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A Rare Case of Primary Colonic Leiomyosarcoma in a Patient with Neurofibromatosis Type 1

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Background	This is a case report of a 65-year-old woman referred to our tertiary level teaching hospital for investigation of symptomatic anaemia and weight loss.
Summary	The patient was known to have neurofibromatosis type 1 (NF1) left ventricular hypertrophy, hypertension, and gout. Her surgical history included a previous resection of an anterior abdominal wall liposarcoma 12 years prior. Computed tomography (CT) demonstrated a 65 mm mass in the ascending colon, which was confirmed on colonoscopy. Following an initial inconclusive biopsy, the patient underwent a laparoscopic right hemicolectomy. Histopathological examination of the lesion showed a high grade, pleomorphic spindle cell sarcoma, with immunohistochemical staining consistent with an organ-confined leiomyosarcoma.
Conclusion	This case highlights the under-recognised, but significant, increased risk of non-neurogenic sarcomas in NF1 patients.
Keywords	Neurofibromatosis type 1, NF1, von Recklinghausen disease, leiomyosarcoma, sarcoma

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Case Description

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is a multisystem autosomal dominant disease caused by germline mutations of the *neurofibromin 1* (*NF1*) gene on chromosome 17q11.2.[1] NF1 accounts for approximately 97 percent of neurofibromatosis (NF) cases, with an incidence of approximately one in 2600 to 3000 people.[2]

NF1 has a widely variable phenotype, with hallmark pathognomonic features of benign neurofibromas, multiple café-au-lait macules, axillary or inguinal freckling, and Lisch nodules.[3] NF1 patients also have an increased risk of malignancy compared to the general population. Malignant peripheral nerve sheath tumors (MPNST) are by far the most common malignant complication, arising in an estimated 8–13 percent of NF1 patients, often from a preexisting benign neurofibroma.[4,5]

Less recognized is that NF1 also carries an increased risk of non-neurogenic sarcomas, including gastrointestinal stromal tumors (GIST), leiomyosarcoma, somatostatinoma, periampullary tumor, breast carcinoma, osteosarcoma, rhabdomyosarcoma, pheochromocytomas, and leukaemia-myelodysplasia syndrome.[5-7]

We present a rare case of NF1-associated with a leiomyosarcoma arising in the ascending colon. To our knowledge, this is the first report of primary colonic leiomyosarcoma occurring in a NF1 patient. This case highlights the under-recognised, but significant, increased risk of non-neurogenic sarcomas in NF1 patients.

A 65-year-old woman was referred to the surgical outpatients' clinic at our tertiary level teaching hospital for investigation of symptomatic anaemia and five kilograms of unintentional weight loss over two months. She reported no alteration in bowel habits or perirectal bleeding. The patient's medical history was otherwise significant for NF1, left ventricular hypertrophy, hypertension, and gout. Her surgical history included a previous resection of an anterior abdominal wall liposarcoma 12 years prior.

Computed tomography (CT) of the chest, abdomen and pelvis demonstrated a 65 mm mass in the ascending colon and polypoid lesions in the terminal ileum (Figure 1).

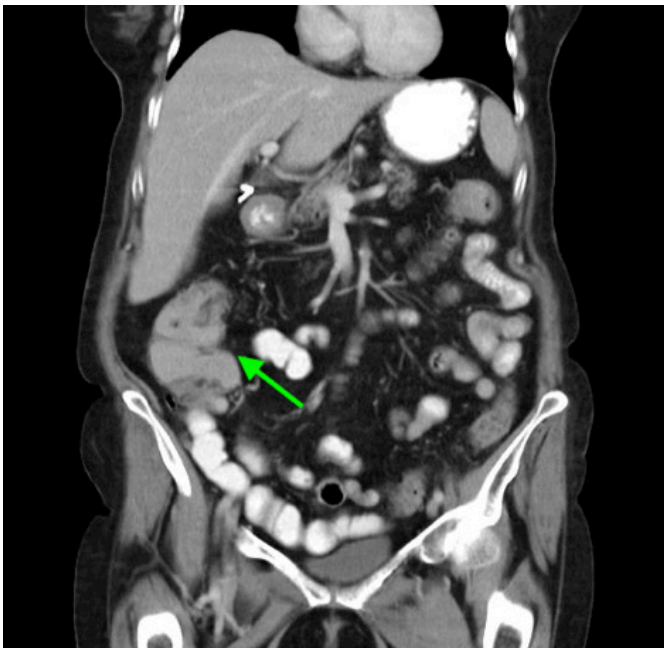


Figure 1. Preoperative CT scan of the abdomen showing ascending colon mass (see arrow) measuring 65 mm in diameter.

