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A case report

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EPCephalic duodenopancreatectomy for neurofibromatosis associated with gastrointestinal stromal tumor. A case report

BACKGROUND: *Neurofibromatosis is a genetic autosomal dominant disease characterized by multiple skin nodules and hyperpigmentation. This condition is frequently associated with a large variety of neoplasia, including gastrointestinal stromal tumors (GIST) in about 6% of cases. We present a case of neurofibromatosis associated GIST.*
CASE REPORT: *A 57 year-old male patient with Von Recklinghausen disease was referred into our service after he was discovered with a 7 mm nodular formation in contact with the pancreatic head, during a routine abdominal ultrasonography. Ultrasound examination performed into our service reveals a nodular formation with hypoechoic circumference, central translucency, with central necrosis, contrast medium uptake and dimensions at about 78/49/77 mm, without peritoneal fluid content. Trans-gastric biopsy specimen shows mesenchymal proliferation with spindle cells and elongated nuclei and c-kit intensely positive. The diagnosis was gastrointestinal stromal tumor. Delimitation towards pancreatic head was unclear. A cephalic duodenopacreatectomy was performed. Morphopathology confirmed a multifocal GIST of low grade G1, in the second stage.*
CONCLUSION: *A rare case of neurofibromatosis associated GIST with multifocal localization was successfully treated by cephalic duodenopancreatectomy.*

KEY WORDS: Neurofibromatosis type 1 (NF1), Retroperitoneal Gastrointestinal Stromal Tumor (GIST).

Introduction

Neurofibromatosis (NF) also called Von Recklinghausen disease is a genetic autosomal dominant disorder, and patients usually present multiple neurofibromas and pigmented skin spots. In this disease was observed loss of neurofibromin gene, a tumor suppressor gene, on both alleles [1]. Patients with neurofibromatosis type 1 (NF1) usually have associated different forms of neoplasia such as optic glioma, nerve sheath tumors, pheochromocytoma (in 1-5% of NF1 patients) [2], breast cancer (5-8%) [3] or GIST tumors (associated in 25% of NF1 patients) [4]. The prevalence of GIST tumor in patients with NF is around 6%, and the risk of developing the tumor is 200 times higher compared to the general population [1]. GIST is a tumor with origin in the interstitial pacemaker cell of Cajal, cells with a role in peristalsis [5]. The most common site for this malignancy is the stomach (60-70%), followed by small intestine (20-30%) [6], while duodenal localizations are rare (3-7%) [7]. Multiple localization is also rare in patients with primary GIST, and this condition is more frequent in GIST associated with neurofibromatosis where multiple tumors are more common [1,8]. The primary GIST is associated in 80% of cases with mutations in

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the KIT gene and 10% with mutations in PDGFRA (platelet activated receptor alpha) gene [9]. This behavior is not seen in GISTs associated with NF1 where the KIT and PDGFRA mutations are less frequent [1]. That is the reason why Imatinib therapy did not always work correctly in patients with NF1 and associated GIST. Gupta et al. describe a case of two siblings, both suffering from NF1 associated GIST, with positive expression of CD117 and CD 34 (both of them), but only one responded according to stabilization of gastrointestinal disease (progression stopped for at least one year) [10]. Valencia and Saif recommend the evaluation of the c-Kit mutations before beginning Imatinib therapy, as they can predict the therapeutic response. Surgical treatment seems to be the best option for the patient in an early stage with a hereditary disease that can influence the genetic profile of the tumor [5].
We present a case of a 57 years old male with neurofibromatosis type 1 and a multifocal GIST tumor, a rare case of NF1 associated with GIST.

