Impaired bowel healing in surgical patients with neurofibromatosis

Corresponding Author: Joanna W Etra

Tel: (303) 724-4790; Email: Joanna.Etra@cuanschutz.edu

Isabelle Roseto; Taryn I Ketels, NP; Kristy Hawley, MD; W Aaron Marshall, MD; Whitney R Jenson, MD, MPH; Mitchell J Cohen, MD; Michael W Cripps, MD, MSCS; Catherine Velopulos, MD; Joanna W Etra, MD*

University of Colorado School of Medicine, Department of Trauma and Acute Care Surgery, Aurora CO, USA.

Introduction

Tissue healing is of vital importance to surgical outcomes, and alterations can have devastating consequences. Understanding a patient's healing patterns is crucial for preoperative planning and patient counseling. While not fully understood or previously published, we here present a series of cases leading us to hypothesize that neurofibromatosis may be associated with poor bowel healing.

Neurofibromatosis (NF) is a neurocutaneous syndrome that typically causes tumor growth on nervous tissue [1]. NF encompasses multiple distinct autosomal dominantly inherited disorders including neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2) and schwannomatosis [2-4]. NF1 is the most common subtype, accounting for 96% of cases of NF and has an incidence of 1 in 2600-3000 people [1,5,6]. NF1 is caused by a mutation in NF1, a tumor suppressor gene that encodes neurofibromin, a GTPase-activating protein that negatively regulates the RAS/MAPK pathway [7,8]. Neurofibromas are a hallmark finding of NF1, as are café-au-lait spots, freckling in skinfolds, bone dysplasia, osteopenia, and Lisch nodules [9-13]. NF2 accounts for 3% of cases, with an incidence varying from 1

in 25,000-46,000 people [1,5,6]. Like NF1, NF2 is a tumor suppressor. It encodes merlin (also called schwannomin) which is a membrane-cytoskeleton scaffolding protein [14,15]. Clinical characteristics of NF2 include bilateral vestibular schwannomas, meningiomas, gliomas, ependymomas, and posterior subcapsular cataracts [16-19]. Schwannomatosis is the least common subtype, accounting for <1% of all cases, and has a highly variable reported incidence of 1 in 68,000 to 1 in 1,800,000 people [6,20,21]. The most common genetic mutations implicated in schwannomatosis are SMARCB1 and LZTR1 [22-24]. Schwannomatosis has incomplete penetrance, unlike NF1 and NF2. It is related to NF2, and they were originally thought to be one clinical entity. However, schwannomatosis is genetically distinct from NF2 and is defined as multiple non-vestibular schwannomas in the absence of other features of NF2 [25,26].

NF has consequences for many different physiologic processes. One effect that is not fully understood is the impact of NF on tissue healing. Though there have been a number of wound healing studies in NF, there have been no known studies reporting specifically on the potential impact of NF on bowel healing.

Regardless of the technique to repair or anastomose the bowel (hand sewn, stapled), there is a risk of leak, which allows egress of bowel contents into the peritoneal cavity and result in significant morbidity. In this report, we present three recent cases of patients with NF who had multiple complications related to healing following bowel injury. While we cannot prove association or causality, it is crucial to know whether these disease processes result in higher risk of anastomotic leak, as these patients would need to be approached with extra care in planning and executing abdominal operations. We present three surgical cases in patients with different NF subtypes, each of whom experiences abnormal bowel healing. These cases, along with a review of the literature, suggest that NF may impair bowel healing and increase the risk of post-surgical complications.

Case presentations

Patient 1

This patient is a 63-year-old female with a family history of NF who has a longstanding history of NF1. Her manifestations at the time of presentation included many cutaneous and subcutaneous neurofibromas and osteoporosis. She had a fibroma removed from her inferior aortic arch and had an adrenalectomy due to a pheochromocytoma.

