Case Report

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Surgery Section

Synchronous Cystic Duct and Duodenal Neuroendocrine Tumours in a Patient with Neurofibromatosis 1: A Case Report

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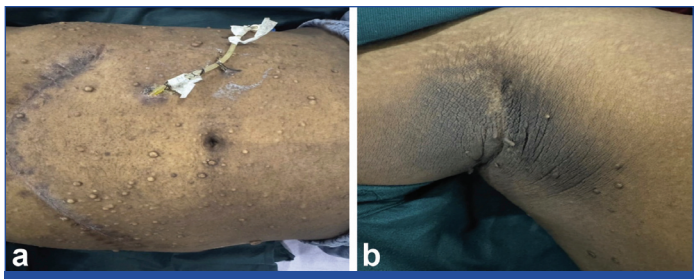
ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominant tumour-predisposition syndrome associated with various tumours. Amongst gastrointestinal tumours, Gastrointestinal Stromal Tumours (GISTs) and periampullary Neuroendocrine Tumours (NET) are most common. The authors describe a 43-year-old male with long-standing NF1 who presented with chronic dyspepsia and episodic right upper-quadrant pain. Imaging revealed an enhancing lesion at the cystic duct-common hepatic duct junction and a peri-duodenal lesion. ^{68}Ga-DOTANOC PET/CT demonstrated somatostatin receptor-avid lesions in the duodenum and a regional lymph node, suggesting multifocal neuroendocrine neoplasia. The patient underwent classical pancreaticoduodenectomy. Histopathology subsequently confirmed synchronous primary neuroendocrine tumours of the cystic duct and duodenum, with the regional lymph node showing involvement by the cystic duct neuroendocrine tumour. Histopathology demonstrated a well-differentiated grade 2 NET of the cystic duct and a separate microscopic grade 2 duodenal tumour. This represents an exceptionally rare synchronous occurrence; to our knowledge, no previous report has described this co-existence, thereby expanding the spectrum of NF1-associated gastrointestinal NETs.

Keywords: Ampulla, Biliary tract, Classical pancreaticoduodenectomy, Ki-67 index, Prognosis, Syndromic predisposition

CASE REPORT

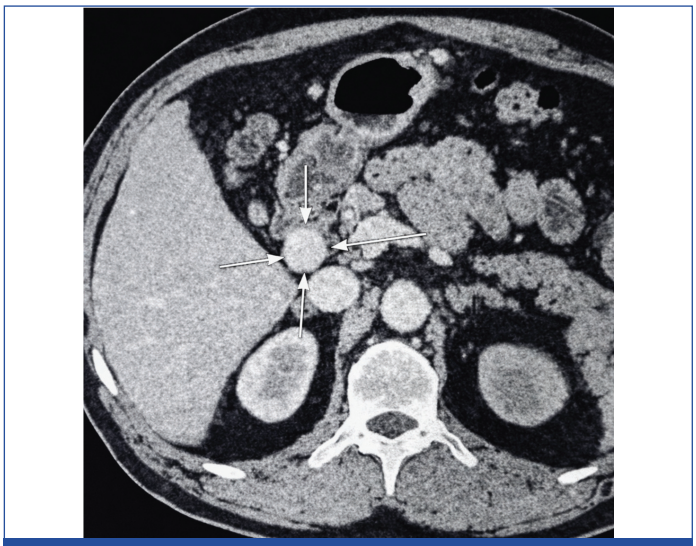
A 43-year-old male presented with the chief complaint of recurrent dyspepsia for two years. Patient was apparently asymptomatic two years back, following which he presented with dyspepsia associated with intermittent non bilious vomiting and right upper-quadrant abdominal pain for one year. There was no history of jaundice, pruritus, gastrointestinal bleeding or weight loss. He had a known history of NF1 diagnosed clinically since childhood. However, there was no family history of NF1 with no history of prior surgeries or NF1-associated tumours. Clinical examination revealed multiple cutaneous neurofibromas [Table/Fig-1a] and axillary freckling [Table/Fig-1b]. No other associated NF1 co-morbidities were present.



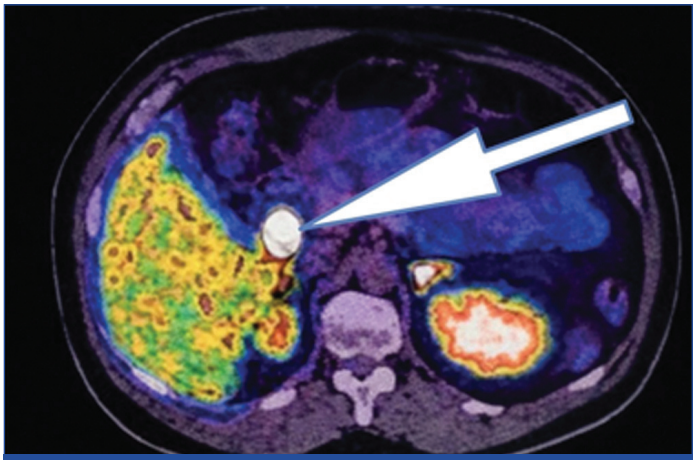
[Table/Fig-1]: a) Clinical photograph revealing multiple cutaneous neurofibromas in the trunk region, with bilateral subcostal incision and in situ feeding jejunostomy tube; b) Clinical photograph revealing axillary freckling.

