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Case Report

Malignant small intestinal stromal tumor combined with thoracic intraspinal and posterior mediastinal tumor in a patient with neurofibromatosis-1

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Abstract: This report presents a case of metachronous double tumors formation of gastrointestinal stromal tumor (GIST) and thoracic intraspinal and posterior mediastinal tumor in a patient with neurofibromatosis-1 (NF-1). A 31-year old woman who had no family history of NF-1 was admitted to our hospital because of unexplained anemia. The physical examination revealed numerous café-au-lait patches and multiple cutaneous neurofibromas on the upper extremities and trunk. CT revealed a peripheral enhanced irregular tumor in the abdomen and a metastatic tumor in the left liver lobe. The patient underwent tumor resection combined with intestine and liver surgery. The histopathological diagnosis was GIST and metastatic GIST. 21 months later, CT revealed an irregular intraspinal and posterior mediastinal tumor, like a dumbbell. Surgical excision was performed again and the tumor was found to be neurofibroma.

Keywords: Gastrointestinal stromal tumor, neurofibromatosis-1, intraspinal and posterior mediastinal tumor

Introduction

Neurofibromatosis-1 (NF-1), also called von Recklinghausen's disease, is a dominantly inheritable disease with an normality at chromosome 17q11.2, with a prevalence of approximately 1 in 3000 individuals [1]. The clinical features include systemic pigmented skin spots(café-au-lait spots), skin and subcutaneous multiple neurofibromas, and Lisch nodule. NF-1 is associated with the formation of various benign and malignant neoplasms [2].

GISTs are the most common tumors of mesenchymal origin in the gastrointestinal tract, mesentery, omentum, and retroperitoneum. The most significant risk factor for development of these tumors is the presence of NF-1 [3]. The majority of GISTs are isolated neoplasm and they are sporadically noted in non-NF-1 individuals without histopathological features that can help reliably distinguish NF-1-associated cases from sporadic cases. However, previous research pointed out that tumors associated with NF-1 frequently showed multiplicity, jejunal location, and abundant skeinoid fibers [4, 5].

Posterior mediastinal tumor sources are very complex, and the main neurological sources are schwannomas and neurofibromas. The intraspinal tumors usually are meningiomas, schwannomas and neurofibromas, but tumors stretch to posterior mediastina through intervertebral foramen are commonly schwannomas and neurofibromas.

The current study examined not only the clinical and pathological features, but also the treatment in a patient with NF-1 merged malignant GIST combined intraspinal and posterior mediastinal tumor.

Case report

A 31-year old woman who had no family history of NF-1 from the age of 14 years was admitted to our hospital because of unexplained anemia. The physical examination revealed numerous café-au-lait patches and multiple cutaneous

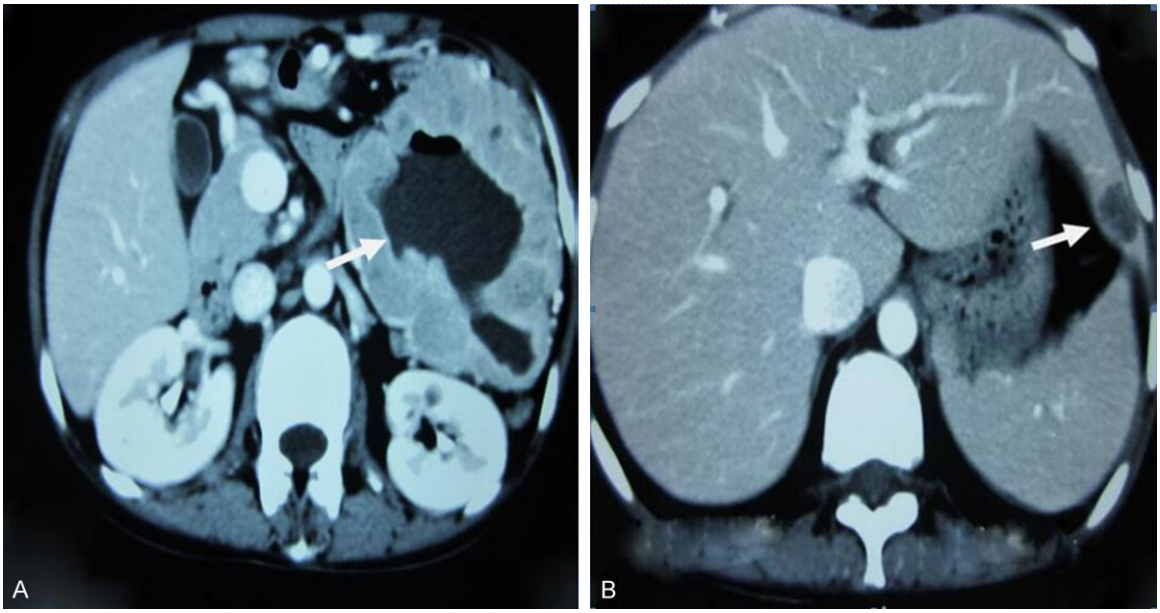

Figure 1. A. Small-bowel GIST with a thickened wall. The solid and peripheral enhanced tumor has an area of necrosis in the center, with air present within the necrotic cavity that communicates with the lumen of the small bowel. B. The metastatic tumor in the liver, which is enhanced like a ring.

