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Pancreaticoduodenectomy in patients with type 1 Neurofibromatosis: Report of two cases and literature review

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ABSTRACT

INTRODUCTION: Type 1 Neurofibromatosis (NF1) is one of the most common autosomal dominantly inherited multisystem disorders. It is associated with an increased risk of developing neurologic and gastrointestinal (GI) malignant neoplasms. The incidence of GI involvement is reported in 10–25% of patients. Less than 5% of NF1 patients with GI neoplasms manifest symptoms. The presence of synchronic gastrointestinal stromal and neuroendocrine tumors is rare in these patients.

PRESENTATION OF CASES: The first case is a 37 year-old male patient with a history of abdominal pain for a few months. Imaging study showed a periampullary mass and a solid lesion at the third duodenal portion. He was submitted to a pancreatoduodenectomy and histological anaylisis showed two low-grade neuroendocrine tumors and a gastrointestinal stromal tumor. The second case is a 47 year-old female patient with a routine computed tomography scan showing a duodenal and a jejunal lesion. Duodenopancreatectomy was performed and histological analysis showed a neuroendocrine adenocarcinoma of the duodenum and two jejunal lesions compatible with GI tumors.

DISCUSSION: GI symptoms such as jaundice, pain and bleeding in NF1 patients should prompt urgent admission Occasionally, associated gastrointestinal tumors may be incidentally found in asymptomatic NF1 patients. The presence of a periampullary or duodenal neoplasia such as neuroendocrine tumors should be evaluated.

CONCLUSION: Although rare, the synchronic presentation of gastrointestinal tumors in patients with NF1 should be ruled out since it can lead to higher morbidity and mortality rates. Single-stage surgical management is feasable and yields satisfactory results.

1. Introduction

Neurofibromatosis type 1 (NF1) is one of the most common autosomal dominant inherited multisystem disorders affecting 1 of 3500 births. Itís main features are dermal neurofibromas and pigmentary abnormalities such as café au lait patches, axillary freckling and Lisch nodules of the iris. Also, NF1 is also associated with an increased risk of developing neural neoplasms such as malignant peripheral nerve sheath tumors and optic pathway gliomas. The gastrointestinal (GI) tract is also affected.

The incidence of GI tract involvement is sometimes difficult to assess in NF1 patients, although reports have indicated the presence of tumors in 10–25% of patients, and can be divided into 3 groups: neural intestinal neoplasms (neurofibromas, ganglioneuromatosis, gangliocytic paragangliomas), duodenum and periampullary neuroendocrine tumors, and gastrointestinal stromal tumors (GIST) [1–5].

GIST are the most common tumors of mesenchymal origin in the GI tract. NF1 has been associated with the presence of multiple GIST throughout the GI tract, most commonly in the small bowel and stomach. Approximately 60% of patients develop multiple tumors or multiple tumor sites. GIST alone have been reported in 5–25% of NF1 patients. The largest series indicates a 7% incidence of GIST

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[6]. Less than 5% of NF1 patients with GI neoplasms have presented with symptoms [5].

Neuroendocrine tumors (NET) may be either functioning or non-functioning, depending on their hormonal activity. Periampullary tumors have also been recognized in patients with NF1[7]. NF1 association with duodenal neuroendocrine tumors, particularly somatostatin-producing endocrine tumors, although unusual, has recently become more widely recognized as a distinct neuroendocrine syndrome [8].

We present two cases of patients with NF1 that developed neuroendocrine tumors of the ampulla of Vater and small bowel GIST, simultaneously.

2. Presentation of cases

First case is a 37-year old male patient presenting to the emergency department in March 2010 complaining of acute right-sided upper abdominal pain, fever, jaundice, pale-colored stool and dark urine for four days. He had a history of NF1. His physical exam showed cutaneous neurofibromas, café au lait maculae and upper right side tenderness, with no signs of peritonitis. Laboratory assay showed direct hyperbilirubinemia, elevated alkaline phosphatase levels and anemia. No other significant abnormalities were noted on urine and blood tests.

