

Multiple Small Intestinal Stromal Tumors Associated with Neurofibromatosis-1

Mee Joo¹, Hye Kyung Lee², Hanseong Kim¹, Min Kyung Kim¹, and Je G. Chi¹

Department of Pathology, ¹Ilsanpaik Hospital and ²Seoul Paik Hospital, Inje University College of Medicine, Seoul, Korea.

Gastrointestinal stromal tumors (GISTs) are rarely noted in association with neurofibromatosis-1 (NF-1, von Recklinghausen disease) as an individual gastrointestinal manifestation. We report here a case of multiple GISTs with an abundant skeinoid fiber in the jejunum of a 43-year-old woman diagnosed as NF-1. Histologically, the tumors were composed of uniform spindle-shaped cells with a fascicular pattern, almost indistinguishable from the histology characteristic of usual GISTs. However, multiple synchronous tumor occurrence, abundant skeinoid fiber, and presence of microscopic miniatures of stromal tumors are additional characteristic features of this case.

Key Words: Gastrointestinal stromal tumor (GIST), Neurofibromatosis 1 (von Recklinghausen disease), multiple.

INTRODUCTION

Gastrointestinal manifestations of neurofibromatosis-1 (NF-1) can be divided into four main groups: neuronal dysplasia; gastrointestinal stromal tumors (GISTs); endocrine cell tumors of the duodenum and periampullary region; and a miscellaneous group of other tumors.^{1,2} GIST is referred as the majority of all gastrointestinal mesenchymal tumors, excluding tumors showing a definite differentiation toward the smooth muscle or schwann cells.³ The majority of GISTs are isolated neoplasm and they are sporadically noted in non-NF-1 individuals without histological features that can help reliably distinguish NF-1-associated cases from sporadic cases. However,

previous reports pointed out that tumors associated with NF-1 frequently showed multiplicity, jejunal location, and abundant skeinoid fibers.^{4,5} Here, we report a case of multiple small intestinal stromal tumors with abundant skeinoid fibers and spindle cell hyperplasia of the myenteric plexus, presenting like miniatures of stromal tumors, in the jejunum of a 43-year-old woman diagnosed as NF-1.

CASE REPORT

Clinical summary

A 43-year-old woman, who had no family history of NF-1, was admitted with abdominal pain and unexplained anemia. The physical examination revealed numerous café-au-lait patches and multiple cutaneous neurofibromas on the upper extremities and trunk. Esophagogastroduodenoscopy showed mild erosive gastritis, and the small bowel study showed an intraluminal protruding mass in the jejunum (Fig. 1). The abdominal exploration revealed multiple solid nodules in the jejunum, located from 30 cm to 75 cm distally from the Treitz ligament, and the segmental resection of the jejunum was performed.

Pathological findings

The resected segment of the small intestine showed nine subserosal solid masses (Fig. 2 and 3). The largest mass measured 3 × 2.5 × 2 cm, showing a short stalk and hemorrhagic appearance. The second in size mass had a dumbbell shape, with a diffuse mucosal ulceration. The remaining

Received August 20, 2003
Accepted December 1, 2003

Reprint address: requests to Dr. Mee Joo, Department of Pathology, Ilsanpaik Hospital, Inje University, 2240 Daelwa-dong, Ilsan-gu, Koyang-city, Kyeong-gi 411-706, Korea. Tel: 82-31-910-7141, Fax: 82-31-910-7139, E-mail: meeah@hitel.net



Fig. 1. Radiograph of the small bowel examination showing an intraluminal protruding mass in the jejunum.