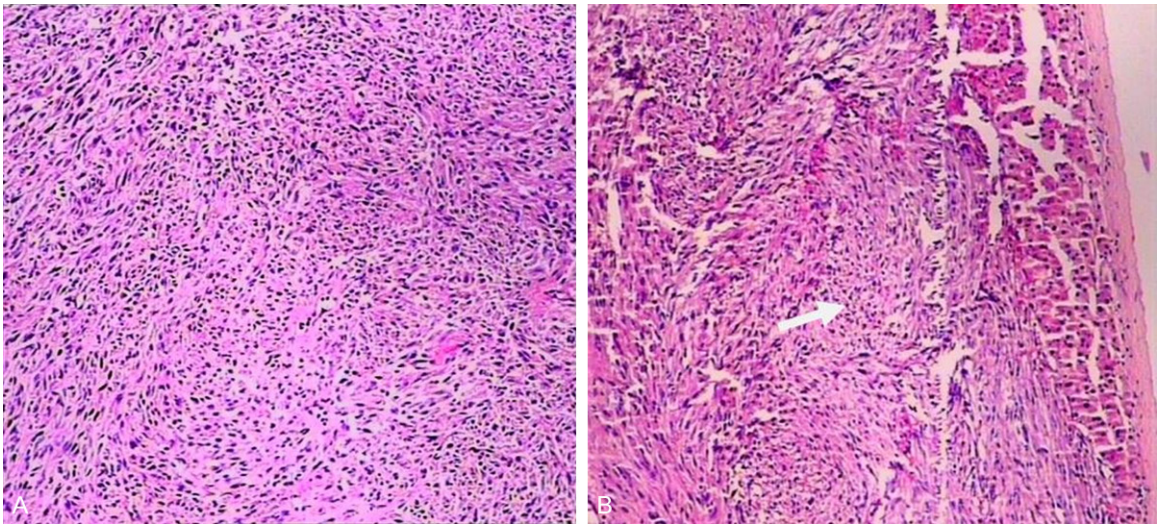

Figure 2. A. The small-bowel GIST was composed of spindle cells arraged in fascicles (×100). B. Similar cells developed the metastatic tumor in the liver (×100).

neurofibromas on the upper extremities and trunk. An irregular hard lump measuring approximately 15×10 cm was palpable in the left abdomen. When admitted, CBC showed leukocytes 12.7/mm^3 (segmented neutrophils 85%), hemoglobin 75 g/l, and platelets 948/mm^3. Other laboratory test results were normal, including tumor markers and hormonal levels. A contrast enhanced CT scan was performed and it revealed a soft tissue mass in the small bowel suggesting a diagnosis of GIST. Furthermore, there was a metastatic tumor in the left liver lobe (**Figure 1**).

The patient was successfully treated with surgical excision, including the GIST and the metastatic tumor. The main tumor was 15×10×8 cm and located between the transverse colon and the jejunum (20 cm distally from the Treitz Ligament). Because the mass invaded the transverse colon and the jejunum, parts of them were resected, and then we made digestive