Tumor markers including carcinoembryonic antigen (CEA), CA 19.9 and CA-125 were within normal limits. Subsequent colonoscopy confirmed a 50 mm pedunculated tumor in the ascending colon (Figure 2). Initial biopsy of the lesion revealed only granulation tissue. Given the clinical uncertainty of this result, the patient underwent an uncomplicated laparoscopic right hemicolectomy.

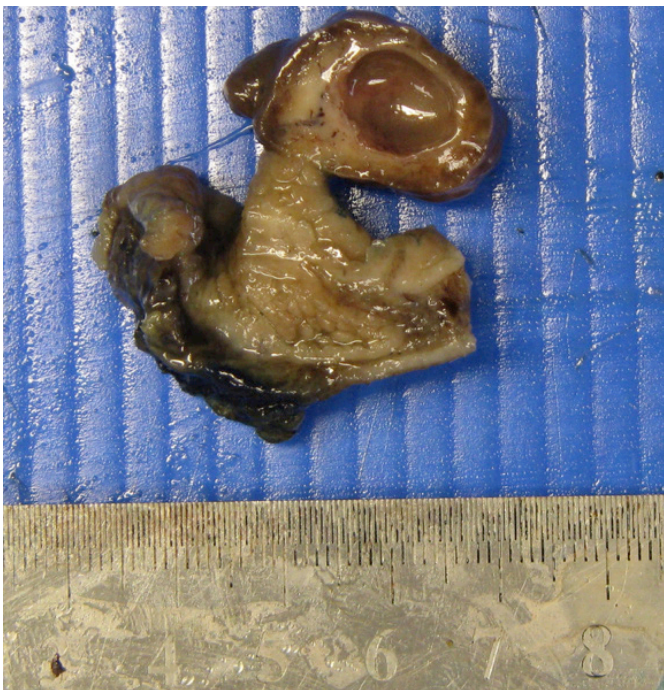


Figure 2. Macroscopic of the pedunculated tumor from the ascending colon

Following formaldehyde fixation for 24 hours, macroscopic examination showed a pedunculated polypoid tumor, 25 x 20 x 15 mm. Representative sections of the lesion were embedded in paraffin and subsequently stained with haematoxylin and eosin. Histopathological examination showed a high grade, pleomorphic spindle cell sarcoma, with cells arranged in short intersecting fascicles (Figure 3).

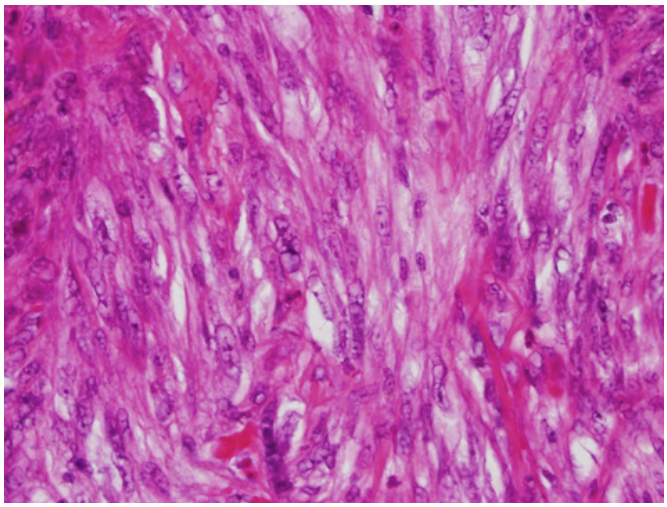
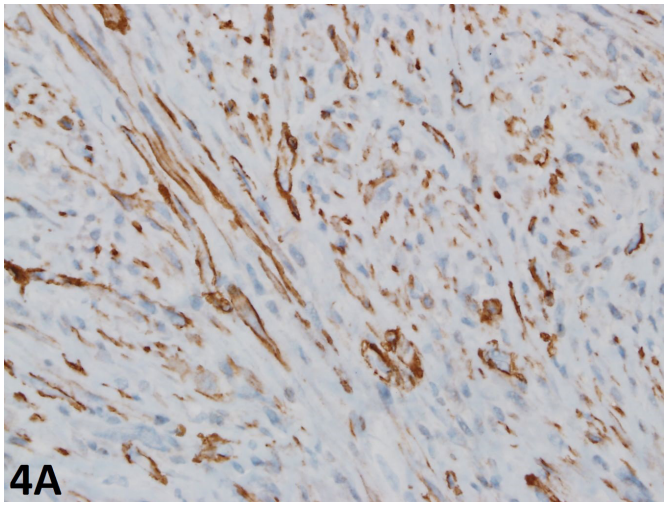
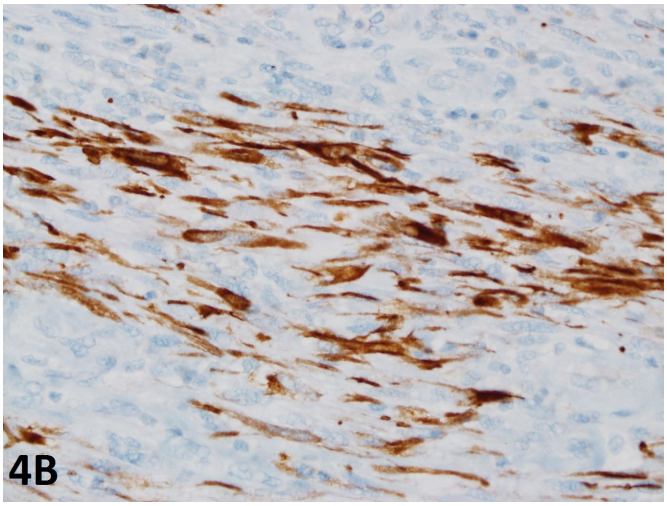


