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CASE REPORT OPEN ACCESS

Clinical heterogeneity in pancreatic neuroendocrine tumors: A case series of eight patients and their outcomes

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Abstract

Pancreatic neuroendocrine tumors (NETs) are rare neoplasms, accounting for less than 3% of all primary pancreatic tumors, with an annual incidence of ≤1 per 100,000 population. They may occur sporadically or in association with hereditary syndromes such as multiple endocrine neoplasia type 1 (MEN-1), neurofibromatosis type 1 (NF-1), tuberous sclerosis, or Von Hippel–Lindau syndrome. Clinically, NETs are categorized as functioning (F-NET) or non-functioning (NF-NET) based on hormone secretion and associated symptoms. We retrospectively analyzed eight patients with pancreatic NETs managed in the Department of Endocrinology. Four patients had functioning tumors (insulinomas), all presenting with symptomatic hypoglycaemia, confirmed by low plasma glucose with inappropriately elevated insulin and C-peptide levels. These patients underwent surgical or minimally invasive procedures, resulting in complete resolution of symptoms. The four non-functioning NET cases presented with features related to mass effect or metastasis, including two patients with underlying hereditary syndromes. Management included surgical resection and, in advanced cases, systemic therapies such as somatostatin analogues (octreotide LAR) and peptide receptor radionuclide therapy (PRRT). Clinical outcomes ranged from stable disease to progression-free intervals depending on tumor grade and stage. This case series highlights the clinical heterogeneity of pancreatic NETs and underscores the importance of multimodal imaging, histopathological grading, and individualized therapeutic strategies. While surgery remains curative for most insulinomas, advanced NF-NETs often require multimodal systemic management. Long-term surveillance is essential due to the potential for recurrence or disease progression.

Keywords: pancreatic NET; insulinoma; functioning NET; non-functioning NET; MEN-1; NF-1; octreotide LAR; PRRT

Introduction

Pancreatic neuroendocrine tumors (pancreatic NETs) are rare neoplasms with an estimated incidence of ≤1 per 100,000 population per year, accounting for less than 3% of all primary pancreatic tumors [1]. These tumors may occur sporadically or in association with hereditary syndromes such as multiple endocrine neoplasia type 1 (MEN-1), neurofibromatosis type 1 (NF-1), tuberous sclerosis, and Von Hippel–Lindau syndrome [2]. Pancreatic NETs are broadly classified into functioning (F-NET), which secrete bioactive peptides leading to characteristic clinical syndromes, and non-functioning NETs (NF-NET), which may secrete peptides such as pancreatic polypeptide but do not produce overt clinical symptoms [3, 8].

Given their heterogeneity in clinical presentation, biological behavior, and therapeutic response, early diagnosis and individualized management plays a crucial role in improving outcomes. Advancements in cross-sectional imaging, endoscopic ultrasound, functional imaging, and histopathological grading have significantly improved diagnostic precision and treatment planning in recent years [4–7].

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In this case series, we retrospectively analyzed eight patients with pancreatic NETs managed in the Department of Endocrinology. Four patients had functioning tumors (insulinomas), all presenting with symptomatic hypoglycaemia, confirmed by low plasma glucose with inappropriately elevated insulin and C-peptide levels. The objective of this report is to describe their clinical profiles, diagnostic approaches, management strategies, and outcomes to highlight the heterogeneity of pancreatic NETs and the importance of comprehensive multidisciplinary care.

Case presentations

We retrospectively collected data from eight patients diagnosed with pancreatic neuroendocrine tumors (NETs) in the Department of Endocrinology, Krishna Institute of Medical Sciences Hospital, between March 2022 and February 2024. Clinical presentations, biochemical profiles, imaging findings, histopathology, staging, treatments, and follow-up outcomes were analyzed. Data were obtained from inpatient medical records, outpatient follow-up documentation, and laboratory databases.