She had a history of ventral hernia repairs complicated by infected mesh and subcutaneous abscesses that had been treated nonoperatively. She presented for the first time to us with sepsis and underwent exploratory laparotomy with extensive lysis of adhesions, abdominal mesh explantation, excision of antimesenteric jejunal mass, appendectomy, segmental ileal resection with stapled side-to-side anastomosis, and abdominal wall debridement with abdominal closure. At the time, it was noted that her small bowel had fistulized to the mesh, which was the source of her multiple mesh infections. The postoperative course was complicated by an anastomotic leak, sepsis, and enterocutaneous fistula formation. Six months later, percutaneous closure of the fistula was performed but closure failed three days later. Over the following months, the enterocutaneous fistula intermittently closed and formed multiple subcutaneous abscesses.

She presented six months later for an exploratory laparotomy with extensive lysis of adhesions and fistula takedown with small bowel anastomosis. Enterolysis was unusually difficult due to the extensive adhesions. Her postoperative hospital course was complicated by wound dehiscence and new enterocutaneous fistulas requiring negative pressure wound therapy. Secondary skin closure occurred after two months of hospital admission, and she was discharged in a stable condition. She was treated outpatient with parenteral nutrition and local wound care. She had one subsequent admission for bacteremia which was treated with antibiotics and an exchange of her central line. Over the course of months of treatment with suppressive antibiotics and parenteral nutrition, she had resolution of the enterocutenous fistula.

Patient 2

Patient 2 is a 55-year-old male originally diagnosed with NF1 at age 10 with peripheral neurofibromas and café-au-lait spots. Manifestations at the time of presentation include plexiform neurofibromas, right ulnar neuropathy, right-sided motor deficits, and abnormal gait. He has had multiple cervical tumor decompressions, a right ulnar nerve transposition, and many (30+) superficial neurofibromas excised.

He presented to a hospital outside our institution with unrelenting abdominal pain and a small amount of pneumoperitoneum on Computed Tomography (CT) scan. Subsequent exploratory laparotomy revealed a perforated prepyloric ulcer, and an open gastric antrectomy with gastrojejunostomy was performed and a JP drain was placed. Extensive intraperitoneal and retroperitoneal neurofibromas were noted during surgery. A CT scan on Postoperative Day (POD) 5 showed an inflamed duodenal stump with surrounding fluid, concerning for a stump leak. On POD8, a percutaneous biliary drain was placed for ongoing bile leak from the duodenal stump. On POD14, an intraperitoneal percutaneous drain was placed for a parasplenic abscess. He was discharged on POD22.

He presented to an outside hospital approximately two months later with constipation, dizziness, and CT evidence of fecal impaction. He developed a small bowel obstruction and septic shock requiring vasopressors. He was also found to have another duodenal stump leak, which was managed with an over-the-endoscope clip for repair. He was transferred to our institution for evaluation due to persistent bilious output from drains. Subsequent cholangiogram was negative for persistent duodenal leak and CT showed no new intra-abdominal lesions. He was discharged in a stable condition.

Patient 3

This patient is a 63-year-old male with probable NF2 (not definitively distinguished from schwannomatosis) that manifested with many central and peripheral schwannomas, including spinal lesions in the cervical, thoracic, and lumbar regions, a right vestibular schwannoma, and multiple schwannomas on his right upper extremity, as well as diffuse right-sided peripheral neuropathy. He had multiple schwannoma resections.

