□ Case Report □

Gastric neurofibroma in von Recklinghausen disease : a cause of upper gastrointestinal bleeding

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Neurofibromatosis type 1 (von Recklinghausen disease, NF1) involves the central and peripheral nervous systems as well as the skin, bone, endocrine, gastrointestinal and vascular systems. The gastrointestinal neurofibroma associated with NF1 has been infrequently reported. We report our experience with a 15-year-old boy who had a gastric plexiform neurofibroma with upper gastrointestinal bleeding and underwent a tumorectomy because of massive upper gastrointestinal bleeding. We conclude that gastrointestinal bleeding and anemia in the setting of NF1 mandates complete endoscopic examination of the digestive tract to rule out neurofibromas. Surgical resection is the standard treatment. **(Korean J Pediatr 2006;49:203-207)**

Key Words : Neurofibromatosis, Plexiform neurofibroma, Stomach, Gastrointestinal bleeding

Introduction

Von Recklinghausen disease (neurofibromatosis, NF1) is one of the most common neurogenetic diseases affecting children and adults, occurring in 1 per 3,500 to 4,000 individuals. NF1 is inherited in an autosomal dominant pattern with a spontaneous mutation rate, estimated to be as high as 50%. NF1 has variable manifestations and can involve the central and peripheral nervous system as well as the skin, bone, endocrine, gastrointestinal and vascular system[1, 2]. Diagnostic criteria for NF1 include : pigmentary lesions (cafe-au-lait macules, skin fold freckling and Lisch nodules), neurofibroma, optic pathway gliomas and bony dysplasias[3]. Gastrointestinal involvement has been described in about one-fourth of patients with multiple neurofibromatosis, whereas among patients with intestinal neurofibroma only 15% also have systemic NF1[4]. The gastrointestinal neurofibroma associated with NF1 has been infrequently reported[5-7]. Gastrointestinal bleeding associated with neurofibroma has never been reported in Korean children. We report a case of gastric neurofibroma with massive gastrointestinal bleeding and severe anemia.

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Case report

A 15-year-old man presented with a 1-week history of melena. He was diagnosed with von Recklinghausen disease because of multiple cafe-au-lait spots, ranging in size from 1 to 2 cm and Lisch nodules at birth as well as family history of NF1. At the age of 12 years, he complained of headache, vomiting and chest tightness and had been treated with antacid and fluid therapy with the presumption of gastric ulcer disease at a primary care clinic. He did not have a gastric endoscopy.

During that admission, oliguria was detected. He was diagnosed as having idiopathic chronic renal failure and he was started on hemodialysis. At that time, abdominal pain developed and he was suspected to have acute pancreatitis because of the additional findings of high amylase and lipase levels and low attenuation of peripancreatic fatty tissue on the abdominal CT scan. He recovered with fasting and conservative treatment. However, epigastric discomfort persisted and a gastric polyp without associated bleeding

was detected at esophagogastroduodenoscopy. He remained well since this episode. Ten days prior to admission, he had a cough and rhinorrhea and took over the counter medications. Seven days prior to admission, he was admitted for persisted melena of sudden onset.

The past medical history showed that he was born at home without perinatal problems. He goes to high school and is considered to have mild mental retardation. His mother and sister also have neurofibromatosis. His mother died of a traffic accident.

On admission the patient was pale. His body weight was 31.5 kg (<3 percentile), his height 148 cm (<3 percentile). His blood pressure was 122/76 mmHg, pulse rate 90/min, respiratory rate 20/min and body temperature 35.8 ℃. His conjunctivae were pale. His sclerae were not icteric. He had dry oral mucosa. He had a Perm-cath catheter in left external jugular vein. Breath sounds were clear, heart rate was regular without audible murmur. The abdomen was soft and flat. Bowel sounds were normoactive. There was neither tenderness nor rebound tenderness. Liver and spleen were not palpable. He had multiple cafe-au-lait spots over the trunk and extremities, ranging in size from 1 to 2 cm. The arteriovenous fistulas were observed in the bilateral radial arteries.

One month prior to admission, the hemoglobin level was 10.8 g/dL, the hematocrit 32.7%, the leukocyte count 5,510/mm^3, the platelet count 201,000/mm^3.

On admission the hemoglobin level was 4.0 g/dL, the hematocrit 12.9%, the leukocyte count 5,140/mm^3, the platelet count 219,000/mm^3. After a packed-red cell transfusion the hemoglobin level and the hematocrit were 9.2 g/dL and 29.2%. The direct and indirect Coombs' tests were negative. A peripheral blood smear showed normochromia, normocyte, anisocytosis and polychromasia. Laboratory investigations showed lactate dehydrogenase level (LDH) of 138 IU/L, serum iron level 82 μg/dL, total iron binding capacity (TIBC) 287 μg/dL, serum ferritin <3 ng/mL. The blood urea nitrogen (BUN) value was 11 mg/dL, the creatinine 2.9 mg/dL. All other blood investigations were within normal limits.

