Solitary colonic neurofibroma in a patient with transient segmental colitis: Case report

Vasilios Panteris, Thivi Vassilakaki, Nikos Vaitisis, Ioannis Elemenoglou, Irini Mylonakou, Dimitrios Georgios Karamanolis

CASE REPORT
A 65-year-old Caucasian female came to the emergency department of our hospital complaining of bloody diarrhea. Twelve hours before admission the patient experienced a dull abdominal pain of sudden onset, located at the hypogastrum, and her temperature rose to 37.8°C. She reported 10 bowel movements, which were diarrheal at first and became hemorrhagic later. Physical examination revealed moderate tenderness on palpation of the hypogastrum and increased bowel sounds on auscultation. Inspection of the skin revealed two firm, subcutaneous masses with ill-defined borders, each one located at the apex of the scapula with a diameter of 2 cm. Physical examination of the lungs, heart, skin, and other body systems revealed no abnormal features. It was the first episode of bloody diarrhea experienced by the patient. Her past medical history included essential hypertension, hyperlipidemia, and an acute coronary syndrome and she was receiving an angiotensin-converting enzyme inhibitor, enteric-coated aspirin and a statin. Furthermore, she had atopy to grass, tree pollens and fungal spores, manifested by bronchoconstriction. There was no family history of intestinal diseases.

Laboratory investigation including complete blood count, biochemical examination, tumor markers (CEA, CA 19-9, aFP, CA125, CA 15-3), coagulation tests, microbiological cultures for bacterial and parasites in feces and cultures of the urine were normal except for a slightly elevated blood glucose level (120 mg%) and CRP (12, normal <4). Chest x-ray and ECG had no abnormal features. An abdominal plain radiograph showed only an air-filled large bowel. Colonoscopy was performed after cessation of the hemorrhage. The endoscope reached the hepatic flexure and revealed a segmental colitis. At the splenic flexure and proximal portion of the descending colon there were erythema and edema of the mucosa with hemorrhagic petechiae. A sessile polyp 1 cm in diameter was detected at the descending colon, near the site of inflammation and was endoscopically removed. The transverse colon and the rectum were macroscopically normal. At the sigmoid colon a few, small diverticulae were noticed, without inflammation. Ultrasonography of the abdomen revealed no pathological findings.

INTRODUCTION
Neurofibromas exist rarely in the colon as isolated neoplasms outside the classical clinical picture of von Recklinghausen’s disease (neurofibromatosis type 1, NF1) [1]. Intestinal neurofibromatosis characterized by multiple neurofibromas usually in the small intestine and stomach may rarely present as a sporadic case in a patient without features of the generalized neurofibromatosis. Isolated colonic neurofibromatosis is even more unusually described in the literature [2]. Here we describe a rare case of a solitary colonic neurofibroma in a patient without features of NF1 or isolated colonic neurofibromatosis.

Pathology findings
Microscopically, the biopsy from the polyp showed fragments of mucosa of the large bowel lined by normal epithelium. In the lamina propria there was a nodule, with ill-defined borders, which was composed of longitudinal cells with elongated, pointed nucleus. These cells were...
deposited in interlaced bundles and in near proximity with collagen fibers. There were no signs of atypia, nor significant mitotic activity. Immunohistochemical stains were positive for vimentin and S-100 protein but negative for desmin, smooth muscle actin, c-kit and CD34. The above morphological and immunohistochemical characteristics were consistent with the diagnosis of neurofibroma (Figures 1A-C). Biopsy samples from the site of colitis showed focal erosions of the surface mucosal epithelium and focal decrease in mucus production. The architecture of the glands was intact. There was edema and dense infiltrate of inflammatory cells (lymphocytes, polymorphonuclear and plasma cells) in the lamina propria. There was an increased number of eosinophils in the same area. Crypt abscesses were rarely encountered. Granulomas were not recognized microscopically. These findings could not support a definite diagnosis of idiopathic inflammatory bowel disease and were classified as nonspecific colitis (Figures 2A-C).

