Neurofibromatosis Type 1 and GIST: Is There a Correlation?

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Abstract. *Background: Neurofibromatosis type 1 (NF1) is a hereditary cancer predisposition syndrome characterized by neurologic, dermatologic and orthopedic manifestations. There is a spectrum of tumors that affects individuals with NF1 at an increased incidence compared to the general population, such as neurofibromas, malignant peripheral nerve sheath tumors (MPNST) and gliomas. There has been a growing number of literature reporting an association between NF1 and gastrointestinal stromal tumors (GIST). Case Report: We herein report a case of recurrent asymptomatic GIST in a 50-year-old woman with a history of neurofibromatosis type 1. Discussion: NF1-associated GIST has been described to comprise a minority of cases, in which there is an alternative molecular pathogenesis. This difference between NF1-related GISTs and that of the general population has important therapeutic implications. The presence of kinase mutations has been shown to be predictive of clinical response to imatinib, a tyrosine kinase inhibitor.*

Neurofibromatosis type 1 (NF1) is a hereditary cancer predisposition syndrome characterized by its neurologic, dermatologic and orthopedic manifestations. It is the most common genetic syndrome with an incidence of 1 in 2,500 to 3,000 and a prevalence of 1 in 4,000 to 5,000 (1). It has an autosomal dominant pattern of inheritance with complete penetrance; however, as many as 50% of affected individuals have been reported to be sporadic cases (2, 3). NF1 is further defined by its variable expression, resulting in a wide array of clinicopathological features and a varying, unpredictable disease course (1, 2).

There is a spectrum of tumors that affects individuals with NF1 at an increased incidence as compared to the general population. In addition to the NF1-distinguishing neoplasms, such as neurofibromas, malignant peripheral nerve sheath tumors (MPNST) and gliomas, there has been a growing number of literature reporting an association between NF1 and gastrointestinal stromal tumors (GIST). Although it is a relatively rare entity, occurring at an incidence of 6 to 15 *per* one million, GIST is the most common mesenchymal tumor of the gastrointestinal (GI) tract (5). It is only in recent years that the molecular pathogenesis of GIST has been demonstrated, with aberrant tyrosine kinase activity identified as the key modulator in the majority of cases. This advancement has allowed for molecularly targeted therapy *via* imatinib, a tyrosine kinase inhibitor (5, 6, 9). NF1-associated GIST, however, has been described to comprise a minority of cases, in which there is an alternative molecular pathogenesis. This difference between NF1-related GISTs and that of the general population has important therapeutic implications (9).

We herein report a case of recurrent asymptomatic GIST in a 50-year-old woman with a history of neurofibromatosis type 1.

Case Report

A fifty-year-old Nigerian woman with NF1 (Figure 1) was incidentally diagnosed with GIST in 2008 following routine monitoring of an intra-abdominal neurofibroma. Computed tomographic (CT) imaging revealed that the intra-abdominal neurofibroma had enlarged from 1 cm to 3.9 cm as compared to a 2.5 year prior CT scan. The patient was asymptomatic; however, given the concern for malignant transformation, a surgical wedge resection was performed, during which a solitary 2.5 cm retrogastric mass was removed. Pathology revealed involvement of the gastric muscularis propria and serosa, uniform spindle cell morphology and a mitotic count of 5 *per* 50 high power fields. Immunohistochemical analysis was positive for CD 117 and desmin expression; whereas staining for smooth muscle actin, S-100 protein and neurofilament was negative. Mutation testing of platelet derived growth factor receptor alpha (PDGFRA) exon 18 was negative for a D842 mutation. *KIT* mutation analyses were wild type for exons 9 and 11. These findings were

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consistent with the diagnosis of wild-type GIST with a low risk prognosis, based on the maximum diameter of the tumor, in combination with the mitotic count, *per* National Institute of Health consensus NIH guidelines (5, 16). The patient was treated with adjuvant imatinib for one year at a dosage of 400 mg daily.

The patient was routinely monitored for recurrence over the following four years. In 2012, CT imaging revealed interval gastric wall thickening adjacent to the previous wedge resection. The patient did not manifest any symptoms; but, in the setting of her history of GIST, further work-up was pursued. Surgical exploration was significant for four gastrointestinal masses: a 3.8 cm inferior gastric mass, a 2 cm lesser curvature gastric mass, a 1.4 cm duodenal mass and a 1.7 cm small bowel mass. The former three masses had a spindle cell morphology, while the small bowel mass had an epithelioid morphology. All four masses had a mitotic count of 1 to 3 *per* 50 high power fields. Immunohistochemistry demonstrated CD 117 expression in each of the masses. In addition, the inferior gastric mass expressed S-100, neurofilament and a Ki-67 proliferation index of 1 to 2%. The small bowel mass also expressed a Ki-67 proliferation index of 1 to 2%. These findings rendered a diagnosis of multifocal GIST with a low risk prognosis (5, 16). Mutation analyses for each of the GISTs yielded the same results: wild type *KIT* exon 9, wild type *KIT* exon 11, and *PDGFRA* exon 18 negative for D842 mutation.