Initial abdominal ultrasound evaluation demonstrated dilation of intra and extrahepatic bile ducts. Abdominal computerized tomography (CT) and Magnetic Resonance Cholangiopancreatography (MRCP) revealed an abrupt narrowing of the distal part of the main bile duct, a distended gallbladder, a periampullary mass and a solid lesion at the third duodenal portion, both contrast-enhanced (Fig. 1). The patient underwent an oesophagogastroduodenoscopy (OGD) (Fig. 2) revealing a partially obstructing and infiltrative duodenal lesion and an irregular mass at the ampulla of Vater. Biopsy of the mass showed neuroendocrine cells at the duodenal lamina propria with positive chromogranin immunohistochemical stain.

The patient was explored by laparotomy. Intraoperative findings revealed a palpable lesion at the duodenum and a one-centimeter lesion at the anti-mesenteric aspect of the jejunum, 80 cm distally to the Treitz ligament. We performed pancreaticoduodenectomy, resection of the jejunal lesion, and Roux-en-Y reconstruction. Pathology findings of the lesions were consistent with two low grade periampullary neuroendocrine tumors, one of 2.6 cm and another of 2.3 cm, and a 0.9 cm GIST of the jejunal segment (Fig. 3).

The patient had an uneventful recovery. Last follow-up three years postoperative he was doing well with no evidence of disease and was satisfied with the outcome.

Second case is a 45-year old female previously diagnosed with NF1 and grade 2 fusocellular sarcoma of the thoracic wall admitted to our reference service in January 2007 for post-operative follow-up. She was asymptomatic at the time.

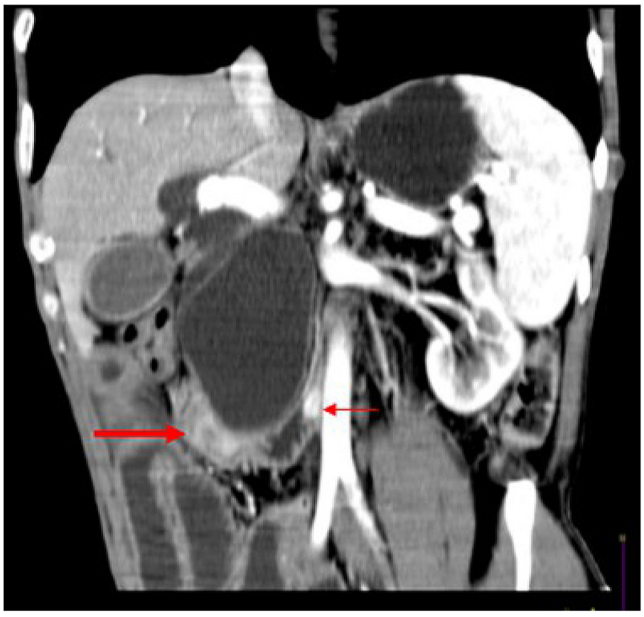

Fig. 1. This coronal CT image of patient 1 nicely reveals the large periampullary mass (large arrow), the contrast-enhanced duodenal GIST (small arrow) and a dilated gallbladder.

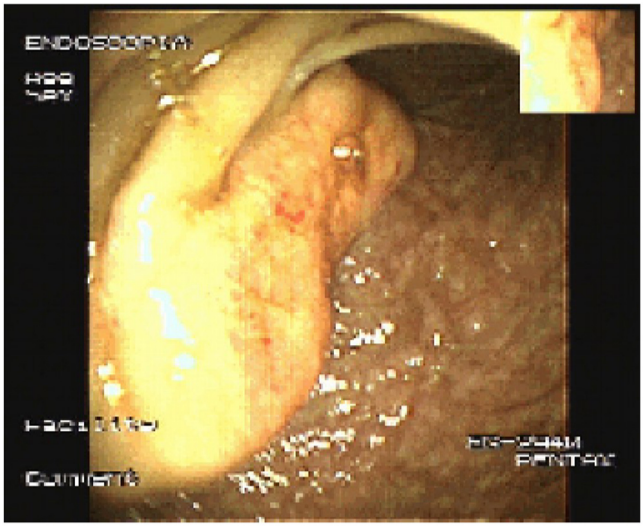

Fig. 2. The OGD for patient 1 shows a bulging mass at the periampullary region.