Clinically the patient had no café-au-lait spots on her skin, axillary freckling or peripheral neurofibromas. Also there were no pigmented hamartomas of the iris and no family history of neurofibromatosis. The patient received crystalloid solutions, antibiotics and mesalazine, had an uneventful recovery and was discharged 5 d later. Two months later in a follow-up examination, the patient had no symptoms from the intestine and her physical examination was unremarkable. Colonoscopy was again performed and the colon was examined to the hepatic flexure. The previous findings were absent and the mucosal surface was normal. The patient was advised to have a barium enema done for the visualization of the remaining large bowel which showed only diverticula of the right colon and sigmoid. Due to the polypoid neurofibroma the patient underwent spiral CT of the brain, thorax and abdomen for pathological features associated with neurofibromatosis. No abnormalities were found. Biopsy samples, taken from one of the subcutaneous masses located at the back of the patient showed a lipoma with fibrous components and S-100 negative immunoreactivity. New serum laboratory tests were normal except glucose, which was 142 mg%. Gastroscopy revealed erosive duodenitis and no other suspicious pathologic lesion.

DISCUSSION

Neurofibromas are usually manifestations of the von Recklinghausen's disease. They are benign neoplasms consisting of neural and connective tissue components like Schwann and perineural cells and myofibroblasts. They are usually multiple on presentation and are part of a hereditary disorder with two clinical forms: Nf1 (or von Recklinghausen's neurofibromatosis or peripheral neurofibromatosis, Nf1) and neurofibromatosis type 2 (or central neurofibromatosis or bilateral acoustic neurofibromatosis). These disease entities have variable clinical expressions with manifestations involving the skin, nervous system, eyes, bones, gastrointestinal tract, and other body parts. Cardiovascular disease manifested as hypertension, myocardial infarction, hemorrhage, or cerebral ischemia, are the most frequent causes of death in Nf1 patients[3]. Survival is lesser than expected in the normal population as much as 15 years. There is also a disease type called segmental neurofibromatosis, which involves a specific
body organ without the variety of multiple pathologic expressions of the generalized form.

Neurofibromas of the digestive system are usually found as part of the NF1. This is a relative common inherited disorder based on genetic transmission of the autosomal dominant type. The incidence of the disease is 1:3 000 births and the population prevalence is 1:5 000[4]. The diagnostic criteria for NF1 include the following: (1) the so-called “café-au-lait” spots (at least six spots, size ≥1.5 cm in postpubertal patients), (2) the characteristic neurofibromas (at least two or one plexiform), (3) axillary or groin freckling, (4) pigmented hamartomas of the iris, the so-called Lisch nodules (at least two), (5) an osseous lesion which may include thinning of the long bone cortex or sphenoid wing dysplasia, (6) first degree relative with NF1, (7) optic glioma. The patient should have at least two of the previous criteria to be considered as NF1. The penetrance of the disease is 100% until age 5[5]. The majority of patients have café-au-lait spots (95%), neurofibromas (95%), Lisch nodules (95%) and axillary freckling (70%). Optic gliomas affect 15% of the patients[6]. Café-au-lait spots most commonly present before 2 years of age[6].

Neurofibromas may be cutaneous, nodular derived from peripheral nerves or plexiform with aggressive, infiltrative growth that extends outside the nerve sheath to the surrounding tissue. Although benign, neurofibromas of the nodular and particular the plexiform type may demonstrate a malignant transformation in 2-16% of affected individuals[8,9,10]. About 50% of the cases of NF1 are not familial but sporadic as a result of germ-cell mutations. Segmental NF seems to involve a group of somatic cells that have exclusively acquired the specific neurofibromatosis mutations presenting a mosaicism[4]. The NF1 gene has been located on chromosome 17q11.2 and produces a peptide of 2 818 aminoacids, called neurofibromin, which works as a tumor suppressor[11,12]. Neurofibromin seems to interact with the RAS/GTP membrane-signaling pathway in cells by activating the GTPase that converts GTP to inactive GDP and therefore shutting down the RAS effector system which is involved in cell growth and differentiation. Mutations of the NF1 gene result in deficient neurofibromin, which in turn seems unable to control responses to proliferation signaling thus giving birth to neoplastic growth.