Discussion

NF1 is one of the most common autosomal dominant conditions in which affected individuals have an increased risk of malignancy. It is mostly characterized as a neurocutaneous disorder, with both *café au lait* patches and cutaneous neurofibromas occurring at frequencies greater than 99% (1, 2). However, NF1 is a multi-system and variable disease with clinicopathological features that encompass a much broader spectrum.

The genetic basis of this disease is a mutation in the *NF1* gene located on chromosome 17q11.2. *NF1* encodes neurofibromin, a tumor suppressor protein. Neurofibromin regulates cellular proliferation *via* inactivation of RAS, a protein that stimulates signal transduction through the MAP-kinase pathway when activated. The resultant loss of function of neurofibromin predisposes to the development of benign and malignant tumors (1, 2, 7).

The major neurological disease manifestations can be divided between the central nervous system (CNS) and the peripheral nervous system (PNS). CNS involvement includes cognitive impairment, learning disability, attention deficit hyperactivity disorder (ADHD), epilepsy, structural malformations and cerebrovascular abnormalities. The most frequent CNS malignancy observed is glioma, which has a predisposition for the optic pathway, the brainstem and the cerebellum. Neurofibromas are the chief feature of PNS. They are benign tumors that develop along the peripheral nerve sheath and occur in multiple types: focal cutaneous or subcutaneous, and diffuse or nodular plexiform. Malignant peripheral nerve sheath tumors (MPNST) are the predominant PNS cancers, with an 8-13% lifetime risk in NF1. MPNST usually arise from preexisting plexiform or subcutaneous neurofibromas (1, 2).

Those affected with NF1 also carry the potential for disease manifestations beyond the neurological system. Lisch nodules, which are benign hamartomas of the iris, constitute the major pathology of the eye. The musculoskeletal system can also be involved with scoliosis, tibial bowing and pseudoarthrosis most frequently observed. The predominant dermatologic features are café au lait spots, followed by skin-fold freckling (1, 2). Cardiovascular disease, including congenital heart disease, vasculopathy and hypertension, as well as other malignancies, such as leukemia, rhabdomyosarcoma and pheochromocytoma, are reported to be associated with NF1 at greater frequencies than the general population (7, 11).

In addition to the aforementioned disease hallmarks, GI involvement in NF1 has been reported in as many as 25% of affected individuals (17). NF1-related GI disease has been described to occur in three principle forms: neurogenic tumors, stromal tumors and neuroendocrine tumors (10, 17, 18). The most common of these GI manifestations in NF1 is GIST. Further, NF1 has been associated with an increased risk of developing GIST, with one study indicating an incidence of 7% in the NF1 population and another study reporting a 150-fold increased risk as compared to the general population (7, 19).

GIST is a soft-tissue sarcoma that likely arises from the interstitial cells of Cajal (ICC), GI pacemaker cells with a role in motility. Its origin was elucidated by the discovery that both the ICC and the majority of GISTs express the receptor tyrosine kinase *KIT* (CD 117) (5, 6). Approximately 85% of GISTs are characterized by a sporadic activating mutation in the gene KIT, leading to the constitutive activation of KIT. *KIT* mutations most commonly occur in exon 11 (60%), but can also occur in exons 9 (15%), 13 or 17 (5%). Less commonly, GISTs harbor a mutation in the platelet derived growth factor receptor alpha (*PDGFRA*) gene, which also encodes a receptor tyrosine kinase. These mutations can occur in exons 12 or 18 (5, 6). Both tyrosine kinases play key roles in the tumorigenesis of GIST *via* signal transduction through the PI3K-AKT, MAP-kinase, and JAK-STAT3 pathways (12).

In addition to mutation analysis, GIST is further characterized by its pathology. The majority of cases occur as a solitary tumor, with the stomach as the most common site (60%), followed by the small intestine (25%). Tumor morphology can be classified as one of three types: spindle

