

## Case Report

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# A rare case presentation of neurofibromatosis type 1 with multiple gastrointestinal stromal tumors: a case report

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## ABSTRACT

Neurofibromatosis type 1 (NF1), a hereditary cancer predisposing syndrome is an autosomal dominant disorder. Gastrointestinal stromal tumor (GIST) is the most prevalent non-neurological tumor in these individuals. In NF1-associated GIST, KIT and platelet-derived growth factor receptor  $\alpha$  (PDGFRA) mutations might not be present, and Imatinib may not be effective. Surgical resection is the first-line treatment. The primary aim was to include the possibility of rare tumors including GIST in neurofibromatosis patients in the differential diagnosis of GIT pathology/presentation. A 50-year-old male with neurofibromatosis came with complaints of dull aching abdominal pain and on further investigation was found to have lesions in the distal small bowel, suspicious of nerve sheath tumors, in abdominal computed tomography. A laparotomy was performed and the jejunum containing nodular lesions was resected and pathologically diagnosed as GIST. The patient was then started on Imatinib. At the 6-month follow-up, no tumor recurrence was visible. The rare and unusual location of multiple GIST in neurofibromatosis patients underscores its importance in differential diagnosis, and our case report on the patient's therapy and the clinical outcome could aid in patient care.

**Keywords:** Neurofibromatosis type 1, Gastrointestinal stromal tumours, NF1 gene

## INTRODUCTION

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen's disease, is an autosomal dominant disorder caused by genetic mutations in certain oncogenes. It is a hereditary cancer predisposition syndrome characterized by neurologic, dermatologic, and orthopedic manifestations. The incidence is of 1/3000 to 1/4000.<sup>1</sup> NF1 is clinically diagnosed when at least two of the following conditions are met: (1) at least six café-au-lait patches, each larger than 5 mm in diameter in prepubertal children and over 15 mm in diameter in postpubertal individuals and adults; (2) freckles in the axilla or inguinal region; (3) two or more neurofibromas or one plexiform neurofibroma; (4) optic glioma; (5) two or more Lisch nodes or iris hamartomas; (6) bone lesions; and (7) first-degree relative with NF1.<sup>3</sup> The most prevalent mesenchymal neoplasm of the GI tract is the

gastrointestinal stromal tumors (GIST). They are derived from the intestinal cells of Cajal, a GI pacemaker cell. They mostly arise in the stomach (60–70%) or small intestine (20–30%). GISTs can manifest at any age but are mostly seen after 50 years of age. 5% of GISTs are associated with an underlying heritable mutation such as familial GIST syndrome, neurofibromatosis 1, or Carney-Stratakis syndrome. Multiple GISTs are uncommon, but can be seen in familial GIST.<sup>4</sup> We report an NF1 patient with dull aching abdominal pain with a small intestinal nodular mass who underwent laparotomy and was diagnosed with multiple GISTs.

## CASE REPORT

### *Clinical history*

A 50-year-old male with neurofibromatosis came to outpatient department (OPD) with complaints of dull

aching abdominal pain for the last 5-6 days, in the perumbilical region, intermittent and not associated with nausea, vomiting, fever, and altered bowel and bladder habits. The patient is a known case of neurofibromatosis with no other comorbidities or past illness, and no history of any surgical interventions. He did not have any addictions. He did not have any significant family history.

#### Physical examination

On physical examination, the patient exhibited soft cutaneous nodular masses (neurofibromas) of 0.2 to 3 cm in diameter on the head, face, trunk, and limbs as well as multiple café-au-lait patches, and a plexiform neurofibroma over the left flank (Figure 1). There were freckles in the axilla and inguinal region. The patient had scoliosis. Nothing abnormal was detected in the examinations of the cardiovascular and respiratory systems. Hearing tests were done and were normal. No lymphadenopathy was detected in the neck, axilla, or inguinal region. The abdomen was soft and without tenderness or palpable masses. Bowel sounds were normal. The digital rectal exam was unremarkable.



