# Multiple Gastrointestinal Stromal Tumors and Their Association with Other Rare Tumors: Case Report

## Multipl Gastrointestinal Stromal Tümör ve Diğer Nadir Tümörler ile Birlikteliği

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**ABSTRACT** We identified four patients with multiple gastrointestinal stromal tumors (GIST) in small bowel. Three of the adult patients have neurofibromatosis type 1 (NF1) and one patient have neither NF1 nor any other familial disorder. Immunostains for CD117, CD34, desmin, actins, S-100 protein, and keratins were performed on all of the tumors. Patient's ages/genders were 65/F, 66/M, 36/M and 65/F. All of the patients had multiple GISTs in small bowel; at least three nodules at the size of average 3.0 cm (0.2 mm-12 cm). The first patient had incidental somatostatinoma in ampulla vatery at the same time, and the second one had synchronously adenomyoma in ampulla vatery and gastric adenocarcinoma metachronously, third one was found incidentally during his invagination operation and the fourth one had gastrointestinal stromal tumor metastasis in liver and had thyroid papillary carcinoma (TPC) twenty years before. GISTs may present with other rare tumors.

**Key Words:** Gastrointestinal stromal tumors; neoplasms, multiple primary; neurofibromatosis 1

**ÖZET** İnce barsak baskın Gastrointestinal stromal tümörleri (GİST) olan 4 erişkin hasta sunulmaktadır. Hastaların 3'ünde Nörofibromatozis Tip 1 (NF1) bulunmakta iken diğer hastada NF1 veya herhangi bir ailesel hastalık mevcut değildi. Tüm hastalara ait tümörlerde immunohistokimyasal olarak CD117, CD34, dezmin, aktin, S-100 protein ve keratin çalışıldı. Hastaların yaşları ve cinsiyetleri 65/K, 66/E, 36/E ve 65/K şeklindeydi. Multiple GİST hastalarımızın tümünde ince barsak yerleşimli çok sayıda ortalama 3.0 cm (0.2 mm-12 cm) çapta olmak üzere en az 3 nodül bulunmaktaydı. İlk hastamız aynı zamanda rastlantısal olarak ampulla vateri bölgesine yerleşmiş somatostatinomaya, ikinci hastamız yine ampulla vateride adenomyomaya ve farklı zamanda gastric adenokarsinomaya sahipti. Üçüncü hastamızda invaginasyon operasyonu sırasında tesadüfen multiple GİST tespit edildi. Aynı zamanda karaciğer metastazları da olan son hastamızın 20 yıl önce tiroid papiller karsinomu nedeni ile opere edildiği bulundu. Multiple GİST'lerin ve diğer nadir tümörlerin birlikteliği tartışıldı.

**Anahtar Kelimeler:** Gastrointestinal stromal tümör; neoplasm, multiple primer; nörofibromatozis Tip 1

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Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors that arise throughout the gastrointestinal tract and, rarely, in the mesentery or retroperitroneum. They are characterized by strong immunohistochemical staining for CD117 and most contain activating mutations in the KIT receptor thyrosine kinase, particularly at exons 9,11,13 and 17.[1,2] Approximately one-third of tumors that are wild type at the KIT gene harbor mutations in the juxtamembrane and thyrosine kinase domains of a related thyrosine kinase receptor, platelet-derived growth factor re-

ceptor-alpha (PDGFRA).[3] Although most of the GISTs patients have solitary lesion, especially in neurofibromatosis type 1 (NF1) patients may have multiple GISTs.[4]

NF1 is an autosomally inherited disorder occurring with an incidence of about 1 per 3000 births, equally involving males and females. Genetically it is caused by a mutation at the NF1 gene located on chromosome 17q11.2.[5] Its gene product-neurofibromin-acts as a tumor suppressor. Functionally neurofibromin reduces cell proliferation by accelerating the inactivation of the protooncogene p21-ras, which plays a cardinal role in mitogenic intracellular pathways.[6] Although genetic mutations have been described and the responsible gene product-neurofibromin- has been fully characterized, no frequently recurring mutation has been identified, and diagnosis is still based on established clinical criteria. The "classical triad" of symptoms is "café au lait" spots, cutaneous neurofibroma, and neoplasms of the peripheral or central nervous system. Malignancies are found in 3% to 15% of patients.[7] They usually occur in three principal forms: hyperplasia of submucosal or myenteric nerve plexus, GIST and periampullary neuroendocrine tumors, sometimes associated with pheochromocytoma.[6]

