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Case report

Atypical Intestinal Lesions in a Patient with Neurofibromatosis Type 1: A Case Report

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Abstract

Neurofibromatosis type 1 (NF1) is a neurocutaneous disorder that can manifest as multiple tumors or plexiform lesions in the gastrointestinal tract and extra-intestinal sites. Gastrointestinal involvement occurs in 10%–25% of patients, with neurofibromas being the most common lesions, typically located in the small intestine. When multiple tumors are found in the small intestine, they are often gastrointestinal stromal tumors (GISTs). This case report presents a 55-year-old woman with a history of NF1, characterized by neurofibromas and café-au-lait spots across her body. She was evaluated as an outpatient in the endoscopy unit at Unión de Cirujanos S. A. S. in Manizales, Colombia, within the Gastroenterology Surgical Clinic Service at Universidad de Caldas. The patient underwent ileocolonoscopy after a positive fecal occult blood test. She denied abdominal pain, hematochezia, rectal bleeding, or melena. Ileocolonoscopy revealed nodular lesions ranging from 3 to 5 mm in the distal ileum. Endoscopic resection was performed on one lesion, which was sent for histopathological examination.

Keywords

Neurofibromatosis, neurofibroma, gastrointestinal stromal tumor, atypical intestinal lesions.

INTRODUCTION

Neurofibromatosis type 1 (NF1), or Von Recklinghausen disease, is a neurocutaneous disorder that may manifest as multiple tumors or plexiform lesions within the gastrointestinal tract as well as in extraintestinal locations. It is an autosomal dominant condition with a prevalence of 1 in 3,000 individuals. Approximately half of all cases have a family history, while the other half arise spontaneously. Gastrointestinal involvement occurs in 10%–25% of patients. The upper intestinal tract is the most commonly affected region, with neurofibromas representing the predominant lesion type, usually located in the small intestine. When multiple tumors appear in the small intestine, particularly in the jejunum, they are typically gastrointestinal stromal tumors (GISTs) associated with NF1. Additionally, other gastrointestinal lesions may arise in patients with NF1 and should be considered as differential diagnoses. Abdominal lesions in NF1 are often asymptomatic and, consequently, underrecognized in clinical practice[1,2].

CLINICAL CASE

We present the case of a 55-year-old woman with a medical history of NF1, characterized by neurofibromas and café-au-lait macules distributed across her body (**Figures 1** and **2**).

