Clinical Medicine: Endocrinology and Diabetes

CASE REPORT

Intestinal Obstruction and Pheochromocytoma in a Patient Suffering from von Recklinghausen's Disease

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Abstract: GISTs are rare neoplasms, which were recently identified to be a distinct pathologic entity. They can develop in patients with neurofibromatosis type 1 (NF1) or may be sporadic. NF1 is one of the most common inherited diseases and is a complex disease, with patients having an increased prevalence of benign and malignant tumors, including pheochromocytomas. The association of pheochromocytoma(s) and GISTs in NF1 is very rare. We report an additional case of this triple association in a normotensive 60-year-old female with NF1 admitted for intestinal obstruction: a pheochromocytoma of the left adrenal gland was discovered and surgical resection is performed. We provide an overview of the literature. The coexistence of NF1-related pheochromocytoma and GISTs is uncommon, but perhaps not fortuitous, and endocrinologists should be aware of this.

Keywords: pheochromocytoma, neurofibromatosis type 1, gastrointestinal stromal tumors

Clinical Medicine: Endocrinology and Diabetes 2009:2 35–41

This article is available from http://www.la-press.com.

Introduction

The association between neuroendocrine tumors in neurofibromatosis type 1 (NF1), also called von Recklinghausen disease, and gastrointestinal stromal tumors (GISTs) is generally reported by gastroenterologists or surgeons, endocrinologists being less aware that this association may occur. GISTs are rare neoplasms, which were recently identified to be a distinct pathologic entity. Their incidence varies from 1 to 2 per 100 000 people each year.[1] GISTs can be sporadic or may develop in patients with neurofibromatosis type 1 (NF1). NF1 is one of the most common inherited diseases, occurring in approximately 1 in 3000 individuals.[2] It is a complex disease, with patients having an increased prevalence of benign and malignant tumors, including pheochromocytomas.[3] The association of pheochromocytoma(s) and GISTs in NF1 is very rare.[4–9] Here, we report an additional case of this triple association and provide an overview of the literature.

Case Report

A 60-year-old female with NF1 was admitted for abdominal pain and nausea due to intestinal obstruction. There was no family history of NF1. A laparotomy was previously performed in 2005 for biopsy of multiple gastrointestinal tumors. Immunohistochemical analysis showed that the biggest tumor in the mesenterial region was a GIST. At this time, treatment with imatinib was the preferred strategy to incomplete surgical resection. A new CT scan in 2007 showed that the size of the main tumor had increased to 55 mm in diameter and showed the presence of two other smaller intestinal tumors (25 mm and 6 mm in diameter). In 2005, CT imaging suggested nodular hyperplasia of the left adrenal gland; in 2007, however, the CT scan also showed a new, partially cystic tumor of the left adrenal gland of 35 mm in diameter, suspected to be a pheochromocytoma. The intestinal obstruction resolved with medical treatment. The patient was referred to our department before gastrointestinal surgery to diagnose the pheochromocytoma. The patient's clinical features included multiple "café au lait" spots and cutaneous neurofibroma, but she did not suffer from hypertension or hyper-adrenergic symptoms (such as headache, palpitations or sweat). She was normotensive without any treatment. She underwent Ambulatory Blood Pressure Monitoring, giving the following results: mean 24-hour-SBP/DBP was 111/63 mmHg; diurnal BP was 113/64 mmHg; and nocturnal BP was 106/60 mmHg without any paroxysm (Spacelab Healthcare Redmond WA USA). Urinary metanephrine concentrations were elevated, with normetanephrine measured at 650 µg/24 h (normal $<$ 600) and metanephrine at 885 µg/24 h (normal $<$ 350). Plasma-free metanephrine was also high (105 pg/ml (normal $<$ 90)). The patient was preoperatively treated with alpha and beta blockers. A prompt surgical resection of the left adrenal gland was performed and a 156 cm segment of the small bowel with a parietal tumor 5.5 cm in diameter was removed via transversal laparotomy. The adrenal gland, 25 g in weight and 4 cm in diameter, had a hemorrhagic cyst. Immunohistochemical analysis confirmed pheochromocytoma, with expression of S-100 protein and chromogranin but not of c-Kit (immunoperoxidase stain for CD117). The pheochromocytoma was also immunohistochemically negative for PDGF-RA. The parietal tumor was not associated with the mucosal surface and demonstrated histologic features characteristic of GIST. It showed strong staining for CD117 and CD34 but gave negative staining results for S-100 protein or PDGF-RA. MIB-1 staining showed proliferative activity for 3% of tumor cells.