He presented for a C5/C6 laminoplasty due to worsening right-sided weakness. On POD4, general surgery was consulted for concern for an ileus and colonic dilation that improved with conservative management. On POD9, he began having severe abdominal pain and distension. Imaging demonstrated pneumoperitoneum and a significantly dilated colon. He underwent a laparotomy, which revealed Ogilvie's syndrome with transverse colon perforation. An extended right hemicolectomy with primary ileocolic anastomosis was performed. On POD7 from the laparotomy, a CT scan showed concern for an anastomotic leak. He returned to the OR the next day for an abdominal washout with colorrhaphy and diverting loop ileostomy. A drain was placed for intra-abdominal abscesses. He was discharged to rehab approximately five weeks after the initial laminoplasty but returned a week later with hypovolemic shock and acute kidney injury. During this admission, there was evidence of a fistula of his abscess cavity to adjacent small bowel. An indwelling drainage catheter followed by fibrin glue were used to repair the fistula. Contrast enema showed no anastomotic leak or strictures, and a colonoscopy was unremarkable.

He returned a year later for an elective ileostomy takedown and small bowel resection with primary anastomosis. The postoperative course was complicated by an ileus and gram-negative rod bacteremia. He had a right lower quadrant abdominal drain placed for loculated ascites with concern for peritonitis. Imaging showed no anastomotic leak. He was discharged with improved ileus and bacteremia.

He returned to the emergency room three weeks later with a Richter's hernia involving colon wall just distal to the ileocolic

anastomosis herniating through the site of the previous drain. He underwent a diagnostic laparoscopy which was converted to a laparotomy and revealed colon perforation at the herniated bowel and severe intra-abdominal adhesions and interloop abscesses. He had extensive lysis of adhesions and ileocolic resection with primary anastomosis. He returned to the operating room 10 days later for an abdominal washout and drain placement due to deep surgical site infection not amenable to percutaneous drainage . He was extubated postoperatively but required re-intubation for airway protection and hypoxia. He was found to have pneumonia and pulmonary edema. He was subsequently extubated for two days and then required endotracheal intubation for recurrent respiratory failure. Per family wishes, he was transitioned to comfort measure only care, and he died three days later.

Discussion/Conclusion

Our patients all presented with variations of neurofibromatosis and what we believe to be abnormal gastrointestinal healing. We performed a systematic review for published articles on wound healing in NF (Table 1). Wound healing is known to be altered in patients with NF. Multiple animal and human studies have been conducted in an attempt to characterize this relationship, the results of which have been inconsistent. Atit et al found that in *NF1* knockout mice, fibroblasts produced an abnormal pattern and amount of granulation tissue in response to injury. They also noted that these mice continued to have fibroblast proliferation past the normal wound remodeling phase [27]. In contrast, another study found that people with NF1 seemed to have less scar proliferation in response to injury, as shown by the finding that they were significantly less likely to develop a hypertrophic or keloid scar compared to those with a solitary neurofibroma [28]. They found low rates of wound healing complications. Ademiluyi et al. [29] found a decreased incidence of hypertrophic and keloid scars; however, they found poor wound healing and many cases of wound dehiscence in their cohort of thirty NF1 patients. Another study found no difference in epidermal and dermal wound healing in people with NF1 compared to healthy controls [30]. Golomb et al. [31] report two children with NF1 who had poor wound healing following pial synangiosis. Cell studies from Arima et al. [32] revealed that cells from NF1-associated neurofibromas have an abnormal upregulation of transcription factors involved with epithelial-to-mesenchymal transition, which shows a potential etiology of this abnormal healing. NF1 also appears to impact bone healing, as about 50-80% of individuals with pseudoarthrosis following fracture have NF1 [33]. Five percent of people with NF1 have pseudoarthrosis, most commonly in their tibia [33]. In multiple studies, NF1 knockout mice have an increased likelihood of abnormal bone healing with diminished cartilage formation, thickened periosteal bone, accumulation of fibrous tissue [34-36]. Rat models have shown significant down-regulation of NF1 with non-union bone fractures [37].

NF2 has also been shown to be implicated in healing, as it was found that NF2 mutated cells have defects in migration in a wound-healing assay [38]. Also, NF2 knockout mice promote neointima hyperplasia following vascular injury [39]. Regarding schwannomatosis, liver cells with SMARCB1 loss of function had reduced cell proliferation and wound healing capacity *in vitro* [40].