Case report

A 57-year-old male patient was referred to our surgery department in October 2017 for evaluation of an abdominal mass identified at a routine abdominal ultrasound examination. The patient was known with NF1, lumbar scoliosis, asthma, and gallbladder lithiasis. The history of the relatives revealed the presence of skin nodules but in a smaller number at his grandmother (maternal line). The patient is an ex-smoker (quit 15 years ago) and uses alcohol occasionally. At clinical examination he presented hyperpigmented skin, with numerous soft, painless, and mobile pseudotumoral lesions, without epithelial lesions, covering the whole body, randomly distributed (Fig. 1).
The tumoral mass was asymptomatic at presentation (only a small weight loss, about 3 kg in the previous six months) and was discovered during a routine abdominal ultrasound examination. The tumoral formation was described as a nodule with a hypoechogenic circumference, inhomogeneous structure, with central translucency, of approximately 73 mm in diameter. The lesion was localized between the liver and the pyloric antrum, and covering the pancreatic head. Gallbladder was described with hyperechogenic content (Fig. 2).
Fine needle aspiration was performed, and histopathological examination showed mesenchymal proliferation with hemorrhage and inflammatory elements. Spindle cells arranged in fascicles with an elongated nucleus and pale eosinophilic cytoplasm were identified. C-Kit (CD 117) was intensely positive while DOG1 (deletions of guanine-rich DNA) was weakly positive.
The computer tomography examination shows a heterogeneous 78/49/77 mm mass with central necrosis and contrasts medium uptake. Delimitation towards pancreatic head was unclear without any sign of peritoneal fluid content.
A subcostal rooftop incision followed by hemostasis, isolation, and exploration of the peritoneal cavity was performed. Several neurofibromatosis nodules were found along the serous layer of the bowel, without liquid content in the peritoneal cavity. A solid mobile mass of 8 cm in diameter (Fig. 3) was found at the level of the duodenum, with no penetration of duodenal serosa, and without any permeation nodules. Local lymph nodules from hepatic hilum and retro-portal localization were biopsied, and no invasion at their level was identified. No secondary determinations were found. Choledocus was of normal caliber. A cephalic duodenopancreatectomy was done due to the proximity with pancreatic head, duodenum and bile ducts with a terminolateral pancreaticojejunal anastomosis, terminolateral liver to jejunum anastomosis and terminolateral transmesocolic gastro-jejunal anastomosis. The mesocolonic breach was closed to prevent an internal hernia, and a Stamm jejunostomy was left to secure

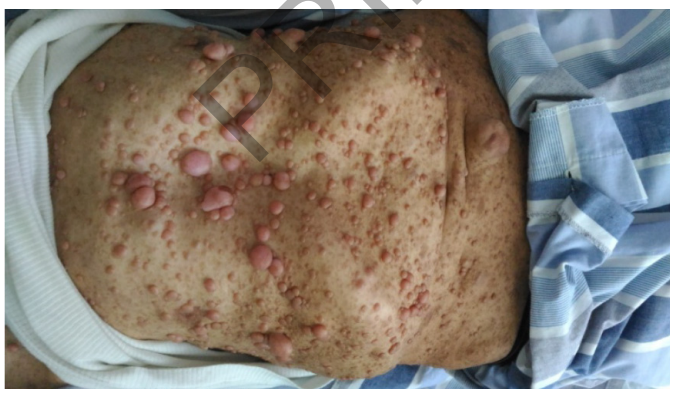

Fig. 1. Presence of multiple pseudo-tumoral skin nodules in the context of neurofibromatosis.

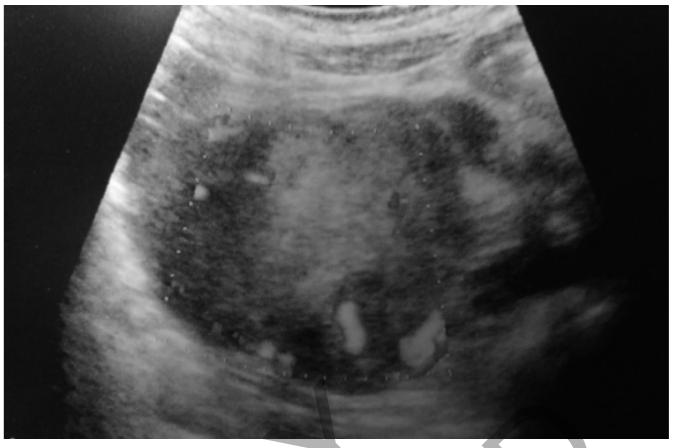

Fig. 2. Abdominal ultrasonography was showing a nodular mass with hypoechoic circumference and inhomogeneous structure.