**Figure 1: Preoperative clinical image, red arrow shows multiple cutaneous nodular masses or neurofibromas, black arrow shows plexiform neurofibroma, green arrow shows café-au-lait patches.**

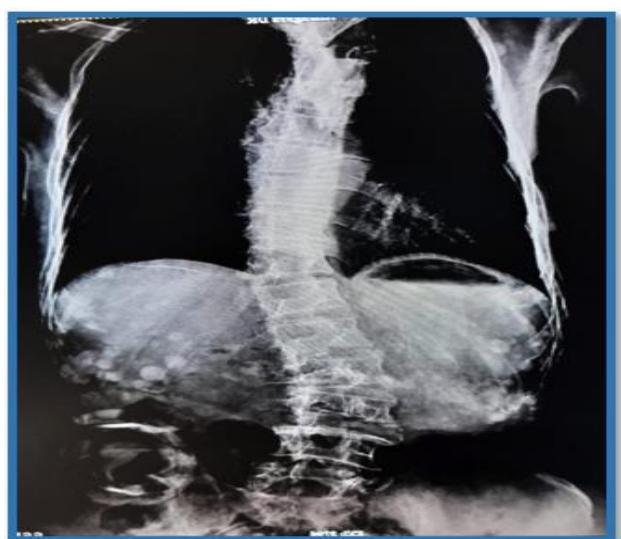
#### Investigations

Routine hematological tests were done and were within normal limits. X-ray spine showed scoliosis (Figure 2). Contrast-enhanced computed tomography of the abdomen (Figure 3) showed 3 well-defined heterogeneously enhancing mural lesions with endoluminal and exophytic growth in distal small bowel loops suggestive of nerve sheath/neuroendocrine tumors. It also mentions multiple cutaneous and subcutaneous heterogeneously enhancing

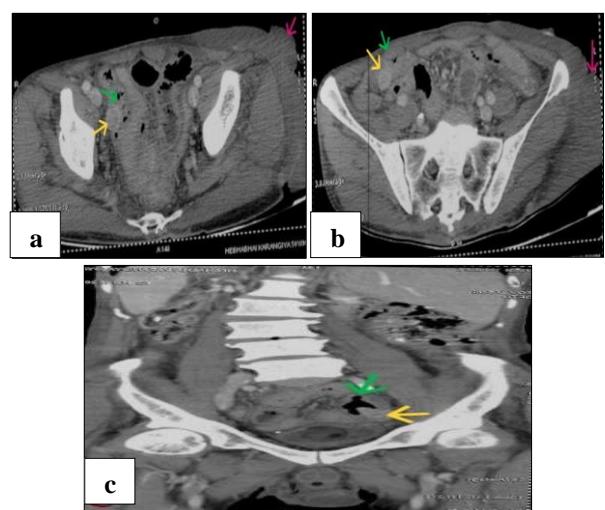
soft tissue lesions suggestive of neurofibromas. Serum serotonin was done and was within normal range.

#### Treatment

After multidisciplinary team consultation, laparotomy was performed. There were multiple inter-bowel adhesions and three extra luminal nodular growths of size 1-2 cm were found in the jejunum, roughly 80 cm from the ligament of Treitz. Adhesions between this part of the bowel and the sigmoid colon were separated. There was a minor injury in the sigmoid colon while removing adhesions. This was repaired. Then the jejunum containing the nodular growth was resected with a 5 cm margin on either side (Figure 4). Then jejuno-ileal side-to-side stapler anastomosis was done, followed by sigmoid diversion transverse loop colostomy. Postoperative recovery was uneventful.



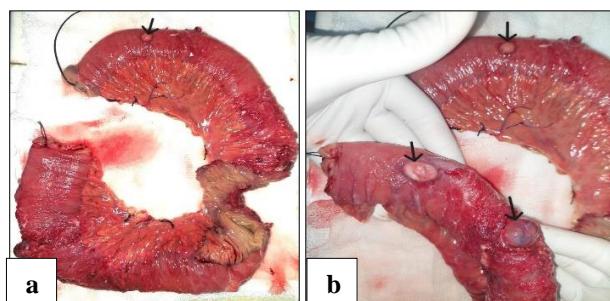
**Figure 2: X-ray dorso-lumbar spine AP view showing scoliosis.**