After our systematic review of the current literature, we believe that this report is the first to identify bowel healing implications in patients with NF. This association has the potential to impact preoperative planning, decision making, and patient counseling in patients with NF who might have higher risk of complications in bowel operations. While wound healing derangements are known and reported in multiple studies, further work must be done to elucidate the impact of NF on bowel healing and potential clinical consequences when operations are considered or required in patients with this condition.

Table 1: Systematic review for published articles on wound healing in NF.

PubMed			
Concepts	**Neurofibromatosis**	**Bowel injury, ulcer, obstruction**	**Complications, healing, outcomes**
Entry Terms and Keywords Title/Abstract =[tiab] Textwords (title,abstract,keywords)=[tw] *= all word endings " "= strict phrase	Neurofibromatosis [tw] OR Neurofibromatoses[tw] OR Schwannomatosis[tw] OR Schwannomatoses[tw] OR NF1[tiab] OR NF2[tiab] OR von Recklinghausen's disease[tw] OR	Intestinal Obstruction*[tw] OR Bowel obstruction*[tw] OR Ileus[tw] OR Intestinal Pseudo-Obstruction*[tw] OR Colonic Pseudo-Obstruction*[tw] OR Peptic Ulcer*[tw] OR Gastroduodenal Ulcer*[tw] OR Prepyloric ulcer*[tw] OR Pre-pyloric ulcer*[tw] OR Bowel injur*[tw] OR Intestinal injur*[tw] OR	Healing[tw]
MeSH (Medical Subject Headings)	"Neurofibromatoses"[Mesh] OR "Schwannomatosis" [Supplementary Concept]	"Intestinal Obstruction"[Mesh] OR "Peptic Ulcer"[Mesh] OR "Intestine, Large/injuries"[Mesh] OR "Intestine, Small/injuries"[Mesh]	

Find and Replace for OR: **FIND** ^p **REPLACE** _OR_
OR – combining synonyms
AND – combines separate concepts
Results: 231
Google Scholar: neurofibromatosis "bowel injury" | "intestinal obstruction" | "peptic ulcer" "hospital stay" | healing | outcome | complications

References

1. Korf BR. Neurofibromatosis. Handb Clin Neurol 2013; 111:333-340.

2. Nix JS, Blakeley J, Rodriguez FJ. An update on the central nervous system manifestations of neurofibromatosis type 1. Acta Neuropathol 2020; 139(4):625-641.

3. Coy S, Rashid R, Stemmer-Rachamimov A, Santagata S. An update on the CNS manifestations of neurofibromatosis type 2. Acta Neuropathol 2020; 139(4):643-665.

4. Merker VL, Esparza S, Smith MJ, Stemmer-Rachamimov A, Plotkin SR. Clinical features of schwannomatosis: a retrospective analysis of 87 patients. Oncologist 2012; 17(10):1317-1322.

5. Lee TJ, Chopra M, Kim RH, Parkin PC, Barnett-Tapia C. Incidence and prevalence of neurofibromatosis type 1 and 2: a systematic review and meta-analysis. Orphanet J Rare Dis 2023; 18(1):292.

6. Tamura R. Current Understanding of Neurofibromatosis Type 1, 2, and Schwannomatosis. Int J Mol Sci 2021; 22(11).

7. Ars E, Kruyer H, Morell M, Pros E, Serra E, Ravella A, et al. **Recurrent mutations in the NF1 gene are common among neurofibromatosis type 1 patients**. J Med Genet 2003; 40(6):e82.

8. De Luca A, Bottillo I, Sarkozy A, Carta C, Neri C, Bellacchio E, et al. NF1 gene mutations represent the major molecular event underlying neurofibromatosis-Noonan syndrome. Am J Hum Genet 2005; 77(6):1092-1101.

9. Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 1997; 278(1):51-57.