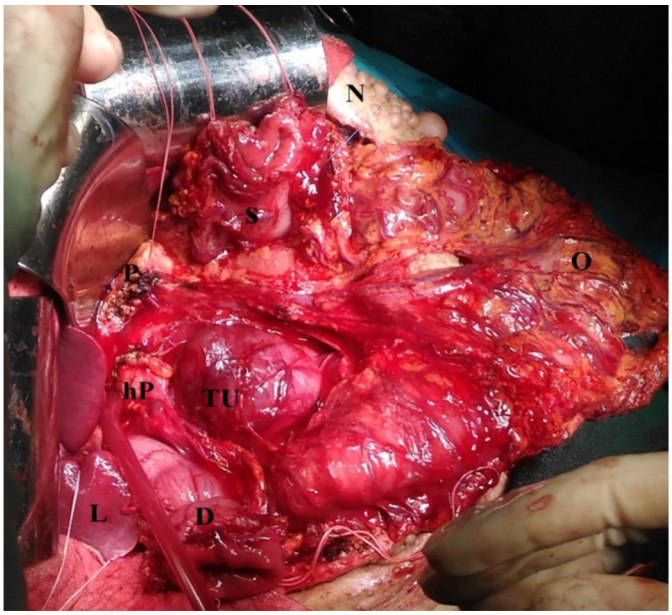

Fig. 3. Intraoperative picture showing the GIST tumor (TU), in contact with the pancreatic head (hP), liver (L), duodenum (D), body of the pancreas (P), stomach (S), greater omentum (O) and some neurofibromatosis nodules of the external abdominal wall (N).

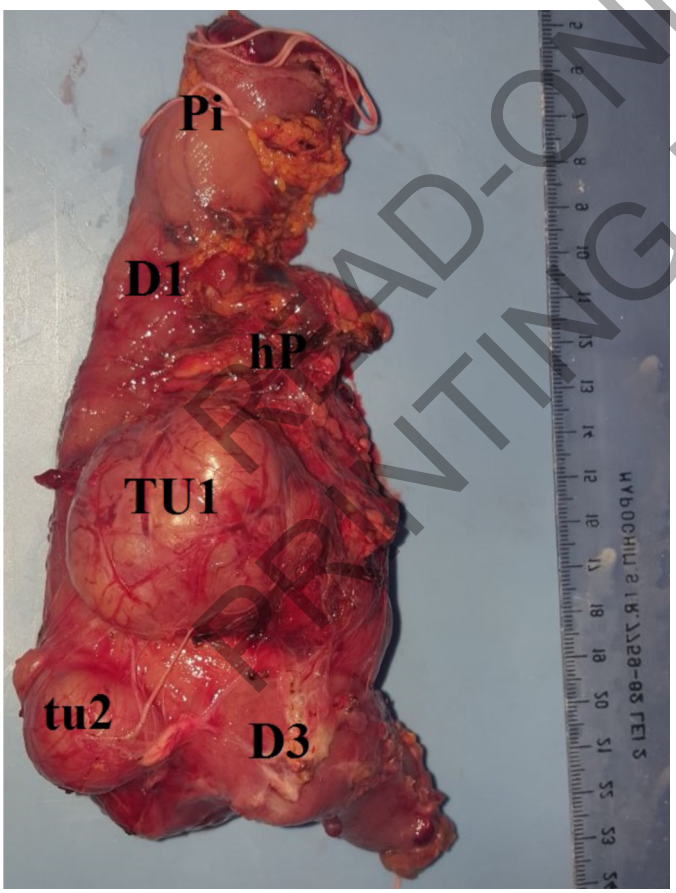

Fig. 4. Resection specimen presented two nodular formations (TU1 and tu2), head of the pancreas (hP), pyloric antrum (Pi) and duodenum (D1, D3).

Fig. 5. Dark hemolysis calculi from the gall bladder.

alimentation. Two drainage tubes were placed into subhepatic space, and a retro-gastric space, with drains at Douglas and splenic lodge. The intervention last 4 hours and the estimated blood loses were of 300 ml. Drains were suppressed in the fourth day after surgery, suture wires were removed in the tenth day, and the patient was discharged after wires removal. The patient complained by nausea and vomiting in the third day after surgery.

The sectioned specimen presented two nodular formations, stomach antrum, and the duodenum, pancreatic head, extrahepatic biliary tree below the bifurcation, the gall bladder and connective tissue (Fig. 4). The main nodular formation has polylobulated with the following dimensions 9.5/6.5/6.0 cm. Central brown masses of low consistency were described. Tumor seems to have the origin in the submucous layer of the duodenum, without invading the serosa, without invading the pancreas, at about 6.4 cm of proximal resection margin. Proximal, at about 5 cm from the resection margin, a second nodular formation with brown necrosis areas and dimensions at 2.3/1.5/1.0 cm were described. Several white 0.2-0.4 cm nodular formations at the serous level, described as neurofibromatosis nodules were reported. Free margins towards stomach, duodenum, pancreas and biliary tree were described by pathological examination. Microscopically, spindle cells were found, with elongated nuclei, with positivity DOG1 and C-kit and a Ki67 of 3%. Five lymph nodes were found on the resected specimen, without tumor invasion. The conclusion was multifocal GIST, of low-grade G1, in the second stage (pT3N0MxL0V0R0).

