The coexistence of neuroendocrine papillary tumor and gastrointestinal stromal tumor in neurofibromatosis Type 1: A case report

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ABSTRACT

Introduction: Neurofibromatosis Type 1 (NF-1, Recklinghausen disease) is the most common hereditary multitumor syndrome with an incidence at birth of approximately 1/3000. In type 1 neurofibromatosis, gastrointestinal tumors are relatively infrequent and generally correspond with a hyperplasia of neural cells in the myenteric and submucosal plexus, gastrointestinal stromal tumors (GIST) and periamillary neuro endocrine tumors. However, the association of GIST, the neuro endocrine tumor of ampulla of Vater and neurofibromatosis is rare. Case Report: The case reports a 66-year-old woman without a familial history of neurofibromatosis diagnosed with neuro endocrine tumor of ampulla and GIST of the duodenum. She underwent cephalic duodeno pancreatectomy. A working diagnosis of NF-1 was made and the patient was referred to genetic counseling. Conclusion: The case clearly points out the important value of gastrointestinal findings in identifying undiagnosed NF-1.

Keywords: Gastrointestinal stromal tumor, Neurofibromatosis Type 1, Neuroendocrine tumor

INTRODUCTION

Type 1 neurofibromatosis is an autosomal dominant disease with an incomplete penetrance. It mainly affects the nervous system in the form of benign or malignant tumors [1]. The clinical diagnosis is generally posed for observation “cafe au lait” spots and cutaneous neurofibroma. Gastrointestinal involvement is observed in 25% of patients [2]. Carcinoids of the ampulla of Vater are infrequent tumors (only 100 cases have been documented) of which a quarter of cases have been detected in patients with type I neurofibromatosis [3, 4]. This hereditary disease is also associated with gastrointestinal stromal tumors (GIST). However, the coincidence of these three entities together has only been formerly detected in nine cases [5].

CASE REPORT

A 66-year-old woman diagnosed with neurofibromatosis Type 1, showed four months before her hospitalization, generalized icterus and sporadic pain at the level of the right hypochondre. She had a
good general state (OMS score = 1), her body mass index was 19. The physical examination showed the presence of multiple cutaneous nodules and café au lait spots but no other pathological findings. Hepatic tests were perturbed. Alkaline phosphatase was 630 U/l and gamma glutamyl transferase was 380 U/l. Aminotransferase aspartate (AST) was 95 U/l and alanine aminotransferase (ALT) was 102 U/l. No other biochemical abnormality was found.

The abdominal ultrasonography showed an important dilatation of the extra and intra hepatic bile duct with important dilatation of Wirsung without obvious obstacle.

The computed tomography (CT) scan also showed extra and intra hepatic bile duct dilatation with wirsung dilatation upstream of a hyper vascular tissular mass raising intensely in the arterial and portal time sitting at the level of the ampullar region measuring 12 mm. Presence of a second hyper vascular tissular mass sitting at the level of the angle of Treitz measuring 27x17x16 mm. The kinetic of raising of 2 masses evokes neuro endocrine tumors. There was no metastasis Figure 1(A and B). Duodenoscopy showed the presence of regular oblong, non-stenosing, budding formation about 2 cm long in the ampulla of Vater. Presence of a second tumor lesion at D IV, umbilicated at the center about 3 cm long Figure 2(A and B). Histological examination of the D IV lesion revealed a proliferation of tangles of fusiform cells showing moderate atypia, an abundant eosinophilic cytoplasm, and a hyper chromatic nucleus. These cells were C-Kit +, Dog1 +, PS100-, AML-. The diagnosis of GIST was retained. The biopsy of the papilla was within the histological limits of normal. The patient underwent surgery. The laparotomy disclosed a palpable ampullary mass (approximately 2 cm in diameter) and another one located in the duodenal wall (D IV). There was no evidence of either hepatic or peritoneal metastatic disease. A cephalic duodeno pancreactectomy was performed. The postoperative course elapsed without complications.

The definitive histological study of the surgical piece showed, surprisingly in the bulb of Vater, tissue of neuroendocrine origin with positive staining for chromogranin A and synaptophysin with grading NET G1 and infiltrating the duodenal muscularis classified PT2NO.