The patient subsequently underwent esophagogastroduodenoscopy to the third portion of duodenum. Normal esophagus was observed. A round-shaped polypoid mass with a broad base was noted at the greater curvature side of the lower body in the stomach. The surface of the mass was smooth and reddish (Fig. 1). The mass was suspected to be a submucosal lesion. A small amount of bleeding persisted. Multiple brownish macules were observed in the body of the stomach. There were multiple small nodules in the duodenum, suspected to be lymphoid follicles. The abdominal radiography showed non-specific findings. The barium study in the upper gastrointestinal series showed one polypoid mass with adjacent fold thickening in the greater curvature side of the lower body of the stomach. There was 3-4 cm sized, lobulated mass (Fig. 2). There

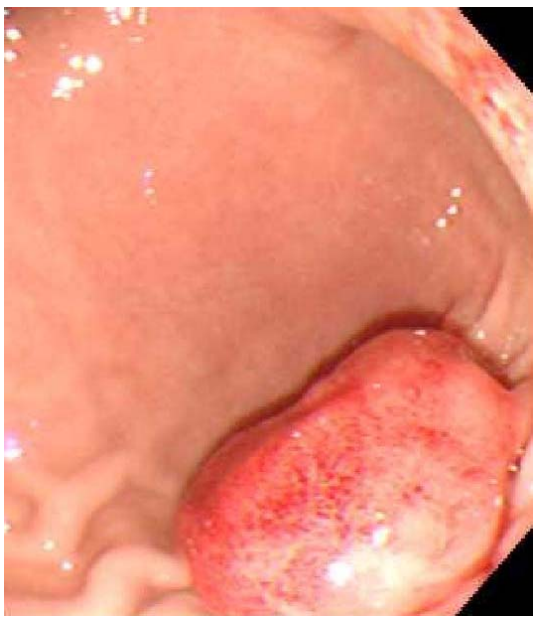

Fig. 1. Endoscopic findings show that a round-shaped polypoid mass with a broad base is noted at the greater curvature side of the lower body in the stomach.

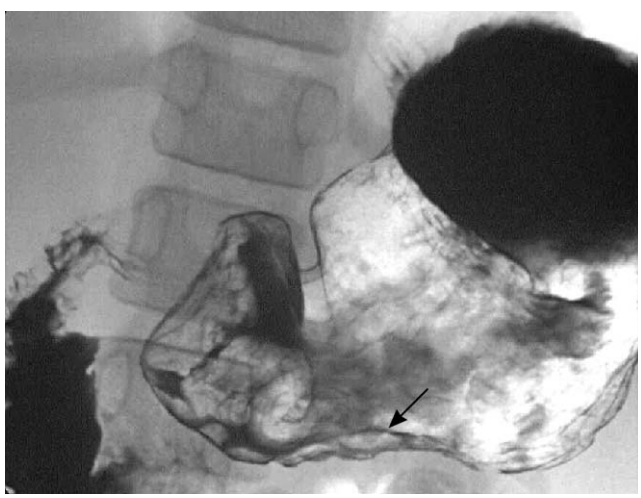

Fig. 2. The barium study shows one polypoid mass with adjacent fold thickening in the greater curvature side of the lower body in the stomach.

was no mass like lesion in the small bowel series. Ultrasonography of the abdomen showed no remarkable finding except bilateral small kidneys. The brain computed tomography was normal. His melena persisted after medical treatment. The patient emergently underwent esophagogastroduodenoscopy but the endoscopic removal of the bleeding mass was impossible. The patient was referred for surgical consultation and he underwent a tumorectomy. The pathologic specimen showed two masses; a 3×1.2×1 cm ash-colored, firm, lobulated, well capsulated mass and a 2×0.5×0.5 cm submucosal mass in the body of the stomach (Fig. 3). Microscopically these tumors consisted of interlacing strands of fusiform cells. These findings of the polyps were compatible with the diagnosis of a plexiform neurofibroma (Fig. 4A, 4B). The postoperative course was uneventful and the patient was discharged after 6 days. Two years later he remains well without anemia, hematemesis or melena. He is followed in the outpatient department with no evidence of gastrointestinal bleeding on stool samples for occult blood.

