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Case Report

Concurrent gastrointestinal stromal tumor and small bowel adenocarcinoma in neurofibromatosis type 1: A rare case report

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Abstract

Introduction: Neurofibromatosis type 1 (NF1) is an inherited associated with increased tumorigenic potential, particularly in the nervous and gastrointestinal systems. Gastrointestinal stromal tumors (GISTs) are the most frequent gastrointestinal neoplasms in NF1, typically affecting the small bowel. However, the synchronous occurrence of GIST and small bowel adenocarcinoma in NF1 patients is exceedingly rare and presents unique diagnostic and therapeutic challenges.

Case presentation: We report the case of a 68-year-old male with a known history of NF1 and previously treated GIST, for which he had been receiving imatinib (400 mg twice daily) until his death. There was no family history of cancer. His initial GIST episode, in 2018, involved a 6 cm small bowel mass, classified as high-risk according to Miettinen's criteria and staged as pT3. In 2023, he was admitted for persistent periumbilical abdominal pain, general health deterioration, fever, weight loss, and signs of systemic inflammation. Physical examination revealed localized tenderness in the periumbilical region. Imaging studies identified a large intraperitoneal mass. During surgical exploration, a total colectomy was performed due to mesenteric extension. Intraoperatively, a circumferential ileal tumor infiltrating approximately 5.5 cm of the bowel wall was observed, along with 20 serosal nodules ranging from 0.4 to 2 cm in size. Histopathological analysis confirmed a low-grade adenocarcinoma not otherwise specified (NOS), staged as T4aN2, with studies of the serosal nodules revealed multiple GISTs, showing strong positivity for DOG1 and CD117. The patient received adjuvant chemotherapy with the FOLFOX regimen. As of the last follow-up in December 2024, the patient remains clinically stable.

Discussion: This case illustrates a rare convergence of synchronous GIST and small bowel adenocarcinoma in an NF1 patient. It highlights the need for heightened clinical awareness and suggests the potential utility of routine gastrointestinal surveillance in patients with NF1, particularly those with a history of gastrointestinal neoplasms. The overlapping tumor biology warrants further molecular investigation to inform surveillance protocols and therapeutic strategies.

Conclusion: Synchronous GIST and small bowel adenocarcinoma in NF1 is an exceptionally rare presentation. Early recognition through vigilant monitoring and multidisciplinary management is essential to optimize outcomes. Future studies should explore the shared molecular pathways to improve diagnostic precision and guide targeted treatment.

Keywords: Neurofibromatosis Type 1, GIST, Adenocarcinoma, Small bowel, Synchronous tumors

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1. Introduction

Neurofibromatosis type 1 (NF1), also known as Von Recklinghausen disease, is an autosomal dominant disorder resulting from mutations in the NF1 gene on chromosome 17 (1–3), with an incidence of 1 in 3,000 births (1,4–6). Clinically, NF1 manifests through a variety of features (4,7). It is characterized by diverse clinical manifestations and a predisposition to both benign and malignant tumors, particularly affecting the nervous system, skin, muscles, and gastrointestinal tract (7). Among these, gastrointestinal stromal tumors (GISTs) are the most frequent neoplasms, occurring in 10–25% of NF1 patients (8). Small bowel adenocarcinoma (SBA), although rare, represents a notable risk in NF1—particularly in the duodenum, jejunum, or ileum.

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Despite an incidence of only 7.3 cases per million, SBA constitutes approximately 40% of all small bowel malignancies (5,9–11). Its relative rarity may be attributed to the unique immunological and microbial environment of the small intestine (12). In NF1, SBA can present with severe complications such as gastrointestinal bleeding or gastric outlet obstruction, often complicating diagnosis and management (10,13–15). While GIST and small bowel adenocarcinoma each carry individual significance in NF1, synchronous presentation of both tumors remains exceptionally rare. This case describes a patient with NF1 diagnosed with concurrent duodenal GIST and small bowel adenocarcinoma—an unusual tumor constellation. The report underscores the diagnostic complexity of such cases and highlights the need for heightened clinical vigilance in NF1 patients due to their susceptibility to multifocal and histologically distinct malignancies.

