Abdominal Pain: A Unique Presentation of Neurofibromatosis and Updated Review of the Condition

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Abstract
Neurofibromatosis type 1 (NF1) is a common, autosomal-dominant neurocutaneous disorder affecting 1 in 3,000 people. It often presents with myriad cutaneous features, including neurofibromas, Lisch nodules, café-au-lait macules, axillary freckling, and plexiform neurofibromas. Many other non-cutaneous manifestations have been observed in NF1. Gastrointestinal stromal tumors (GIST), malignant peripheral nerve sheath tumors (MPNST), and adenocarcinoma are commonly found in the gastrointestinal tracts of NF1 patients and can manifest as complaints of abdominal pain. We present a unique case of NF1 with an initial presenting symptom of abdominal pain caused by plexiform neurofibromas located outside the gastrointestinal tract.

Introduction
Neurofibromatosis is a common condition, with a reported incidence of approximately 1 in 3,000.1-3 The diagnostic criteria originally established by the NIH in 1988 (Table 1, p. 14) has proved very specific and sensitive in correctly diagnosing NF1 patients in early childhood; however, many patients are not diagnosed until adolescence or early adulthood.4,5 As with our patient, many NF1 cases are identified through incidental imaging from a seemingly unrelated and somewhat unusual complaint.6 Exotic presentations of NF1 have been reported in the literature and range from signs of spinal cord compression, incontinence due to tumor growths in the bladder, breathing difficulties, epigastric pain, and gastric outlet obstruction.3,7-12 Abdominal complaints related to NF1 tumors are fairly common; however, the etiology is often due to gastrointestinal tumors, which are reported in 2% to 25% of NF1 patients.1,2

Case Report
A 17-year-old female was admitted for evaluation of non-radiating right upper quadrant abdominal pain that had been present for three days. The patient did not have a significant medical history or family history of NF1; however, during the initial patient interview, her mother was found to have multiple café-au-lait macules. Physical examination revealed 24 café-au-lait macules on her limbs and torso, ranging in size from 0.5 cm to a 7 cm macule on her left lateral thigh (Figures 1 and 2). Additionally, she was found to have axillary freckling and three subcutaneous nodules on the face and neck. Preliminary ophthalmologic examination had shown multiple yellow-to-brown pigmented macules within the irises, clinically consistent with Lisch nodules (Figure 3). CT scan of the abdomen and pelvis with IV contrast was obtained and noted the presence of solid masses within the pelvis and surrounding the celiac and superior mesenteric arteries.

Magnetic resonance imaging was subsequently performed to further classify the nature of these masses and confirmed multiple plexiform neurofibromas within the retroperitoneum and pelvis (Figures 4 and 5). Numerous plexiform neurofibromas surrounding and extending into thoracic and lumbar neuroforamina were incidentally noted. Ultimately, MRI studies and subsequent esophagogastroduodenoscopy were negative for gastrointestinal tumor involvement. Based on the imaging results obtained, the patient’s abdominal discomfort was secondary to external compression of abdominal structures by plexiform neurofibromas. Despite the extensive neurological findings on MRI, the patient lacked any clinical signs or symptoms of neurological involvement. Neurosurgical consultation...
Neurofibromatosis is a common genetic condition caused by inactivation of the NF1 gene on chromosome 17.\textsuperscript{1,3,13} It is inherited in an autosomal-dominant fashion, though approximately half of NF1 cases are due to spontaneous mutations with no family history.\textsuperscript{14} The diagnostic criteria is based upon the NIH consensus of 1988 (Table 1).\textsuperscript{4} Patients are prone to multisystem disease complications including but not limited to cutaneous and plexiform neurofibromas, MPNST, scoliosis, pseudoarthrosis of the tibia, learning disabilities, short stature, renal artery stenosis, pheochromocytoma, epilepsy, optic and cerebral gliomas, sphenoid wing dysplasia, and aqueduct stenosis.\textsuperscript{15} These complications necessitate the involvement of a multi-disciplinary team including geneticists, pediatricians, neurologists, and dermatologists who specialize in the condition, as well as a neurofibromatosis specialty clinic, if available.\textsuperscript{16}