Participation of the gastrointestinal tract has been documented in 25% of patients with NF1. Ganglioneuromatosis and neurofibromatosis are the pathologic forms of gastrointestinal involvement[8]. Ganglioneuromatosis refers to extended hyperplasia and hypertrophy of the nerve plexuses and ganglion cells in the mucosa or throughout the intestinal wall. Characteristic neurofibromas have been found in the digestive tract in 11% of patients with NF1[5].

Intestinal neurofibromatosis exists, in the majority of cases, in association with NF1 and only rarely presents outside this disease as a separate pathologic entity (familial or sporadic)[5]. Multiple neurofibromas are discovered in the gut, more often located in the jejunum, stomach, ileum, duodenum, and colon according to the frequency of their appearance[13,14]. Neurofibromas are usually originating from either the plexus of Meissner in the submucosa or the plexus of Auerbach’s in the muscularis propria or even from the serosa[15,16]. The lesions are often sessile and wide based but also pedunculated polyps have been observed[5]. These lesions most often are discovered in the 4th-6th decade of life[10-12]. It is common to remain clinically silent and rarely cause symptoms before puberty. NF1 is also associated with the occurrence of other neoplasms that involve the gastrointestinal tract. These include carcinoids and somatostatinomas that are located mainly in the duodenum and ampulla of Vater, stromal tumors mainly leiomyomas and sarcomas and pancreatic adenocarcinomas[8,9,10]. The clinical picture includes abdominal pain, palpable masses, hemorrhage due to necrosis or ulceration of the mucosa, obstruction due to intussusception or extraluminal pressure, perforation, megacolon, peptic ulcer disease, diarrhea, steatorrhea, obstructive jaundice and obstruction of the pancreatic tract. Iron deficiency anemia has also been reported and caused by occult blood loss[9,11].

Neurofibromatosis of the colon as part of the NF1 is rare[7-10,13-14]. Isolated colonic neurofibromatosis without other features suggestive of NF1 has been very rarely encountered in the clinical practice. Only 13 such cases of isolated colonic neurofibromatosis with no evidence of NF1 have been documented in the literature[13-15]. Isolated neurofibromas of the colon are even rarer and only two such cases have been published[15]. In the first case an asymptomatic polyp was discovered to represent a neurofibroma while in the second case the neurofibroma presented as a large polypoid mass in the transverse colon. The mass had intussuscepted into the rectum causing massive bleeding of the gastrointestinal tract. There are also other parts of the digestive tract in which solitary neurofibromas have been detected. There have been 8 cases of solitary mesentery neurofibroma (7 ileal, 1 gastrocolic) [6], 1 case of ileal isolated neurofibroma[16], 3 cases of the anal canal[17], 1 case of the esophagus[18], 1 case of the soft palate[19], 7 cases of the gallbladder[20], and 1 case of the common bile duct[21].

Isolated neurofibromas in other body organs are also very rare. Very few cases have been reported so far, namely to the kidney[22], spermatic cord[23], nasal cavity[24], palatine tonsil[25], parapharyngeal space[26], larynx[27], humerus[28], submandibular salivary gland[29], conjuctiva[30], retroperitoneal space[31], cranial ventricles[32], and chest wall[33].

In our case a solitary neurofibroma was discovered in the descending colon in the form of a sessile polyp. The patient has no associated features of von Recklinghausen’s disease. The patient presented with lower gastrointestinal bleeding. In colonoscopy a segmental colitis was revealed, involving the splenic flexure and associated proximal part of the descending colon. Although a definite diagnosis of ischemic colitis cannot be made, there are many clues that support this explanation. The medical history of atherosclerotic disease including hypertension, ischemic heart attack, diabetes and hyperlipidemia (syndrome X), which justify the presence of predisposing factors for the development of vascular blood flow defects as a pathogenetic mechanism for ischemic attacks. The age of the patient is compatible with ischemia. The symptoms and physical findings are among those found in ischemic, perfusion-compromised bowel: sudden onset of pain in the lower
abdomen, passage of red blood with stools within 24 h and abdominal tenderness. The endoscopic findings of transient, segmental colitis located around the splenic flexure are a characteristic pattern in 11% of colonic ischemia. The histologic evaluation of the biopsy specimens revealed a nonspecific inflammatory process, which is mostly encountered in mild cases of ischemic colitis. The clinical course with remission of symptoms within 72 h and the reversal of mucosal damage after 8 wk correlates with the clinical presentation in these cases has included, among others, abdominal pain, distention, and pyrexia. Endoscopy has revealed erythema, friability and ulcers and the histologic examination included an eosinophilic infiltrate and crypt abscesses. Many of the above symptoms and signs also exist in our case and therefore aspirin colitis may also be an explanation for our findings.