Patient demographics such as age, sex, and presenting symptoms were reviewed along with biochemical evaluation, including plasma glucose levels assessed in correlation with simultaneously measured insulin and C-peptide concentrations to confirm endogenous hyperinsulinism in functioning NETs (insulinomas). Imaging modalities included contrast-enhanced computed tomography (CECT), Ga-68 DOTATATE PET/CT, Ga-68 Exendin PET/CT where indicated, and endoscopic ultrasound (EUS) for localization and staging. Histopathological analysis provided tumor grade, Ki-67 (MIB-1) proliferation index, and immunohistochemical characteristics. Therapeutic interventions included surgical resection, somatostatin analogues (octreotide LAR), and peptide receptor radionuclide therapy (PRRT) for advanced or unresectable disease. Clinical outcomes were monitored in relation to symptom resolution, disease progression, and long-term follow-up.

A total of eight pancreatic NET cases were evaluated, comprising four functioning and four non-functioning tumors. The study was approved by the Institutional Ethics Committee, and informed consent was obtained from all participants.

Case 1

A 30-year-old female with BMI 22.7 kg/m^2 presented with episodes of sweating and palpitations. Random blood glucose was 43 mg/dl, with markedly elevated insulin (109 µU/ml) and C-peptide (7.2 ng/ml), confirming endogenous hyperinsulinism. CECT abdomen was normal, but Ga-68 Exendin PET-CT localized a 3 × 4 cm hypermetabolic lesion (SUVmax 8.3) in the pancreatic tail. She underwent distal pancreatectomy, and histopathology confirmed WHO grade 1 NET with MIB-1 index of <3%, T2N0M0 (stage 2, AJCC 9). Postoperatively, the patient had no further hypoglycaemic episodes.

Case 2

A 36-year-old female with a BMI of 26 kg/m^2 presented with recurrent convulsions attributable to hypoglycaemia, with lowest documented RBS at 30 mg/dl. Insulin (39.9 µU/ml) and C-peptide (6.67 ng/ml) levels confirmed endogenous hyperinsulinism. CECT showed an exophytic lesion in the pancreatic tail, further characterized by EUS as a 1.2 × 1.3 cm hypoechoic lesion. The patient underwent laparoscopic distal pancreatectomy. Histopathology confirmed a WHO grade 1 NET with MIB-1 index of 2%, T1N0M0 (stage 1, AJCC 9). On follow-up, no further hypoglycaemic episodes were reported.

Case 3

A 45-year-old female with a BMI of 34.4 kg/m^2 presented with recurrent episodes of sweating and altered sensorium, with random blood glucose documented at 29 mg/dl. On examination there was grade 4 Acanthosis nigricans with skin tags as shown in figure 1.

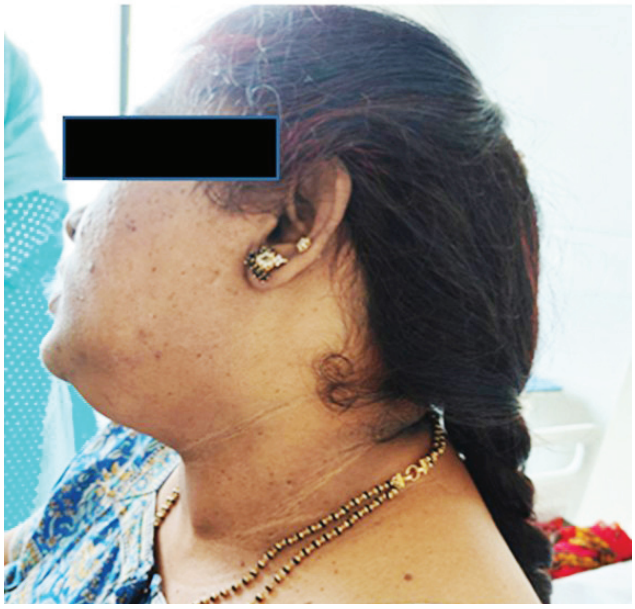

Figure 1: Case 3 with grade 4 acanthosis in insulinoma.