Familial GISTs have been observed in kindred's harboring germline mutations of either KIT or PDGFRA. Affected individuals may develop multiple GISTs, which are generally indolent but may behave aggressively.[8]

Kang et al emphasize the strong correlation between multifocal GISTs and specific settings such as familiar and type 1 neurofibromatosis-related GISTs and, by contrast, the rare occurrence of multiple sporadic GISTs not previously reported in the literature.[4]

The coincidence of a gastrointestinal stromal tumor (GIST) and a somatostatinoma in NF1 is described only four times in the literature.[9,10]

Numerous synchronous and asynchronous cases of GIST and other neoplasms have been reported. Associated malignancies (mostly carcinomas) were gastrointestinal/pancreatic in origin.[11] Most GISTs (16/18) represented benign or low-risk lesions (innocent bystanders) detected during evaluation for the known cancer, either during staging, intra-operatively or on follow-up (24). There was a tendency toward more common localization of a GIST in the small intestine in patients with other neoplasms than in patients with a GIST alone. Tumors with very low risk of aggressive behavior were more frequent in patients with a GIST accompanied by other neoplasms than in the other group.[11]

We report four adult patients with multiple GISTs in small bowel; the first one had incidental somatostatinoma in ampulla vatery at the same time and this case is the fifth case in the literature. The second one had gastric adenocarcinoma metachronously, third one was found incidentally during his invagination operation and the fourth one had gastrointestinal stromal tumor metastasis in omentum and liver and had thyroid papillary carcinoma twenty years before the diagnosis of GISTs.

## CASE REPORTS

The study group consisted of four patients with multiple GISTs: three of them with NF1 and one sporadic nature. (All the patients were prospectively identified from the Erciyes University Medical Faculty Department of Pathology during the time period of 2004-2008). Our patient who had multiple GISTs with NF1 has somatostatinoma, synchronous adenomyoma and asynchronous gastric adenocarcinoma.

All of the patients were treated with surgical resection at the time of diagnostic procedure. Clinical information regarding the patients' gender, age, medical history, presenting symptoms, and outcome was obtained from the patients' physicians, medical records, surgical pathology reports, and operative notes.

Our patients have multiple GIST nodules. All of them had more than two tumor nodules, and resected surgically, demonstrated histologic features characteristics of GISTs and stained strongly for CD117 and CD 34.

Hematoxylin and-eosin-stained slides from routinely processed (10% buffered formalin) paraffin-embedded tissue sections were available for review in all cases. İmmunostains for a panel of antibodies (Table 1) were utilized to evaluate the tumors and performed on 4 μm thick formalin fixed paraffin embedded tissue sections using the standard avidin-biotin complex technique. Sections of normal colon served as positive controls for vimentin, muscle actins, desmin, keratin, S-100 protein, CD34, and CD117.

**TABLE 1:** Antibodies and dilutions utilized in the evaluation of GISTs.

| Antibody | Dilution | Source | Antigen retrivel |
|---|---|---|---|
| Vimentin | 1:20 | Dako | Heat |
| CD117 | 1:40 | Dako | Heat |
| Smooth muscle actin | 1:100 | Dako | Heat |
| Desmin | 1:140 | Dako | Heat |
| S-100 | 1:1000 | Dako | Heat |
| CD34 | 1:20 | Dako | Heat |
| Keratin (AE 1.3) | 1:30 | Dako | Heat |

## CASE 1

The patient was 46-year-old woman with a history of NF1 who presented with back pain and jaundice. She had multiple cutaneous neurofibromas and pigmented macules. Her family members did not have NF1. Radiographic imaging revealed a 3 cm mass in the body of the pancreas and Whipple operation was performed (Figure 1). In operation: there were many (greater than 10) serosal and mural nodules in the small intestine, four of GISTs were resected and determined to be GISTs. Examination of Whipple operation material revealed a pancreatic endocrine neoplasm in periampullary region (somatostatinoma) at the same time (Figure 2). Immunohistochemistry confirmed somatostatinoma with expression of the ChromograninA, Synaptofizin and Somatostatin.

Based upon morphologic differences between the largest and smaller tumors in the small intestine, the lesions were interpreted to represent synchronous primary lesions rather than metastases. The patient is alive after 32 months after the operation and she doesn't have any symptom.

