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Case Report

Synchronous gastrointestinal stromal tumour and neuroendocrine tumour in a patient with neurofibromatosis type 1: a rare clinical association

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ABSTRACT

Type 1 Neurofibromatosis (NF1) is an autosomal dominant disorder caused by germline mutation of the NF1 gene. While it typically manifests as multiple cutaneous neurofibromas and café-au-lait macules, patients also have an inherent predisposition to neoplasms arising from neural crest–derived tissues and the gastrointestinal tract. GISTs are relatively well-recognized in NF1, whereas neuroendocrine tumours (NET) are uncommon. The synchronous occurrence of both NET and GIST in an NF1 patient is exceedingly rare. We present a 53-year-old female with known NF1 who developed synchronous small-bowel GIST and pancreatic NET. The patient presented with intermittent jaundice. Imaging suggestive of periampullary carcinoma. During Whipple's procedure, lesions suggestive of periampullary carcinoma and small bowel GIST were identified. Both tumours were resected. Histopathology confirmed high grade spindle-cell GIST and well-differentiated NET. The postoperative course was uneventful. NF1-associated GISTs are not uncommon, but coexistent NETs are rare and easily overlooked. This case underscores the need for heightened vigilance and a broadened differential diagnosis in NF1 patients presenting with gastrointestinal symptoms, as synchronous multifocal tumours may be missed without careful evaluation.

Keywords: Neurofibromatosis type 1, GIST, Neuroendocrine tumour

INTRODUCTION

NF1, first described by von Recklinghausen, is a multisystem genetic disorder caused by a mutation in the NF1 tumor-suppressor gene located on chromosome 17q11.2. It affects approximately 1 in 3000 individuals.[1] While the hallmark features include multiple cutaneous neurofibromas, axillary freckling, lisch nodules, and skeletal abnormalities, NF1 patients also have a significantly increased risk for tumors such as malignant peripheral nerve sheath tumors, pheochromocytomas, and various gastrointestinal neoplasms. Gastrointestinal manifestations occur in 10-25% of NF1 patients, with GISTs being the most common.[2,3] However, NETs are far less frequently described in association with NF1. The synchronous presentation of both GIST and NET is extremely rare, with only a small number of cases documented. Here, we report a patient with NF1 presenting with synchronous NET and GIST, highlighting the importance of thorough intra-abdominal evaluation in NF1 patients.

CASE REPORT

A 53-year-old female with a known history of neurofibromatosis type 1 presented to our department with complaints of pain in the epigastric and right hypochondrial region associated with on and off

yellowish discoloration of eyes. The patient had cutaneous neurofibromas throughout the body (Figure 1). No significant family history.

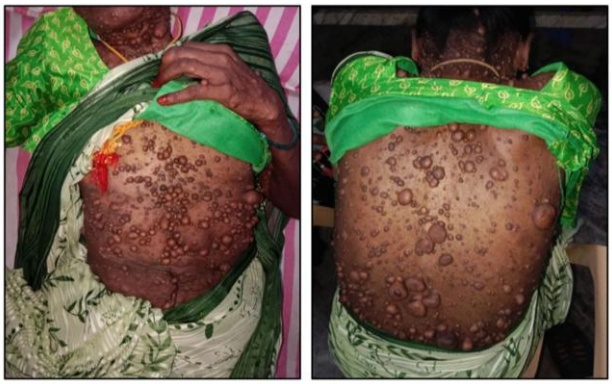

Figure 1: 53-year-old female with cutaneous manifestations of neurofibromatosis type 1.

Investigations

Routine laboratory tests revealed elevated liver enzymes including significant rise in ALP. Except for elevated CEA, other specific tumour markers such as CA 19-9 and serum chromogranin were normal contrast-enhanced CT showed heterogeneously enhancing soft tissue lesion in periampullary region causing infiltration and narrowing of the Common bile duct (CBD) and main pancreatic duct (MPD) (Figure 2). Upper GI endoscopy revealed prominent ampulla with ulcerations.

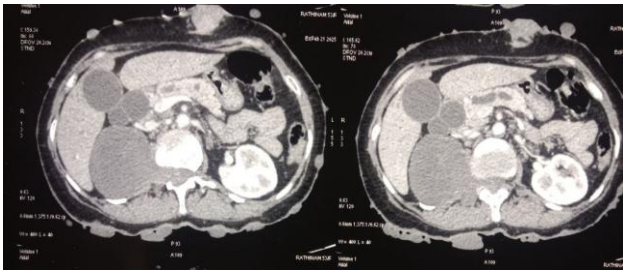

Figure 2: Contrast-enhanced CT of the abdomen.