Contrast-enhanced Computed Tomography (CECT) demonstrated a well-defined, homogeneously enhancing lesion measuring approximately 19 mm at the cystic duct-common hepatic duct junction, along with a second peri-duodenal enhancing lesion measuring 9 mm [Table/Fig-2].

^{68}Ga-DOTANOC PET/CT showed intense somatostatin receptor uptake in the duodenal lesion and a regional lymph node, suggesting multifocal neuroendocrine neoplasia [Table/Fig-3]. Oesophagogastroduodenoscopy (EGD) revealed multiple tiny nodular lesions with central umbilications in some lesions seen throughout the second part of duodenum



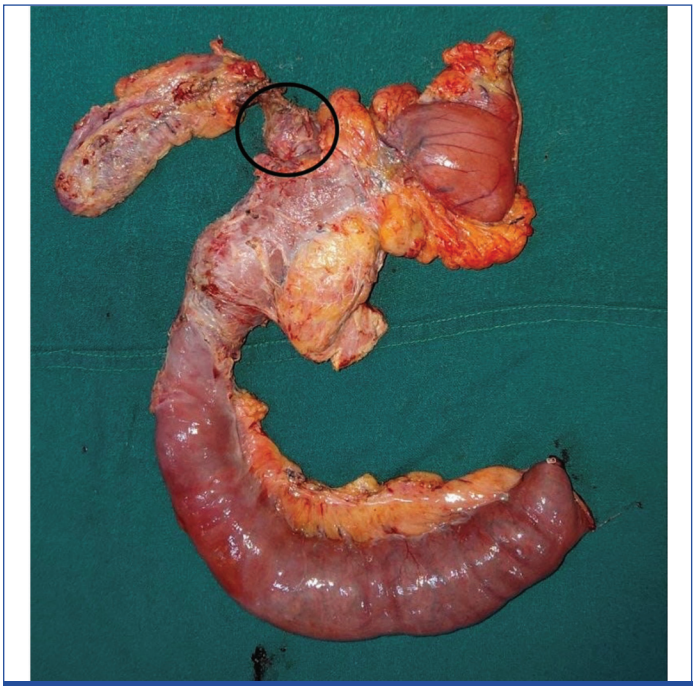
[Table/Fig-2]: CECT axial section revealing a tumour located at cystic duct-common hepatic duct junction (white arrows).



[Table/Fig-3]: DOTANOC PET/CT abdomen and pelvis with MRI screening showing DOTANOC avid duodenal lesion (white arrow).
MRI: Magnetic resonance imaging

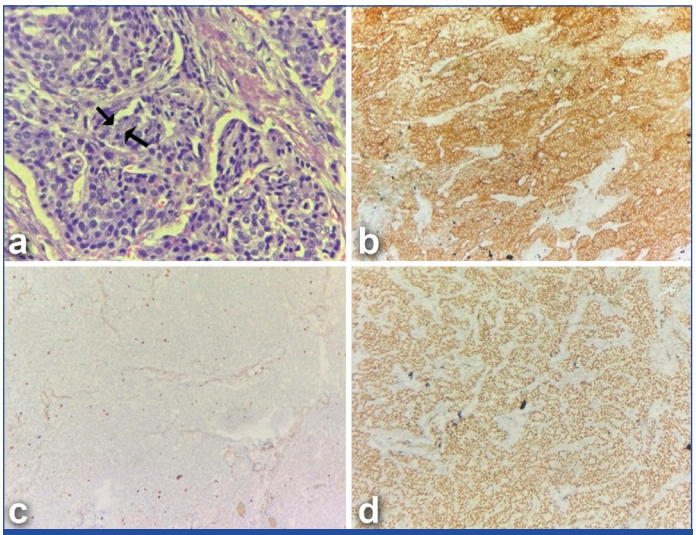
Tumour markers, such as chromogranin A and serotonin, were not measured preoperatively. The patient underwent a classical pancreaticoduodenectomy. The pancreaticoduodenectomy was challenging because of the multi-organ involvement and the need for associated biliary tract resection. Reconstruction was further complicated by the presence of a soft pancreas, which increased the technical difficulty of the pancreatic anastomosis and the risk of postoperative pancreatic leak. These factors required meticulous operative planning and close perioperative management.

Intraoperatively, a firm lesion was noted near the D1-D2 junction with desmoplastic reaction in the hepatoduodenal ligament. Gross examination revealed a 2×2×1.8 cm tumour arising from the cystic duct wall and two microscopic nodules within the duodenum [Table/Fig-4].



