Spontaneous Rupture of Recurrent Gastrointestinal Stromal Tumor Associated with Neurofibromatosis Type 1

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The incidence of gastrointestinal stromal tumor (GIST) among neurofibromatosis type 1 (NF-1) patients is approximately 3.9–25%, and this relationship is generally considered to be non-coincidental. We report a patient with NF-1 who underwent laparotomy 3 times due to recurrent intra-abdominal tumor rupture with internal bleeding in the space of 13 years. The pathologic diagnoses were schwannoma, malignant peripheral nerve sheath tumor and GIST. Because of the similar histologic features of these tumors, we considered them to be of the same nature. Immunohistochemical staining can help in the differential diagnosis. We suggest that NF-1 patients with gastrointestinal symptoms receive further survey to rule out GISTs. [J Chin Med Assoc 2005;68(11):538–541]

Key Words: gastrointestinal stromal tumor, hemoperitoneum, neurofibromatosis-1

Introduction

Neurofibromatosis type 1 (NF-1) is one of the most common neurogenetic disorders, affecting approximately 1 in 3,000 individuals worldwide. Complications arising from gastrointestinal lesions have been reported in 25% of patients with NF-1. The incidence of gastrointestinal stromal tumor (GIST) among NF-1 patients is approximately 3.9–25%, and this relationship is generally considered to be non-coincidental.

We report a male patient with NF-1 who underwent repeated laparotomies due to recurrent retroperitoneal and intra-abdominal tumor rupture. According to the histologic features and immunohistochemical (IHC) stain results, the tumors represent recurrent GISTs.

Case Report

In June 1991, a 50-year-old man with NF-1 associated with multiple cutaneous neurofibromas and café-au-lait spots presented with epigastric pain and oliguria for 20 days. He experienced an episode of near-fainting and was sent to our emergency department. On arrival, he was pale and ill-looking, with a blood pressure of 80/50 mmHg. Physical examination revealed abdominal distension and diffuse tenderness with signs of peritoneal irritation. Abdominal computed tomography (CT) scan showed plenty of intra-abdominal fluids compatible with internal bleeding. A space-occupying mass with an enhanced capsule was found over the lower pelvis just above the urinary bladder, suggesting a tumor with bleeding (Figure 1). The patient underwent emergency laparotomy. An estimated 2,000 mL of bloody ascites was drained and a huge tumor, adhering to the jejunum, colon and omentum, was resected. The postoperative period was uneventful. Pathology revealed an encapsulated tumor mass measuring 16 × 14 × 10 cm in size, with a ruptured hemorrhagic area measuring 4 × 4 cm and areas of peritoneal attachment. Microscopically, the tumor was composed of long fascicles of spindle cells
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with focal nuclear palisading. Mild nuclear pleomorphism, common mitotic figures and frequent hemorrhage were seen. The features were consistent with well-differentiated malignant schwannoma.

The patient remained asymptomatic until 7 years later, when he suffered from abdominal fullness for 1 month and abdominal pain for 5 days. Abdominal CT revealed a retroperitoneal space-occupying lesion and mild bloody ascites. In the second laparotomy, a $12 \times 9 \times 5$ cm mass was found at the fourth portion of the duodenum, just below the Treitz ligament. Due to the tumor’s adhesion to the duodenal wall, en bloc resection of the tumor and part of the duodenal wall was performed. The postoperative period was smooth. On microscopic examination, the tumor was cellular, composed of pleomorphic and spindle cells with wavy nuclei. It had invaded the duodenal wall but spared the mucosa. IHC stain showed tumor cells positive for S-100 but negative for smooth muscle actin (SMA). The pathologic diagnosis was malignant peripheral nerve sheath tumor (MPNST).

Six years later, the patient experienced right lower quadrant pain for a few days. Abdominal CT revealed a pelvic tumor and mild hemoperitoneum (Figure 2). Recurrent malignancy with tumor rupture was highly suspected, and during the third laparotomy, 3 tumors were found. A hemorrhagic ruptured tumor measuring $4 \times 5 \times 3$ cm was found invading the posterior wall of the urinary bladder, a $7 \times 6 \times 5$ cm tumor was found in the mesenteric side of the jejunum, and a $1.5 \times 1 \times 1$ cm tumor was found attached to the ileum. On microscopic section, the 3 tumors were composed of spindle cells with moderate to high cellularity. Nuclear atypia was mild to moderate. Mitoses were occasionally seen in the jejunal tumor (about 2–5/50 high-powered field, HPF), and more frequently seen in the pelvic mass (5/50 HPF). All 3 tumors were positive for CD117, focally positive for CD34, SMA and S-100, and negative for desmin. The pathologic diagnosis was malignant GIST with focal smooth muscle and neurogenic differentiation.

