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Mixed Neuroendocrine - Non-Neuroendocrine Neoplasm (MiNEN) - A Rare Heterogenous Malignancy of the Pancreas

Dr. Kharidehal Durga[1], Dr. Nandam Mohan Rao[2], Dr. Byna Syam Sundara Rao[3], Dr. Grandhi Bhavana[4], Dr. Muramreddy Vijayalakshmi[5], Dr. Baru Ramakrishna Rao[6]

[1]Professor & HOD, Department of Pathology, Narayana Medical College, Nellore (A.P), India
[2,3,4,5]Professor, Department of Pathology, Narayana Medical College, Nellore (A.P.), India
[6]Professor & HOD, Department of Radiology, Narayana Medical College, Nellore (A.P), India

Corresponding Author: Dr. Kharidehal Durga

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ABSTRACT

Introduction: Pancreatic mixed neuroendocrine non-neuroendocrine neoplasms are extremely rare tumours accounting for 0.5% of all the pancreatic malignancies and 5% of all pancreatic neuroendocrine neoplasms. These tumors are rarely diagnosed preoperatively and they have a poor prognosis. Pancreatic MiNEN is characterized by 2 malignant lesions adenocarcinoma and Neuroendocrine tumour with each constituent involving more than 30% of the tumour.

We report a case of 57yr old male with dullaching abdominal pain radiating to back. CA 19-9 was mildly elevated. Other laboratory tests are within normal limits. CECT abdomen revealed bulky pancreas with specks of calcification in the head of the pancreas and few tiny non enhancing hypodense areas and a well defined isodense lesion measuring 1.2x1.4cm in the second part of duodenum with enhancement in post contrast images associated with thickness of duodenal wall.

The patient underwent Whipple's pancreaticoduodenectomy with regional lymphadenectomy. Histopathological examination of specimen revealed an infiltrating acinar adenocarcinoma of the pancreas interspersed with a well differentiated neuroendocrine tumour component which made up of more than 45% of the tumour. The features were consistent with Mixed Neuroendocrine Non-Neuroendocrine Neoplasm of the pancreas.

KEY WORDS: MiNEN, Pancreas, Neuroendocrine, Non-neuroendocrine, Adenocarcinoma

INTRODUCTION

MiNEN is a rare and heterogenous malignancy of the pancreas which has been defined as the histological presence of both neuroendocrine and exocrine acinar or ductal adenocarcinoma components. Both components should account for atleast 30% of the tumour,[1] and both components should be malignant.[2]

MiNEN can involve various organs including stomach, colon, biliary tract and the uterine cervix, but has been infrequently reported in the pancreas.[3]

The histological features of MiNEN were newly defined in 2017, in the WHO classification of Tumours of Endocrine Organs 4th edition, from the old definition of mixed adeno neuroendocrine carcinoma (MANEN).[4] Its main characteristic feature is the presence of two neoplastic components a neuroendocrine and an epithelial one, each accounting for at least 30%of the tumour mass.[5]

CASE REPORT

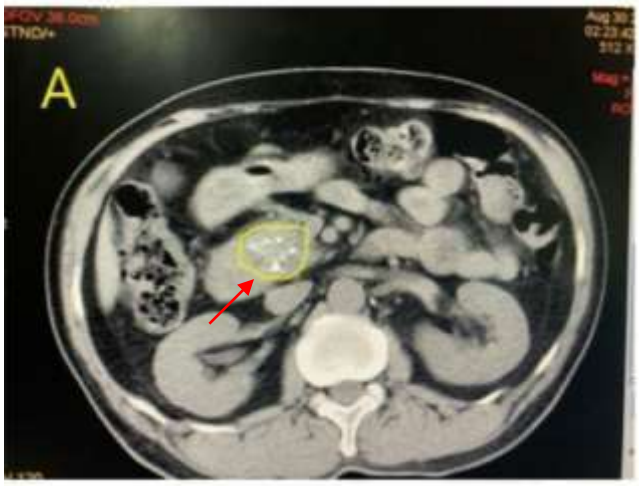
A 57 year old male presented with dull aching abdominal pain radiating to the back with loss of weight and loss of appetite. He has past history of acute pancreatitis 6 months back. There was no history of fever, jaundice or alcoholism. Physical examination was unremarkable.

Lab investigations including serum electrolytes, LFT, complete hemogram were within normal limits. Screening for tumour markers showed a mildly elevated CA 19-9 of 42U/ml, CEA was within normal limits. Upper GI endoscopy findings were unremarkable.