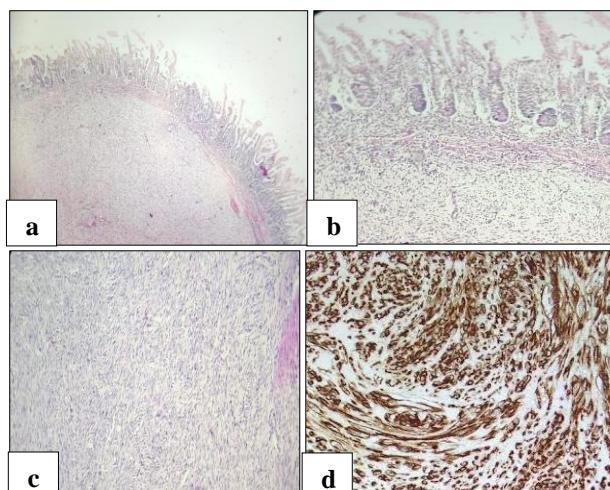
**Figure 3: Contrast enhanced CT images in various sections of the abdomen, (a), (b) and (c) yellow arrow depicts three heterogeneously enhancing endoluminal**

and exophytic growths, green arrow shows the bowel loop, pink arrow shows neurofibromas, and (c) scoliosis.

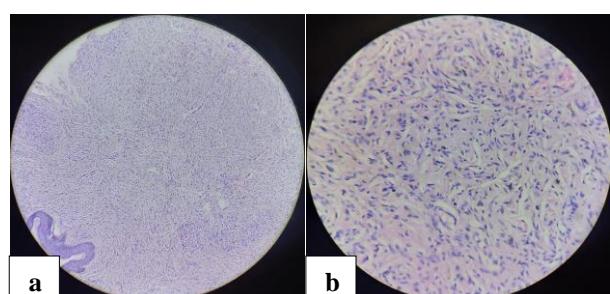
Histopathology of the 3 nodular masses in the jejunum was consistent with GIST with spindle cell type (Figure 5). The tumor was categorized as low risk using modified National Institutes of Health standards. CD117 and DOG-1 staining were positive. S-100 staining was negative. The final diagnosis was multiple NF1-associated GISTS.



**Figure 4: Intraoperative image showing excised specimen of jejunum with three extra luminal nodular growths (shown by arrows), around 1 cm with clear borders.**



**Figure 5: (a) Postoperative histopathology image of nodular mass from the specimen of small bowel showing diffuse spindle cells with rod shaped nuclei (haematoxylin-eosin X 10), (b) in (X 20), (c) in (X 40), and (d) immunohistochemistry showing diffusely strong expression of DOG1 (X 40).**



**Figure 6: Histopathology image from cutaneous nodules showing spindles cells with wavy nuclei with strands of collagen, consistent with neurofibromas.**

#### Outcome and follow-up

The patient was discharged on day 14 after surgery. The patient then consulted the oncology department and was started on the tablet Imatinib 400 mg once a day. No complications occurred. No sign of tumor recurrence or metastasis was present at the 6-month follow-up, by contrast-enhanced abdominal CT.

**Table 1: Distinguishing features of neurofibromatosis 1-associated and sporadic gastrointestinal intestinal stromal tumor.**

Features	NF1 with GIST	Sporadic GIST
<b>Age of presentation</b>	Younger age	Elderly
<b>Most common location</b>	Small bowel (90%)	Stomach (60-70%)
<b>Number of tumors</b>	Often numerous	Often isolated
<b>Rate of tumor growth</b>	Slow	Rapid
<b>Gene mutation such as KIT and PDGFRA</b>	Occasional	Frequent
<b>Imatinib treatment</b>	Ineffective	Effective
<b>Disease progression</b>	Gradual	Brisk
<b>Postoperative recurrence rate</b>	Low	High
<b>Prognosis</b>	Good	Common