Laboratory investigations revealed elevated insulin (31.8 µU/ml) and C-peptide (2.28 ng/ml), confirming endogenous hyperinsulinism and fulfilling Whipple's triad. Contrast-enhanced CT and Ga-68 DOTATATE PET/

CT were normal, but endoscopic ultrasound detected a 1.8 × 1.6 cm hypoechoic lesion in the pancreatic body as shown in figure 2. Histopathology confirmed a WHO grade 1 neuroendocrine tumor with an MIB-1 index of 2%, T1N0M0 (stage 1, AJCC 9). The patient underwent endoscopic ultrasound-guided radiofrequency ablation (EUS-RA) at 30W for 12 seconds per spot. Post procedure there was complete resolution of hypoglycaemic episodes. No recurrence of symptoms on follow-up.

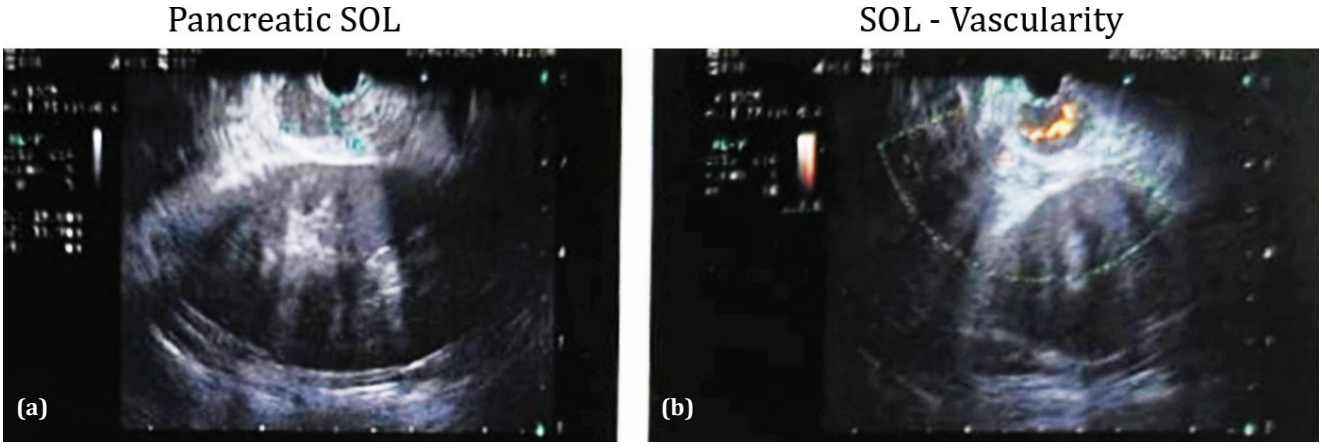

Figure 2ab: Case 3, endoscopic ultrasound.

Case 4

A 46-year-old male (BMI 28 kg/m^2) presented with recurrent episodes of sweating and fatigue, with documented blood glucose of 34 mg/dl. Laboratory evaluation showed elevated insulin (60.7 µU/ml) and C-peptide (5.69 ng/ml), confirming endogenous hyperinsulinism. CECT abdomen revealed a 1.9 × 1.6 cm lesion in the uncinate process of the pancreas, with no evidence of regional or distant disease on nuclear imaging. The patient underwent minimally invasive enucleation of the insulinoma. Histopathology confirmed a WHO grade 1 NET with an MIB-1 index <3%, staged as T1N0M0 (AJCC 9). On follow-up, he remained asymptomatic with complete resolution of hypoglycaemic episodes.

The presenting features and outcome data of the 4 functioning neuroendocrine tumor cases are enumerated in table 1 and 2 respectively.

Non-functioning pancreatic neuroendocrine tumors

Case 5

A 37-year-old female (BMI 24.5 kg/m^2), known to have Multiple Endocrine Neoplasia type 1 (MEN-1) with a history of pituitary macroadenoma and acromegaly, presented with backache. CT abdomen revealed an ill-defined isodense-to-hypodense lesion involving the head and uncinate process of the pancreas, along with multiple enlarged lymph nodes encasing the extrahepatic portal vein. Ga-68 DOTATATE PET/CT demonstrated multiple pancreatic lesions with metastatic deposits in the liver and regional lymph nodes. Histopathology confirmed a WHO grade 2 neuroendocrine tumor with a mitotic rate of 4/mm^2, staged as T3N1M1 (stage IV; AJCC 9). The patient was kept under active surveillance and continued to have stable disease on imaging at 2-year follow-up.