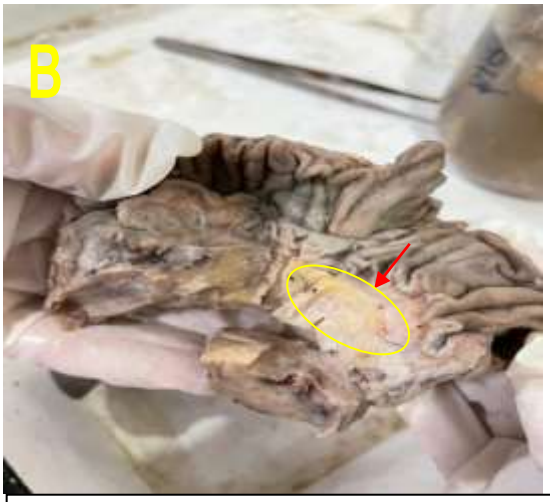
CECT abdomen revealed a partially distended gall bladder with dilated CBD of 13.8mm. Pancreas was mildly bulky with tiny specks of calcification in the head of the pancreas along with non enhancing hypodense areas. A well defined isodense lesion measuring 1.2x1.4cm was noted in the second part of duodenum with enhancement in post contrast images associated with thickness of duodenal wall reported as possibly duodenal mass/ periampullary lesion. In view of CECT findings (Fig 1A) showing a periampullary lesion/ duodenal mass, patient underwent Whipple's pancreaticoduodenectomy with regional lymphadenectomy.

Grossly pancreas measured 4.5 cm with thickening of the periampullary region and showing multiple grey white to grey yellow nodules in the pancreatic body and tail on cut section (Fig 1B). 8 lymph nodes were resected largest measuring 2x1cm and smallest measured 1x0.5 cm which were grey white on cut section.

Fig 1



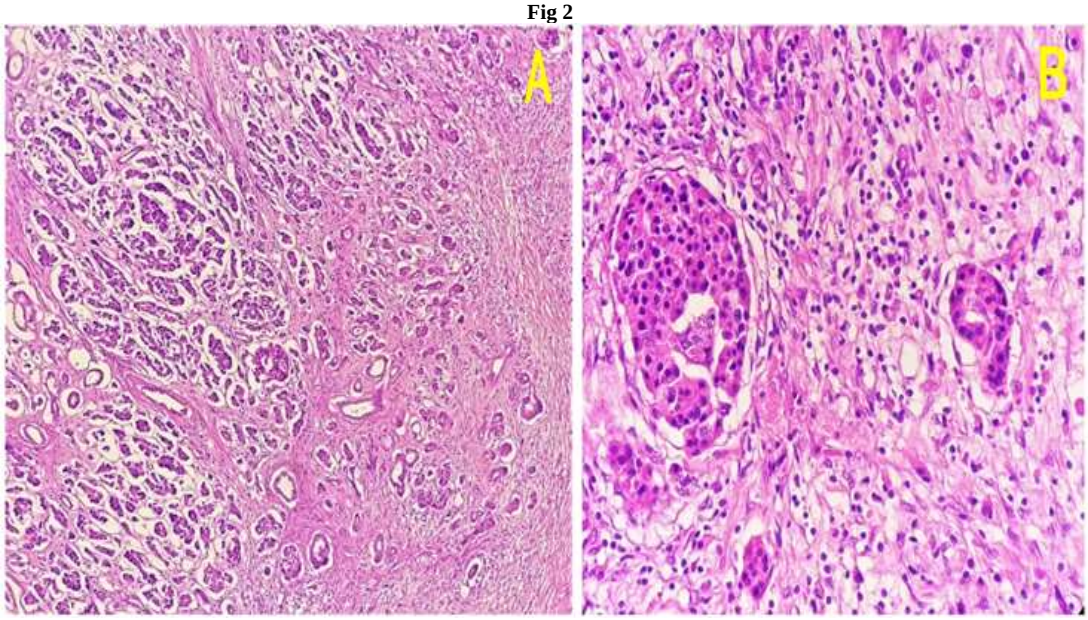
CECT findings showing non enhancing hypodense areas in the head of pancreas



Cut section showing grey white to grey yellow areas in pancreas

Histopathological examination of the pancreas revealed a tumour consisting of 2 neoplastic populations with sheets, ribbons and trabecular pattern of neuroendocrine cells making up >45% of the tumour, with mitotic rate <2 mitosis/2 mm square (Grade G1). Interspersed within these neuroendocrine tumour cells were infiltrating adenocarcinoma cells in acinar pattern (Fig2A, 2B). Evidence of infiltration noted extending through the duodenal mucosa upto the muscularis propria. Each component accounted for >30% of the tumour. All resected margins were free from tumour. All the 8 lymphnodes examined showed reactive follicular hyperplasia without the evidence of metastasis. The Pathological stage was $pT_2N_0M_x$.

