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Brunei International Medical Journal
2026;22:53-56

Brunei International Medical Journal

Case Report

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A Rare Colonic Neurofibromal Polyp in Neurofibromatosis Type 1

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Abstract

Gastrointestinal involvement in Neurofibromatosis type 1 (NF1) is uncommon and colonic neurofibromas are rarely reported. We report an interesting case of a colonic neurofibroma in a patient with NF1, highlighting its clinicopathological features and differential diagnoses. The lesion manifested as a mucosal polyp in the sigmoid colon and on histopathologic examination showed fascicles of spindle cells with wavy nucleus and S100 positivity, confirming a neurofibroma. Recognition of this uncommon manifestation is important to distinguish it from other mesenchymal lesions of colon and guide appropriate clinical management and follow-up.

Keywords: Colonic neoplasm, Neurofibromatosis; Neurofibroma; Polyp.

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INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant tumour predisposition syndrome characterised by a pathogenic variant in NF1 gene and a constellation of clinical criteria. Gastrointestinal manifestations of NF1 are heterogeneous and range from completely asymptomatic or incidental findings, to symptomatic neoplasms that with abdominal pain, bleeding, and symptoms related to the presence of a mass. Colonic neurofibromas are infrequently reported and may pose diagnostic difficulty due to morphologic overlap with other spindle cell lesions of gastrointestinal tract. Histopathological evaluation and immunohistochemistry aids in correct diagnosis and appropriate management.

CASE REPORT

A 67-year-old gentleman who is a known case of NF1, hypertension and hyperlipidaemia was found to have anaemia (Hb 13.2 g/dL) on routine health check-up. On further evaluation, stool occult blood was positive and

was referred for screening for colorectal cancer. Colonoscopy showed diverticular disease and an adenomatous looking polyp in the sigmoid colon which was removed. Upper gastrointestinal endoscopy showed mild gastritis in the antrum and fundus. Biopsy was positive for *Helicobacter pylori* on rapid urease test and was later started on eradication therapy that consisted of omeprazole 20 mg, amoxicillin 1 gm and clarithromycin 50 mg, all twice daily for 14 days.

The resected specimen consisted of a single 3 x 3 mm smooth surfaced tan polypoid tissue. Histopathological examination showed the polyp consisting of fascicles of proliferated neural cells extending into lamina propria with scattered spindle cells with tapered nuclei (**Figure 1a & b**). Scattered eosinophils and mast cells were seen in the lamina propria. No ganglion cells were seen. The overlying mucosa showed features of ischaemic injury. There was no dysplasia or malignancy. The spindle cells were positive for S100 (**Figure 1c**). A diagnosis of neurofibromal polyp of sigmoid colon was made. The patient remained well and continued to be on follow up.