Case 6

A 53-year-old male (BMI 20 kg/m^2) presented with abdominal pain. CT imaging revealed a 2 × 3.4 cm lesion in the uncinate process of the pancreas, along with a metastatic lesion in the liver. Ga-68 DOTATATE PET/CT confirmed pancreatic and hepatic involvement with nodal metastases (figure 3). Histopathology showed a WHO grade 2 NET with a mitotic rate of 8 per 10 HPF, staged as T2N1M1 (stage IV;AJCC-9). The patient underwent surgical resection of the liver lesion and was initiated on octreotide LAR therapy. Due to progressive disease on follow-up imaging, he subsequently received three cycles of ^{177}Lu-DOTATATE PRRT (150 mCi). Post-treatment Ga-68 DOTATATE PET/CT demonstrated a reduction in lesion size and metabolic activity as shown in figure 4, and he achieved 2 years of progression-free survival following therapy.

Case 7

A 56-year-old male (BMI 19 kg/m^2) with clinical features suggestive of Neurofibromatosis type 1 (NF-1) including multiple cutaneous neurofibromas, café-au-lait macules, and palmar freckling (Figure 5) presented with jaundice. Ultrasonography of the abdomen revealed a 1.2 × 1.5 cm mass in the periampullary region

Table 1: Clinical and laboratory features of cases with functioning neuroendocrine tumor.

Age (yrs)/ Gender	*Presenting complaints*	*BMI (kg/m^2)*	*RBS (mg/dl)*	*Insulin (μU/ml) (NR=2.6-24.9)*	*c-peptide (ng/ml) (NR=0.81-3.85)*	*Diagnosis*
30/F	Sweating, palpitations	22.7	43	109	7.2	Endogenous hyperinsulinism
36/F	Convulsions	26	30	39.9	6.67	Endogenous hyperinsulinism
45/F	Episodes of sweating, altered sensorium	34.4	29	31.8	2.28	Endogenous hyperinsulinism
46/M	Sweating, Fatigue	28	34	60.7	5.69	Endogenous hyperinsulinism

Table 2: Functioning NETs cases localization methods, treatment and follow-up.

CECT abdomen	*Nuclear scan*	*Endoscopic ultrasound*	*HPE*	*MIB-1*	*Stage AJCC9*	*First line treatment*	*Follow-up*
Normal	68Ga-Exendin PET-CT: 3x4 cms lesion in tail (8.3-SUVmax)	-	NET WHO-Grade1	<3%	T2N0M0 (stage2)	Distal pancreatectomy	No further hypoglycaemic episodes
Normal	Exophytic Lesion in tail of pancreas	1.2x1.3 cms hypoechoic lesion in tail of pancreas	NET WHO-Grade1	2%	T1N0M0 (stage 1)	Laparoscopic Distal pancreatectomy	No further hypoglycaemic episodes
Normal	68Ga-DOTATATE PET-CT: Normal	1.8x1.6cms Lesion in body of pancreas	NET WHO-Grade1	2%	T1N0M0 (Stage1)	EUS guided Radio-Frequency ablation	No further hypoglycaemic episodes
1.9x1.6cms Lesion in uncinate process of pancreas	-	-	NET WHO-Grade1	<3%	T1N0M0 (stage1)	Minimally invasive enucleation of insulinoma	No further hypoglycaemic episodes

of the pancreas. Ga-68 DOTATATE PET/CT localized a corresponding somatostatin receptor–avid 1.9 × 1.5 cm lesion without evidence of metastasis (figure 6). Histopathological examination confirmed a WHO grade 1 neuroendocrine tumor with a mitotic rate <2/ mm^2, staged as T1N0M0 (stage I; AJCC-9). The patient underwent surgical resection of the periampullary mass and remained disease-free at 2-year follow-up.