The nodule on D IV wall measured about 3 cm and showed a cell proliferation located in the muscular layer, formed by spindled cells, with few mitotic figures (three per 50 high power fields).

These cells were CD 117-positive, S-100 protein and CD34 negative. The pathological diagnosis was carcinoid tumor of ampulla of Vater and duodenal GIST. One year after the surgery was performed; the patient remained symptom free and showed no evidence of a relapse.

DISCUSSION

Type 1 neurofibromatosis is a disease that is transmitted with dominant autosomal inheritance and is caused by a mutation in the NF1 gene, located in chromosome 17q11.2. This gene codifies the neurofibromin that acts as a neoplastic suppressant, accelerating the inactivation of the proto-oncogene protein p21-ras, which plays an important role in the mitogenic intracellular pathways [6].

The association von Recklinghausen disease, NET and GIST is not coincidental and corresponds to the clinical spectrum of neurofibromatosis Type I [7].

The gastrointestinal condition in Type 1 neurofibromatosis mainly takes place in one of three ways: (i) the hyperplasia of neural cells in the myenteric and submucosal plexus; (ii) GIST and (iii) endocrine tumors of the ampulla of Vater [2, 8].

The main clinical demonstrations of carcinoids of the ampulla of Vater are jaundice (in two-thirds of cases), abdominal pain (40% of cases) and occasionally an acute pancreatitis. Contrary to those located in the jejunum and ileum, the carcinoids of the ampulla of Vater rarely show clinical or biochemical data of carcinoid syndrome [4, 9].

The majority of NF-1 associated neuroendocrine neoplasms are ampullary somatostatinomas, other endocrine tumors including gastrinoma [10], insulinoma and gangliocyticparaganglioma have been rarely reported [11, 12].

In a previous review, 12 of 28 (43%) periampullary somatostatinomas reported in the literature occurred in patients with NF-1 as opposed to only 6% of their pancreatic counterparts [12].
In 30% of cases, the tumors are not secreting but immunohistochemistry allows the differentiation highlighting the peptide they produced without secreting [13].

Dayal compared immunostaining of somatostatinomas ampullary in patients with NF1 and those free of this disease. It shows that there is a particular form of tumor having an almost exclusive synthesis of somatostatin when associated with Von Recklinghausen disease [14].

The surgical treatment is always indicated as good results are obtained even in the presence of metastatic disease, the preferred surgical option being the cephalic duodenopancreatectomy [15].

GISTs are mesenchymal tumors arising from a common precursor, the interstitial cells of Cajal. They are positive for CD117 (95% of cases), CD34 (60–70%), smooth muscle actin (30–40%), and desmin (2%) [16].

Gastrointestinal neurofibromas resembling leiomyomas in NF-1 patients were first reported by Lukash& Johnson [17]. The incidence of GIST in patients with neurofibromatosis varies from 4 to 25%, while the rate of neurofibromatosis in patients with GIST is 6% [18, 19]. GISTs associated to neurofibromatosis are often small in size and show little mitotic activity. Another fact differentiating GIST associated to neurofibromatosis is that the most frequent place to find them is the jejunum, that in two-thirds of cases they are multiple [18, 19].

Similar to KIT/PDGFRA wild type sporadic GISTs, NF-1-associated GISTs show a variable but generally incomplete response to the tyrosine kinase inhibitor [20, 21].

The European Society for Medical Oncology (ESMO) guidelines indicates that the standard treatment of localised GISTs is complete surgical excision of the lesion, without dissection of clinically negative lymph nodes. Adjuvant treatment with imatinib for three years must be considered if resection R1 or high risk of relapse. In locally advanced inoperable and metastatic patients, imatinib is standard treatment.

CONCLUSION

The association of neurofibromatosis with Gastrointestinal Stromal Tumor or with an endocrine tumor of ampulla of Vater is not excessively unusual, but the concurrency of the three entities is very sparse, as far as we know, this case report is only the tenth that has ever been documented in medical literature.

REFERENCES


Author Contributions
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Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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