Fig. 2. The resected segment of the small intestine shows multiple, mainly subserosal, solid masses, measuring up to $3 \times 2.5 \times 2$ cm.

seven tumors were small in size, and ranged from 4 to 10 mm. Histologically, the tumors were composed of interlacing fascicles of the uniform spindle cells with elongated cytoplasm (Fig. 4). The tumor cells lacked pleomorphism, and mitotic figures were extremely rare. The results of the immunohistochemical stainings revealed that the tumor cells were diffusely positive for CD117, CD34, neuron specific enolase (NSE), and vimentin; and negative for smooth muscle actin, S100 protein, and desmin. Prominent skeinoid fibers, which were amorphous and eosinophilic materials

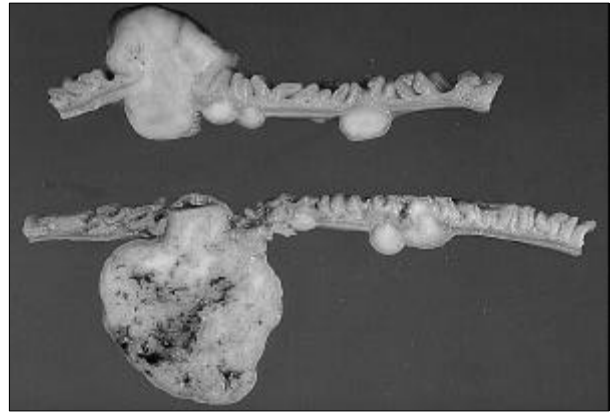


Fig. 3. Cut sections show multiple stromal tumors either protruding to the serosa or having a 'dumbbell' appearance. The largest one has a lobulated appearance and diffuse hemorrhage.

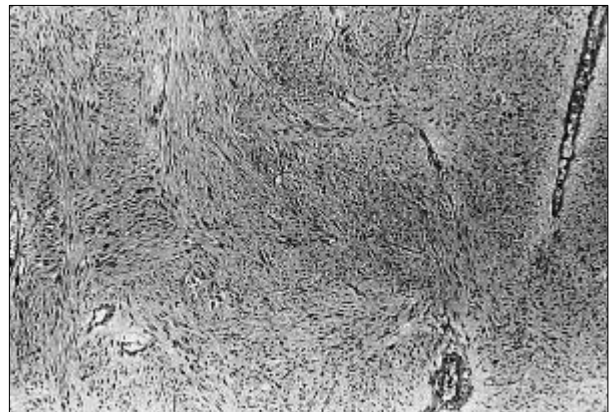


Fig. 4. Histologically, the tumors were composed of interlacing fascicles of uniform spindle cells with eosinophilic elongated cytoplasm.

in Hematoxylin-Eosin stain and positively stained with Periodic Acid Schiff (PAS) stain, were noted in the tumorous stroma (Fig. 5). Some of the tumors were directly continuous to the adjacent hyperplastic myenteric plexuses, and nodular proliferations of the spindle cells, like miniatures of the stromal tumors, were also noted in the region of the myenteric plexus (Fig. 6), and showed the same immunoreactivity patterns as the main tumors (Fig. 7).

DISCUSSION

Neurofibromatosis type-1 (von Recklinghausen

disease) is an autosomal dominant hereditary disease that may affect the gastrointestinal tract in up to 25% of the patients.^{2,6,7} Stromal tumors have been reported to be the most common lesion of the gastrointestinal tract, but the symptomatic cases account for less than 5% of patients.^{1,2} These tumors may cause obstruction, volvulus, intussusception, ulceration, bleeding or perforation. In our patient, the presumable cause of anemia was the overlying mucosal ulceration and bleeding of the tumor.

GISTs also occur sporadically in non-NF-1 individuals, and there is no histological difference

between the NF-1-associated cases and the sporadic cases. However, tumors associated with NF-1 frequently show multiplicity, jejunal location, and abundant skeinoid fibers.^{4,5,8} We found nine cases of GISTs with abundant skeinoid fibers in patients with NF-1 in the literature in English,^{4,5,8-11} and all of these tumors were noted in the small intestine, predominantly in the jejunum (8 of 9 cases). Five of the nine cases were multiple; the number of tumors in each case was 2, 4, 7, over 50, and about 100, respectively.^{4,5,8} Our case seems to be a typical presentation of NF-1 associated GISTs, demonstrating the entire

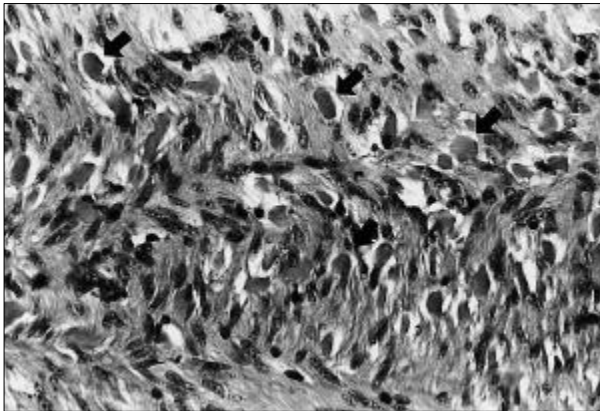


Fig. 5. Prominent skeinoid fibers were noted in the tumorous stroma.

