# **Multiple Gastrointestinal Stromal Tumors Associated with Neurofibromatosis Type 1: A Case Report**

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**Consent statement**

Written informed consent was obtained from the patient to publish this report in accordance with the journal’s patient consent policy.

## **Abstract**

## Neurofibromatosis type 1 (NF1), is a complex multisystemic autosomal dominant disorder caused by mutation in tumor suppressor gene NF1 and therefore, has increased tendency to develop neural (peripheral and central) tumors and gastrointestinal stromal tumors (GISTs). In this article, we report a 57-year-old male with NF1, who presented with recurrent episodes of melena and fresh blood in stool, and loss of consciousness who was initially managed conservatively with two pints of blood. The CT-scan of his abdomen depicted multiple lesions suggesting GISTs in the jejunum and was managed with surgical resection and anastomosis of the jejunum, and Imatinib as an adjuvant therapy. The management of multiple and wide spreading, and chemotherapy resistant GISTs can be quite challenging.

Keywords: *gastrointestinal stromal tumors; GISTs; neurofibromatosis type 1; treatment of GISTs; tumors of intestine*

## **Introduction**

## Neurofibroma is a benign peripheral nerve sheath tumor which is composed of a variable mixture of Schwann cells, perineurial-like cells, and fibroblasts.1 There are two types of neurofibromatosis: type 1 and type 2. Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is a complex autosomal dominant disorder caused by germline mutations in the NF1 tumour suppressor gene and has a frequency of about 1 in 3000. The disease affects both male and female affected in equal frequency and severity.2,3

The NF1 exhibits a wide range of clinical manifestations, the most common findings being café-au-lait nodules, neurofibromas, Lisch nodules, optic nerve pathway tumor and inguinal freckling.4 Though relatively uncommon, peripheral nerve sheath tumors of different histological subtypes may develop in the gastrointestinal organs from in patients with NF-1. These tumors may occur at any site from the esophagus to the anorectum as well as the omentum, mesentery and retroperitoneum.4

Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal tumors predominantly found in the gastrointestinal tract (GIT) that develop due to the gain-of-function mutations in c-KIT proto-oncogene. People with NF1 are at higher risk of developing a variety of benign and malignant tumors since NF1 gene acts as a tumor suppressor gene in certain group of human cells.5 Studies have shown that, compared to normal individuals, GISTs are 34 times more common in patients with NF-1.6 GISTs in the patients with NF1 are most found in the small intestine and are rarely seen in the stomach. However, in the latter, incidental GISTs are common.7

Though cases of GISTs as manifestations of NF1 have been reported in other countries, there are no reported cases in Nepal to the best of our knowledge. Herein, we report an unusual case of co-occurrence of multiple GISTs in a patient with NF1 and who was managed by surgical resection and adjuvant chemotherapy.

**2. Method:**

We reported this case following the updated consensus-based Surgical Case Report (SCARE) Guidelines.8

## **Case presentation**

A 57-year-old Buddhist male from urban Nepal with Neurofibromatosis type-1 for the last 30 years, presented to our center with the complaint of two episodes of melena. The patient did not complain of abdominal pain, yellowish discoloration of skin and mucous membranes, hematemesis and abdominal mass. On examination, the patient had diffuse lesions of neurofibromatosis over his upper and lower limbs. The hematological profile indicated anemia with hemoglobin concentration of 7.3 gm%. The upper GI endoscopic evaluation of the patient showed duodenitis and healing gastric ulcer. He was managed conservatively with two pints of blood.