NF1: Neurofibromatosis 1; GIST: gastrointestinal stromal tumor

#### DISCUSSION

The NF1 gene is found in chromosome 17q11. The related neurofibromin protein may not be able to be produced as a result of mutations. Because of the aberrant activation of the RAS/RAF/MAP signaling pathway caused by deletion, neurofibromin's tumor suppressor function is lost, and tumors like neurofibroma, optic glioma, neuroblastoma, pheochromocytoma, and breast cancer are more likely to develop.<sup>1,2</sup> Roughly 7% of NF1 individuals develop GIST, which is an uncommon condition.<sup>5</sup> Its mesenchymal origins are found in the stomach and small intestine, where spindle and epithelioid cells are the most common pathological features. Ninety percent of GISTS have KIT mutations, but only five percent have PDGFRA mutations.<sup>6</sup> These two genes' mutations are the primary reason, though BRAF mutations may be present in a few. Less than 5% of GISTS are multiple. NF1 and familial GIST are often linked to multiple GISTS.<sup>7,8</sup> GIST is the most prevalent non-neurological malignancy in NF1 patients. GIST is 45 times more common in NF1 patients than in the general population. NF1-associated GIST is distinct from sporadic GIST in that it manifests at an earlier age and is more prevalent in women, with the majority of tumors (90%) being numerous and situated in

the small intestine.<sup>9,10</sup> Pathologically, NF1-associated GIST behaves like a low-grade malignancy with a slow progression and is mostly composed of spindle cells. PDGFRA and KIT mutations are often absent, indicating an independent pathogenesis from the sporadic variant. NF1-associated GIST has a better prognosis than the sporadic variant. Anemia, gastrointestinal hemorrhage, intestinal obstruction, nausea, vomiting, and abdominal discomfort are all possible symptoms of GIST. But it might also be asymptomatic and discovered incidentally. Gastroscopy is usually negative for NF1-associated GIST since it usually occurs in the small intestine. Consequently, abdominal CT or magnetic resonance imaging should be performed on middle-aged and elderly NF1 patients who have gastrointestinal symptoms. A CT scan of the abdomen can show metastases as well as the size, position, border, and relationship of the tumor with the surrounding tissues. Necrosis and calcification can occur in GIST which becomes visible on CT scans.<sup>11</sup> Exophytic tumors are more common than intraluminal tumors and can be seen on CT scan. Intraluminal tumors appear as punched out ulcers on CT scan.<sup>12</sup> The diagnosis can also be made by capsule endoscopy and small intestinal endoscopy, and it is confirmed by pathologic evaluation, immunohistochemical analysis, and genetic testing of a tumor sample.

Most NF1-associated GIST patients have positive CD117 and CD34, which helps in diagnosis. Recent studies show that DOG1 is more sensitive and specific than CD117.<sup>13</sup> Prognostic variables for GIST include tumor location, size, and mitotic activity. Survival and recurrence are related to the Ki-67 index.<sup>14</sup> Because most NF1-associated GISTS lack PDGFRA and KIT mutations, imatinib is less successful in treating them.<sup>15</sup> Depending on the size of the tumor, the initial course of treatment is surgical excision of the tumor or intestinal segment. Generally, a 1 cm resection margin is enough.<sup>16</sup> Complete removal without lymph node dissection is recommended.<sup>17</sup>

Relapse occurs in around 50% of individuals even after radical surgical treatment.<sup>18</sup> Patients with NF1 and those with sporadic GIST have similar recurrence rates. Laparoscopic surgery is also becoming common, with less procedure-related pain, faster recovery, and shorter hospital stays. Table 1 given below lists the distinguishing features of neurofibromatosis 1-associated and sporadic gastrointestinal intestinal stromal tumors.

## CONCLUSION

GIST is the most common GIT tumor associated with NF1. It should always be considered in the differential diagnosis of GIT pathology in those with NF1. It is usually asymptomatic but can present with vague abdominal complaints and GIT bleeding. NF1-associated GIST is distinct from sporadic GIST in that it does not exhibit multifocality, known genetic alterations, or effectiveness to tyrosine kinase inhibitors. Surgery is the mainstay of treatment. Unlike sporadic GIST, which most commonly

occurs in the stomach, the small intestine is the most common location of GIST in NF1 patients.

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