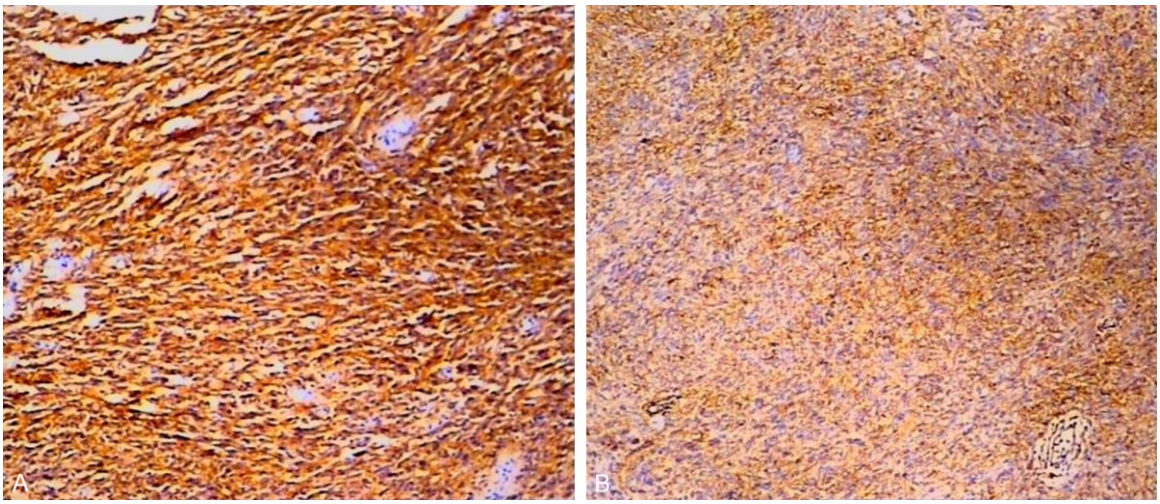

Figure 3. Immunohistochemistry (×100). A. c-kit (CD117) is very positive. B. CD34 is slightly positive.

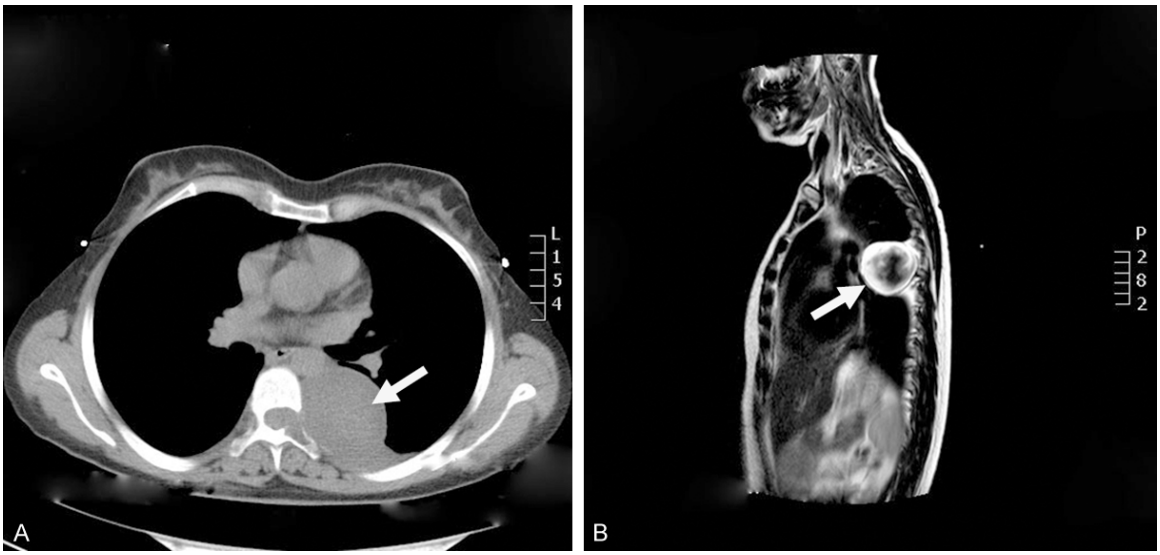

Figure 4. A. Chest CT confirmed an irregular intraspinal and posterior mediastinal tumor, like a dumbbell, and The 7th intervertebral foramen was damaged by this tumor. B. MRI revealed a high signal in the spinal canal and posterior mediastina.

tract reconstruction. The metastatic tumor was in the left liver lobe, measuring 3×2×2 cm. We made an irregular part liver resection for this metastatic tumor. The postoperative course was good without any major complications.

The histopathological diagnosis of these tumors are GISTs. The tumors were composed of interlacing fascicles of the uniform spindle cells (**Figure 2**). The results of the immunohistochemical staining revealed the tumor cells were diffusely positive for CD117, CD34 (**Figure 3**), but negative for SMA, S-100 protein and desmin.

Because of economic factors, the patient did not receive imatinib therapy. 3 months later, the anemia was cured and all of laboratory test results were normal. She went to work like normal people and received a careful follow-up every 3 months.

Twenty on months later, Chest CT confirmed an irregular intraspinal and posterior mediastinal tumor, like a dumbbell (**Figure 4**). The 7th intervertebral foramen was damaged by this tumor, but the patient did not have any symptom. Surgical excision was performed again and we found the tumor originated the 7th spinal nerve

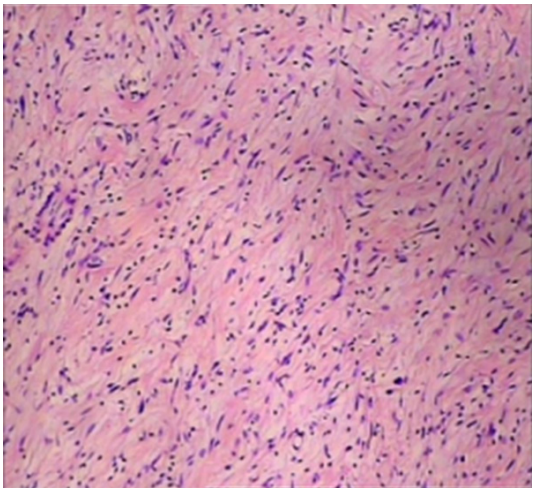

Figure 5. Histologically, the tumor was compsed of interlacing fascicles of uniform spindle cells (×100).