To confirm the impression of recurrent GIST, the specimen from the first laparotomy was reviewed and IHC staining performed. The tumor was strongly positive for CD117 (Figure 3), CD34, SMA and S-100, but negative for desmin. It fulfilled the criteria for GIST.

Discussion

NF-1, also known as von Recklinghausen’s disease, is characterized by multiple peripheral neurofibromas,
café-au-lait macules, skinfold freckling, and iris hamartoma (Lisch nodules). The gastrointestinal lesions arise during midlife, later than cutaneous lesions. The predominant lesions are benign neurofibromas or leiomyomas involving the jejunum and stomach, with rare involvement of the colon. The incidence of these tumors, which tend to be multiple in the gastrointestinal tract, is uncertain because the diagnosis is made only in symptomatic patients. A significant number of patients with NF-1 never manifest gastrointestinal bleeding, obstruction or abdominal pain, which are the 3 most common symptoms of these tumors.

In the 1960s, Stout and Kay and Still used the terms “leiomyoma”, “leiomyosarcoma”, “leiomyoblastoma” and “bizarre leiomyoma” to describe gastrointestinal stroma cell tumors. With the introduction of IHC staining in the 1980s and the discovery of CD117 in the 1990s, GIST has become a generic name for primary nonepithelial tumors of the gastrointestinal tract.

Surgery is the mainstay of treatment for GIST. Radiation and chemotherapy with currently available agents are of uncertain value. Recent dramatic improvements have been achieved using STI571 (Glivec, Novartis AG, Basel, Switzerland) in cases of metastatic, recurrent or unresectable GIST. Glivec inhibits mutant KIT tyrosine kinase, which appears to play a critical role in the pathogenesis of GIST.

Generally, the combination of size less than 2 cm and low mitotic rate (< 5/50 HPF) translates to a benign clinical course. Tumors larger than 5 cm in diameter or with mitotic activity exceeding 5 mitoses per 50 HPFs show high potential for intra-abdominal and liver metastasis. It has been reported that the 5-year survival rate after complete GIST resection is 63%, compared to 10% after incomplete resection. Furthermore, the 5-year survival rate for completely excised low-grade GIST is 72%, compared to 18% for high-grade GIST. Tumor rupture, whether spontaneous or iatrogenic, is associated with a decreased overall survival rate and an increased rate of early recurrence, because intraperitoneal seeding and metastasis may occur after tumor rupture.

Although the tumors are often soft, fragile, and prone to rupture during resection, only a few cases presenting with hemoperitoneum have been reported. Cystic change is often found in GIST, even when the tumor is small. Cheon et al claimed that cystic degeneration within the mass may cause weakness of the tumor capsule. Karatzas et al postulated that hemoperitoneum might be related to the rupture of the capsular vessel on the tumor surface. Examination of our specimens showed no cystic degeneration; erosion of the friable neovascularity associated with extensive intratumoral hemorrhage and rapid expansion of the tumor mass may have caused the spontaneous tumor rupture.

Due to the nature of the local recurrence of malignant GIST, and the similar histologic features of our tumors, we considered them to be of similar type. IHC staining can help us to differentiate schwannoma, MPNST and GIST. Almost all GISTs are CD117-positive, 70% are CD34-positive, a minority are positive for S-100, occasionally positive for SMA and desmin, and negative for glial fibrillary acidic protein (GFAP). Schwannomas are almost always positive for S-100 and GFAP, occasionally positive for CD34, and negative for CD117, SMA and desmin. MPNSTs are positive for neuron-specific enolase and GFAP, and they also exhibit a mixed proliferation of cells positive for S-100 protein, epithelial membrane antigen and CD34, indicating a heterogeneous composition of the constituents.

Gastrointestinal manifestations of NF-1 have been well described. Some authors estimate that 3.9–25% of patients with NF-1 have gastrointestinal tumors, but less than 5% actually have associated symptoms. Although this is generally considered to be non-coincidental, the definite relationship between NF-1 and GIST based on molecular biology remains to be determined. We, therefore, recommend that non-epithelial tumors of the gastrointestinal tract in patients with neurofibromatosis be reviewed to exclude the possibility of GIST, a tumor that is highly responsive to target therapy. We also suggest that NF-1 patients with gastrointestinal complaints receive further survey to rule out GIST.
References