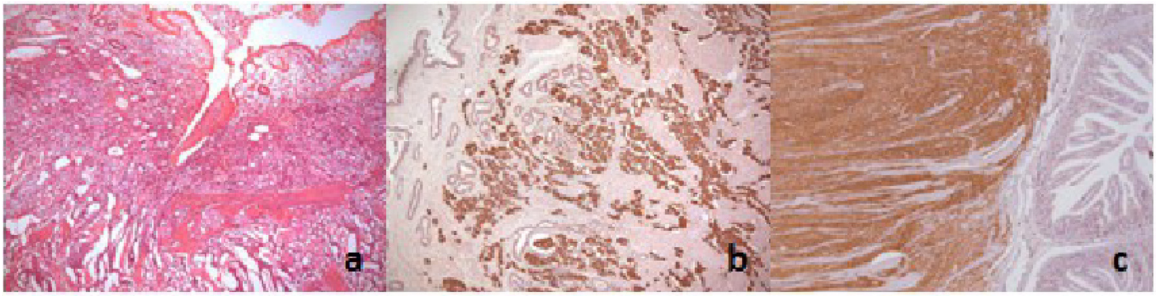

Fig. 3. Ampulla and jejunal well-differentiated neuroendocrine tumor.Proeminente acinar growth patern are seen in this example, in jejunal ressection (a). Somatostatin staining in Immunohistochemistry (b). CD117/c-Kit expression in GIST, with cytoplasmic and membranous labeling (c). (Hematoxilin and eosin, original magnification x 50 [a], immunohistochemistry, ×100 [b, c]).

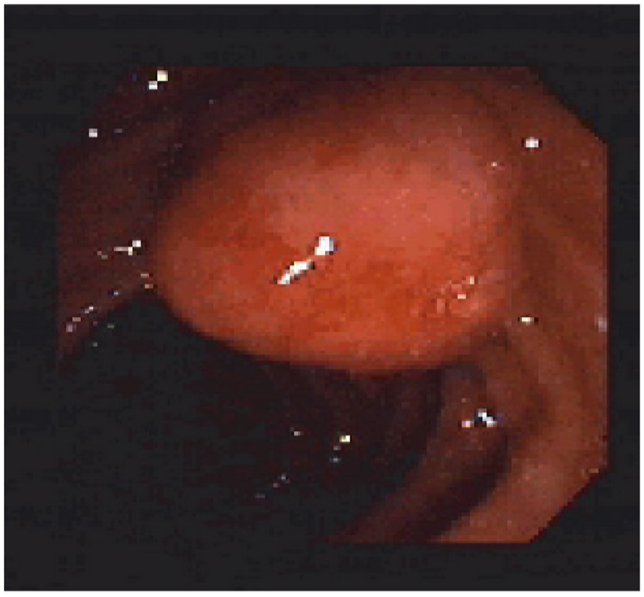

Fig. 4. OGD view of a polypoid intraluminal lesion of 1.5 cm at the second duodenal portion of Patient 2.

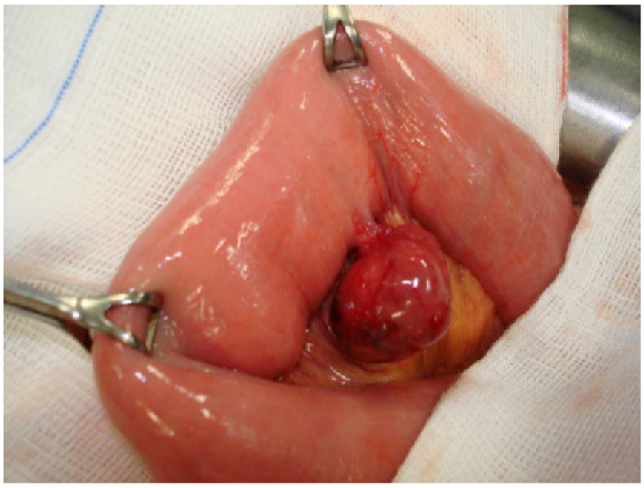

Fig. 5. Pedunculated GIST of the jejunum of Patient 2.