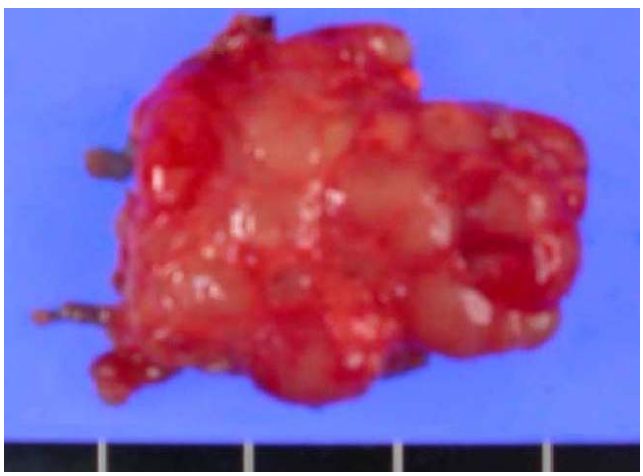

Fig. 3. Gross pathologic findings show multiple, lobulated and capsulated polyps (3×1.2×1 cm) and submucosal nodules.

Discussion

Neurofibromas are benign peripheral nerve sheath tumors characterized by unpredictable patterns of growth, variable cellular composition and diverse appearance. Patients with NF1 will develop neurofibromas at some time during their lives[1, 8, 9]. Such lesions may be present at birth.

Clinically, neurofibromas may present as discrete tumors (dermal neurofibromas), diffuse tumors, plexiform neurofibromas, or tumors associated with spinal nerve sheaths (spinal neurofibromas).

Neurofibromas are composed of neoplastic Schwann cells, perineural-like cells and fibroblasts in a matrix of collagen fibers and mucosubstances[10]. Growth of neurofibromas is initially along the course of nerve fibers. If the tumor arises from a relatively large nerve, it may be enclosed by the thickened epineurium and be confined to the nerve. Tumors arising from small nerves may spread diffusely into the dermis and soft tissue. Plexiform neurofibromas involve multiple nerves or fascicles and are expanded by tumor cells and collagen.

Solitary plexiform neurofiromas may occur in patients without other stigmata of NF1. In a recent review, 8 of 124 patients with plexiform neurofibromas had no other evidence of NF1[10]. The pathogenesis of such lesions is unclear, but they may result form mosaicism of the NFI or a related gene.

Neurofibromas can develop throughout the digestive

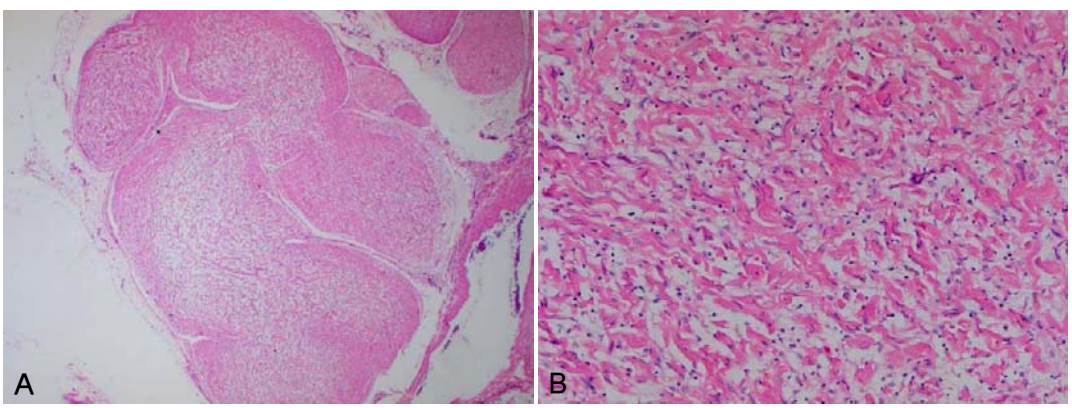

Fig. 4A, 4B. Histopathologic finding of the polyp is compatible with the diagnosis of plexiform neurofibroma (H&E stain, ×100 & ×400).

tract, but are mainly found in the proximal part. Bleeding associated with these neurofibromas, caused by ulceration of the mucosa, is important complication as it can produce gross intestinal hemorrhage and/or melena[11, 12]. Other reported complications are obstruction, abdominal pain and perforation[13].

Benign tumors of the stomach are relatively rare; they account for less than 2% of all gastric neoplasms. Neurogenic tumors consist of two subtypes : Schwannomas and neurofibromas. Schwannomas are usually encapsulated, are almost always solitary, and generally exist without generalized neurofibromatosis. Schwannomas are seen much more commonly than neurofibromas.

NF1 is characterized by abnormal pigmentation (cafe au lait spots) and multiple subcutaneous tumor nodules. These nodules may involve virtually any part of the body, including the skin, skeleton, retroperitoneum, central and peripheral nervous systems and even bone. Ghrist et al[14]. conducted 27,149 autopsies and 12 patients satisfied the criteria for NF1. Only three of these patients had gastrointestinal involvement as well.