2. Case Presentation

In this report, we present a case of a 68-year-old man with no family history of cancer and with a medical history of type I neurofibromatosis, who underwent surgery in 2018 for a ruptured intra-abdominal stromal tumor. It involved a 6 cm small bowel mass, classified as high-risk according to Miettinen's criteria and staged as pT3. He has been on targeted therapy (Imatinib 400 mg x2) since. In 2023, he was re-admitted to the general surgery department due to abdominal pain associated with a general health deterioration, fever, weight loss, and a biological inflammatory syndrome. Physical examination revealed localized tenderness in the periumbilical region. The CT scan (Fig. 1) revealed a large, hypodense, poorly delineated intraperitoneal mass infiltrating the mesenteric fatty tissue. It was associated to several, round, well-demarcated, hypoisodense pelvic lymphadenopathies. Intraoperative findings included the small intestine and colon with multiple neurofibromas and a 10 cm lesion located 1.5 meters from the duodenojejunal junction, communicating with the terminal ileum. A total colectomy was then indicated.

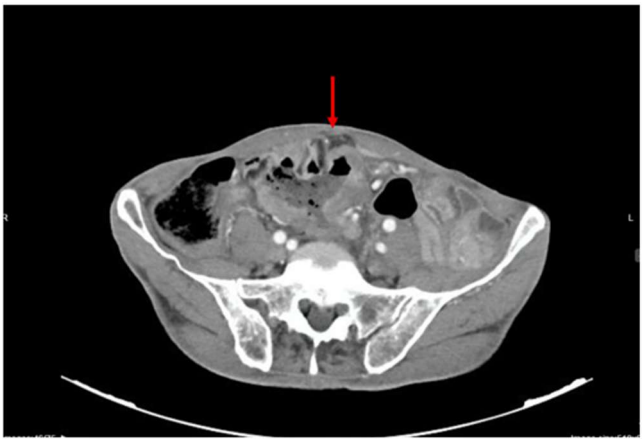

Fig. 1. CT scan image showing an irregular circumferential tumoral process involving the small intestine, centrally located, causing acute intestinal obstruction with feces sign (arrow).

During surgical exploration, extensive intra-abdominal mass was noted. A large 10 cm lesion was identified approximately 1.5 meters distal to the duodenojejunal junction, involving the terminal ileum and communicating with adjacent bowel loops. The tumor appeared circumferential, infiltrating approximately 5.5 cm of the ileal wall. In addition, multiple nodular lesions consistent with serosal involvement were observed, totaling around 20 nodules ranging from 0.4 to 2 cm in size. The small bowel and colon also exhibited numerous neurofibromas, consistent with the patient's underlying NF1. Given the mesenteric extension of the tumor and the diffuse involvement of the colonic segment, a right colectomy was initially performed. However, due to the broader colonic pathology and anatomical considerations, the surgical team proceeded with a total colectomy to achieve complete resection and minimize recurrence risk.

Macroscopic examination revealed a 63 cm long ileum with a 4 cm circumference, its outer surface dotted with approximately twenty nodules ranging from 0.4 to 2 cm, projecting slightly on the serosal surface (Fig. 2). At 40 cm from the ileocecal valve and 18 cm from the ileal margin, there was a stenotic area with adhesion of two intestinal loops. Opening the intestine showed a 5.5 cm circumferential tumoral process infiltrating the entire wall and peri-intestinal fat (Fig. 3).

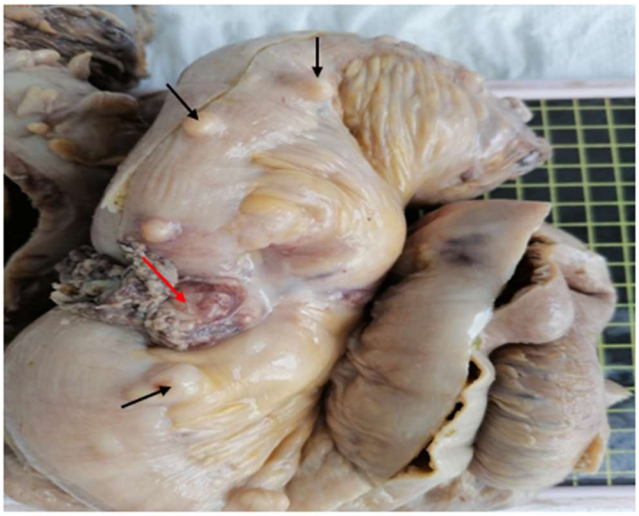

Fig. 2. Macroscopic image showing an ileal specimen with a serosal surface marked by multiple whitish nodular formations of varying sizes (black arrows). Additionally, a protruding mass is observed, causing ulceration of the serosa (red arrow).