[Table/Fig-4]: Clinical photograph revealing a Whipple's specimen showing lesion in the cystic duct near its insertion at the lateral wall of Duodenum D1-D2 (Black circle).

Histopathology showed well-differentiated NETs composed of uniform cells with finely stippled chromatin. Immunohistochemistry demonstrated diffuse synaptophysin positivity and strong nuclear INSM1 (Insulinoma Associated Protein 1) positivity [Table/Fig-5a-d]. The cystic duct tumour had a Ki-67 index of 10-12%, while the duodenal lesion showed a Ki-67 index of 4%, both consistent with grade 2 NETs according to the World Health Organisation (WHO) classification [1]. All surgical margins were free of tumour. The patient had grade 1 Delayed Gastric Emptying (DGE) during the postoperative period, which was managed conservatively, following which he was discharged two weeks after surgery. He was started on long-acting somatostatin analogue therapy in view of a high rate of recurrence after discussion in the multidisciplinary board. The patient was kept on monthly follow-up. Patient is currently asymptomatic with no evidence of tumour relapse after eight months of follow-up.



[Table/Fig-5]: a) High-power view of NET revealing chromatin stippling and characteristic salt and pepper pattern (black arrows) (H&E , 400×); b) Synaptophysin stained NET showing diffuse, strong, cytoplasmic and membranous positivity (100×); c) Ki-67 stained NET biopsy showing 10-12% positivity (100×); d) Insulinoma Associated Protein 1 (INSM1) stained NET showing diffuse, strong nuclear positivity (100×).

DISCUSSION

The NF1 is a common autosomal dominant neurocutaneous disorder with an estimated incidence of approximately one in 3000-4000 people worldwide [2]. It results from pathogenic variants in the NF1 gene, leading to a deficiency of neurofibromin, a tumour suppressor protein that negatively regulates the Rat sarcoma/Mitogen-activated protein kinase (RAS/MAPK) signalling pathway [2].

Well-differentiated NETs are divided into three grades. Grade 1 (G1) tumours are defined by a Ki-67 index of <3% and fewer than two mitoses per 10 high-power fields, reflecting low proliferative activity and typically indolent behaviour. Grade 2 (G2) tumours demonstrate a Ki-67 index between 3% and 20% or 2-20 mitoses per 10 high-power fields, indicating intermediate biological activity and a higher likelihood of recurrence compared to G1 lesions. Grade 3 (G3) well-differentiated tumours have a Ki-67 index greater than 20%, signifying high proliferative potential [1]. In the present case, the tumour showed a Ki-67 index of 10-12%, clearly placing it within the Grade 2 category.

Ben Rejeb S et al., documented a 51-year-old male who underwent laparoscopic cholecystectomy for presumed acute cholecystitis. Histopathological examination unexpectedly revealed a well-differentiated grade 1 NET involving the cystic duct margin with subserosal invasion (pT2). Histopathological analysis of the resected specimen demonstrated no residual tumour and no lymph node involvement. The patient did not receive adjuvant therapy and remains free of disease recurrence after five years of follow-up [3].

Saito Y et al., described a woman in her 40s who presented with jaundice and elevated hepatobiliary enzymes. Imaging revealed a 17 mm enhancing nodule at the junction of the cystic and common hepatic ducts. Endoscopic Ultrasound (EUS) and Intraductal Ultrasound (IDUS) demonstrated a well-circumscribed hypoechoic submucosal lesion, raising suspicion for a NET. She underwent cholecystectomy with extrahepatic bile duct resection, and histopathology confirmed a WHO grade 1 NET. The patient remained recurrence-free at the 2-year follow-up [4].

The present case adds to the knowledge on the presentation of cystic NETs, which was similar to the above-mentioned cases. As per authors' knowledge, this represents the first reported case of synchronous NETs involving both the cystic duct and the duodenum in a patient with NF1.

Cristescu B et al., reported a 63-year-old male presented with acute gangrenous cholecystitis and underwent laparoscopic cholecystectomy. Histopathology unexpectedly revealed a 4-5 mm grade 1 NET obstructing the cystic duct, with positive cystic duct margins, Ki-67 <3%, and no lymph node involvement [5].

The lesions in the present case are both primary synchronous lesions and not metastatic as shown by their varying Ki67 indices, the cystic duct NET showing Ki-67 index of 10-12%, whereas duodenal lesion showing 4% Ki-67 positivity, as they have different Ki-67 indices, distinct anatomical locations, and absence of vascular features suggestive of metastasis. A limitation of this report is that it describes a single case, thereby limiting the generalisability of the findings. In addition, preoperative biochemical evaluation with NET markers such as chromogranin A and serotonin was not performed, which may have further supported the diagnostic workup.

CONCLUSION(S)

Cystic duct NETs are rare biliary neoplasms and their co-existence with NF1 appears to be exceptionally uncommon. By reporting this case, the authors highlight a previously unrecognised manifestation within the tumour spectrum of NF1. Recognition of such rare presentations broadens clinical awareness and may facilitate timely diagnosis and individualised management in similar patients.

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