The patient had melena for three days five years back as well. He was investigated with a CT scan of the abdomen which showed multiple gastrointestinal stromal tumors (GISTs). He was suggested for surgery which was refused. Seven months back, the patient again presented with melena, fresh blood loss per rectum and loss of consciousness. The CT scan of the abdomen of the patient showed multiple exophytic masses in the small intestine suggesting GISTs. He was surgically managed with exploratory laparotomy with jejunal resection and anastomosis. An oval mass of size 6-7 centimeters (cm) was found during the procedure in the antimesenteric border of the proximal jejunum about 50 cm distal to duodeno-jejunal flexure. Multiple small nodules were found over the proximal jejunum. The length of the small bowel in the patient was short (300 cm) and the transverse colon was posterior to proximal jejunum. The jejunal segment 10 cm proximal and 5 cm distal to the mass was resected and sent for histopathological evaluation. Imatinib was prescribed to the patient as an adjuvant therapy. The histopathology of the excised mass from the jejunum showed seven spindle type multifocal GISTs, the largest one being 10.5 cm. Also, the patient tested positive for DOG1, CD 117/C-KIT which are the most specific and sensitive tumor markers of GIST.9

## **Discussion**

## Neurofibromatosis type 1 is a multisystemic autosomal dominant disorder characterized mainly by the formation of numerous neurofibromas associated with spinal, peripheral or cranial nerves. The disease manifestations, which include pigmentary abnormalities, low-grade gliomas and skeletal dysplasias in addition to the neurofibromas, are gradually progressive. The patient with this disorder is managed symptomatically as no definitive treatment is available at present.2 A study has shown that as many as 25% of patients with NF1 had presented with GI complaints with or without involvement of other systems. These GI complaints are found to be related to neurogenic tumors, stromal tumors and neuroendocrine tumors.10,11 GISTs are KIT-positive and KIT- or PDGFRA-driven a soft-tissue sarcomas that arise from the interstitial cells of Cajal, the GI pacemaker cells.12 The exact mechanism of increased tendency for development of GISTs in patient with NF1 is still unclear. However, a recent study has shown the mutation of KIT and PDGFRA genes in addition to the mutation of tumor suppressor NF1 gene in patients with coexisted NF1 and GISTs.13

## The common presentation of GISTs is GI bleeding, often chronic or intermittent with or without signs and symptoms of anemia.5 The patient in our case had multiple episodes of recurrent melena and was anemic. Therefore, when a patient with NF1 presents with signs and symptoms of anemia, GISTs should be suspected and further evaluated. The mechanism of GI bleeding in patients with GISTs is the necrosis of the GI mucosal wall due to the pressure effect of the growing tumor to the vessel supplying the wall. Also, the invasion and erosion of vessel wall by the tumor leads to blood leakage.14

Upper GI endoscopy and colonoscopy are the investigations of choice in a patient with complaints of blood in the stool. The findings of these endoscopies were non-significant in our case. So, the patient was further investigated with a CT scan of the abdomen which showed multiple GISTs in the jejunum. The management of the GISTs in patient with NF1 is quite challenging as surgical resection is not effective in cases with multiple and widely spreading GISTs and locally advanced and metastatic lesions exhibit resistance to chemotherapy.15

The first-line treatment of primary operable GISTs is complete surgical resection with or without adjuvant chemotherapy. The location of the tumor and its extent are the principal determining factors to select the mode of surgery. The duodenal lesion of <2cm in size is managed with local resection while pancreaticoduodenectomy may be required for duodenal GISTS of size >5cm and GISTS near to ampulla of Vater.16 As the tumors in the reported case appear to be primary (not metastatic), we managed the case with complete surgical removal of the tumor with jejunal resection and anastomosis. Imatinib, a potent and specific inhibitor of KIT, was prescribed as an adjuvant therapy to suppress the growth of other unresectable tumors and prevent recurrence.17

## **Conclusion**

When a patient with NF1 presents with blood in stool and/or signs and symptoms of anemia and hypovolemia, the possibility of bleeding GISTs should be considered early. Multiple GISTs along different regions of the GIT and locally advanced chemotherapy-resistant tumors make the management is quite challenging. The treatment of these patients is symptomatic relief and the surgical resection of the primary tumor with or without chemotherapy. As the patient is more likely to develop recurrent and metastatic lesions, vigilant postoperative surveillance with regular follow-ups is a must.

**Key clinical message**

Neurofibroma is a benign peripheral nerve sheath tumor that exhibits a wide range of clinical manifestations. There are no reported cases in Nepal to the best of our knowledge. Herein, we report an unusual case of co-occurrence of multiple GISTs in a patient with NF1 and who was managed by surgical resection and adjuvant chemotherapy.