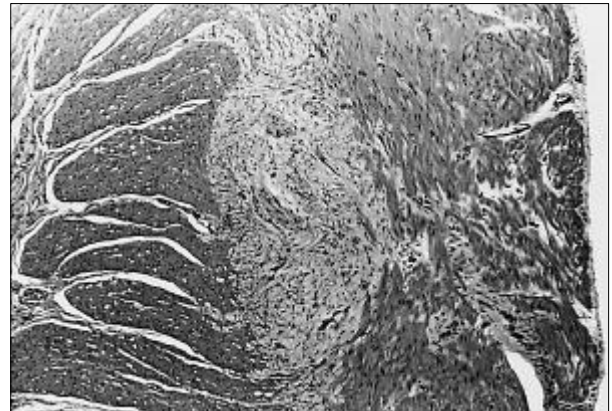


Fig. 6. A minute nodular proliferation of the spindle cells is noted between the inner circular and outer longitudinal muscle layers of the macroscopically normal intestinal wall.

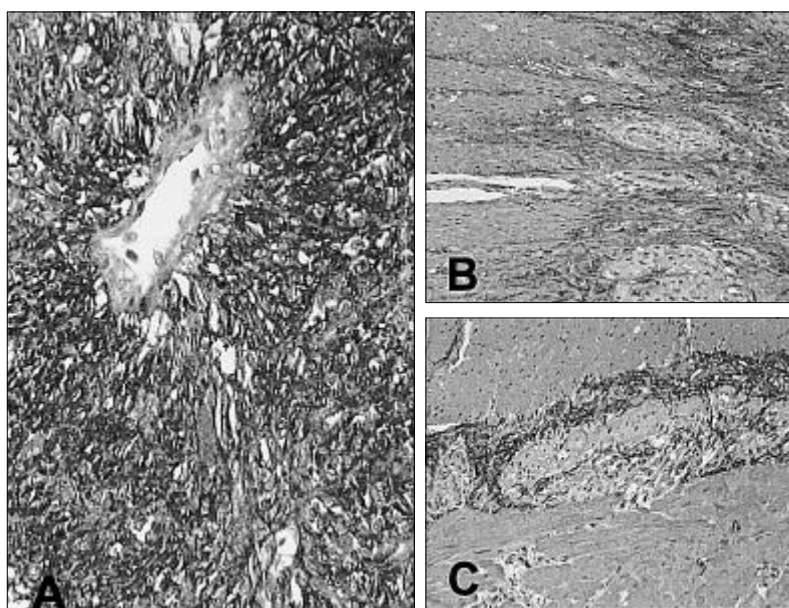


Fig. 7. Immunohistochemistry showing strong and diffuse CD117 positivity in neoplastic cells (A), and proliferative spindle cells within hyperplastic myenteric plexus (B & C).

spectrum of features mentioned in previous reports.

Up to the present time, 6 gastrointestinal tumors associated with NF-1 have been reported in Korean literature: two types of synchronous biliary tract cancers in a patient with solitary, incidentally found jejunal stromal tumors¹²; one case of cholangiocarcinoma¹³; and one case of metachronous tumors (breast cancer, small bowel sarcoma) in the same patient.¹⁴ The features of one out of the two cases reported by Park et al.¹⁵ were very similar to those noted in the present case: multiple stromal tumors were present in the small intestine, the largest one measured 11 cm and the remaining about 0.5 cm. They described these tumors as neurofibromas arising in the Auerbach's myenteric plexus; however, no additional immunohistochemical or ultrastructural data was presented.