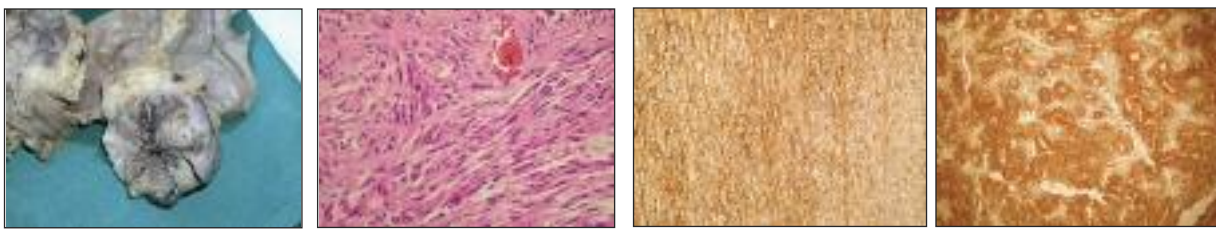

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**FIGURE 1: a.** Macroscopic appearance of large intestinal GIST that was involving the intestinal wall. **b.** Tumor consisted of spindle cells, HE, x400. **c, d.** The spindle cells showed cytoplasmic positive reactivity for CD 117 (c-kit) and CD34 on immunohistochemical examination.

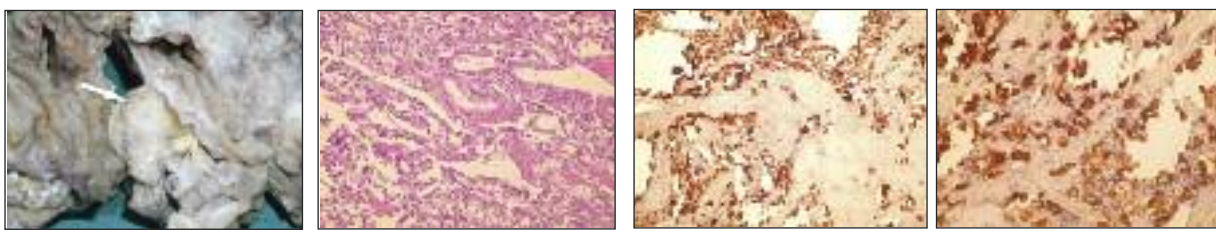

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**FIGURE 2: a.** A 0.8-cm tumor of the papilla of Vater as observed (arrow). **b.** The tumor was solid, and tumor cells densely proliferated in acinar form were observed from the papilla of Vater mucosa, HE, x200. **c.** The tumor cells stained uniformly for synaptofisin and somatostatin. Psammoma bodies were observed within the tumor cells.

## CASE 2

66-year-old man presented with abdominal pain and jaundice. Radiographic imaging revealed a 1 cm mass in the head of the pancreas and Whipple operation was performed. Examination of the operation material revealed that, the lesion was 0.5 cm in diameter and, was located in the ampulla region, diagnosed as adenomyoma. During the operation, innumerable subserosal nodules involving the small intestine was found, ranging from 0.3 to 3 cm in diameter and seven of them were resected and determined to be GISTs. During the surgical procedure four lymph nodes were dissected and were diagnosed as reactive lymph nodes.

Surprisingly after 8 months of his operation, a neurofibroma, which was located in his back is found and resected. The patient or his family members did not have any lesions of NF1.

Three years later, the patient was diagnosed as gastric adenocarcinoma; signet ring cell type and operated. Total gastrectomy specimen had five GISTs nodules (0.2-0.8 cm) and hiperplastic interstitial cell of Cajal (ICC) at the same time (Figure 3). After the operation, our patient died.

## CASE 3

The patient was 36-year-old man with a history of NF1 (Figure 4). He had severe abdominal pain and admitted emergency. He was operated and an invagination was seen in small intestine and his small intestine was resected. Examination of the surgical operation material revealed three lesions that were 0.3-3 cm in diameter and, the lesions were diagnosed as GISTs. He had multiple cutaneous neurofibromas and pigmented macules. His family members had no NF1.