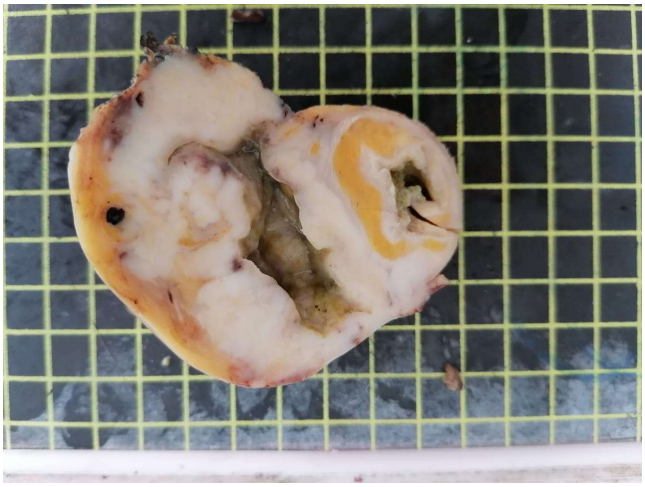

Fig. 3. Macroscopic image showing that on section, the ileal tumor is circumferential, infiltrating all the parietal tunics.

Microscopically, the stenosing lesion identified macroscopically was found to be a moderately differentiated infiltrating adenocarcinoma. It exhibited irregular glandular structures arranged in trabeculae and occasionally forming solid masses (Fig. 4). The tumor cells demonstrated moderate eosinophilic cytoplasm and atypical nuclei (Fig. 5), with proliferation infiltrating the entire wall up to the serosa. Surgical margins were clear; however, vascular emboli and numerous perineural invasions were observed. Of the nine mesenteric nodules examined, three were metastatic lymph nodes (3N+/9N). No histological lesions were identified in the colonic segment or appendix. The nodules observed on the external surface of the ileum were diagnosed as a GIST tumor (Fig. 6 and 7), subsequently confirmed through immunohistochemical analysis using DOG1 and CD117 markers (Fig. 8).

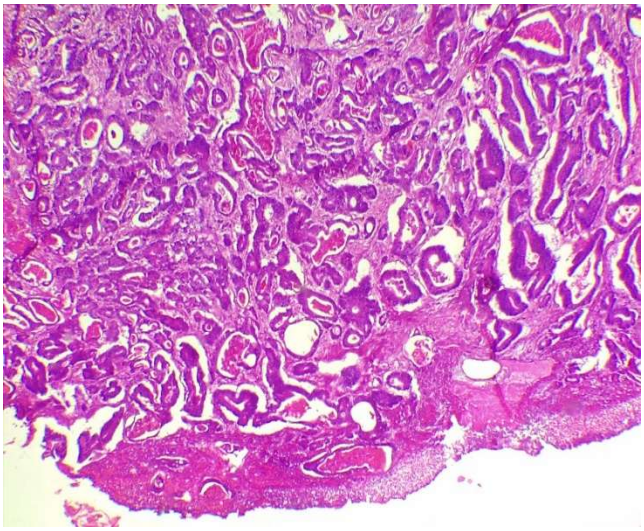

Fig. 4. Microscopic examination using hematoxylin and eosin staining (H&E, x100) reveals an infiltrating carcinomatous proliferation composed of tubulo-glandular structures.

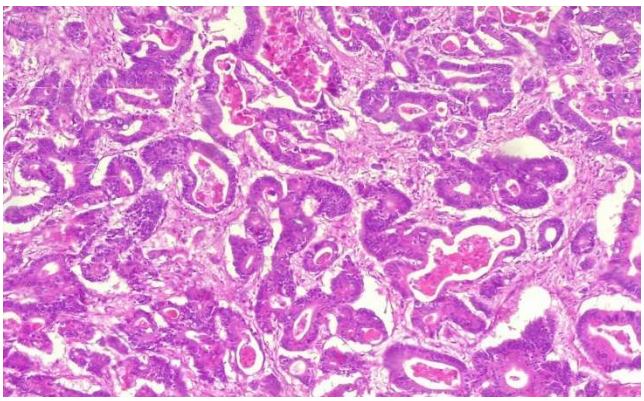

Fig. 5. Microscopic examination using hematoxylin and eosin staining, at higher magnification (H&E, x400) showing tubule-glandular structures with comedonecrosis, frank nuclear atypia and high mitotic rate.

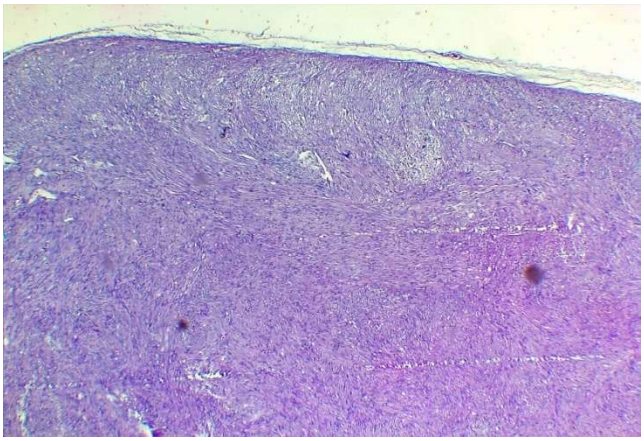

Fig. 6. Microscopic examination using hematoxylin and eosin staining (H&E, x100) showing an infiltrative tumor proliferation arranged in storiform bundles.