Routine follow-up abdominal CT showed a polypoid intraluminal lesion of 1.5 cm at the second duodenal portion, and a 2.0 cm jejunal nodule, both exposing contrast enhancement. An OGD (Fig. 4) was performed and biopsy of the first lesion revealed a well – differentiated neuroendocrine tumor of the ampulla of Vater, positive for somatostatin. Further evaluation by endoscopic ultrasound revealed a 1.5 × 1.0-cm hypoechoic ampullary mass confined to the mucosa and submucosa.

Pylorus-preserving pancreaticoduodenectomy and resection of the jejunal lesion (Fig. 5) was performed. Pathology findings were well-differentiated neuroendocrine adenocarcinoma at the level of the papilla, and two jejunal lesions of 2.5 cm and 0.6 cm, positive for CD-117, S-100 protein and smooth muscle actin, consistent with GIST (Fig. 6).

The patient had an uneventful postoperative recovery. Last follow-up eight years postoperative she was doing well with no evidence of disease. She exposed no concerns about the course of treatment and was pleased with the outcome.

3. Discussion

Patients with NF1 are predisposed to both benign and malignant tumors of neurogenic and nonneurogenic origin. Several pathways are thought to be involved in the development of tumors associated with NF1. The protein associated with NF1, neurofibromin, is involved in the downregulation of the rat sarcoma viral oncogene homologue (RAS)– mitogen activated protein kinase (MAPK) pathway and NF1 belongs to the group of RAS–MAPK disorders that include Noonan, cardio fasciocutaneous, Costello, LEOPARD, and NF1-like syndrome [9].

GIST are the most common mesenchymal tumors of the GI tract. They are strongly associated with NF1 and detected in approximately 7% of the patients. Lifetime risk for patients with NF1 might be as high as 6% [6]. A review of 167 duodenal GIST from the AFIP found that 6% were associated with NF1 and, although usually clinically indolent, severe GI bleeding was a distinctive complication of this group [6,8]. The clinicopathological characteristics of GIST in patients with NF1 are different from the characteristics of sporadic GIST. NF1 GIST are most often small, multiple, and most commonly distributed in the small bowel. Histologically, the tumors usually have low mitotic rates. About 22–31% of GISTs in NF1 patients are found in the duodenum, and approximately 60% of patients harbor tumors at multiple sites [10]. We found two GIST in the proximal jejunum in our second patient.

Miettinen et al. showed that, in 45 patients who had NF1 and GIST, none of the 16 tumors from 15 patients had a *KIT* mutation in exon 9, 11, 13, or 17 or a *PDGFRA* mutation in exon 12 or 18 as is typical in sporadic GIST. These data clearly indicate that GIST in NF1 patients have a different pathogenesis than sporadic GIST [6]. The molecular event underlying GIST development in this patient group may be a somatic inactivation such as LOH of the wild-type *NF1* allele leading to inactivation of neurofibromin and subsequent activation of the MAP-kinase pathway [11,12].

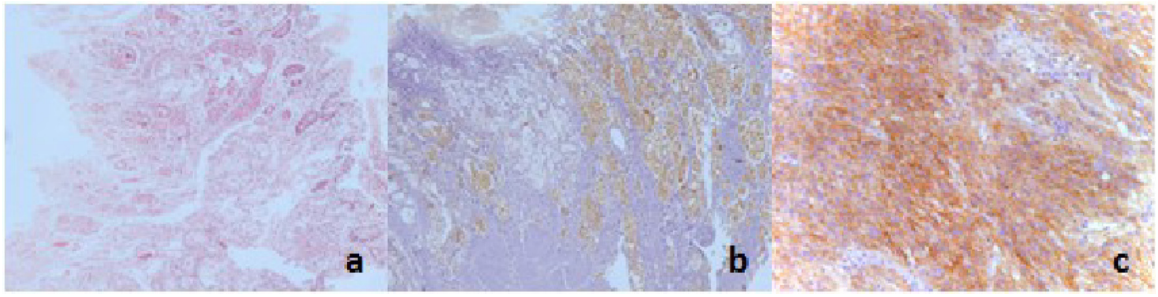

Fig. 6. Duodenal well-differentiated neuroendocrine tumor. This example shows a proeminent nest growth pattern (a). A chromogranin stain highlight the neoplastic cell (b).Gastrointestinal stromal tumor cells highlited by CD117/c-KIT stain(c) (Hematoxilin and eosin, original magnification ×100 [a], and immunohistochemistry,×100 [b] and ×200 [c]).