## CASE 4

Sixty-five year-old woman presented with right upper quadrant pain, and a 20 pound weight loss. Radiographic imaging revealed 8 cm mass in small intestine and the patient was operated (Figure 5A). Examination of resected 105 cm length small intestine material revealed that 19 serosal nodules involving the small intestine, they were ranging from 0.2 to 8 cm in diameter (Figure 5B). Pathologic evaluation of the small intestinal tumors confirmed the diagnosis of multiple GISTs. Two months after resections of the GISTs, the patient developed multiple liver metastases from her GISTs. After 18 months, she was operated and diagnosed as GIST metastases to liver. This patient's first huge nodules in jejunum and adjacent five GISTs nodules were intermediate grade for aggressiveness and GIST nodule in liver had same characteristic future. But the rest of GISTs (7/19) nodules were very low risk.

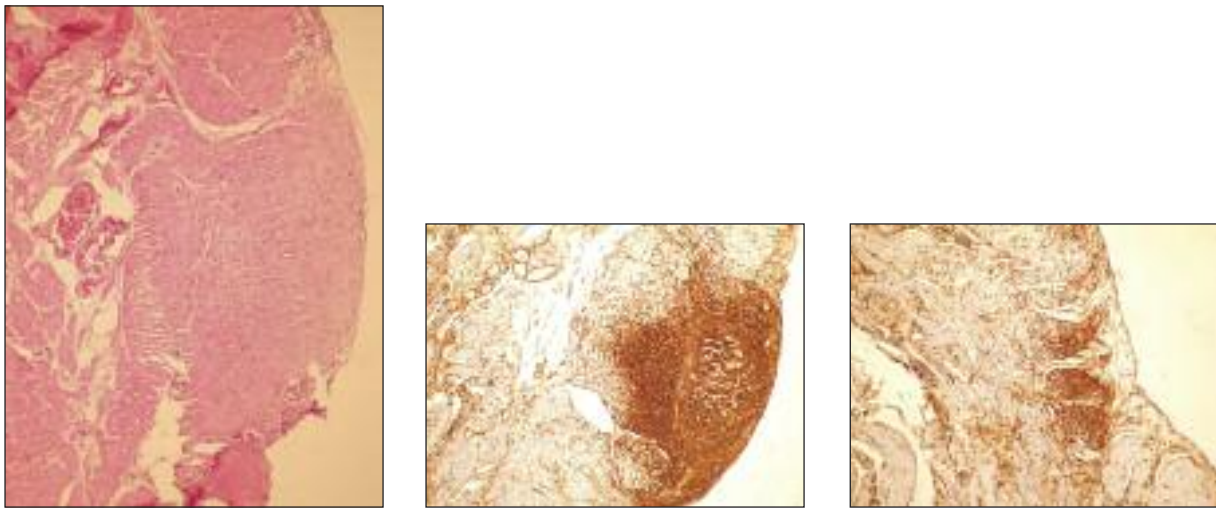


**FIGURE 3: a.** Small GISTs within the outer longitudinal layer of the muscularis propria and serosa of the stomach. **b, c.** Lesions strongly positive for CD34 **(b)** and also showing immunoreactivity for CD117 **(c).**