Operative findings

The patient underwent Whipple's procedure. Intraoperatively, 2x2 cm periampullary mass noted with grossly dilated MPD and CBD (Figure 3). Incidentally, multiple serosal nodules noted arising from proximal jejunum; one such serosal nodule was excised and sent for histopathological examinations (Figure 4).

Histopathology

Periampullary mass showed a well-differentiated grade 1 NET. On Immunohistochemistry (IHC) the tumour had Ki-67 <1% and it was positive for synaptophysin (Figure 5 and 6). The small bowel serosal nodule revealed GIST of spindle-cell type with Ki-67 of 30-40% and positive for CD117 and DOG1 (Figure 7 and 8).

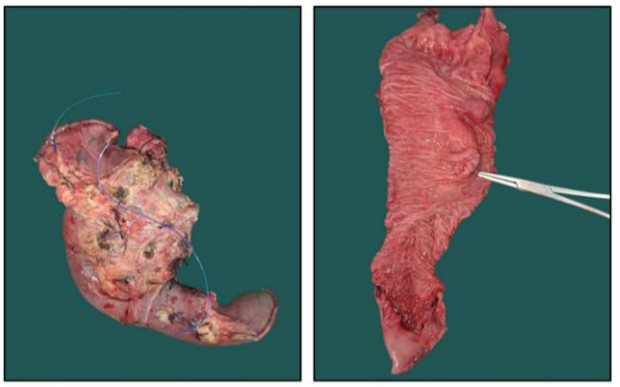

Figure 3: (A) gross pancreaticoduodenectomy specimen and (B) cut open specimen shows a 2x2 cm periampullary growth.

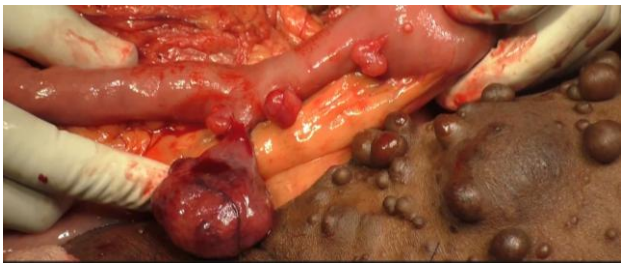

Figure 4: Proximal jejunum. Multiple serosal nodules noted.

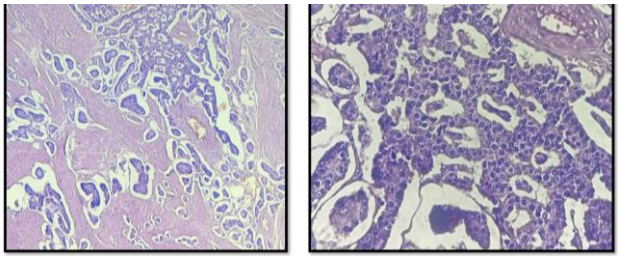

Figure 5: Growth in periampullary region shows a well differentiated grade 1 NET (PT2 PN1): (A) 10X magnification and (B) 40X magnification.

Postoperative course

The recovery was uneventful. The patient was discharged on postoperative day 7. At 1 month follow up, 68-GaDOTANOC PET was done which showed no significant 68-GaDOTANOC avid lesions noted at the operative bed or anywhere else in the body.

Patient was started on adjuvant therapy with tab. imatinib 400 mg once daily for 3 years. At 6-month follow-up, the patient remains asymptomatic with no NET recurrence on imaging.

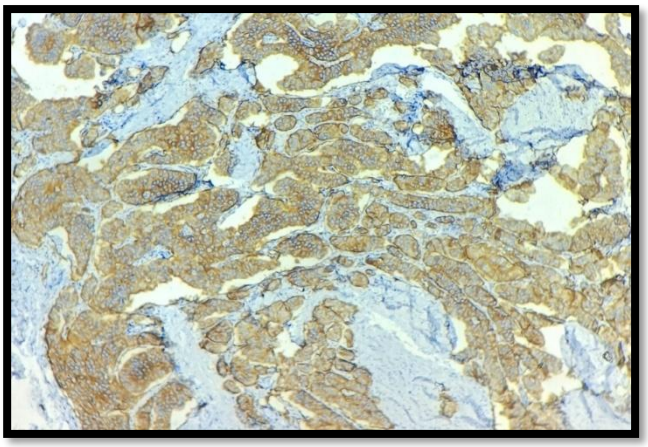

Figure 6: IHC for synaptophysin positive.