The post operative evolution was uneventful: blood pressure remained stable and pharmacologic treatment was stopped a few weeks after surgery. Intestinal resection caused the patient to have diarrhoea, which was treated with medication. Laboratory findings normalized and imatinib was maintained. Twenty-four months after the initial evaluation, the patient was in good condition and had no new symptoms. Hormonal findings remained normal and functional imaging using whole-body^{131} metaiodobenzylguanidine (MIBG) scintigraphy revealed no abnormal hyperfixation.

Discussion

The incidence of pheochromocytomas in NF1 patients varies between 1% and 5.7% and GISTs occur in approximately 7% of NF1 patients.[3,10] To our knowledge, only 10 cases of the triple association of pheochromocytomas, GIST and NF1 have been previously reported[4–9] (Table 1).

Table 1. Characteristics of the 11 NF1 patients with associated GIST(s) and pheochromocytoma(s).

Age (yrs) M/F References	Reasons for initial examination leading to discovery	Reasons for suspicion of pheo(s)	Reasons for suspicion of GIST(s)	Pheochromocytoma location and diameter	GIST location and diameter	Treatment	Outcome during follow-up
60 M[4]	Follow-up for NF1	ND	Found during surgery on pheo	Bilateral pheo ND	Duodeno-jejunal; ND for diameter	Surgery on pheo ND for GIST	ND
58 F[5]	ND	ND	Incidental finding at autopsy	ND	Jejunum; One tumor, 5 cm	ND	Patient died with hydrocephalus, dementia, pulmonary embolism
71 M[5]	Pheo 12 years earlier	ND: pheo removed 12 years earlier	Incidental finding at autopsy	ND	Ileum; 3 tumors 0.3 cm; 2 cm; 5 cm	ND	Patient died from pulmonary embolism
68 F[5]	Gastric retention	Incidental finding at autopsy	Gastric retention	ND	Duodenum; small intestine Multiple tumors 0.5–2 cm	4 year follow-up; ND for treatment of pheo or GIST	Patient died from pneumonia and pulmonary embolism
64 M[5]	ND	ND	Incidental finding at surgery	ND	Stomach, small intestine and colon; Multiple tumors (>100) 0.1–3.5 cm	Surgery on pheo	Patient was alive and well at 1 year
53 F[6]	Follow-up of NF1	Tumor found on CT scan	Found during surgery on pheo	Pheo of left adrenal gland 5 cm	Small intestinal sub mucosal tumor 3 cm	Surgery on pheo Resection of the GIST	ND
82 F[7]	Follow-up of NF1; Epilepsy associated with old brain infarction; obstruction during hospitalization	Tumor found on CT scan; No symptoms; normal blood pressure	Obstruction, managed conservatively	Pheo of left adrenal gland 2.5 cm	Sub mucosal surface of stomach; Multiple tumors, 3–5 mm	Surgery on pheo Biopsy of GIST	Alive after 2 months
63 F[8]	Follow-up of NF1: Recurrent hypertension, palpitations, headache, nausea	Recurrent hypertension, palpitations, headache, nausea	Found during surgery on pheo	Pheo of left adrenal gland 5 cm	Terminal Ileum and mesenterial region 6.5 cm	Surgery on pheo Complete resection of the GIST with resection of 9 cm of ileum	

(*Continued*)

Table 1. (*Continued*)