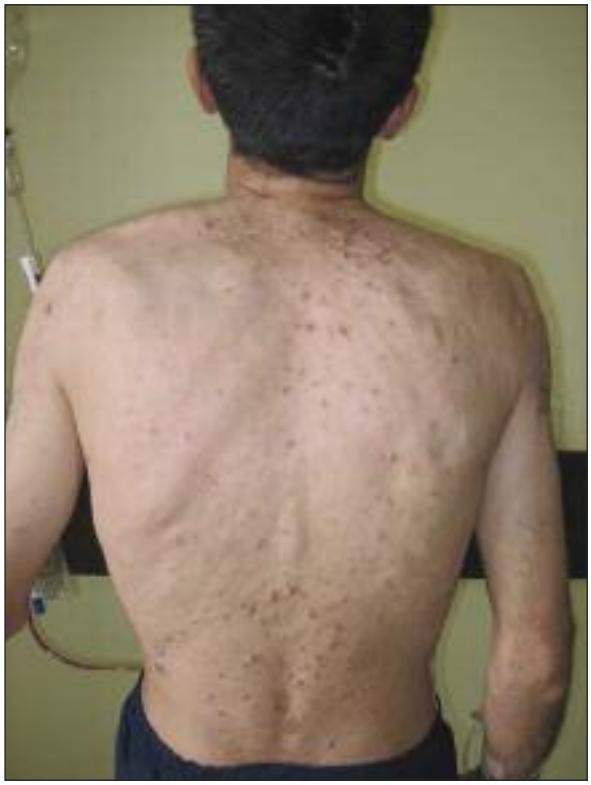


**FIGURE 4:** Cutaneous lesions in the NF1 patient (patient 3).

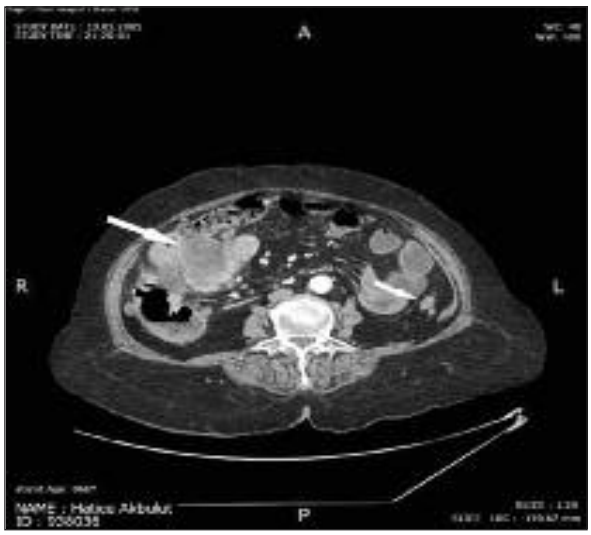
The patient was treated with imatinib 400 mg/day. The initial response to treatment continued for 20 months. Then a huge mass appeared in abdomen and extirpation was performed. This mass was recurrent GIST from liver. The patient's disease has been controlled with imatinib for 37 months.

Pathologic examinations were performed in each of the 39 GISTs. The nodul sizes were ranging between 0.2-8 cm. Tumor nodules were predominantly subserozal (33/39) (Table 2). The neoplastic cells were predominantly spindle shaped in 35 of 39 GISTs (89.7%), mixed cell type 2 GISTs (5.1%), and epithelioid cell type in 2 GISTs (5.1%). Mitotic figures were low <5/50 high-power fields (HPF) in 32 GISTs, and the others had high mitotic counts (5/50-25/50HPF). Although the cellular atypia and cellularity were minimal in most of the GISTs, especially prominent high mitotic count lesions in which, the size of these lesions were 0.3-8 cm diameters. The necrosis was present in six tumor nodules.

Pathologic risk of aggressive behavior included very low risk for 25 GISTs, low risk for 7 GISTs, intermediate risk for 5 GISTs, and high risk for one GIST. Immunohistochemically, CD117 and CD34 were diffusely positive in 100% of multiple GISTs. Smooth muscle actin (SMA), S-100 protein, and desmin were negative.

## DISCUSSION

An association between the development of multiple GISTs and type 1 neurofibromatosis has al-

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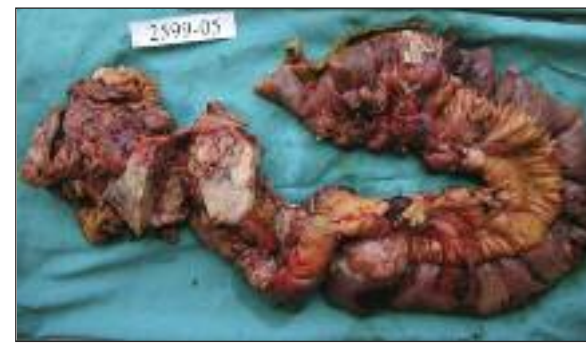

b

**FIGURE 5: a.** The contrast-enhanced computed tomography revealed multiple GISTs nodules (arrows). **b.** Photograph of opened resected small intestine shows innumerable gastrointestinal stromal tumors (arrows) extending through to serosal surface of ileum and jejunum.