Aspirin, which is a drug implicated in the induction of inflammatory colitis, might have attributed to the patient’s symptoms. In a recent review, 5 cases of inflammatory colitis have been attributed to hypersensitivity reactions caused by salicylates. In a recent review, 5 cases of inflammatory colitis appear at a site distal to the colitis. The clinical course with remission of symptoms within 72 h and the reversal of mucosal damage after 8 wk correlates with the histologic examination included an eosinophilic infiltrate and crypt abscesses. Many of the above symptoms and signs also exist in our case and therefore aspirin colitis may also be an explanation for our findings.

REFERENCES
1 Reynolds RM, Browning GG, Navorz I, Campbell IW. Von Recklinghausen’s neurofibromatosis: neurofibromatosis type 1. Lancet 2003; 361: 1552-1554.

2 Bononi M, De Cesare A, Stella MC, Fiori E, Galati G, Atella F, Angelini M, Cimian A, Lemos A, Cangemi V. Isolated intestinal neurofibromatosis of colon. Single case report and review of the literature. Dig Liver Dis 2000; 32: 737-742.

3 Friedman JM, Arbiser J, Epstein JA, Gutmann DH, Huot SJ, Lin AE, McManus B, Korf BR. Cardiovascular disease in neurofibromatosis 1: report of the NF1 Cardiovascular Task Force. Genet Med 2002; 4: 105-111.

4 Hirsch NP, Murphy A, Radcliffe JJ. Neurofibromatosis: clinical presentations and anaesthetic implications. Br J Anaesth 2001; 86: 555-564.

5 Pinski J, Dukhno O, Ovnat A, Levy I. Gastrointestinal complications of von Recklinghausen’s disease: two case reports and a review of the literature. Scand J Gastroenterol 2003; 38: 1275-1278.

6 Magro G, Piana M, Venti C, Lacagnina A, Ruggieri M. Solitary neurofibroma of the mesentery: report of a case and review of the literature. Pathol Res Pract 2000; 196: 713-718.

7 Kim HR, Yiju Y. Neurofibromatosis of the colon and rectum combined with other manifestations of von Recklinghausen’s disease: report of a case. Dis Colon Rectum 1998; 41: 1187-1192.

8 Gogus S, Sarikayalar F, Akkoren Z, Yalnizoglu D, Hisczewicz A. Intestinal involvement and vasculopathy in von Recklinghausen’s neurofibromatosis. Turk J Pediatr 1997; 39: 117-122.

9 Jacob S, Prabhakar BR, Singh SK, Mammen KJ. Neurofibromatosis of the colon: an unusual manifestation of von Recklinghausen’s diseases—a case report. Indian J Pathol Microbiol 1998; 41: 113-116.

10 Giuly JA, Picard R, Giuly D, Monges B, Nguyen-Cat R. Von Recklinghausen disease and gastrointestinal stromal tumors. Am J Surg 2003; 185: 86-87.

11 Abramson LP, Orkin BA, Schwartz AM. Isolated colonic neurofibroma manifested by massive lower gastrointestinal bleeding and intussusception. South Med J 1997; 90: 952-954.

12 Barri A, Bayle JJ, Boucheron S, Dano P, Meley J. Colonic localization of pseudopolypoid type disclosing Recklinghausen’s neurofibromatosis. Semin Hop 1982; 58: 2665-2668.

13 Grouls V, Vaith S, Bindewald H. Involvement of the large intestine in neurofibromatosis type 1. Pathologie 1996; 17: 133-138.

14 Finkel M, Finkel ER, Harris AI. Von Recklinghausen’s disease with involvement of the colon: an endoscopic view. Mt Sinai J Med 1978; 45: 387-389.