In conclusion, the findings indicated a moderately differentiated intestinal-type adenocarcinoma of the ileum, staged as pT4a N2 (AJCC 2017), with multiple low-risk gastrointestinal stromal tumors of the small intestine. The patient received adjuvant chemotherapy with the FOLFOX regimen. As of the last follow-up in December 2024, the patient remains clinically stable.

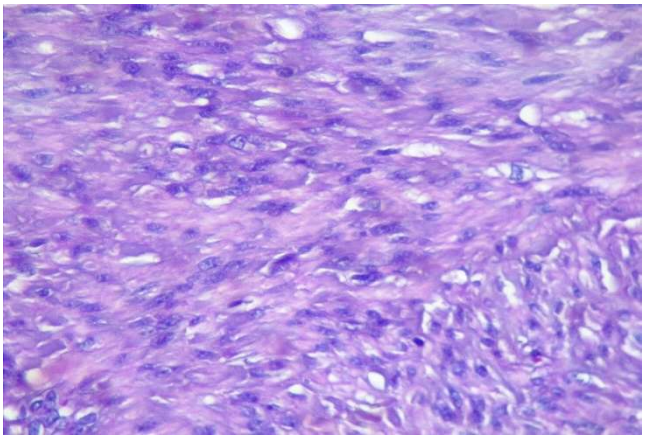

Fig. 7. Microscopic examination using hematoxylin and eosin staining at higher magnification (H&E, x400) reveals a tumor composed of spindle cells with atypical nuclei and infrequent mitotic figures.

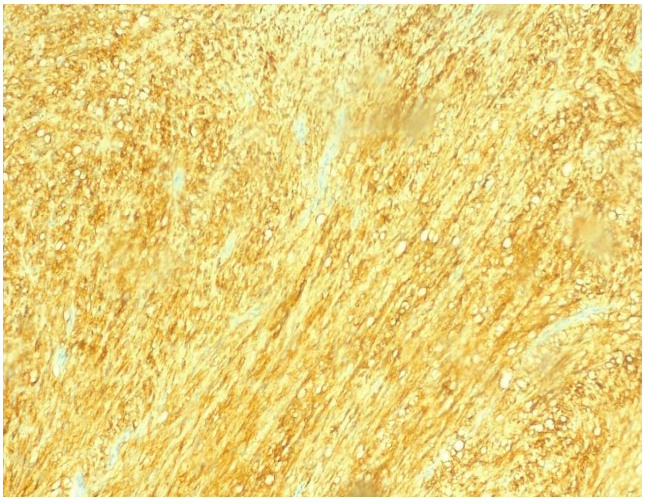

Fig. 8. Microscopic examination using immunohistochemical staining (IHC, x400) reveals strong positivity for CD117 in the tumor cells.

3. Discussion

Neurofibromatosis type 1 (NF-1), also known as von Recklinghausen's disease, is an inherited disorder caused by a mutation in the NF1 gene on chromosome 17q11.2, which functions as a tumor suppressor. NF-1 follows an autosomal dominant pattern, affecting approximately 1 in 3,000 births in the general population (1,5). Patients with NF-1 frequently develop multiple benign and malignant tumors, with an increased prevalence of nervous system and non-nervous system tumors, such as neurofibromas, malignant peripheral nerve sheath tumors, and gliomas (1,5,16).

The manifestations of NF-1 often develop progressively with age. Intra-abdominal symptoms and tumors generally appear later in life, typically after the appearance of cutaneous manifestations in middle age. Some studies indicate that males with NF-1 may have a slightly higher risk of certain types of tumors compared to females, although the overall frequency and severity of the disease can vary widely across patients regardless of gender (1).

NF-1 is considered a tumor susceptibility syndrome due to the elevated risk of multiple tumors associated with the underlying defect in the NF1 gene. This gene mutation leads to dysfunctional neurofibromin 1 protein, impairing its regulation of RAS proteins via GTPase activity (1,17).

Consequently, patients with NF-1 have a substantially higher lifetime cancer risk, with a cumulative cancer risk of 38% by age 50 and a 59.6% lifetime risk, compared to 3.9% and 30.8%, respectively, in the general population (16,18,19). Cancers associated with NF-1 include malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors (GISTs), breast cancer, pheochromocytoma, and, though rare, small bowel adenocarcinoma (SBA) (5).