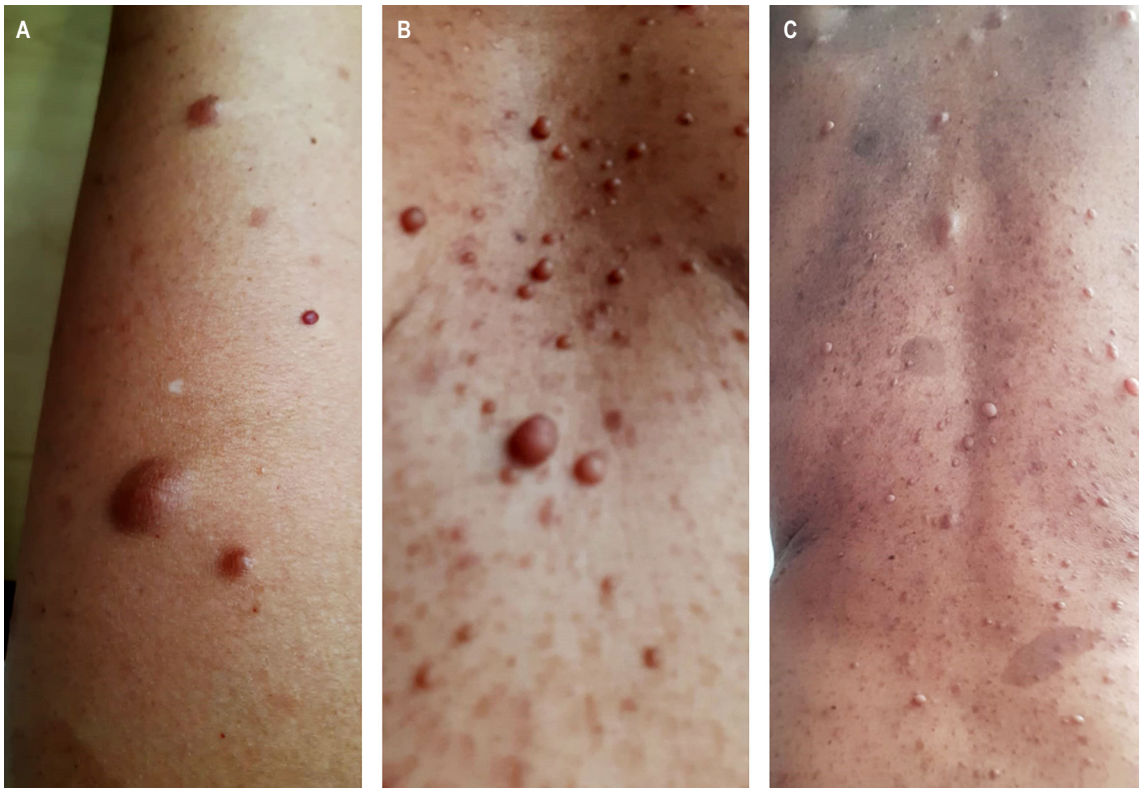


Figure 1. Café-au-lait Macules and Neurofibromas on the Skin of a Patient with Neurofibromatosis Type 1. **A.** Upper limb. **B.** Abdomen. **C.** Dorsal region. Images courtesy of Dr. Fabián Eduardo Puentes-Manosalva, Unión de Cirujanos S. A. S., Clinical-Surgical Gastroenterology Service, Universidad de Caldas, Manizales, Colombia.

The diagnosis was clinically confirmed during a genetics consultation. The patient was managed on an outpatient basis at the endoscopy unit of Unión de Cirujanos S. A. S. in Manizales, Colombia, part of the Clinical-Surgical Gastroenterology Service, Universidad de Caldas. She underwent ileocolonoscopy for the evaluation of a positive fecal occult blood test. The patient denied any abdominal pain, hematochezia, rectal bleeding, or melena.

The ileocolonoscopy revealed nodular lesions measuring 3 to 5 mm in the distal ileum (**Figures 3** and **4**). Endoscopic resection of one of the lesions was performed (**Figure 4**), and the sample was sent for histopathological analysis. The remaining segments examined, including the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum, showed no evidence of inflammatory or tumoral lesions. Haustral markings and colonic motility were preserved. Internal hemorrhoids were observed in the anal canal, without dilation or other abnormalities.

Immunohistochemical analysis of the lesion from the ileum revealed cellular proliferation, with positivity for CD68 and focal positivity for vimentin, along with negativity for CKAE1/AE3, CD34, and cytomegalovirus. The immunophenotypic profile corresponded to reactive histiocytic cellular proliferation. Additional testing with S100 markers showed occasional positivity in histiocytes, while SOX-10 was negative. The final diagnosis indicated acute inflammation and reactive fibroblastic and histiocytic proliferation, with no evidence of neoplasia.

DISCUSSION

Neurofibromatosis is classified into three types: type 1 (NF1), also known as Von Recklinghausen disease, accounting for 90%–95% of cases; type 2 (NF2), comprising less than 10%; and type 3 (NF3), or schwannomatosis[3]. NF1 is a genetic autosomal dominant disorder with a prevalence of 1 in 3,000 individuals. It arises from a mutation in the tumor suppressor gene NF1, located on chromosome 17q11.2. This mutation leads to a reduction in the intracellular protein neurofibromin, resulting in uncontrolled activation of the RAS gene and cell proliferation pathways, along with inhibition of apoptotic pathways[3–5].

The diagnosis of NF1 is primarily clinical, with neurocutaneous manifestations being the most frequent. Diagnosis