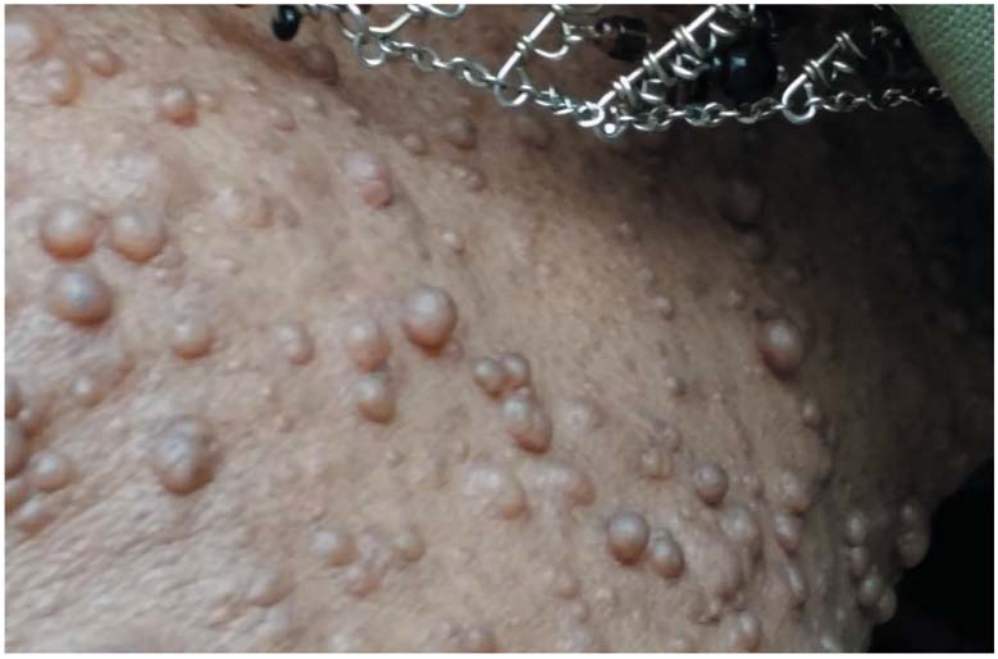

Figure 1. *Dermatological manifestations of neurofibromatosis in the presented case are displayed.*

cell-type (70%), epithelioid-type (20%) and mixed-type (10%). Approximately 95% of tumors have CD 117 (KIT) expression. GIST can also demonstrate expression of BCL-2 [human proto-oncogene located on chromosome 18] (80%), CD34 [hematopoietic progenitor cell antigen CD34] (70%), muscle-specific actin (50%), smooth muscle actin (35%), S-100 (10%) and desmin (5%).

The cases of GIST observed in the NF1 population also demonstrated CD 117 expression; however, in contrast, the NF1-related cases appear to constitute a subset of wild-type cases, in which neither *KIT* or *PDGFRA* are mutated, implying a different molecular pathogenesis (5, 7, 8). NF-1 related GIST occurs as a result of somatic inactivation of the wild-type NF1 allele in the tumor, leading to increased signal transduction *via* the MAP-kinase pathway (7, 8). There has been evidence to suggest that the *NF1* mutation can result in the overexpression of *KIT* and/or *PDGFRA*; thus, explaining positive CD 117 (KIT) expression on immunohistochemistry, despite the absence of a mutation in either *KIT* or *PDGFRA* (20). NF1-related GIST differs from its sporadic counterpart in several other ways, including its propensity to be multifocal and to occur in the small bowel, as well as its higher frequency of spindle cell morphology and CD34 expression (6, 7).

The management of GIST depends on the extent of disease. Surgery constitutes the mainstay treatment for primary resectable disease. For unresectable and metastatic disease, targeted-therapy with imatinib mesylate, a tyrosine kinase inhibitor with activity at both KIT and PDGFRA, has shown promising effects. In 2002, the US Food and Drug Administration (FDA) approved targeted-therapy with imatinib, following the landmark CSTIB2222 trial, which demonstrated significantly improved median time-to-progression (TTP), median overall survival (OS) and 5-year survival rates. Imatinib was also approved as adjunctive therapy for primary resected GISTS >3 cm in size, after a randomized phase III trial conducted by the American College of Surgeons Oncology Group, demonstrated an improved 1-year recurrence-free survival, compared to placebo. With regards to predictive markers, the CSTIB2222 trial demonstrated that imatinib has highest efficacy in GISTs with exon 11 *KIT* mutations, when compared to GISTs with exon 9 mutations or wild-type *KIT*. In addition, imatinib was shown to have no effect in patients with *PDGFRA* D842V point mutations (5, 6). Specifically for wild-type cases, such as NF1, adjuvant therapy with imatinib should be considered on an individual case-by-case basis, as the benefit may be variable. The dosage of imatinib is approved at 400 mg *per* day; however, studies have demonstrated increased benefit for exon 9 mutations at a dose of 800 mg *per* day. The optimal duration of treatment is undetermined. Initial trials demonstrated benefit with one year of imatinib treatment, whereas the Scandinavian Sarcoma Group recently demonstrated an increased benefit with 3 years of treatment, specifically in the setting of advanced disease (21).

With regard to surveillance for disease progression and recurrence, it has been recommended to perform CT imaging every 6 months during imatinib therapy. The highest risk of GIST recurrence is in the 2 years following treatment, so patients should be followed with CT imaging every 3 to 4 months. After the initial 2-year period, CT imaging should be performed every 6 months for 3 years and then annually. The risk of recurrence after the 10 years substantially decreases, such that the risk of radiation associated with CT imaging may out-weigh its benefit after that period (21).

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