Our case illustrates the exceptional coexistence of both GIST and SBA in a single NF1 patient, with both tumors arising in the duodenum. This synchronous presentation is extremely rare and highlights the diverse tumor spectrum associated with NF1. To our knowledge, very few reports have documented such a combination, emphasizing the unique biological behavior of NF1-related neoplasia.

The association between gastrointestinal stromal tumors (GISTs) and neurofibromatosis type 1 (NF1) is well-documented and illustrates the unique pathogenic mechanisms of NF1-related tumors (20). Unlike sporadic GISTs, which commonly result from mutations in the KIT or PDGFRA genes, NF1-associated GISTs arise due to mutations in the NF1 gene. This gene encodes neurofibromin, a protein that normally regulates cell growth by inhibiting the RAS signaling pathway. In NF1, the inactivation of neurofibromin leads to uncontrolled RAS activation, which then stimulates downstream pathways, particularly the mitogen-activated protein kinase (MAPK) pathway. This aberrant signaling promotes cellular proliferation and contributes to tumor development (21,22).

Studies indicate that NF1-related GISTs are most commonly found in the small bowel and are predominantly of the spindle cell type, contrasting with sporadic GISTs, which typically occur in the stomach (5). NF1-associated GISTs generally exhibit a lower malignancy risk and a better prognosis than their sporadic counterparts, although they are notably resistant to Imatinib, a treatment effective in many sporadic GIST cases (23). This resistance further highlights the distinct molecular pathogenesis of NF1-associated GISTs, rooted in NF1 mutations rather than KIT or PDGFRA mutations. Consequently, the development of NF1-related GISTs is primarily attributed to the dysregulation of RAS-MAPK signaling, underscoring the need for alternative therapeutic strategies for these patients (5,24).

Small bowel adenocarcinoma (SBA) is often associated with deficiencies in DNA mismatch repair (dMMR), particularly in the context of Lynch syndrome, a hereditary cancer syndrome. In the largest retrospective study on SBA to date, dMMR proteins were found in 26% of cases, with 10% of these linked to Lynch syndrome (25,26). Interestingly, a notable association between SBA and neurofibromatosis type 1 (NF1) has also been observed (5). Research by Schrock and colleagues demonstrated a significantly higher mutation rate of the NF1 gene in SBA compared to both gastric and colorectal cancers. This suggests that the NF1 mutation, known for its tumor-suppressing role, may be an influential factor in the development of SBA under certain conditions.

The potential involvement of NF1 mutations in SBA pathogenesis points to a unique molecular pathway, distinct from the dMMR deficiency typical of Lynch syndrome (5,27,28). Consequently, genetic analysis in SBA cases, especially those associated with NF1, could provide deeper insights into the molecular underpinnings of SBA and further clarify the relationship between NF1 mutations and this rare, aggressive form of cancer.

In summary, this rare case underscores the importance of comprehensive and ongoing surveillance in NF1 patients, not only for common tumor types but also for rare, synchronous malignancies. Enhanced awareness and early recognition of such tumor combinations may improve diagnostic accuracy, inform treatment strategies, and ultimately contribute to better outcomes in this high-risk population.

Conclusion

In conclusion, this case study expands the limited body of literature on neurofibromatosis type 1 (NF1) by highlighting the complex relationship between NF1 and gastrointestinal tumors, specifically the rare co-occurrence of gastrointestinal stromal tumors (GISTs) and small bowel adenocarcinoma (SBA). NF1 patients exhibit a distinctive tumor susceptibility profile that includes both common benign tumors such as neurofibromas and rare, aggressive malignancies like SBA. The presence of SBA poses significant clinical challenges due to its poor prognosis and limited treatment options.

The distinct pathogenic mechanisms underlying NF1-associated GISTs and SBAs, largely driven by NF1 mutations leading to dysregulated RAS-MAPK signaling,—primarily involving NF1 mutations and dysregulation of the RAS-MAPK signaling pathway—underscore the need for personalized surveillance and treatment strategies.

Prospective registries and molecular profiling studies in NF1 patients could help clarify tumor co-occurrence patterns and guide risk-adapted management. This case highlights the importance of comprehensive monitoring for a broad range of malignancies in NF1 and points toward the potential for targeted therapies tailored to the specific molecular alterations observed in this high-risk population.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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None.

Conflict of interest

The authors declare that there are no conflicts of interest.

Authors' contribution

The authors participated equally.

Availability of data and materials

All data underlying the manuscript are available as part of the article.

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