Case 8

A 63-year-old male (BMI 18 kg/m^2) presented with progressive jaundice. CT abdomen revealed a 4.3 × 3 cm mass involving the head and uncinate process of the pancreas. Ga-68 DOTATATE PET/CT demonstrated somatostatin receptor–avid lesion in the pancreatic head and duodenum, with involvement of regional lymph nodes. Histopathology confirmed a WHO Grade 2 neuroendocrine tumor with a mitotic rate of 5 per 10 HPF, staged as T3N1M0 (stage III;AJCC-9). The patient underwent pancreaticoduodenectomy and was subsequently initiated on octreotide LAR therapy every 4 weeks. Due to disease progression, he later received four cycles of ^{177}Lu-DOTATATE PRRT (150 mCi). Follow-up Ga-68 DOTATATE PET/CT demonstrated reduced lesion size and markedly decreased tracer uptake, and he achieved 2 years of progression-free survival after therapy.

The presenting features and outcome data of the 4 non-functioning neuroendocrine tumor cases are enumerated in table 3 and 4 respectively.

Discussion

Optimal management of pancreatic NETs depends on tumor functionality, grade, and stage. Functioning tumors such as insulinomas cause hypoglycaemia due to autonomous insulin secretion. When clinical suspicion for insulinoma is high, localization strategies include functional imaging such as glucagon-like peptide-1 receptor PET/CT, endoscopic ultrasound, and, when required, selective arterial calcium stimulation with

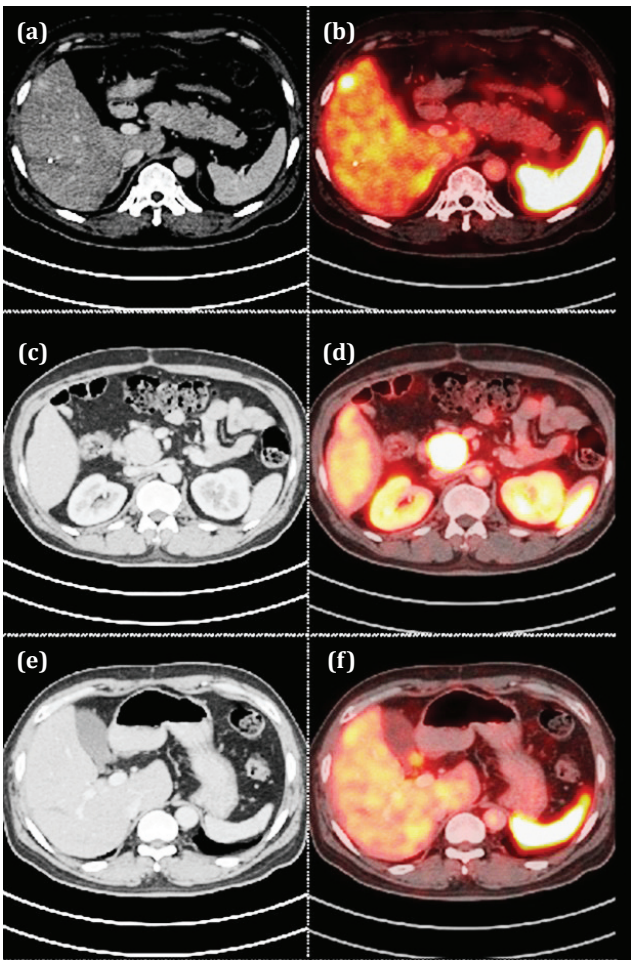

Figure 3a-e: Case 6- 68Ga DOTATATE PET/CT before PRRT showing lesion in pancreas.

