Duodenal Gastrointestinal Stromal Tumor Treated by Wedge Resection in a Patient with Neurofibromatosis Type 1: Report of a Case and Review of the Japanese Literature

Hideya Takeuchi^{a, c} Toshihumi Matsumoto^{a, c}

Tetsuya Kusumoto^{a, c} Yasuji Yoshikawa^{b, c} Yoichi Muto^{a, c}

^aDepartment of Surgery, ^bDepartment of Pathology and ^cClinical Research Institute, National Hospital Organization Beppu Medical Center, Beppu, Japan

Key Words

Gastrointestinal stromal tumor · Neurofibromatosis type 1 · Wedge resection

Abstract

A case of duodenal gastrointestinal stromal tumor (GIST) treated by wedge resection in a patient with neurofibromatosis type 1 (NF-1) is reported. A 55-year-old man with a history of NF-1 was admitted for surgery for a duodenal tumor. Upper gastrointestinal endoscopy revealed a 2.5 cm duodenal submucosal tumor. Abdominal computed tomography showed a homogeneously enhanced mass in the third portion of the duodenum. The patient successfully underwent wedge resection of the duodenal tumor. Histological examination revealed proliferation of spindle tumor cells arranged in a bundle pattern. This tumor was immunohistochemically positive for c-Kit and CD34, and negative for S-100 and α -SMA. A mitotic count showed 3 mitoses per 50 high-power fields. The tumor was diagnosed as a low-risk GIST. The patient's postoperative course was uneventful. GIST in a patient with NF-1 is rare, only 27 cases being reported in the Japanese literature.

Introduction

Neurofibromatosis type 1 (NF-1), also called von Recklinghausen's disease, is the most common autosomal dominant disorder with a prevalence of approximately 1 in 3,000 individuals. NF-1 is associated with a variety of benign and malignant neoplasms [1].

Malignant tumors have been reported four times as often in NF-1 patients as in the general population. A gastrointestinal abnormality is reported to occur in up to 10–20% of NF-1 patients [2].

Although gastrointestinal stromal tumor (GIST), arising from Cajal's cells and expressing c-Kit, is the most common gastrointestinal mesenchymal tumor, the occurrence of GIST in patients with NF-1 is rare. A case of GIST in a NF-1 patient is reported, and the Japanese literatures is reviewed to elucidate its clinicopathological characteristics.

Case Report

A 55-year-old man with a history of NF-1 at the age of 20 years had been followed for GIST in the duodenum at another hospital. His mother also suffered from NF-1. Since the GIST was found to have grown to 2.5 cm, he was admitted to our department for surgery. Physical examination revealed multiple cafe au lait spots and discrete cutaneous neurofibromas over the patient's body. Preoperative laboratory tests were normal. Upper gastrointestinal endoscopy revealed a submucosal tumor, covered with normal mucosa with a central depression in the third portion of the duodenum (fig. 1). Abdominal computed tomography showed a homogeneously enhanced mass in the duodenum and no evidence of metastases in the abdomen (fig. 2). The patient was successfully treated with wedge resection of the duodenal tumor. At laparotomy, no liver or lymph node metastases were found, and a submucosal tumor with a clear border was found in the duodenum about 7 cm above the ligament of Treitz. After the Kocher method had been performed, the tumor, with a 1 cm circumference of normal full-thickness duodenal mucosa, was extracted, and the duodenum was sutured using a two-layer method. The tumor, measuring 25 × 25 × 23 mm, was covered by a normal mucosa, and the cut surface was smooth and white in appearance. Histological examination revealed proliferation of spindle tumor cells arranged in a bundle pattern (fig. 3a). The mitotic count showed 3 mitoses per 50 high-power fields. Immunohistochemical stains were positive for c-Kit (fig. 3b) and CD34 (fig. 3c), and negative for S-100 and α-SMA. The tumor was diagnosed as a low-risk GIST. The postoperative course was uneventful, and the patient remains completely asymptomatic after 24 months.

Discussion

NF-1, which was first reported by von Recklinghausen in 1882, is characterized by abnormal skin pigmentation, cutaneous and plexiform neurofibromas, skeletal dysplasias, and Lisch nodules. NF-1 is caused by mutations of the NF-1 gene on chromosome 17, which encodes neurofibromin, a member of the GTPase-activating protein ras regulatory family [1].

