. On immunohistochemistry, Cytokeratin 19, 20 and X2 were positive on the exocrine portions while Synaptophysin and Chromogranin were positive on the neuroendocrine portions of the tumor (Figures 4 and 5). Ki67 Index was more than 20%. Furthermore, prostatic specific phosphatase was negative, ruling out prostatic metastases. The percentage of small cell neuroendocrine tumor was 60% while that of adenocarcinoma was 40%.

Comment [13]: A monotonous

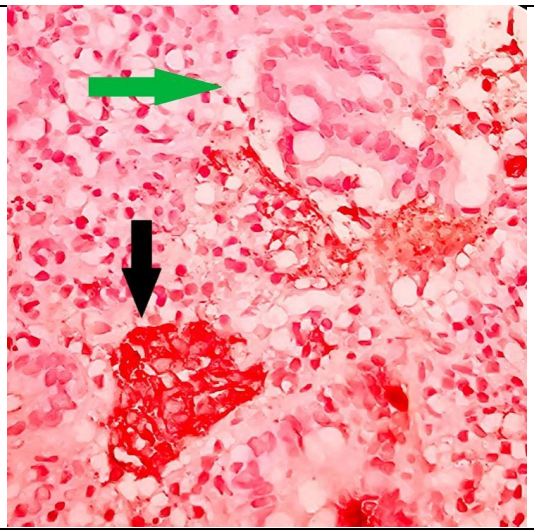

Figure 4: Synaptophysin stain positive on neuroendocrine component (black arrow) and negative on the adjacent adenocarcinoma component (green arrow)

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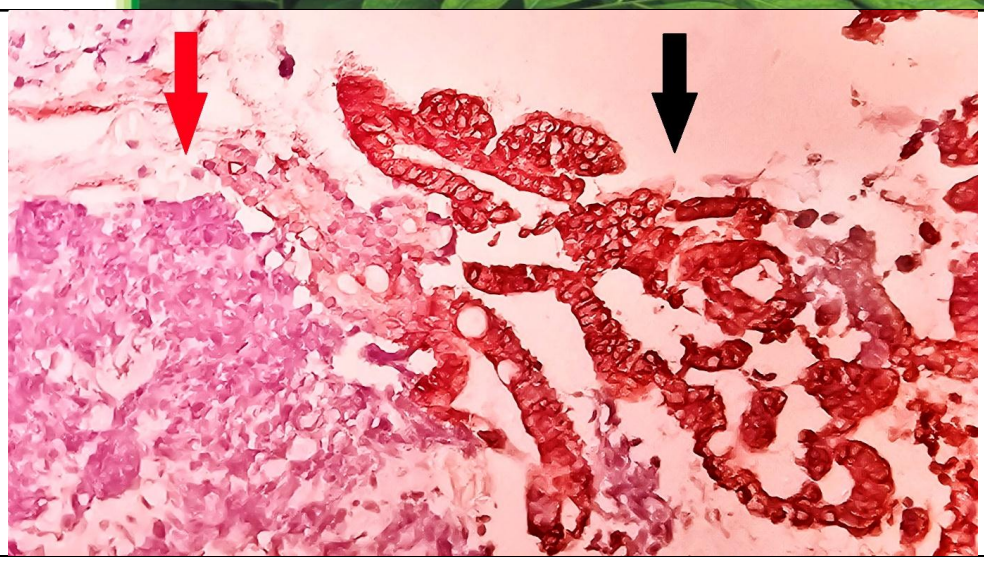

Figure 5: CK 20 staining positive staining on adenocarcinoma component (black arrow) and negative in the adjacent neuroendocrine component (red arrow)

Considering poor performance status and preexisting advanced malignancy, the patient was not deemed a candidate for curative surgery or palliative chemotherapy. A percutaneous transhepatic biliary drainage (PTBD) was performed by the interventional radiology team and a drain was placed in the left main duct (highlighted in Figure 1c).
He was readmitted 2 weeks later with bilious vomiting. His liver function tests had markedly improved and the external drain was fully functional. He was given symptomatic treatment and intravenous fluids. During the course of his admission, he continued to deteriorate and eventually expired a week later.