NET represent a group of neoplasms arising from neuroendocrine cells of the diffuse endocrine system. Most NET are sporadic. However, some NETs, may occur as part of familial (inherited) syndromes, such as the multiple endocrine neoplasia 1 (MEN-1) syndrome, von Hippel Lindau (VHL) syndrome, neurofibromatosis, and tuberous sclerosis (TSC). NET of the ampulla of Vater comprise a broad spectrum of morphologically and biologically diverse tumors, such as various subtypes of well-differentiated endocrine tumors, well-differentiated endocrine carcinomas, and poorly differentiated endocrine carcinomas.

Periampullary NET were first described in association with NF1 in 1982 by Cantor et al. [13]. In 1989 Klein et al. identified 37 cases of NF1 patients with periampullary neoplasms reported in the literature and noted that 54% were found in the ampulla, 38% in the duodenum. Histologically, most tumors were NET (41%) [7]. In a review of the literature Relles et al. found 76 cases of periampullary tumors in NF1 patients. Most patients were symptomatic (92%). In this review, 47% of periampullary tumors were neuroendocrine in origin [5]. Comparing duodenal somatostatinomas of patients with NF1 (27 patients) and non-NF1 patients (29 patients), Capelli et al. showed that the non-NF1 patients were less likely to have tumors with multiple hormonal production (4.7% vs. 16%) [8].

Corresponding to their location, NET of the ampulla of Vater cause jaundice in approximately two-thirds of patients. If jaundice or abdominal pain occurs in patients with NF1 then the possibility of a NET should be considered. Approximately 26% of all patients with NET reported in the literature had NF1 [14].

The presence of synchronous malignant GI tumors in NF1 patients (periampullary NET and small bowel GIST) is rarely reported in the literature [2,15]. Sometimes during resection of the periampullary NET, incidental small bowel GIST may occasionally be found. In patient 1, we found two periampullary NETs and on small bowel subcentimetric GIST. In patient 2, two jejunal GIST were found.

4. Conclusion

GI symptoms such as jaundice, pain and bleeding in NF1 patients are causes of emergency department admissions. Occasionally, associated GI tumors are incidentally found in asymptomatic NF1 patients. A thorough evaluation to rule out the presence of periampullary or duodenal neoplasia must be performed. Surgical intervention is the definitive treatment in both situations. During laparotomy careful inspection and palpation of the small bowel should be done. Incidental finding of small bowel GIST during pancreaticoduodenal resection in NF1 patients has been reported, either isolated or as multiple lesions. Meticulous investigation associated with a careful operative technique could lead to early diagnosis and treatment of these patients with satisfactory results.

Consent

Patient consent of both the subjects of this case report with literature review was obtained prior to the submission.

Conflict of interest

The authors state no conflict of interest.

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Ethical approval

Our work has been approved prior to submission by Comissao de Etica para Analise de Projetos de Pesquisa – CAPPesq (Ethical Comission for Analysis of Research Projects), under the reference number 101/16.

Author contribution

Frederico Teixeira: study concept and design, data analysis and writing the manuscript, data collection.

Carlos Augusto M Menegozzo: data analisys, writing the manuscript.

Sérgio Dias do Couto Netto: study concept and design, data analysis.

Gustavo Scapini: data collection.

Eduardo Hiroshi Akaishi: data collection, study design.

Marcela Pereira Silva Vasconcelos: pathological data collection, interpratation and legends writing of pathology figures.

Edivaldo Massazo Utyiama: study design, data analysis.

Guarantor

Frederico Teixeira, the first author.

Care statement

The authors state that the manuscript is being reported in line with the CARE criteria, as reported in Gagnier J, Kienle G, Altman DG, Moher D, Sox H, Riley DS, and the CARE group. The CARE guidelines: consensus-based clinical case report guideline development.*Journal of Clinical Epidemiology*;67(1),46-51.

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