

## Research

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# Neurofibromatosis Type I and Multiple Gastrointestinal Stromal Tumors: A Unique Identity

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## INTRODUCTION

Von Recklinghausen's disease (VRD) is a genetic disorder characterized by the growth of multiple noncancerous tumors of nerves and skin (neurofibromas) and areas of hypo or hyperpigmentation of the skin. It is also known as *Neurofibromatosis type I (NF1)* and represents one type of VRD. It is an autosomal dominant disorder with a rate of occurrence of 1 in 3000 in the general population.<sup>1</sup> The cause of *NF1* is a mutation in the *NF1* gene, located at the chromosome 17q11.2, which encodes the tumor suppressor gene, neurofibromin. Loss of neurofibromin function results in activity of Ras oncogene and consequently tumor formation.

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. The prevalence of GISTs in *NF1* varies from 5 to 30%. They are more common in the small intestine (90%) and only 5% occur in the stomach, and they don't metastasize immediately.<sup>2</sup> The majority are c-kit and PDGFRA wild-type, which means that are not related to oncogenic mutations. In this paper, we report a case of a man with a late diagnosis of neurofibromatosis and multiple GISTs.

## CASE REPORT

We report a 75-years single-old man with the diagnosis of VRD - Neurofibromatosis Type I since 2000. He had multiple cutaneous neurofibromas and pigmented macules (*café-au-lait* spots) over the entire body surface. In his past history he was also diagnosed with epilepsy and occasional seizures and benign hypertrophy of the prostate gland. His usual medication was tegretol 400 mg, kepra 1000 mg. He had learning disabilities. He had no history of hypertension, diabetes mellitus, cardiovascular or pulmonary disease or previous gastrointestinal pathology. He had no other relevant past medical history. No known family history of diagnosis of Von Recklinghausen disease. He lives in a social center and always accompanied by a social assistant.

This patient reported to the emergency room in 2011 with abdominal pain and an abdominal computed tomography (CT) scan was performed and solid mass with 57×44 mm in the left hypochondrium was diagnosed. He was submitted to surgery with no complications. Histological analysis revealed a gastrointestinal stromal tumor with 7 cm long, tumor capsule was intact, 3 mitosis/50 HPF and was classified with an intermediate risk, according to the National Institutes of Health (NIH) classification, with 24% risk of recurrence.<sup>3</sup> The patient stayed in surveillance.

Three years later in 2014, a second tumor was diagnosed in the duodenum, jejunum as well as in the mesentery. Histology revealed once again a GISTs. The duodenum fragment revealed 2 nodules with 7 and 15 mm long, 1 mitosis/50 HPF and free margins. Immunohistochemical staining revealed: positive for CD117 (oncogene c-kit), negative for CD34, protein S100 and SMA. It was classified as pT1, very low risk. The jejunum nodule was 8 mm long; no mitosis were identified, free margins. Immunostaining was positive for CD117 and CD34,

negative for protein S100 and SMA. It was classified as pT1 with very low risk. The mesentery nodule was 9 mm longest axis, spindle cell proliferation like the ones above and with the same immunostaining characteristics. In the three samples no c-kit mutations were identified, because of which resistance to imatinib has been described and the patient stayed in surveillance once again.

A year later, an abdominal CT scan showed a solid mass with 21 mm was identified in the lateral wall of the first portion of the duodenum. The mass shows exocentric growth from the duodenum wall. Cleavage was maintained with other proximal structures. He was once again submitted to surgery with no complications. Histology revealed the following characteristics: the Duodenum nodule was 20×18×11 mm, spindle cell proliferation, mitotic index was inferior to 5 mitosis/50 HPF; proliferative index (Ki67) inferior to 1%. Immunostaining was positive for CD117 (c-kit) and CD34, poorly positive for desmin, negative for protein S100, keratin 7 and SMA. It was classified as pT1, low risk. The 3 jejunum nodules each with 5 mm long showed smooth muscle, spindle cell proliferation. No mitotic figures were identified. Immunostaining was positive for CD117 and no mutations of c-kit were identified once again. The patient until today is in surveillance, with no more recurrences diagnosed up to last image evaluation.

## DISCUSSION

GISTs are the most common mesenchymal tumor in the digestive tract, which originate from the cells of Cajal.<sup>4</sup> The most common cases are the sporadic GISTs which harbor c-kit gene mutations in 75%. Another group of patients without c-kit mutations may harbor mutations of the *PDGFRA* gene in 10%.<sup>5</sup>

GISTs associated to *NF1* differ in many ways, and only 5-25% arise in *NF1*. They are typically localized to the small intestine, show multiplicity, strongly positive for KIT by Immunohistochemistry (IHC), but have neither mutations of c-kit or *PDGFRA* gene. These GISTs are commonly accidental findings during other abdominal surgeries. According to the NIH classification, they are frequently low grade, small size and with few or mitotically inactive. The presence of multiple small tumors is not associated with progressive disease. Most patients in the follow-up have a good prognosis.

Consequently, *NF1* cases don't have any oncogene mutations which could be targeted by a "shut down" molecule as is imatinib mesylate, a tyrosine kinase inhibitor which acts in

sporadic cases with oncogene mutations. Therefore, point mutations of c-kit (exon 9,11,13 and 17) and *PDGFRA* (exon 12 or 18) gene may play a small role in the tumorigenesis pathway of *NF1* associated to GIST.<sup>5</sup> In other words, the pathogenetic mechanisms arise via a distinct way.

We report a case of a late known diagnosis of *NF1* associated with multiple GISTs submitted to three surgeries. He was never submitted to imatinib treatment, as previously explained, and with a good prognosis and with good quality of life (QoL).

This is a unique identity of Gist's that clinicians have to be aware of. It appears within the Von Recklinghausen disease, as Neurofibromatosis Type I, and are distinct from the usual GISTs, thus require different care approaches. This case report has some interesting particularities which in this case, spares the patient from molecular target therapy and its toxicities, and on the other hand, spares the country's health system from a heavy economic burden.

## CONSENT

The author has taken oral consent from the patient.

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