10. Vazquez-Osorio I, Duat-Rodriguez A, Garcia-Martinez FJ, Torrelo A, Noguera-Morel L, Hernandez-Martin A. Cutaneous and Systemic Findings in Mosaic Neurofibromatosis Type 1. Pediatr Dermatol 2017; 34(3):271-276.

11. Brunetti-Pierri N, Doty SB, Hicks J, Phan K, Mendoza-Londono R, Blazo M, et al. Generalized metabolic bone disease in Neurofibromatosis type I. Mol Genet Metab 2008; 94(1):105-111.

12. Dulai S, Briody J, Schindeler A, North KN, Cowell CT, Little DG. Decreased bone mineral density in neurofibromatosis type 1: results from a pediatric cohort. J Pediatr Orthop 2007; 27(4):472-475.

13. Nichols JC, Amato JE, Chung SM. Characteristics of Lisch nodules in patients with neurofibromatosis type 1. J Pediatr Ophthalmol Strabismus 2003; 40(5):293-296.

14. Rouleau GA, Merel P, Lutchman M, Sanson M, Zucman J, Marineau C, et al. Alteration in a new gene encoding a putative membrane-organizing protein causes neuro-fibromatosis type 2. Nature 1993; 363(6429):515-521.

15. Bretscher A, Chambers D, Nguyen R, Reczek D. ERM-Merlin and EBP50 protein families in plasma membrane organization and function. Annu Rev Cell Dev Biol 2000; 16:113-143.

16. Parry DM, Eldridge R, Kaiser-Kupfer MI, Bouzas EA, Pikus A, Patronas N. Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. Am J Med Genet 1994; 52(4):450-461.

17. Evans DG, Huson SM, Donnai D, Neary W, Blair V, Newton V, et al. A clinical study of type 2 neurofibromatosis. Q J Med 1992; 84(304):603-618.

18. Mautner VF, Lindenau M, Baser ME, Hazim W, Tatagiba M, Haase W, et al. The neuroimaging and clinical spectrum of neurofibromatosis 2. Neurosurgery 1996; 38(5):880-885; discussion 885-886.

19. McLaughlin ME, Pepin SM, Maccollin M, Choopong P, Lessell S. Ocular pathologic findings of neurofibromatosis type 2. Arch Ophthalmol 2007; 125(3):389-394.

20. Evans DG, Bowers NL, Tobi S, Hartley C, Wallace AJ, King AT, et al. Schwannomatosis: a genetic and epidemiological study. J Neurol Neurosurg Psychiatry 2018; 89(11):1215-1219.

21. Antinheimo J, Sankila R, Carpen O, Pukkala E, Sainio M, Jaaskelainen J. Population-based analysis of sporadic and type 2 neurofibromatosis-associated meningiomas and schwannomas. Neurology 2000; 54(1):71-76.

22. Hulsebos TJ, Plomp AS, Wolterman RA, Robanus-Maandag EC, Baas F, Wesseling P. Germline mutation of INI1/SMARCB1 in familial schwannomatosis. Am J Hum Genet 2007; 80(4):805-810.

23. Boyd C, Smith MJ, Kluwe L, Balogh A, Maccollin M, Plotkin SR. Alterations in the SMARCB1 (INI1) tumor suppressor gene in familial schwannomatosis. Clin Genet 2008; 74(4):358-366.

24. Piotrowski A, Xie J, Liu YF, Poplawski AB, Gomes AR, Madanecki P, et al. Germline loss-of-function mutations in LZTR1 predispose to an inherited disorder of multiple schwannomas. Nat Genet 2014; 46(2):182-187.

25. MacCollin M, Woodfin W, Kronn D, Short MP. Schwannomatosis: a clinical and pathologic study. Neurology 1996; 46(4):1072-1079.

26. Gonzalvo A, Fowler A, Cook RJ, Little NS, Wheeler H, McDonald KL, et al. Schwannomatosis, sporadic schwannomatosis, and familial schwannomatosis: a surgical series with long-term follow-up. Clinical article. J Neurosurg 2011; 114(3):756-762.