Fig 2

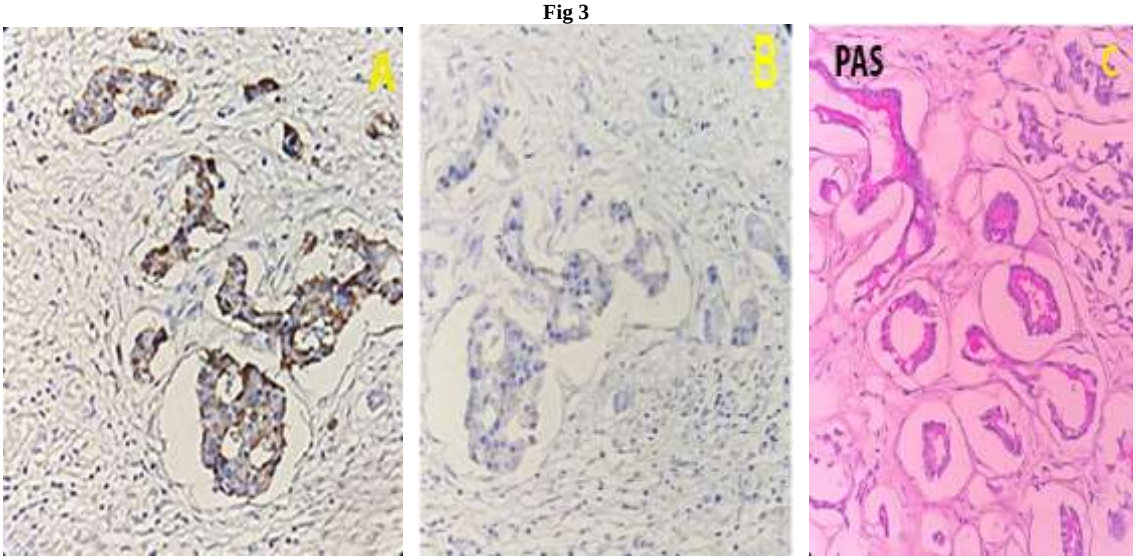


Acini lined by pleomorphic tumor cells along with neuroendocrine cells in glandular pattern (H & E X100)

Neuroendocrine cells with finely granular eosinophilic cytoplasm (H & E X400)

On immunohistochemistry the neuroendocrine component was immunoreactive to Chromogranin and Synaptophysin (Fig 3A & 3B) and the acinar structures were positive for CK7/EMA and negative for CK20, which was consistent with Mixed NeuroEndocrine and Non neuroendocrine Neoplasm of the pancreas. Strong PAS positivity was also noted in the acinar structures.(Fig 3C).

Fig 3



Neuroendocrine cells showing chromogranin positivity (IHC, X400)

Neuroendocrine cells showing synaptophysin positivity (IHC, X400)

Pancreatic ducts showing PAS positive material (PAS, X100)

Post operatively the patient did well and was discharged on the 7th day in a stable condition and was sent for chemotherapy. At the end of one year follow up, CECT abdomen showed no evidence of recurrence or metastasis. Long term follow up is advised.

DISCUSSION

Earlier mixed tumours were defined under the term MANEC (mixed adeno neuroendocrine carcinoma). The WHO Classification of Tumours of the Endocrine Organs 2017 introduced the term MiNEN for the first time and also extended this concept to all gastrointestinal organ mixed neuroendocrine non neuroendocrine tumours.[5]

Pancreatic MiNEN is a heterogenous malignancy characterized by presence of two malignancies neuroendocrine tumour and adenocarcinoma with each constituent involving more than 30% of the tumour. These tumours are usually seen in elderly patients with a median age of 60yrs and can be located in any part of the pancreas.[6]

The histogenesis of MiNEN is controversial though previous studies report origin from totipotential pancreatic stem cells residing in pancreatic islets.[7,8]

MiNEN can be morphologically classified into 3 different categories

1. Collision MiNEN's
2. Composite MiNEN"s
3. Amphicrine MiNEN'S.

Collision MiNEN's include tumours where the two malignant cell populations are juxtaposed without mixing. Composite MiNEN'S where there is an intermingled population of two different tumour cell populations. Amphicrine MiNEN's where cells show phenotype of two different types of malignancies but tumour shows only one cell population.[5,9]

La Rosa et al graded MiNEN's on their degree of malignancy. High grade MiNEN is composed of a non-neuroendocrine carcinoma or adenoma and Neuroendocrine carcinoma where the latter is very aggressive. Intermediate grade MiNEN combines a non-neuroendocrine carcinoma with a well differentiated neuroendocrine tumour and the prognosis depends on the Non neuroendocrine component. Low grade MiNEN combines an adenoma with a well differentiated neuroendocrine tumour.[5,10]

Our case is a composite type of MiNEN, Intermediate grade with intermingled non neuroendocrine infiltrating acinar component with a well differentiated neuroendocrine tumour (mitotic rate <2mitosis / 2 square mm).

Pancreaticoduodenectomy is the standard procedure of treatment. Histopathological examination with IHC is the gold standard to confirm MiNEN. PAS positive acinar structures with positivity for CEA and MUC 1 indicate ductal differentiation and positivity for synaptophysin and chromogranin indicate neuroendocrine differentiation. [11]

According to La Rosa et al, management should focus on the dominant cell type as the outcome follows the more aggressive cell type and the overall prognosis is poor. [12]

CONCLUSION

MiNEN of the pancreas is an extremely rare heterogenous tumour which is challenging to diagnose preoperatively because of its nonspecific clinical presentation. Hence, histopathology and IHC is the gold standard for diagnosis. Our case is a composite type of MiNEN, Intermediate grade showing intermingled non neuroendocrine infiltrating acinar component with a well differentiated neuroendocrine tumour. Immunohistochemically, acinar component was positive for CK7 and negative for CK20 and the Neuroendocrine component was positive for synaptophysin and chromogranin.

Declaration by Authors

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