Discussion

The history of mixed non-neuroendocrine neuroendocrine neoplasm goes back to 1924 when they were first reported in literature as both neuroendocrine and epithelial neoplasms occurring together (3). Since then, it has been given multiple names such as mixed glandular-neuroendocrine compound carcinoma and mixed endocrine-exocrine neoplasia. In 2010, the term mixed adeno-neuroendocrine neoplasia (MANEC) was coined by the WHO to classify tumors that exhibited a neuroendocrine as well as an adenocarcinoma component (4). This term was insufficient as the non-neuroendocrine component was not always adenocarcinoma or always malignant. It occasionally also comprised of squamous cell carcinoma, acinar cell carcinoma or even adenomas. Thus, a more appropriate and inclusive term of Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) was fashioned by La Rosa *et al* and eventually adopted by the WHO (5).
MiNEN is a highly aggressive tumor which is not widely discussed in literature owing to its low incidence and the inconsistency in its diagnostic criteria. As per WHO, MiNEN is diagnosed when each of the neuroendocrine and exocrine portion represents at least 30% of the tumor. This criterion makes an endoscopic or FNA diagnosis difficult as larger and deeper biopsy specimens are likely to yield accurate results. (6) Superficial samples are

Comment [14]: • The section on **MiNEN's** aggressive nature could be expanded. Consider adding more details on the molecular or genetic characteristics of MiNENs that contribute to their poor prognosis.
• The contrast between **adenocarcinoma** and **neuroendocrine components** in the pancreatic MiNEN is interesting. Your observation that the exocrine portion was predominantly adenocarcinoma is valuable and highlights the diversity in MiNEN presentations.
• When discussing the prognosis, it's useful to reference studies that assess the overall survival and treatment outcomes in patients with pancreatic MiNEN.

generally reported as adenocarcinoma or acinar cell carcinoma. A few cases with co-existing neuroendocrine portions that were less than 30% of the biopsy sample could not be confidently classified as MiNEN. This indicates that the incidence of this malignancy might be grossly under reported. So far, most reported cases have been diagnosed on surgically resected specimens.

Moreover, most cases of MiNEN occur in the colon, appendix or stomach. Pancreatic MiNEN is exceedingly rare. Less than 30 cases of pancreatic MiNeNs have been reported worldwide. (7) Most cases of pancreatic MiNEN constitute acinar cell carcinoma as the exocrine portion. Ductal adenocarcinoma has rarely been found (6) Interestingly, in our case, the exocrine portion of the tumor comprised primarily of adenocarcinoma.

Occurrence of multiple primary cancers (MPCs) in men diagnosed with prostate cancer ranges from 1.14% to 8.7 %. (8) Although the mechanism of development of MPCs is unknown, both genetic predisposition and environmental factors are thought to contribute. (9) In a large study conducted between 1992 to 2010, 44,310 (10%) out of 441,504 patients of prostate cancer subsequently developed a second primary malignancy (10). In 4% of these cases the second primary malignancy was of pancreatic origin but the subtype was not specified.

Our case is strikingly distinct as the diagnosis was made through an endoscopic ampullary biopsy in a patient with a preexisting advanced prostatic malignancy. Furthermore, there is no reported publication on pancreatic MiNEN in conjunction with prostate carcinoma, making our case even more unique.

As a result of low evidence and scarce data, management of pancreatic MiNEN remains a question of further research. Considering the aggressive nature of the tumor, surgical resection remains the treatment of choice if there are no distant metastases (11). Pancreatoduodenectomy followed by platinum-based chemotherapy has showed to benefit certain cases but most tumors are advanced at the time of diagnosis (12,13). Prognosis is extremely dismal and further research is warranted to improve management of these patients.

Conclusion

Minens are difficult to diagnose pre operatively. When a mixed population of atypical cells are encountered on biopsy specimens, a high index of clinical suspicion may aid diagnosis. Pancreatic MiNeNs occurring as a second primary tumor in association with prostate cancer is a finding that has not been previously reported. Further research is recommended to ascertain possible interconnecting pathogenesis and novel treatments to improve prognosis.

Comment [15]: •• Including specific references to studies or clinical trials that have explored **pancreatoduodenectomy** and **platinum-based chemotherapy** for **MiNEN** would strengthen your argument.
• The **poor prognosis** section is well-argued, though a note about **palliative care** or symptom management strategies for advanced **MiNEN** cases would add depth to the conclusion

Comment [16]: consider explicitly stating that the co-occurrence of pancreatic MiNEN with prostate carcinoma underscores the necessity for clinicians to consider this possibility, even in the context of pre-existing malignancies.

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