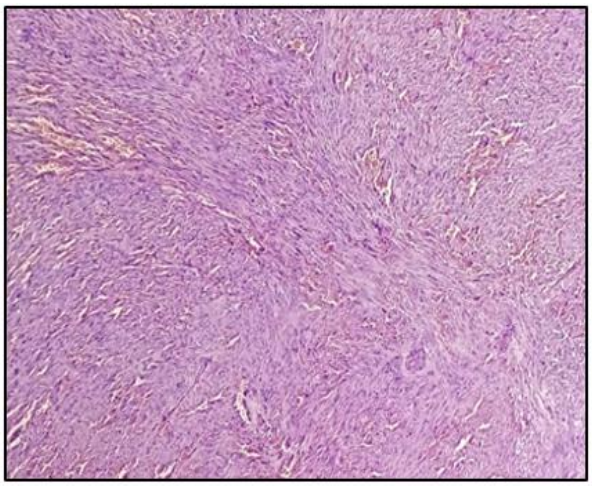

Figure 7: Histopathology of the serosal nodule from the proximal jejunum showed high grade gist, spindle cell type.

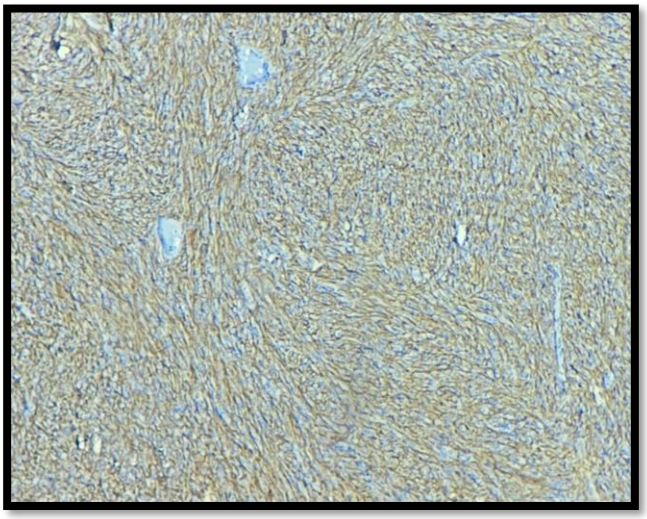

Figure 8: Positive IHC for DOG 1 in the jejunal serosal nodule.

DISCUSSION

NF1 is associated with constitutive activation of the RAS–MAPK pathway, predisposing patients to various tumors.[4] GIST is relatively rare in the general population but develops in approximately 7% of patients with NF1.5 GISTs arise from the mesenchymal tissue of the gastrointestinal tract.

Compared with sporadic cases, NF1-associated GIST typically presents at a younger age, has a female preponderance, and most commonly involves the small intestine, accounting for up to 90% of cases.[6] Multifocal GISTs are uncommon, seen in <5% of sporadic cases, but multiple lesions are frequently seen in NF1-associated GIST. Histopathologically, NF1-related GISTs predominantly exhibit a spindle cell morphology.[7] NF1-associated GISTs often harbor wild-type KIT and PDGFRA, which is associated with a reduced response to imatinib therapy.[8]

NETs in NF1 predominantly occur in the duodenum and periampullary region and may secrete somatostatin, although a large proportion are non-functional. Surgical resection is recommended for well-differentiated periampullary or pancreatic NETs larger than 2 cm or those exhibiting local invasion, as demonstrated in this case. In NF1 patients, a Whipple procedure is preferred owing to the higher likelihood of nodal metastasis and multifocal tumors. This aligns with the management approach taken in the present case.

The synchronous occurrence of GIST and NET is exceptionally rare, and several mechanisms have been proposed to account for this association. One explanation is the shared embryologic origin of neural crest–derived tumours, which may predispose patients with NF1 to develop multiple neoplasms along related developmental pathways.[9] In addition, global tumour predisposition resulting from NF1 gene dysfunction can create a biologic environment that favours the emergence of distinct tumour types within the same individual.[10] A further contributing factor may be a regional "field effect" within the gastrointestinal tract, promoting multifocal neoplasia and thereby explaining the coexistence of lesions such as GIST and NET in NF1 patients.[11]

This case highlights the need for a thorough intra-abdominal evaluation in patients with NF1, as they are prone to developing multiple gastrointestinal lesions that may not be clinically apparent. Clinicians should maintain a high index of suspicion for multifocal or synchronous tumours, particularly combinations such as GIST and periampullary NET. Additionally, histopathological confirmation of all suspicious lesions is essential, as each tumour may exhibit distinct biological behaviour, mutation profiles, and malignant potential, which directly influence management and prognosis.

CONCLUSION

This case underscores, that given the documented predisposition of NF1 to multifocal and biologically distinct tumours, the importance of multidisciplinary management and vigilant follow-up in NF1 patients with gastrointestinal neoplasms. Close follow-up is particularly important, as NF1-associated tumours may arise metachronously, behave differently from their sporadic counterparts.

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