Age (yrs) M/F References	Reasons for initial examination leading to discovery	Reasons for suspicion of pheo(s)	Reasons for suspicion of GIST(s)	Pheochromocytoma location and diameter	GIST location and diameter	Treatment	Outcome during follow-up
	Follow-up: at 6 months, recurrent hypertension, palpitations, headache	CT scan performed	ND	Pheo of right adrenal gland 3 cm	Jejunal; Multiple tumors 3 cm	Enucleation of the right mass; Resection of the GIST and of a jejunal segment; 7 other GIST were removed up to 2 mm	48 months follow-up; no recurrence seen on clinical examination or CT scan
60 F[9]	Hypertension, headache, vomiting	Hypertension, headache, vomiting	Found during surgery on pheo	Pheo of left adrenal gland 3 cm	Small intestine; Multiple tumors 5–20 mm	Left adrenalectomy, with some GISTs removed during the procedure	No recurrence at 15 months
67 F[9]	Follow-up of NF1: hypertension	Hypertension	Found during surgery on pheo	Bilateral pheo	On the mesentery of the descending colon 3 cm	Bilateral adrenalectomy, with GIST removed during the procedure	9 months follow-up: Patient died of secondary infection with ischemic necrosis of intestine
60 F case presented in current report	Follow-up of NF1: acute intestinal obstruction	Tumor found on CT scan; Normal blood pressure	Follow-up of NF1: found in 2005 on CT scan Multiple GIST; laparotomy and biopsies	Pheo of left adrenal gland 3.5 cm	Small intestine and mesentery; Multiple GIST One GIST: 5.5 cm	Left adrenalectomy, with biggest GIST removed during this procedure; resection of 156 cm of small intestine and colon	At 18 months: No recurrence of pheo, diarrhoea

Abbreviations: CT, computerized tomography; M/F, Male/Female; NF1, neurofibromatosis 1; ND, not documented; pheo, pheochromocytoma; GIST(s), gastrointestinal stromal tumor(s).

The clinical expression of NF1 is highly variable, with the occurrence of several various benign or malignant tumors (36% of cases in 70 NF1 patients), including GISTs and pheochromocytomas.[3] NF1 is associated with gastrointestinal manifestations in 10%–25% of cases. These symptoms are sometimes due to stromal tumors, the most common mesenchymal neoplasms of the gastrointestinal tract.[5,11,12] GISTs originate from multipotential precursor cells with characteristics of the interstitial cells of Cajal. These gastrointestinal pace maker cells regulate peristalsis in the digestive tract. As previously reported, GISTs encountered in NF1 are mostly located in the small intestine (as we observed in 10 of 11 subjects), whereas sporadic GISTs are located in the stomach in two third of cases.[13,14] We found multiple tumors in seven of 11 patients with GIST. These findings are consistent with previous reports.[5,13] Pheochromocytomas were bilateral in three of 11 patients (27% of cases); a previous study found pheochromocytomas in 9.6% of 148 patients.[10] We found symptomatic hypertension in three patients (27% of cases).

NF1-related GISTs occur at a younger age (median age: 49 years) than sporadic GISTs (over 55 years of age);[13,15] our patients, however, were older than 58 years. Eight of 11 patients were women, consistent with previous findings of a predominance of NF1-related GISTs among women.[13] Detection of GISTs in the eleven patients was mostly incidental (either intraoperatively or at autopsy for eight patients) and tumors were symptomatic in the remaining three patients. A common clinical manifestation of GISTs in NF1 patients is acute or chronic gastrointestinal bleeding, with or without anemia. However, vague, non-specific and non-localized abdominal symptoms, palpable masses, bowel obstruction and/or perforation have also been reported.[5,13]

Depending on the location of the tumor(s), diagnostic procedures include CT scans and MRI, ultrasonography, upper or lower endoscopy, and more recently PET imaging to characterize malignancy.[16,17] GISTs originate in the bowel wall and may grow into the mucosa causing ulceration and bleeding. Alternatively, they may protrude toward the serosal side; endoscopic biopsies are thus not always useful for diagnosis in such cases.