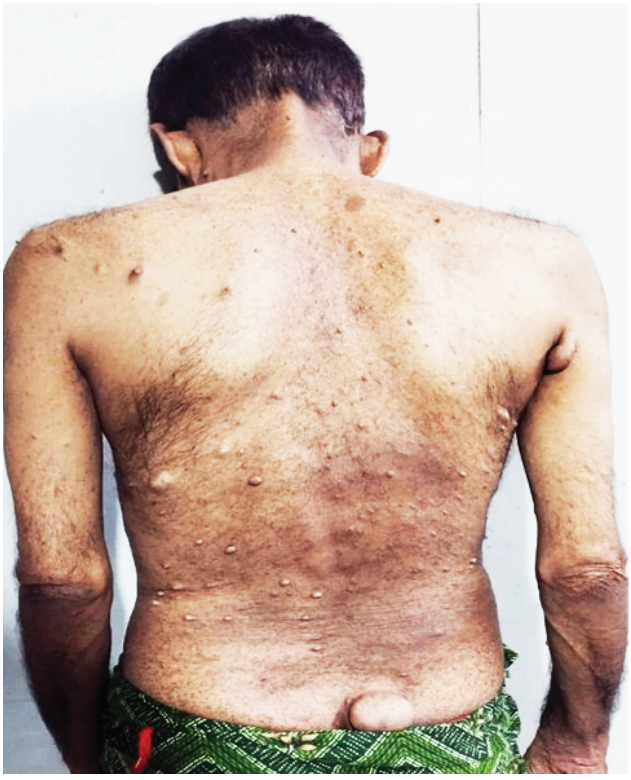

Figure 5: Case 6, NF-1 with neurofibromas and café-au-lait macules.

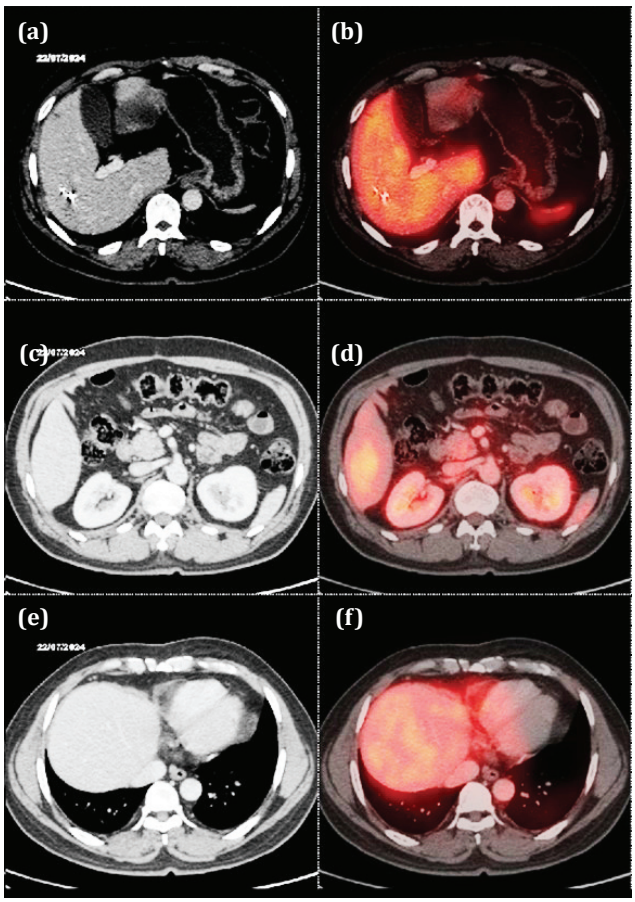

Figure 4a-e: Case 6- 68Ga DOTATATE PET/CT after PRRT, showing decrease in size and uptake of pancreatic lesion.

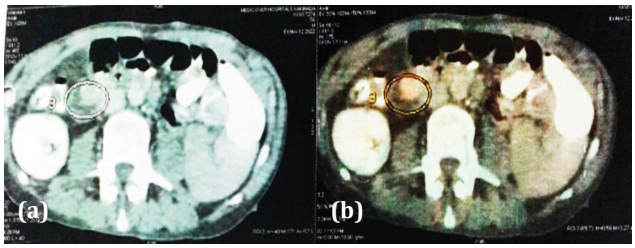

Figure 6a, b: PET CT scan of NF-1 case showing metabolically active lesion in peri-ampullary region measuring approximately 1.9x1.5x1.5 cms.

hepatic venous sampling (ASVS), which remains the diagnostic gold standard [13]. Medical management with diazoxide or somatostatin analogues may be necessary in patients who are not candidates for surgery. Prognosis is generally favorable after surgical resection; however, ongoing surveillance is essential, particularly in cases of malignant or metastatic disease [14]. Surgical excision or minimally invasive ablation aims to achieve cytoreduction, relieve symptoms, and prevent recurrence. Insulinomas typically demonstrate benign histological features and excellent long-term survival outcomes [2, 6, 7].