At the macroscopic examination, the gallbladder present dark biliary stones, with a muriform aspect (Fig. 5).

Discussions

We reported a case of an asymptomatic patient with GIST and NF1. His condition was appreciated with a high risk of malignancy, and surgical treatment was done at an early stage. The incidence of malignant disturbances is higher on NF1 patients than in the general population, and special attention is needed [11].

Adenocarcinomas, neuroendocrine tumors, stromal tumors, accompanied by nerve sheath tumors and gliomas are the main tumoral lesions seen in NF1 patients [3]. Neurofibromatosis-associated GIST is atypical, with multiple and unusual localisations, such as a retroperitoneal tumour as presented in our case-report, that request doudenopancreatectomy. A differential diagnosis can be made with other neuroendocrine tumors, the gangliocytic paraganglioma, that usually presents the same localization such as in our case, the second portion of the duodenum [12]. Also, it is known that GIST in neurofibromatosis context can present a particular mutational profile of CD 117 and an inadequate response to Imatinibe therapy [1,5,10]. Surgical treatment is the most feasible option for these patients.

Evaluating the genetic profile of GIST shows that oncogenic KIT or PDGFRA mutations drive this tumor, but there are also about 10% of the tumors that have not these activating mutations, and they are called wild-type GIST (KIT/PDGFRA wt-GIST). These wild species present other mutations in RAS and MAP-kinase pathway. Deficiency in neurifibromin 1 can activate RAS or MAP-kinase pathway. Neurofibromatosis-associated GISTs are often KIT wt-GIST with different phenotype and inadequate response to Imatinibe [5,13]. Our patient was diagnosed by routine abdominal ultrasonography, and the complete excision with negative margins at an early stage was possible. For the preoperative appreciation of the tumor cellularity, a Fine-Needle Aspiration (FNA) guided by Harmonic Contrast-Enhaced Endoscopic Ultasonography (CH-EUS) should be made [14]. The gold standard in cephalic duodenopancreatectomy is the R0 resection, but a previous study showed that a microscopically positive (R1) resection (distance from tumoral tissue to resection margin ≤ 1 mm) does not affect the three years survival rate in pancreatic adenocarcinoma [15]. However, considering the R0 resection, in our GIST case, no adjuvant therapy is required, but due to the age of the patient age and disposition towards malignant disease, periodical controls is recommended. Most of the GIST recurrences occur in the first two years after surgery. The first two years after the intervention is recommended a four months computer tomography (CT) follow-up. A 6 months CT follow up is recommended in the third year, followed by an annual imagistic evaluation starting with the fourth year. After ten years the risk of recurrence is insignificant, and no further evaluation is required[5].

Conclusion

A rare case of asymptomatic neurofibromatosis-associated GIST, with retroperitoneal localization and significant anatomic relations that required cephalic duodenopancreatectomy was presented.

Riassunto

La neurofibromatosi è una malattia genetica autosomica dominante caratterizzata da più noduli cutanei e iperpigmentazione, e si associa frequentemente – in circa il 6% dei casi a una grande varietà di neoplasie, inclusi i tumori stromali gastrointestinali (GIST). Viene qui presentato un caso di GIST associato a neurofibromatosi. Uomo di 57 anni affetto da malattia di Von Recklinghausen, trasferito nel nostro reparto dopo la scoperta nel corso di una ecografia addominale di routine di una formazione nodulare di 7 mm a contatto con la testa del pancreas. L'esame ecografico eseguito nel nostro servizio rivelava una formazione nodulare con circonferenza ipoecogena, ed translucenza centrale, con necrosi centrale, assunzione del mezzo di contrasto e dimensioni a circa 78/49/77 mm, senza presenza di liquido peritoneale. Il campione bioptico trans-gastrico mostrava una proliferazione mesenchimale con cellule fusate e nuclei allungati e il c-kit intensamente positivo, di qui la diagnosi di tumore stromale gastrointestinale. La delimitazione verso la testa del pancreas non era chiara, per cui è stata eseguita una duodenopacreatectomia cefalica. Lo studio anatomo-patologico ha confermato trattarsi di un GIST multifocale di basso grado G1 al secondo stadio. Conclusioni: un caso raro di GIST associato a neurofibromatosi con localizzazione multifocale è stato trattato con successo mediante duodenopancreatectomia cefalica.

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