Previous histologic and immunohistochemical analyses have shown that GISTs associated with NF1 are similar to sporadic GISTs.[15,18] The tumor cells typically show strong positive signal for the KIT receptor tyrosine kinase (immunoperoxidase stain for CD117), with variable positive staining for alpha smooth-muscle actin, S-100 protein and CD34.[19] One study suggested that CD34 stains more strongly in NF1-associated GISTs than in sporadic GISTs.[5]

The molecular basis of GIST formation in NF1 is not perfectly understood: whereas mutations of the c-kit gene or of the PDGFRA-encoding gene are sometimes detected in sporadic GISTs, they are not generally associated with NF1-related GISTs. Thousands of mutations in the NF1 gene (17q11.2) have been associated with the development of NF1, an autosomal dominant genetic disorder.[20] The gene encodes neurofibromin, a protein of 2818 amino acids, belonging to the GTPase-activating protein family of RAS regulatory proteins. Maertens *et al* suggest that the molecular event underlying GIST development is rather a somatic inactivation of the wild-type NF1 gene in the tumor, resulting in the inactivation of neurofibromin.[5,19] The consequent oncogenic effects involve pathways other than those previously described for sporadic GISTs.[19] This molecular pathogenesis of GISTs in NF1 patients is not consistent with the coexistence of GISTs in NF1 patients being purely coincidental.[19]

Pheochromocytomas were removed in nine of our patients (data about surgery were not available for two patients). Surgery of resectable GIST over 2 cm in size remains the standard curative strategy.[21] In five of 11 patients, GISTs and pheochromocytomas were removed at the same time (one patient had a biopsy of stromal lesions and data were unknown for the remaining patients). We do not know if laparotomy was preferred to endoscopic surgery for NF1-related pheochromocytoma removal for cases in which GISTs were discovered at the preoperative work-up. As the number, location and size of GISTs vary greatly, we cannot recommend one technique over another; indeed, a multidisciplinary team, including surgeons, should be consulted in such cases.

GISTs are unresponsive to conventional chemotherapy. Thus, imatinib, which inhibits the c-kit receptor, is used in cases of unresectable GISTs, partial resection or recurrence of the tumors.[22] Data

about the treatment with imatinib were available for one patient only.

The prognosis for GISTs in NF1 is unknown and highly variable. In a one study, 70 NF1 patients were followed for 12 years, with an average age at diagnosis of 44 years. Of these 70 patients, 31.4% died at a mean age of 62 years. Malignancy was the most common cause of death, occurring in 55% of the patients that died.[23] In another study, 45% of NF1 patients with GISTs were alive and well after a median follow-up of 14 years.[13] Hypertension is significantly associated with mortality; indeed, in a previous study, 10 of 12 patients with hypertension died during follow-up.[23] Patients with NF1 and pheochromocytoma have a relatively high prevalence of malignant disease (12 percent of patients).[24] In a retrospective study of 259 patients with GIST, who underwent surgery before treatment with imatinib, completeness of surgical resection was found to be an independent positive prognostic factor.[21] Prognosis may be improved by treatment with imatinib, but this requires further investigation in NF1 patients.

Conclusion

The coexistence of NF1-related pheochromocytoma and GISTs is uncommon, but perhaps not fortuitous, and endocrinologists should be aware of this. GISTs may be detected before or after clinical expression of pheochromocytoma. The frequency of gastrointestinal manifestations of GISTs in NF1 patients is not known and most of the small GISTs, generally multiple and preferentially located in the small intestine, are discovered incidentally during radiological examinations, laparotomy or autopsy. Specific molecular pathogenic mechanisms underlying the development of GISTs in NF1 patients suggest that their coexistence is not purely coincidental. Surgery on resectable GISTs remains the standard curative strategy, with GISTs and pheochromocytoma generally being removed simultaneously. The efficacy of imatinib requires further study in NF1 patients and the prognosis of GISTs in NF1 is unknown and highly variable.

Acknowledgments

We thank Alex Edelman and Associates for correcting our English.

Disclosures

The authors report no conflicts of interest.

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