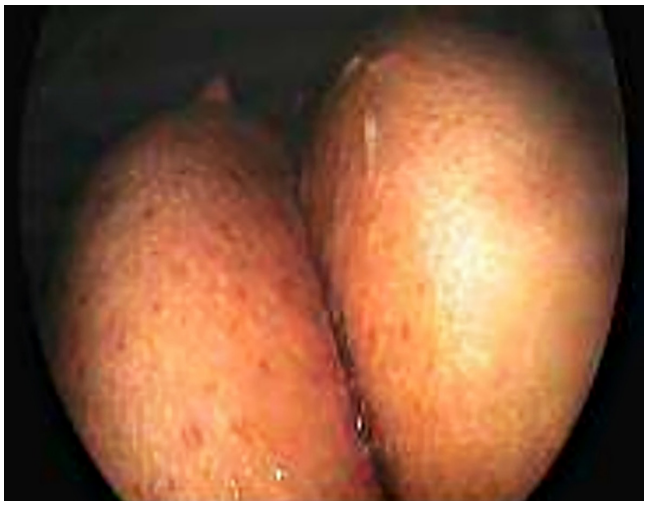


Figure 2. Café-au-lait Macules on the Gluteal Region of a Patient with Neurofibromatosis Type 1. Image courtesy of Dr. Fabián Eduardo Puentes-Manosalva, Unión de Cirujanos S. A. S., Clinical-Surgical Gastroenterology Service, Universidad de Caldas, Manizales, Colombia.

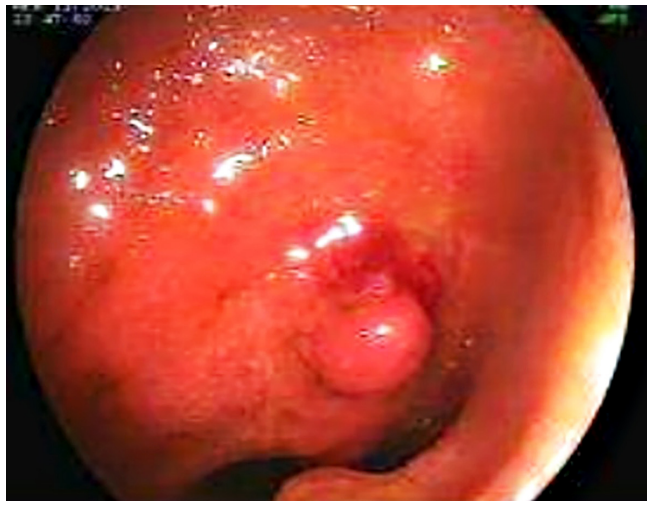
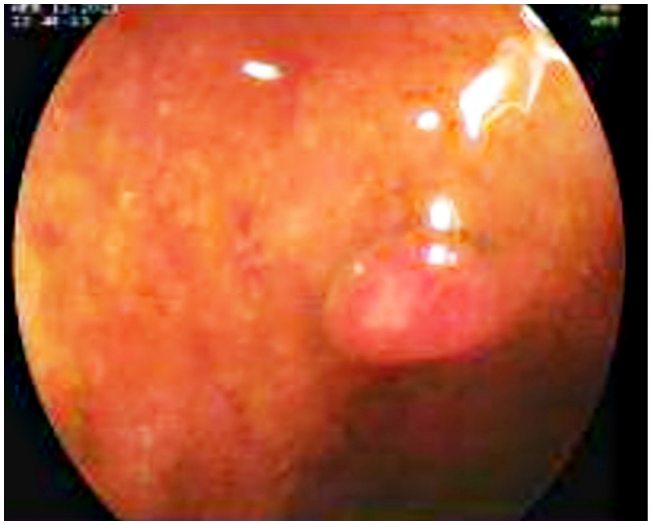


Figure 3. Atypical Nodular Lesion in the Distal Ileum of a Patient with Neurofibromatosis Type 1. Image courtesy of Dr. Fabián Eduardo Puentes-Manosalva, Unión de Cirujanos S. A. S., Clinical-Surgical Gastroenterology Service, Universidad de Caldas, Manizales, Colombia.