GIST is the most common gastrointestinal mesenchymal tumor, accounting for 80% of these neoplasms. Patients' mean age ranges from 55 to 65 years, and there is a slight male predominance [3]. GIST is thought to increase by the activation of tyrosine kinase of the Kit receptor through mutation of the protooncogene c-Kit gene [4]. To the best of our knowledge, only 28 cases of GIST associated with NF-1 have been reported, and they are summarized in table 1 [5–12]. There were 14 males and 14 females (male/female ratio 1.0). Their median age was 56.0 years (range 22–74 years). According to the risk criteria of GIST [2], 7 were at high risk, 2 at intermediate risk, and 10 at very low/low risk. In 4 cases the tumor was found incidentally during unrelated surgery. 6 cases needed emergent surgery because of bleeding, perforation, or bowel obstruction. 4 cases had synchronous combined malignant disease. All cases developed in the small intestine, and most cases were multiple synchronous primary lesions, while GISTs in non-NF-1 patients occur as solitary lesions, most commonly in the stomach (60–70%), followed by the small intestine (20–30%) [3].

Recently, dramatic improvements have been achieved using imatinib mesylate (formerly STI571, Gleevec in the United States/Glivec in Europe) in cases of metastasis or recurrence of GIST [13]. Imatinib mesylate works by inhibiting active mutant c-Kit tyrosine kinase, which appears to play a central part in the pathogenesis of GIST. It is known that the likelihood of response to imatinib mesylate is strictly related to the c-Kit mutational pattern. However, Nemoto et al. [1] reported absence of c-Kit mutation in GIST in an NF-1 patient. These findings support the idea that different mechanisms underlie the tumorigenesis of GIST based on the neurofibromin gene disorder in NF-1 patients and non-NF-1 patients, and treatment of GIST and evaluation of the efficacy of imatinib mesylate should be distinguished between NF-1 and non-NF-1 patients [14]. GISTs without c-Kit mutations appear to respond less well than those with c-Kit mutations. Further examination of the utility of imatinib mesylate in a larger number of NF-1 patients with GIST is needed.

Since lymph node metastasis is very rare in cases with GIST, it is recognized that lymph node dissection is unnecessary, and full-thickness local excision is recommended [3]. Duodenal wedge resection to the duodenal GIST far from the ampulla is considered an appropriate surgical procedure in terms of morbidity and curability without any symptoms.

GIST in a patient with NF-1 is rare; the present case is the 28th reported case in the Japanese literature. Patients with NF-1, particularly those presenting with gastrointestinal symptoms, should be investigated for GIST. In NF-1 patients with GIST, further investigations of the entire body, especially the small intestine, are needed preoperatively and intraoperatively. Use of imatinib mesylate in this subset of patients with GIST may not be appropriate.

Table 1. Summary of 28 reported cases of GIST in patients with NF-1 in Japan

Characteristics	Number of patients
Sex	
Male	14 (50.0%)
Female	14 (50.0%)
Median age, years (range)	56.0 (22–74)
Primary site	
Small intestine	28 (100%)
Number of primary tumors	
Multiple	18 (64.3%)
Single	10 (36.7%)
Median tumor size, cm (range)	6.4 (1.2–25)
Risk stratification (n = 19)	
High	7 (36.8%)
Intermediate	2 (10.5%)
Very low/low	10 (52.7%)
Synchronous combined malignant disease (n = 4)	
Rectal carcinoma	2 (7.1%)
Duodenal carcinoma	2 (7.1%)
Reason for emergent operation (n = 6)	
Bleeding	3 (10.7%)
Perforation	2 (7.1%)
Bowel obstruction	1 (3.6%)
Incidental finding during unrelated surgery	4 (14.3%)

Fig. 1. Upper gastrointestinal endoscopy shows a submucosal tumor with an ulcer scar formed at the top in the duodenal third portion.

Fig. 2. Computed tomography image of the abdomen shows a homogenously enhanced mass in the duodenal second portion with no evidence of direct invasion of neighboring organs or liver metastases.

Fig. 3. Histological examination reveals tumors were composed of spindle cells arranged in a bundle pattern (**a**, $\times 400$), and the cells are immunohistochemically positive for c-Kit (**b**, $\times 400$) and CD34 (**c**, $\times 400$).

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