**Author contributions**

PBSK and BK conceptualized the study. SG and SD were in charge of the case. BK, SG and SD wrote the original manuscript and reviewed and edited the manuscript. MK, SS, AK and PY corrected and edited the original manuscript.

**Ethical approval**

Ethical approval is not required for case reports at our hospital

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**Data Availability**

None

**Conflict of interest**

None

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## **References**

1. Taketomi T, Nakamura K, Teratani Y, Matsuo K, Kusukawa J. Solitary Neurofibroma of the Hard Palate: A Case Report and Literature Review. Am J Case Rep. 2021;22:e929674.

2. Gutmann DH, Ferner RE, Listernick RH, Korf BR, Wolters PL, Johnson KJ. Neurofibromatosis type 1. Nat Rev Dis Primers. 2017;3:17004.

3. Riccardi VM. Von Recklinghausen neurofibromatosis. N Engl J Med. 1981;305(27):1617-27.

4. Agaimy A, Vassos N, Croner RS. Gastrointestinal manifestations of neurofibromatosis type 1 (Recklinghausen's disease): clinicopathological spectrum with pathogenetic considerations. Int J Clin Exp Pathol. 2012;5(9):852-62.

5. Miettinen M, Fetsch JF, Sobin LH, Lasota J. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol. 2006;30(1):90-6.

6. Study links NF1 mutations to GIST tumors, highlighting the need for genetic testing. 2017.

7. Al Momani LA, Abughanimeh O, Shipley LC, Phemister J, Swenson J, Young M. Recurrent Gastric Gastrointestinal Stromal Tumor in a Patient with Neurofibromatosis. Cureus. 2018;10(6):e2854.

8. Agha RA, Franchi T, Sohrabi C, Mathew G, Kerwan A, Thoma A, et al. The SCARE 2020 Guideline: Updating Consensus Surgical CAse REport (SCARE) Guidelines. Int J Surg 2020;84:226–30. https://doi.org/10.1016/j.ijsu.2020.10.034.

9. Wu CE, Tzen CY, Wang SY, Yeh CN. Clinical Diagnosis of Gastrointestinal Stromal Tumor (GIST): From the Molecular Genetic Point of View. Cancers (Basel). 2019;11(5).

10. Cheng SP, Huang MJ, Yang TL, Tzen CY, Liu CL, Liu TP, et al. Neurofibromatosis with gastrointestinal stromal tumors: insights into the association. Dig Dis Sci. 2004;49(7-8):1165-9.

11. Valencia E, Saif MW. Neurofibromatosis type 1 and GIST: is there a correlation? Anticancer Res. 2014;34(10):5609-12.

12. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol. 2004;22(18):3813-25.

13. Takazawa Y, Sakurai S, Sakuma Y, Ikeda T, Yamaguchi J, Hashizume Y, et al. Gastrointestinal stromal tumors of neurofibromatosis type I (von Recklinghausen's disease). Am J Surg Pathol. 2005;29(6):755-63.

14. Trupiano JK, Stewart RE, Misick C, Appelman HD, Goldblum JR. Gastric stromal tumors: a clinicopathologic study of 77 cases with correlation of features with nonaggressive and aggressive clinical behaviors. Am J Surg Pathol. 2002;26(6):705-14.

15. Farag S, Smith MJ, Fotiadis N, Constantinidou A, Jones RL. Revolutions in treatment options in gastrointestinal stromal tumours (GISTs): the latest updates. Curr Treat Options Oncol. 2020;21(7):55.

16. Bauer S, Rutkowski P, Hohenberger P, Miceli R, Fumagalli E, Siedlecki JA, et al. Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib -- analysis of prognostic factors (EORTC-STBSG collaborative study). Eur J Surg Oncol. 2014;40(4):412-9.

17. Thacoor A. Gastrointestinal stromal tumours: advances in surgical and pharmacological management options. J Gastrointest Oncol. 2018;9(3):573-8.