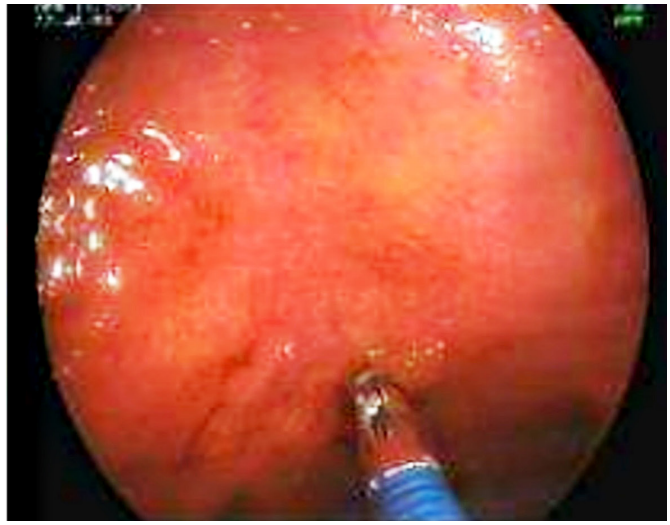


Figure 4. Atypical Nodular Lesion in the Distal Ileum of a Patient with Neurofibromatosis Type 1 and Its Endoscopic Resection. Images courtesy of Dr. Fabián Eduardo Puentes-Manosalva, Unión de Cirujanos S. A. S., Clinical-Surgical Gastroenterology Service, Universidad de Caldas, Manizales, Colombia.

requires the presence of two or more of the following criteria (**Table 1**): six or more café-au-lait macules larger than 5 mm in children or larger than 15 mm in adults, two or more cutaneous or subcutaneous neurofibromas or one plexiform neurofibroma, axillary or inguinal freckling (Crowe's sign), optic nerve glioma, two or more iris hamartomas (Lisch nodules), atypical bone lesions (sphenoid dysplasia, cortical thinning of long bones with or without pseudoarthrosis), and a first-degree family history of NF1[3,4].

The coexistence of multiple tumors of different types is common in NF1 due to the variable penetrance of the autosomal gene. Consequently, patients may present with one or more tumors synchronously or metachronously[2,3]. Gastrointestinal tract lesions are not uncommon in NF1,

occurring in 10%–25% of all cases, though only 5% are symptomatic[2,3]. These manifestations typically appear between the ages of 30 and 40 and can occur at any location within the gastrointestinal tract, although the small intestine is the most frequent site (70%), particularly the jejunum[2,3]. The most common locations of gastrointestinal neurofibromas are the jejunum, followed by the stomach, ileum, duodenum, and colon[4]. These lesions arise in the Meissner's plexus of the submucosa, the Auerbach's plexus of the muscularis propria, or even the serosa. They are generally asymptomatic but, depending on their location and the extent of mucosal involvement, may present clinically with abdominal pain, diarrhea, upper or lower gastrointestinal bleeding, palpable mass, microcytic anemia, intestinal obstruction (due to intussusception or secondary volvulus), perforation, or even obstructive jaundice[2–5].

Table 1. Diagnostic Criteria for Neurofibromatosis Type 1*

Six or more café-au-lait macules larger than 5 mm in children or larger than 15 mm in adults
Two or more cutaneous or subcutaneous neurofibromas or one plexiform neurofibroma
Axillary or inguinal freckling (Crowe's sign)
Optic nerve glioma
Two or more iris hamartomas (Lisch nodules)
Atypical bone lesions (sphenoid dysplasia, cortical thinning of long bones with or without pseudoarthrosis)
First-degree family history of neurofibromatosis type 1

*At least two criteria are required. Adapted from: Gamarra ER, and colleagues. Horiz Med (Lima). 2020;20(4):e1412[3]; SSelfa-Muñoz A, and colleagues. Rev Esp Enferm Dig (Madrid). 2012;104(2):99-100[4].

Gastrointestinal neoplasms are more frequent in patients with NF1 compared to the general population and occur in three main forms: hyperplasia of the submucosal and myenteric nerve plexuses and mucosal ganglioneuromatosis, leading to intestinal motility disorders; GIST with varying degrees of neural or smooth muscle differentiation; and neuroendocrine tumor producing somatostatin (ampullary somatostatinoma), characteristic of the periampullary region of the duodenum, containing psammoma bodies and potentially associated with pheochromocytoma[2].

Gastrointestinal lesions associated with NF1 most commonly include benign neoplasms, such as neurofibromas (52%), leiomyomas (17%), ganglioneurofibromas (5.8%), neuroendocrine tumors, and GISTs (6.5%). In NF1, GISTs are slightly more common in women and tend to appear at younger ages, although they can also manifest later in life. They are usually multiple and predominantly located in the small intestine, unlike in the general population without NF1, where GISTs are more frequently found in the stomach[5,6]. Malignant neoplasms may also occur, with 20% being adenocarcinomas. Among benign tumors, such as neurofibromas, malignant transformation occurs in 5% to 15% of cases[3], particularly in patients over 40 years of age. As a result, surgery is the treatment of choice for symptomatic tumors, while clinical monitoring may be considered for asymptomatic patients[4]. Although rare, gastrointestinal adenocarcinoma has been reported in the stomach, esophagus, duodenum, biliary tract, pancreas, and colon. However, the genetic association between adenocarcinoma and NF1 remains unclear[5]. Gastrointestinal lesions in NF1 can be visualized through endoscopic studies such as esophagogastroduodenoscopy, colonoscopy, enteroscopy, or video capsule endoscopy, as well as imaging studies like computed tomography (CT) or nuclear magnetic resonance imaging (NMRI)[5–7]. The risk of recurrence and cancer-specific mortality appears to be similar between NF1 and non-NF1 patients following surgical resection of GISTs[8].