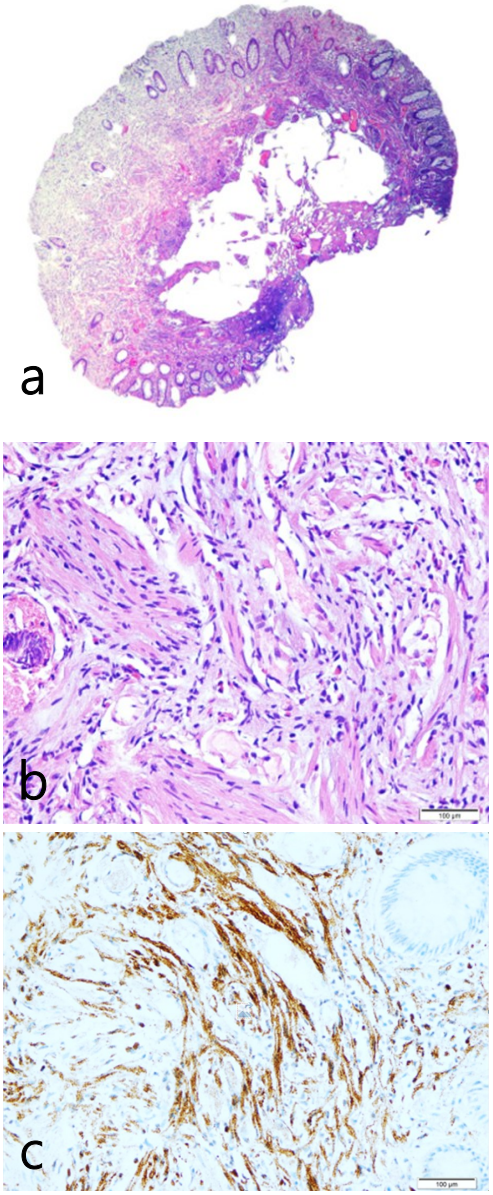

Fig 1: a) Colonic mucosal polyp with expanded lamina propria and surface erosions, H&E, magnification 4X. b) Fascicles and loosely arranged bland spindle cells, scattered eosinophils in the background (H&E, magnification 40X). c) Spindle cells showing nuclear and cytoplasmic staining with s100 (magnification 40X).

DISCUSSION

NF1 known as von Recklinghausen disease, is one of the common inheritable disorders with an autosomal dominant transmission, an incidence of 1:3,000, and a prevalence of 1:4–5,000.[1,2] The pathogenesis of the disease is mutation the NF1 tumour suppressor gene located in Chromosome 17q11.2. NF1 gene codes for neurofibromin protein which controls cellular proliferation by inactivating the p21 RAS and the MAP kinase pathway. The NF1 gene has one of the highest new mutation rates in humans and approximately 50% of NF1 patients have no family history of the disorder.[3] The phenotypic manifestation varies greatly depending on the nature of the mutation, the time at which the mutation occurs, and the presence of additional molecular alterations in other related genes.[3]

The frequency of intra-abdominal (gastrointestinal or retroperitoneal) manifestations of NF1 varied greatly in previous studies ranging from 5%-25%. Most of them are incidentally detected on screening colonoscopy. Only 5% of the cases present with symptoms such as gastrointestinal bleeding, abdominal pain and anaemia. They manifest usually in adult life following the more common cutaneous manifestations like café-au-lait spots, cutaneous neurofibromas, axillary freckling, and ocular Lisch nodules.

Gastrointestinal neurofibromas in NF1 arise from the proliferation of Schwann cells, fibroblasts and perineurial cells in the enteric nerve plexus. They can appear as solitary polypoid lesions, diffuse involvement or as plexiform neurofibromas. According to previously published studies, NF1 associated neurofibromas are the most frequently encountered in the small bowel and retroperitoneum.[4,5] Occurrence in the large bowel is extremely rare with only few cases reported in literature.[6-10] Endoscopy reveals sessile or pedunculated

mucosal or submucosal lesions. Kim *et al*. describes a case of neurofibromatosis diffusely involving the left colon, the sigmoid colon, and the rectum, which resulted in herniation of the mass through the anus, with intestinal obstruction.[6] Baril *et al.* reported a case of 46-year-old female with multiple polypoid neurofibromas from the transverse colon downwards who was managed with total colectomy.[7] Reports on single NF1 associated solitary neurofibromal polyps are not yet published, however there are reports on isolated neurofibromal polyps of colon that are sporadic and not NF1 associated.[11] It remains obscure, whether such lesions represent a segmental or localised visceral form of NF1 limited to the gastrointestinal tract or a distinct disease entity.[12]

The other lesions seen in gastrointestinal tract associated with NF1 include ganglioneuromatosis, gastrointestinal stromal tumours, neuroendocrine tumours and increased risk of development of small bowel adenocarcinoma.[13] Colorectal adenocarcinoma is not a part of the classic NF1 tumour spectrum. Published cases are mainly isolated case reports and brief series, but a definitive association has not yet been established.[14]

Pathological examination of colonic polyp forms an important part of diagnostic workup and histopathology remains the gold standard for diagnosis. Neurofibroma needs to be distinguished from other spindle cell mesenchymal lesions of the colon. The histological differential diagnosis includes schwannoma, gastrointestinal stromal tumour or GIST, inflammatory fibroid polyp, Schwann cell hamartoma and ganglioneuroma. Immunohistochemistry aids in distinguishing these entities. The salient distinguishing features are summarised in **Table 1**.

Malignant transformation of neurofibromas to malignant peripheral nerve sheath tumour (MPNST) have been described in association with NF1, mostly in extraintestinal sites. The occurrence of MPNST in the gastrointestinal tract is exceptionally rare. People with NF1 have a 10% lifetime risk of developing a MPNST compared to 0.001% in non-NF1 patients. Larger tumours and plexiform neurofibromas are more likely to undergo malignant transformation. The prognosis remains poor and depends on tumour size and location, resection margins, adjuvant chemotherapy, distant metastasis, and tumour stage.[14]

Table 1. Comparison of colonic neurofibroma and its histologic differentials.