Dermatologists are often consulted to assist in the diagnosis of NF1 due to the early appearance of cutaneous findings (Table 2).\textsuperscript{15} Specific dermatological manifestations of NF1 include café au lait macules, skin freckling, hypo-pigmented macules, Lisch nodules, and cutaneous and plexiform neurofibromas, all of which were present in our patient. Café au lait macules are localized, light brown, benign areas of hyperpigmentation. The term is derived from the characteristic homogeneous color resembling “coffee with milk.” NF1 patients have shown an increased number of melanocytes in their café au lait spots as well as in their normal skin.\textsuperscript{17} Although café au lait macules are benign and have little propensity to differentiate into melanoma, it’s hypothesized that this proliferation may be related to a slightly increased risk of melanoma in NF1 patients, reported in 0.1% to 5.4% of patients. Lisch nodules are benign, pigmented iris hamartomas. They usually appear in early childhood but become more prominent through adolescence, and by age 20 approximately 80% to 90% of NF1 patients have Lisch nodules.\textsuperscript{18,19}

Although many patients present initially with both dermatologic and non-dermatologic manifestations sufficient to meet the NIH diagnostic criteria (see Table 1), NF1 is often overlooked. The presence of six or more café au lait patches, even in the absence of family history and other manifestations, is strongly predictive of the disease, as more than 95% of these patients will eventually be diagnosed with NF1.\textsuperscript{20} In a study by DeBella et al. involving 1,893 NF1 patients, it was determined that the NIH criteria is both very specific and very sensitive in older children and adolescents, but has a low sensitivity in patients under the age of 1.5 Their data revealed that 46% of infants under the age of 1 initially failed to meet diagnostic criteria; by age 8, 97% of patients met the criteria, and almost all met the criteria by age 20. Though most patients will have clinical features sufficient to meet diagnostic criteria at a young age, many are diagnosed late, when they present for an unrelated concern.

Abdominal complaints related to NF1 are fairly common and often lead to the incidental diagnosis of NF1. Visceral and gastrointestinal tumors are often asymptomatic but may present as pain, palpable masses, GI bleeding, vessel compression, or bowel occlusion.\textsuperscript{21} Patients with NF1 can present with a wide variety of abdominal tumors, including pheochromocytomas, GIST, MPNST, and plexiform neurofibromas. The etiology of the abdominal pain is commonly due to gastrointestinal tumors, which are reported in 2% to 25% of NF1 patients.\textsuperscript{1,2} Our patient was unusual because her only complaint was abdominal distress, which was caused by plexiform neurofibromas located outside the GI tract.

Plexiform neurofibromas are present in approximately 25% of NF1 patients and are one of the most common culprits in morbidity and cosmetic impairment.\textsuperscript{15} Plexiform neurofibromas are benign tumors of peripheral nerves that arise from proliferation of neural cells in the nerve sheath and extend across multiple nerve fascicles. They often become very large, involve major nerves and compress surrounding structures, including the spinal cord.\textsuperscript{15} Plexiform neurofibromas tend to grow during early childhood, when exposed to increased hormones, as in puberty and pregnancy.\textsuperscript{22} Plexiform neurofibromas have a propensity for transformation to MPNST, occurring in approximately 2% of cases.\textsuperscript{15,24,26} As was the case with our patient, it is not uncommon for plexiform neurofibromas to remain clinically undetected for many years. Using imaging studies, Schorry et al. identified thoracic plexiform neurofibromas in nine of 240 children with NF1.\textsuperscript{18} Three of these were symptomatic, but the others would have remained clinically undetected. In another study, Thakkar et al. performed MRI studies on 54 NF1 patients, and 35 were found to have spinal plexiform neurofibromas, with 12
References