The incidence of GIST in NF1 patients is approximately 6%–7%, but the concurrent presence of multiple GISTs is uncommon[9,10]. GISTs are the most common non-neurological tumors in NF1 patients, with an incidence 45 times higher than in the general population. When GISTs are associated with NF1, mutations in the KIT and PDGFRA genes are frequently absent, rendering imatinib ineffective. Consequently, surgical resection is the first-line treatment. The prognosis for NF1-associated GISTs is better than that for sporadic GISTs. Laparoscopic surgery is as effective as open surgery; however, it offers advantages such as reduced procedure-related pain, faster recovery, and shorter hospital stays. The recurrence rate in NF1 patients is similar to that of patients with sporadic GISTs[10]. While neurofibromas can occur in the gastrointestinal tract, they may also be found extraintestinally. Isolated neurofibromas have been documented in patients without NF1 in locations such as the colon and mesentery[11,12].

Currently, no specific treatment exists for neurofibromatosis. Management involves clinical monitoring or surgical intervention to resect neurofibromatous lesions, especially when there is functional impairment or risk of malignancy[13]. Gastrointestinal neurofibromas are generally resistant to chemotherapy and radiotherapy. As a result, pharmacological options, such as thalidomide, pirfenidone, imatinib, and tipifarnib, are being investigated for lesions that cannot be resected due to their proximity to vital structures[14].

Gastrointestinal tumors that are difficult to distinguish from neurofibromas macroscopically and radiologically include lipomas, which account for 5% of all gastrointes-

tinal tumors and 10% of benign gastrointestinal tumors. These lesions are typically located just beneath the mucosa and are usually asymptomatic. However, they can cause obstruction, intussusception, or bleeding. Lipomas may coexist with gastrointestinal neurofibromas, making them an important differential diagnosis to consider[15,16]. In the case reviewed in this article, atypical intestinal lesions were observed in the distal ileum of a 55-year-old female patient with NF1.

CONCLUSION

NF1, or Von Recklinghausen disease, is a neurocutaneous disorder that may present with multiple tumors or plexiform lesions in both the gastrointestinal and extraintestinal regions. Gastrointestinal lesions are not uncommon in NF1, occurring in 10%–25% of cases, with only 5% being symptomatic. These manifestations typically appear between the ages of 30 and 40 and can be found throughout the gastrointestinal tract, although the small intestine is the most commonly affected site. Benign tumors such as neurofibromas may undergo malignant transformation in 5%–15% of cases, particularly in patients over 40 years old. GIST should be suspected in NF1 patients presenting with gastrointestinal symptoms.

Multiple GISTs located outside the stomach should raise suspicion for NF1, and gastrointestinal lipomas should be considered as an important differential diagnosis. A thorough medical history and careful physical examination are essential. Endoscopic studies, such as esophagogastroduodenoscopy, colonoscopy, enteroscopy, or video capsule endoscopy, as well as imaging studies like CT and MRI, are highly valuable for evaluating NF1 depending on the type and location of gastrointestinal lesions. Clinical monitoring or surgical intervention is recommended for neurofibromatous lesions, particularly when functional impairment or risk of malignancy exists. Endoscopic resection or laparoscopy can be useful for both diagnosis and treatment.

The case presented in this article highlights atypical intestinal lesions in the distal ileum of a patient with NF1. Detailed histopathological and immunohistochemical analysis demonstrated acute inflammation and reactive fibroblastic and histiocytic proliferation, with no evidence of neoplasia. This finding is significant as it introduces a new differential diagnosis for gastrointestinal lesions in patients with NF1.

Conflict of Interest

The authors declare no conflicts of interest for this article.

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