15 Becheur H, Marteau P, Lavergne-Slove A, Bouhnik Y, Attar A, Rambaud JC. Isolated and spontaneously regressive colonic neurofibromatosis. Gastroenterol Clin Biol 1995; 19: 718-720.

16 Watanuki F, Ohwada S, Hosomura Y, Okamura S, Kawashima Y, Tanahashi Y, Nakamura S, Iino Y, Jhoshita T, Morishita Y. Small ileal neurofibroma causing intussusception in a non-neurofibromatosis patient. J Gastroenterol 1995; 30: 113-116.

17 Frick EJ Jr, Lapos L, Vargas HD. Solitary neurofibroma of the anal canal: report of two cases. Dis Colon Rectum 2000; 43: 109-112.

18 Saitoh K, Nasu M, Kamiyama R, Hatakeyama S, Maruyama M, Tsuruta K, Takeshita K. Solitary neurofibroma of the esophagus. Acta Pathol Jpn 1985; 35: 527-531.

19 Sinha R, Paul R, Sen I, Siddar B. A solitary huge neurofibroma of the soft palate. J Laryngol Otol 2002; 116: 637-638.

20 Acebo E, Fernandez FA, Val-Bernal JF. Solitary neurofibroma of the gallbladder. A case report and review of the literature. Gen Diag Pathol 1998; 143: 337-340.

21 Carbia S, Pagola J, Flaster N, Guida A, Jufe L, Gonzalez B, Caniparoli A. Isolated neurofibroma of the common bile duct. Medicina 1995; 55: 689-692.

22 Kostakopoulos A, Chorti M, Protogerou V, Kokkinou S. Solitary neurofibroma of kidney: clinical, histological and chromosomal appearance. Int Urol Nephrol 2003; 35: 11-13.

23 Milanthakis KN, Karamanolakis DK, Mpgdanos IM, Trihia-Spyrou El. Solitary neurofibroma of the spenticord. Urol Int 2004; 72: 271-274.

24 Hirao M, Gushiken T, Imokawa H, Kawai S, Inaba H, Tsukuda M. Solitary neurofibroma of the nasal cavity: resection with endoscopic surgery. J Laryngol Otol 2001; 115: 1012-1014.

25 Survald CJ, Salam MA, Rowe RC. A solitary neurofibroma of the palate tonsil. J Laryngol Otol 2002; 116: 1050-1052.

26 Wenke KA, Jeppson MC. Solitary neurofibroma of the parapharyngeal space. HNO 2004; 52: 443-446.

27 Puri R, Berry S, Srivastava G. Solitary neurofibroma of the larynx. Otolaryngol Head Neck Surg 1997; 117: 713-714.

28 Paksoy Y, Sahin M, Avunduk MC, Aksoy F, Odev K. Solitary juxtacortical neurofibroma of the humerus. Skeletal Radiol 2002; 31: 112-115.

29 Tsutsumi T, Oku T, Komatsuzaki A. Solitary pleixform neur-oibroma of the submandibular salivary gland. J Laryngol Otol 1996; 110: 1173-1175.

30 Kalina PH, Bartley GB, Campbell RJ, Buettner H. Isolated neurofibromas of the conjunctiva. Am J Ophthalmol 1991; 111: 694-698.

31 Ameur A, Lezrek M, Jira H, el Alami M, Beddouch A, Abbar M. Solitary giant retroperitoneal neurofibroma. Prog Urol 2002; 12: 465-468.

32 Kocak A, Cayli SR, Sarac K, Aydin NE. Infraventricular solitary fibrous tumor: an unusual tumor with radiological, ultrastructural, and immunohistochemical evaluation: case report. Neurosurgery 2004; 54: 213-216.

33 Kamyoshihara M, Hirai T, Kawashima O, Morishita Y. Primary solitary neurofibroma of the chest wall: report of a case resected with video-assisted thoracoscopic surgery. Kyobu Geka 1997; 50: 421-423.

34 Cappell MS, Colonic toxicity of administered drugs and chemicals. Am J Gastroenterol 2004; 99: 1175-1190.