Non-functioning pancreatic NETs often present at an advanced stage due to mass effect or metastatic

Table 3: Clinical features, imaging of cases non-functioning pancreatic NETs.

Age (yrs)/ Gender	*Presenting complaints*	*BMI (kg/m²)*	*Associated syndrome*	*Imaging findings*
37/F	backache	24.5	MEN-1 (h/o pituitary macroadenoma-Acromegaly)	CT abdomen: ill-defined iso-hypodense lesion in head and uncinate process of pancreas, multiple enlarged lymph nodes encasing extrahepatic portal vein
53/M	Pain abdomen	20	-	CT abdomen- 2x3.4 cms lesion in uncinate process of pancreas and liver lesion
56/M	Jaundice	19	NF-1 (cutaneous neurofibromas, café-au-lait macules, palmar freckling -present)	USG abdomen- 1.2x1.5 cms mass in peri-ampullary region of pancreas
63/M	Jaundice	18	-	CT abdomen: 4.3x3 cms mass in head and uncinate process of pancreas

Table 4: Nuclear scan, histopathology, staging and treatment in NF-NETs.

Ga-68 DOTATATE PET/CT	*HPE*	*Mitotic Rate*	*Staging AJCC9*	*First line treatment*	*Oct LAR*	*At 12 weeks*	*PRRT*	*Follow-up*
Multiple lesions in pancreas, with metastasis in liver and LNs	NET WHO-Grade2	4/ mm2	T3N1M1 (Stage4)	Surveillance	-	Stable disease	-	Stable disease at 2 years
Lesion in the pancreas, liver and LNs	NET WHO-grade2	8/10 hpf	T2N1M1 (stage4)	Resection of lesion in the liver	Every 4 weekly	Progressive	3 cycles	Decrease in size and uptake of lesion in Ga-68 DOTATATE PET/CT and 2 years PFS
1.9x1.5cms periampullary mass	NET WHO-grade1	<2/ mm2	T1N0M0 (stage1)	Surgical resection of periampullary mass	-	-	-	2 years DFS
Lesion in head of pancreas & duodenum, LNs	NET WHO-garde2	5/10 hpf	T3N1M0 (stage3)	Pancreatico-duodenectomy	Every 4 weekly	Progressive	4 cycles done	Decrease in size and uptake of lesion in Ga-68 DOTATATE PET/CT and 2 years PFS

symptoms. Management involves surgical resection when feasible, along with systemic therapies such as somatostatin analogues (octreotide LAR) for tumors that express somatostatin receptors [2, 7, 9]. Clinical studies have reported a median time to tumor progression of 14.3 months in patients treated with octreotide compared to 6 months in those receiving placebo. PET/CT-based assessments have shown partial response rates of approximately 26%, stable disease in 61%, and disease progression in 11%, with a reported 5-year overall survival of nearly 61.8% among treated individuals [3-5, 9].

Peptide receptor radionuclide therapy (PRRT) has emerged as an effective option for unresectable or metastatic NETs with somatostatin receptor overexpression, significantly improving progression-free survival [10]. The NETTER-2 trial demonstrated a marked increase in median progression-free survival—22.8 months with PRRT compared to 8.5 months with placebo—highlighting its therapeutic value [11]. Given the potential for recurrence or progression, lifelong surveillance remains critical for all pancreatic NET patients [7, 8].

Conclusion

This case series highlights the clinical heterogeneity of pancreatic neuroendocrine tumors and underscores the importance of multimodal imaging, histopathological grading, and individualized therapeutic approaches. Functioning insulinomas demonstrate a high curative potential with timely surgical intervention, whereas non-functioning NETs often require systemic therapies such as somatostatin analogues and PRRT in advanced or unresectable disease, contributing to symptom control and improved quality of life. Lifelong surveillance

remains essential, as systemic therapies primarily achieve tumor stabilization or reduction rather than complete cure in advanced NETs.

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Conflicts of interest

Authors declare no conflicts of interest.

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