Figure 3. Histopathology showed a spindle cell tumor with a high-grade sarcomatous morphology.

On immunohistochemical staining, the tumor cells were positive for smooth muscle markers including smooth muscle actin (SMA) (Figure 4A), desmin (Figure 4B) and caldesmon (Figure 4C). Additional stains including S100, SOX10, CD117, DOG1, cytokeratin, CD34, ERG, EMA and ALK were all negative. This profile was consistent with an organ-confined leiomyosarcoma. All surgical margins were clear, and lymph node examination showed no metastatic disease (T1N0M0).





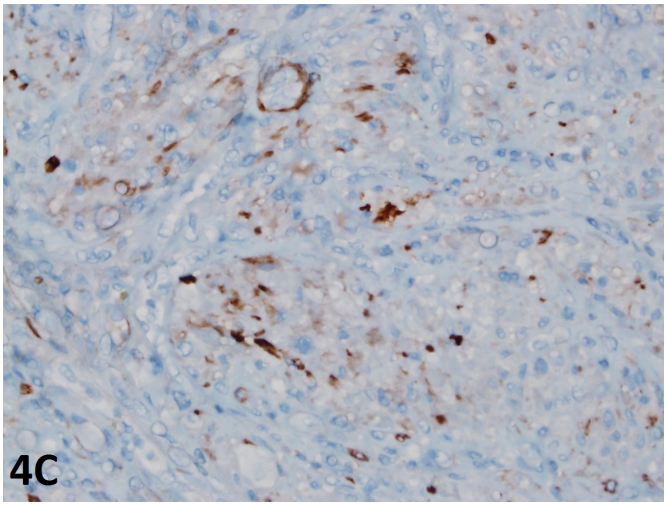


Figure 4A—4C. The tumor cells stained positive for smooth muscle actin (SMA) (4A), desmin (4B) and caldesmon (4C)

The patient had an uncomplicated recovery and was discharged on postoperative day seven. Given her increased risk of future malignancy, consensus was reached in the multidisciplinary meeting that the patient would have annual surveillance with magnetic resonance imaging (MRI) of the abdomen.

Discussion

To our knowledge, this is the first reported case of a primary colonic leiomyosarcoma occurring in the context of NF1. Gastrointestinal leiomyosarcoma is a rare non-neurogenic complication of NF1, but this condition has previously been described in the duodenum,[7] jejunum,[8,9] and ileum.[10] Extra-gastrointestinal cases have also been described in the bladder,[11,12] liver,[13] cranial vault,[14] and sciatic nerve.[15]

NF1 encodes the cytoplasmic tumor suppressor protein neurofibromin, which acts chiefly by negative regulation of the Ras/mitogen-activated protein kinase pathway.[16] In NF1 patients, biallelic silencing of the *NF1* gene results in loss of neurofibromin and activates the pathway to tumorgenesis.[16,17] The development of neurogenic and non-neurogenic sarcomas in NF1 patients is thought to be a complex, multistep process involving additional mutations at multiple genetic loci.[5,18]

To date, no specific mutation has been associated with the occurrence of leiomyosarcoma.[16,18]

Surgical excision with a negative margin remains the primary therapy for organ confined visceral or retroperitoneal sarcomas. This may be followed by radiation therapy for high-grade sarcomas.[19] The main limitation of radiation therapy is its toxicity to surrounding structures, particularly the bowel.[20]

Conclusion

This patient had a prior history of liposarcoma of the anterior abdominal wall. The multitudinous nature of both neurogenic and non-neurogenic sarcomas in NF1 has previously been described.[18,21] As such, for NF1 patients with a previously confirmed malignancy, close long-term surveillance is recommended.

Lessons Learned

This rare case of primary colonic leiomyosarcoma in an NF1 patient reiterates the importance of clinical awareness of the increased risk of sarcomas in this patient group. We emphasize the need for a high index of suspicion and careful investigation in any NF1 patient presenting with gastrointestinal symptoms, especially in the setting of an equivocal initial biopsy and a history of malignancy.

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