Neurogenic tumors and particularly, neurofibromas make up a small percentage of gastric neoplasms. Palmer's classic study[15] of 4,806 gastric neoplasms obtained form autopsy studies revealed only five neurogenic tumors. But Brasfield and Das Gupta[16] reported that approximately 11% of patients with NF1 had neurofibromas in some area of the digestive tract. Therefore, if the patients with NF1 develop gastrointestinal symptoms and signs, gastrointestinal involvement of neurofibroma should be suspected. The usual presenting sign is anemia in these generally healthy patients. An upper gastrointestinal series is helpful but not diagnostic. Bruneton et al.[17] reported that in their series, barium contrast studies diagnosed 10/16 benign gastric tumors of unknown histology. Accordingly, the esophagogastroduodenoscopic exam is needed for the diagnosis of gastrointestinal neurofibromas.

The removal of the neurofibroma is required to prevent recurrence of tumor and to preclude malignant degeneration. Actually, in von Recklinghausen's original report, there was a case of sarcoma that occurred in a presumed neurofibroma. The rate of malignant degeneration is not known but is estimated to be approximately 13%[18]. Unfortunately, conventional endoscopic polypectomy does not allow removal of full-thickness biopsy specimens. For this reason, gastrointestinal dysfunction, particularly anemia, in the setting of NF1 mandates complete radiologic evaluation of the digestive tract to rule out neurofibromas and surgical resection may be considered.

한 글 요 약

Von Recklinghausen disease병 환아에서 상부위장관 출혈로 발현한 위의 신경섬유종 1례

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위장관계의 신경섬유종의 발생빈도는 드물다고 알려져 있다. 저자들은 제1형 신경섬유종증의 15세 남자 환아에서 상부위장관 출혈로 발현한 위에 생기는 신경섬유종을 내시경 및 상부위장관 조영술을 통해 진단을 내리고, 수술적 제거를 시행하였던 1례를 경험하였기에 문헌 고찰과 함께 보고하는 바이다.

References

1) Friedman JM, Gutmann DH, MacCollin M, Riccardi VM. Neurofibromatosis : phenotype, natural history and pathogenesis. 3rd ed. Baltimore : Johns Hopkins University Press, 1999.
2) Huson SM, Harper PS, Compston DAS. Von Recklinghausen neurofibromatosis : a clinical and population study in Southest Wales. Brain 1988;111:1355-81.
3) Packer RJ, Gutmannn DH, Rubenstein A, Viskochil D, Zimmerman RA, Vezina G, et al. Plexiform neurofibromas in NF1; toward biologic-based therapy. Neurology 2002;58: 1461-70.
4) Davis GB, Berk RN. Intestinal neurofibromas in von Recklinghausen's disease. Am J Gastroenterol 1973;60:410-4.
5) Devereux RB, Koblenz LW, Cipriano P, Gray GF. Gastrointestinal hemorrhage : an unusual manifestation of neurofibromatosis. Am J Med 1975;58:135-8.
6) Frank DJ, Majid N, England D. Massive gastrointestinal beeding in a patient with von Recklinghausen's disease : case report. Milit Med 1981;146:438-9.
7) Hochberg FH, Dasilva AB, Galdabini J. Gastrointestinal involvement in von Recklinghausen's neurofibromatosis. Neurology 1974;24:1144-51.
8) Korf BR. Plexiform neurofibromas. Am J Med Genet 1999; 89:31-7.
9) Ruggieri M, Huson S. The clinical and diagnostic implications of mosaicism in the neurofibromatosis. Neurology 2001;56:1433-43.
10) Woodruff JM, Lourea HP, Louis DN, Scheitauer BW. Neurofibroma. In : Kleihues P, Cavenee WK, eds. World Health Organization classification of tumours, pathology and ge-

netics of tumors of the nervous system. Lyon : IARC Press, 2000:167-8.
11) Lawson FE, Latimer EO. Neurofibromatosis (von Recklinghausen's disease) and bleeding from the gastrointestinal tract. Int Surg 1971;55:243-9.
12) Hochberg FH, Dasilva AB, Galdabini J. Gastrointestinal involvement in von Recklinghausens' neurofibromatosis. Neurology 1974;24:1144-51.
13) Warshauwer FN, Nelson RE. Neurofibroma of jejunum with perforation : a case report. Am Surg 1953;19:467-72.
14) Ghrist TD. Gastrointestinal involvement in neurofibromatosis. Arch Intern Med 1963;112:111-6.
15) Palmer ED. Stomach tumors. Medicine 1951;30:116-35.
16) Brasfield RD, Das Gupta TK. Von Recklinghausen's disease : a clinicopathologic study. Ann Surg 1972;175:86-104.
17) Bruneton JN, Drouillard J, Roux P. Neurogenic tumors of the stomach. Fortschr Rontgenol 1983;139:192-8.
18) Ransom HK, Kay EB. Neurogenic tumors of the stomach. Ann Surg 1940;112:700-41.