Table 1. Published reports of gastrointestinal mesenchymal tumors in NF1 patients

	Published reports
Mean (range) age (yr)	51 (10-87)
Male:female (% male)	30:35 (46)
Presenting symptoms	
GI bleeding (%)	25/48 (52)
Obstruction (%)	3/48 (6)
Incidental finding (%)	12/48 (25)
Involved sites	
Gastric (%)	9/65 (14)
Duodenal (%)	20/65 (31)
Jejunal (%)	40/65 (62)
Ileal (%)	12/65 (18)
Multiple tumors/sites (%)	40/65 (62)
Mean (range) tumor size (cm)	3.0 (0.3-28)

root. Histopathological examination showed the tumor was neurofibroma (**Figure 5**). We continue the follow-up after the operation, everything is normal for this patient.

Discussion

NF-1 is mainly caused by mutation of NF-1 gene, which is located in chromosome 17q11.2. The NF-1 gene encodes a 327-kDa protein known as neurofibromin. In most cases, the mutations responsible for NF-1 result in truncations of neurofibromin [6]. NF-1 may affect the gastrointestinal tract in up to 3.9%-25% of the patient [7].

GISTs originate from the intestinal cells of Cajal [8]. GISTs are detected in many patients by chance, and the patients usually present with gastrointestinal bleeding, which is often chronic or intermittent. In addition, they are often found in patients with anemia, constipation or obstruction. The current patient had an unexplained anemia and seek for etiology in many other medical institutes before she came to our hospital. Both the characteristics and the tumor genesis of GISTs in patients with NF-1 are different from those of sporadic GISTs. GIST in NF-1 patients develops in the small intestine and has a tendency to form multiple lesions in most cases, although this patient has only one lesion in the jejunum with a metastatic mass in the liver. On the other hand, sporadic GIST occurs as solitary lesion, most commonly in the stomach [9]. GIST associated with NF-1 has a better prognosis than sporadic GIST with the same size and stage [10]. As c-kit gene mutation is rare in GIST with NF-1 [11], the mechanism of development of this GIST may be explained by loss of heterozygosity of NF-1 gene [12], rather than a mutation of the c-kit gene. There are many Published reports of gastrointestinal mesenchymal tumors in NF1 patients (**Table 1**).

A surgical resection is generally recommended with priority for GIST. However, anticancer drugs, especially imatinib is dramatically important. Imatinib is a selective tyrosine kinase inhibitor of c-kit and PDGFRA, and represents a new paradigm of targeted therapy against GIST, particularly for high risk patients. Imatinib is effective for GIST with the c-kit gene mutation in exon 11, so imatinib shows high resistance when there is no mutation of exon 11 [13]. Because of economic factors, the current patient did not receive imatinib as an adjuvant treatment. We focus on the follow-up every 3 months, emphasizing on abdomen, spinal cord and breasts [14], and we find an intraspinal and posterior mediastinal tumor 21 months later.

Dumbbell tumors of the internal and external thoracic spinal canal account for 10% in posterior mediastinal neurogenic tumors [15], of which most are schwannomas and neurofibromas, and it is neurofibroma in this case. The dumbbell tumors are generally located epidurally, seldom invading along the nerve root subdurally. Clinical symptoms like dysfunction of motion, sensory and reflex are different related to the site of tumor origin and growth direction, and there may exist paroxysmal cough when the main tumor is in the posterior mediastina. However, there is no clinical symptom in this

case, and we find this tumor surprisingly in the follow-up. We employed a combined thoracoscopic and posterior spinal approach [16] to resect the dumbbell tumor with the collaboration of neurological surgeons and thoracic surgeons.

It is unclear whether the NF-1 gene plays a key role in the development of GIST. We can consider the thoracic intraspinal and posterior mediastinal tumor as a clinical manifestation in peripheral nervous system of NF-1, but the metachronous double tumors formation in NF-1 patients is extremely rare.There is no report in China. Because NF-1 easily combines other tumors [17], systemic and careful exploration is essential for detection of malignancies in patients with NF-1 during the follow-up.

Disclosure of conflict of interest

None.

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