Entity	Clinical context	Endoscopic appearance	Histologic features	Immunohistochemistry	Management
Neurofibroma	NF1 associated; rarely sporadic	Smooth surfaced mucosal or submucosal lesion	Poorly circumscribed bland spindle Schwann cells with wavy nuclei, mast cells, shredded carrot like collagen, mixed neural elements	S100 positive in Schwann cells, SOX 10 and CD34 positive Neurofilament P can highlight the axons	Endoscopic or surgical excision if symptomatic. Screening for other NF1 associated lesions
Schwannoma	Usually, sporadic	Smooth, well-circumscribed, sessile (wide-based) nodules or polypoid, submucosal masses.	Encapsulated with cellular Antoni A areas exhibiting palisading of nucleus forming Verocay bodies and less cellular Antoni B areas.	Diffusely positive for S100 and less so for CD34	Excision
Ganglioneuroma	Sporadic or syndromic (NF1, Cowden, MEN2B)	Small, sessile polyps; can be multiple	Mature ganglion cells admixed with Schwann cells and nerve fibres	S100 positive in Schwann cells, Synaptophysin, Chromogranin and NSE highlight ganglion cells	Polypectomy. Evaluate for syndromic association
Gastrointestinal stromal tumor	Sporadic or NF1 associated; risk of malignancy	Smooth, firm, rounded, or lobulated subepithelial lesion. mucosal ulceration in larger tumours	Spindle or epithelioid morphology, variable atypia and mitotic activity	c-KIT and DOG1 positive, S100 negative	Surgical resection, risk based follow up and targeted therapy
Inflammatory fibroid polyp	Non NF1	Often solitary, submucosal, polypoid, or sessile masses.	Onion- skin perivascular pattern, eosinophil rich stroma	CD34 positive, S100 negative	Endoscopic removal; No surveillance needed
Schwann cell hamartoma	Non NF1 associated, incidental	Small (6 mm or less) sessile polyp	Poorly circumscribed mucosal proliferation of spindle cells, with no whorling, no palisading, no fasciculation	S100 positive	Endoscopic removal; No surveillance needed
Leiomyoma	Non NF1 associated	Firm, white, well delineated nodule or polyp, generally < 1 cm	Fascicles of bland smooth muscle cells with cigar shaped nucleus.	SMA, Desmin, Caldesmon positive; S100 and c-KIT negative	Excision

NF1: Neurofibromatosis Type 1, MEN2B: Multiple endocrine neoplasia 2B, CD: Cluster of differentiation, NSE: Neuron-Specific Enolase, SMA: smooth muscle actin

Routine endoscopic examinations, along with imaging techniques like computed tomography and magnetic resonance imaging, could be beneficial for the early detection of gastrointestinal lesions in NF1 patients aged 40 and above. The European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS) guideline recommends that adults with NF1 should be assessed clinically, at least once every three years.[15] Honda *et al*. proposes NF1 patients aged ≥40 years must undergo at least one esophagogastroduodenoscopy and colonoscopy, along with imaging modalities, such as CT and MRI, to screen for gastrointestinal lesions, with the need for further follow-up determined based on individual risk factors. Although no established guidelines currently exist for screening asymptomatic NF1 patients, a follow-up interval of 2–5 years may be reasonable.[16]

CONCLUSION

We report an interesting case of a patient with NF1 with incidental findings of a colonic neurofibromal polyp. Though rare, NF1 is associated with gastrointestinal manifestation including in the colon.

Take Home Message

- Colonic neurofibromas are rare manifestations of NF1 and should be considered in evaluating colonic polyps, especially in patients with known NF1..
- Histopathology and immunohistochemistry will help in distinguishing neurofibromas from other spindle mesenchymal tumours.
- While malignant transformation is rare, recognising the lesion support appropriate management and follow up planning, particularly because NF1 patients may harbour additional gastrointestinal lesions

Abbreviations

NF1	Neurofibromatosis type 1
MPNST	Malignant peripheral nerve sheath tumour

Declarations

All the authors declared no competing interests.

Patient Consent

Written consent was obtained from all patients for publications of the clinical details and accompanying images.

Acknowledgement

None

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