27. Atit RP, Crowe MJ, Greenhalgh DG, Wenstrup RJ, Ratner N. The Nf1 tumor suppressor regulates mouse skin wound healing, fibroblast proliferation, and collagen deposited by fibroblasts. J Invest Dermatol 1999; 112(6):835-842.

28. Miyawaki T, Billings B, Har-Shai Y, Agbenorku P, Kokuba E, Moreira-Gonzalez A, et al. Multicenter study of wound healing in neurofibromatosis and neurofibroma. J Craniofac Surg 2007; 18(5):1008-1011.

29. Ademiluyi SA, Sowemimo GO, Oyeneyin JO. Surgical experience in the management of multiple neurofibromatosis in Nigerians. West Afr J Med 1989; 8(1):59-65.

30. Koivunen J, Karvonen SL, Yla-Outinen H, Aaltonen V, Oikarinen A, Peltonen J. NF1 tumor suppressor in epidermal wound healing with special focus on wound healing in patients with type 1 neurofibromatosis. Arch Dermatol Res 2005; 296(12):547-554.

31. Golomb MR, Smith JL. Poor wound healing after pial synangiosis in 2 children with moyamoya vasculopathy associated with neurofibromatosis type 1. J Child Neurol 2014; 29(10):NP101-104.

32. Arima Y, Hayashi H, Kamata K, Goto TM, Sasaki M, Kuramochi A, et al. Decreased expression of neurofibromin contributes to epithelial-mesenchymal transition in neurofibromatosis type 1. Exp Dermatol 2010; 19(8):e136-141.

33. Stevenson DA, Birch PH, Friedman JM, Viskochil DH, Balestrazzi P, Boni S, et al. Descriptive analysis of tibial pseudarthrosis in patients with neurofibromatosis 1. Am J Med Genet 1999; 84(5):413-419.

34. El Khassawna T, Toben D, Kolanczyk M, Schmidt-Bleek K, Koennecke I, Schell H, et al. Deterioration of fracture healing in the mouse model of NF1 long bone dysplasia. Bone 2012; 51(4):651-660.

35. El-Hoss J, Sullivan K, Cheng T, Yu NY, Bobyn JD, Peacock L, et al. A murine model of neurofibromatosis type 1 tibial pseudarthrosis featuring proliferative fibrous tissue and osteoclast-like cells. J Bone Miner Res 2012; 27(1):68-78.

36. Kuorilehto T, Ekholm E, Nissinen M, Hietaniemi K, Hiltunen A, Paavolainen P, et al. NF1 gene expression in mouse fracture healing and in experimental rat pseudarthrosis. J Histochem Cytochem 2006; 54(3):363-370.

37. Tan Q, Wu JY, Liu YX, Liu K, Tang J, Ye WH, et al. The neurofibromatosis type I gene promotes autophagy via mTORC1 signalling pathway to enhance new bone formation after fracture. J Cell Mol Med 2020; 24(19):11524-11534.

38. Laulajainen M, Muranen T, Carpen O, Gronholm M. Protein kinase A-mediated phosphorylation of the NF2 tumor suppressor protein merlin at serine 10 affects the actin cytoskeleton. Oncogene 2008; 27(23):3233-3243.

39. Sun X, Li S, Gan X, Chen K, Yang D, Yang Y. NF2 deficiency accelerates neointima hyperplasia following vascular injury via promoting YAP-TEAD1 interaction in vascular smooth muscle cells. Aging (Albany NY) 2020; 12(10):9726-9744.

40. Hong SH, Son KH, Ha SY, Wee TI, Choi SK, Won JE, et al. Nucleoporin 210 Serves a Key Scaffold for SMARCB1 in Liver Cancer. Cancer Res 2021; 81(2):356-370.