**TABLE 2:** Multiple GIST patients clinicopathologic characteristics

| Cases | Resected GISTs (number) | Size (cm) | Localization | Other tumor | |
|---|---|---|---|---|---|
| 1 | NF1 | 4 | 0.6- 3 | Duedonum,ileum, jejenum | Somatostatinoma |
| 2a | NF1 | 7 | 0.2-3 | Duedonum,ileum | Adenomyoma |
| 2b | | 4 | | Stomach | Gastric adenocarcinoma |
| 3 | NF1 | 3 | 0.3-3.5 | Jejenum | - |
| 4 | | 19 | 0.2-8 | İleum, jejenum | Thyroid papillary carcinoma |

ready been established and many cases have multiple lesions predominantly involving small intestine. In recent years, examples of familial GIST have been reported in which germline mutations of KIT or PDGFRA result in multiple GISTs, skin disorders, and other abnormalities. Although most of multiple GISTs patients in the literature developed in the setting of NF1,[4,5,12] multiplicity in sporadic GIST patients without family history or NF-1 has been also described.[4] In the present study, we analyzed the histological and immunohistochemical features from three NF1 and one sporadic patient.

All of the tumors stained diffusely for CD117 and CD34, were negative for desmin, actins, S-100 protein, and keratin. The immunoprofile seen in our patient matched the findings described in the 12 patients of Kang et al.[4]

Patients with NF1, develop other signs of the disease, including skin manifestations (axillary freckling, café au lait spots), neurological disorders (cognitive deficits and seizures), extraintestinal neoplasms (pheochromocytomas, tumors of the central nervous system), and the neoplasms of the gastrointestinal tract (ampullary adenomas and adenocarcinomas, somatostatinomas, gangliocytic paragangliomas, colorectal carcinomas, and GISTs).[4-7] In the current series, case 1 had pancreatic somatostatinoma and case 2 had adenomyoma in ampulla vatery and signet ring cell type gastric adenocarcinoma.

Although the association of NF1 with neuroendocrine tumors is established, its association with a non-neurogenic malignancy such as GIST has rarely been described. Because NF1 has been shown to arise from an NF1 gene on the long arm of chromosome 17 and NF1 is a tumor suppressor gene involved in growth regulation, patients with NF1 have an increased risk of developing nonneurogenic malignancies.[6,13] To the best of our knowledge, up to year 2000, only 4 cases of "so called" periampullary somatostatinoma associated with NF1 have been reported. Our patient was the fifth case in literature, multiple GISTs and somatostatinoma in NF1. An association of duodenal somatostatinoma with NF1 has been reported in the literature (n= 36). Among those, 41% had metastases at the time of diagnosis.[13] Our case did not have any symptom or lesion for malignant somatostatinoma; the lesion was only 0.8 cm and found incidentally.

There were GIST cases with gastric adenocarcinoma and there is an early gastric carcinoma patient in literature.[14] However our patient was diagnosed as signet ring cell type gastric carcinoma four years later from his multiple GISTs operation.

Small or microscopic gastrointestinal stromal tumors (GISTs) have been published recently. These lesions may accompany clinically overt GISTs or be found incidentally in resection specimens for gastro-oesophageal malignancies. While the majority of cases consist of single lesions,[15] approximately 30% may be multiple (usually two or three such lesions).[16] Two recent studies have focused on sporadic interstitial cell of Cajal (ICC) hyperplasia and so-called minute sclerosing stromal tumors or GIST tumourlets of the stomach, respectively.[17] In our series only five GISTs nodules were greater than 3 cm (12.8%) and localized predominantly in the small intestine. The ICC hyperplasia and minute sclerosing tumors

have been found in gastric resection specimen in case 2. The lesions tended to occur in the body of the stomach in our patient, ranging from 0.1 to 0.5 mm in size, and were subserosal with variable involvement of the muscularis propria. There were minute tumors localized in small intestine in case 3 at the same time. All cases were composed of spindle cell component.

In our last patient we have found tumor metastasis or multiplicity. The patient had 19 GISTs nodules and most of them were subserosal. The biggest nodule was 8 cm in diameter and had a high mitotic ratio. Although the nodule, the adjacent nodules (5 nodules) and liver metastasis were at different sizes they had high mitotic ratio and similar futures, rest of the GISTs nodules were very low and low risk for aggressiveness. Thus we diagnosed the case as multiple GIST.

In patients with NF-1, the appearance of gastrointestinal symptoms should raise interest to search for gastrointestinal tumors because these patients are at risk for gastrointestinal neoplasms from which symptomatic patients are likely to experience significant morbidity. In accordance with other authors, we also recommend that NF-1 patients with gastrointestinal symptoms receive further survey to rule out GISTs.[18] Further studies including molecular analysis to clarify the relationship of GIST and neurofibromatosis and sporadic multiple GISTs are needed.

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