In this case, some of tumors were continuous to hyperplastic myenteric plexus, and nodular proliferations of the spindle cells, like miniatures of the stromal tumors, were noted in the region of the myenteric plexus, apart from the main masses. Walsh et al.⁸ previously reported such lesions and suggested a possible explanation that the Auerbach's myenteric plexus may be the site of the origin for GISTs in NF-1. The miniatures of the stromal tumors noted in this case can be an additional evidence of this suggestion. However, Handra-Luca et al.¹⁶ reported similar findings in their case of multiple familial gastrointestinal stromal tumors. Thus, such findings might help to understand the histogenesis of multiple GISTs, though they are not limited to the cases associated with NF-1.

REFERENCES

1. Riccardi VM. Neurofibromatosis: phenotype, natural History, and pathogenesis. 2nd ed. New York: Johns Hopkins; 1992.
2. Fuller CE, Williams GT. Gastrointestinal manifestations of type 1 neurofibromatosis (von Recklinghausen's disease). *Histopathology* 1991;19:1-11.
3. Hamilton SR, Aaltonen LA. World Health Organization Classification of Tumours: pathology and genetics of tumours of the digestive system. Lyon: IARC Press; 2000. p.62.
4. Ishida T, Wada I, Horiuchi H, Oka T, Machinami R. Multiple small intestinal stromal tumors with skeinoid fibers in association with neurofibromatosis 1 (von Recklinghausen's disease). *Pathol Int* 1996;46:689-95.
5. Boldorini R, Tosoni A, Leutner M, Ribaldone R, Surico N, Comello E, et al. Multiple small intestinal stromal tumours in a patient with previously unrecognised neurofibromatosis type 1: immunohistochemical and ultrastructural evaluation. *Pathology* 2001;33:390-5.
6. Davis GB, Berk RN. Intestinal neurofibromas in von Recklinghausen's disease. *Am J Gastroenterol* 1973; 60: 410-4.
7. Hochberg FH, Dasilva AB, Galdabini J, Richardson EP Jr. Gastrointestinal involvement in von Recklinghausen's neurofibromatosis. *Neurology* 1974;24:1144-51.
8. Walsh NM, Bodurtha A. Auerbach's myenteric plexus: A possible site of origin for gastrointestinal stromal tumors in von Recklinghausen's neurofibromatosis. *Arch Pathol Lab Med* 1990;114:522-5.
9. McDonnell L. Skeinoid fibers (letter). *Am J Surg Pathol* 1993;17:954-6.
10. Schaldenbrand JD, Appelman HD. Solitary solid stromal gastrointestinal tumors in von Recklinghausen's disease with minimal smooth muscle differentiation. *Hum Pathol* 1984;15:229-32.
11. Min KW, Balaton AJ. Small intestinal stromal tumors with skeinoid fibers in neurofibromatosis: Report of four cases with ultrastructural study of skeinoid fibers from paraffin blocks. *Ultrastruct Pathol* 1993;17:307-14.
12. Sohn TS, Kim YI, Lee JR, Noh JH, Choi SH, Lee BB, et al. Synchronous Biliary Tract Cancers in a Patient with von Recklinghausen Disease. *J Korean Surg Soc* 1998;54:587-94.
13. Kim YA, Lee EW, Kim DH, Kang DG, Park H, Kang MW, et al. A case of cholangiocarcinoma associated with neurofibromatosis type 1. *Korean J Med* 2000;59:463-6.
14. Kim BG, Kim JJ, Cho JS, Park UC. Malignant Metachronous Cancers (Breast Cancer, Small Bowel Leiomyosarcoma) Associated with Von Recklinghausen Disease (NF-1). *J Korean Surg Soc*. 1999;56:300-5.
15. Park MJ, Kim HY, Won NH, Kim IS, Lee KN, Paik SY. Gastrointestinal tumors associated with von Recklinghausen's neurofibromatosis. *Korean J Pathol* 1985;19: 345-9.
16. Handra-Luca A, Flejou JF, Molas G, Sauvanet A, Belghiti J, Degott C, et al. Familial multiple gastrointestinal stromal tumours with associated abnormalities of the myenteric plexus layer and skeinoid fibres. *Histopathology* 2001;39:359-63.