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Case Report

Individual therapy of large small intestinal stromal tumor with Tegafur

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Abstract: Gastrointestinal stromal tumors (GIST) are a common type of digestive tract mesenchymal tumors. Small intestinal stromal tumors (SIST) account for 31% of GIST. The positive expression of CD117 and CD34 is of importance to diagnose GIST but does not relate with prognosis. Tumor size, mitotic Count, primary tumor site and tumor rupture are closely related with the prognosis of SIST and tumor rupture is a high-risk factor for poor prognosis. Here we share a case in which a patient with a high risk SIST was treated successfully with tumor resection and Tegafur. No recurrence was detected during 87 months follow-up.

Keywords: Gastrointestinal stromal tumor (GIST), small intestinal stromal tumors (SIST), Tegafur, microsatellite instability (msi), microsatellite stability (MSS)

Introduction

Small intestinal stromal tumors (SIST) account for 31% of all gastrointestinal stromal tumors (GIST) [1]. The 1-, 3-, and 5-year disease-free survival (DFS) and overall survival (OS) rates of SIST were 85.2%, 53.8%, and 43.7%, and 91.5%, 66.6%, and 50.5%, respectively [2]. Clinical aggressive behavior of the tumor is best predicted by the size and mitotic count [3]. Here we share a case in which a patient with a high risk SIST was treated successfully with tumor resection and Tegafur, a cell cycle inhibitor. The patient was emergently admitted on account of intra-abdominal hemorrhage due to rupture of large SIST. After radical resection of the tumor, microsatellite instability (MSI) test was done and showed microsatellite stability (MSS). Tegafur treatment was given following radical resection of the tumor. No recurrence was detected during 87 months follow-up.

Case report

The patient was a 61 years old Asian male. He suffered from lower abdominal pain accompanied by frequent micturition for 1 week and was admitted on 25th Jan, 2008. He denied urgent micturition, odynuria, nausea, diarrhea, fever or vomitting. His medical history and family history were noncontributory. Physical examination: acute anemic appearance, T 36.5°C, P 80 bpm, R 20 bpm, BP 110/76 mmHg. The heart and lungs were normal. Skin and sclera were not icteric .The abdomen was distent and soft. Neither enlarged liver nor spleen was palpable. Murphy's sign was negative. Mass was palpable from 4 fingers above navel to the pelvic, with uneven surface, hard texture and little mobility. There's mild abdominal tenderness and shifting dullness was positive. Blood routine showed WBC 6.7×10^9/L, NE 6.48%, Hgb 57 g/L. Liver function was normal. Fasting blood glucose was 6.0 mmol/L, NSE 41.54 ng/L, CA125 136.10 u/L. AFP, CEA and CA19-9 were all negative. B-Ultrasound detected heterogeneous masses and pyoperitoneum with largest depth about 70 mm in the lower abdomen. CT scan showed multiple large masses in the abdomen (99 mm×180 mm and 100 mm×133 mm in size) with unclear margin and heterogeneous contrast enhancement. The CT value of masses was 25 to 63 HU. The bladder was pushed aside and hydrops could be found around the liver and spleen. No obvious lymph node enlargement could be seen in the posterior

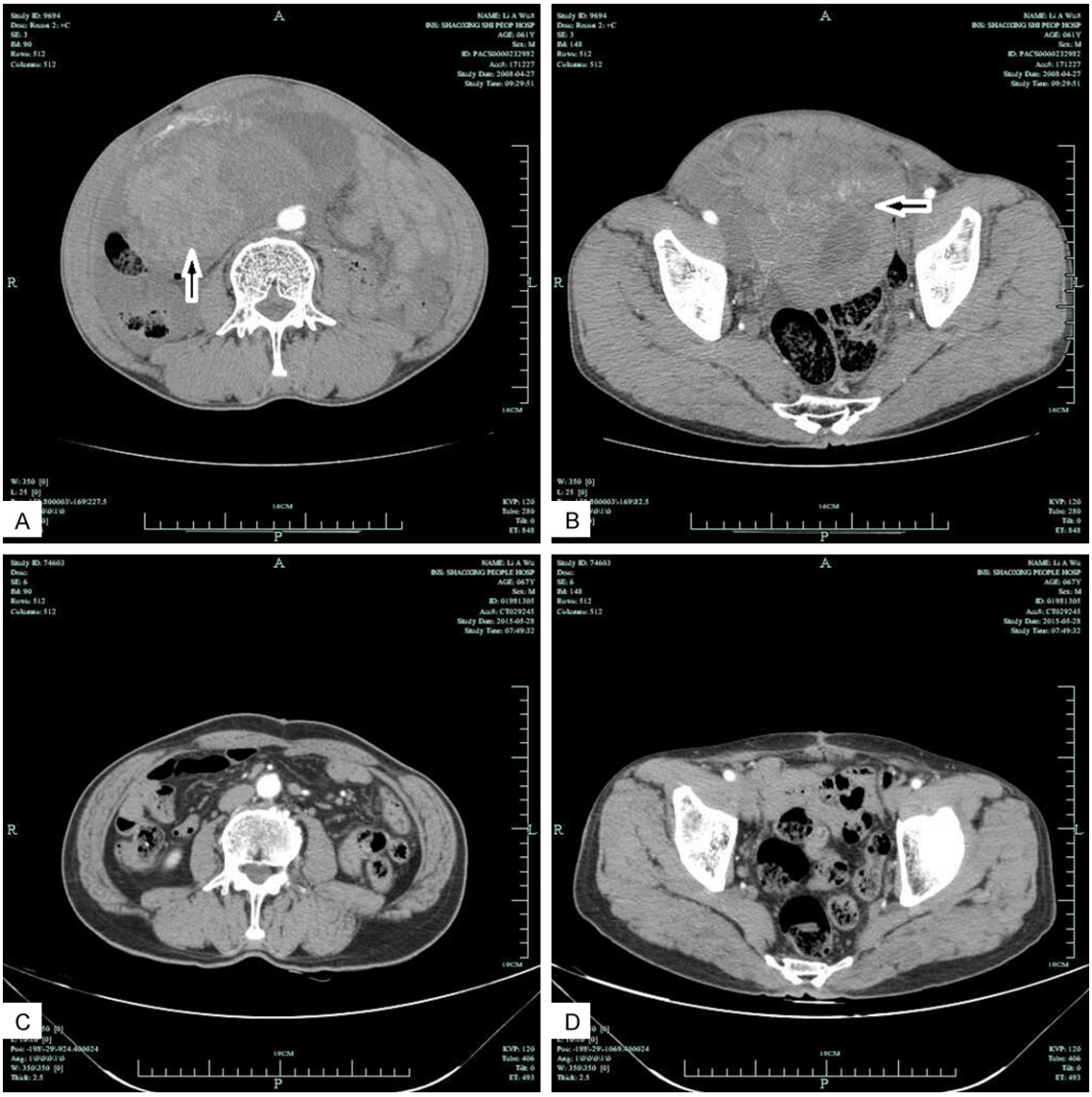

Figure 1. CT scan images of the patient before and after the treatment. Multiple masses (white arrow) can be detected in the abdomen of the patient (A and B). No recurrence of the tumor is found after 87 months follow-up (C and D).

peritoneum and pelvic cavity. So GIST was suggested (**Figure 1A**, **1B**).

We performed an exploratory laparotomy under general anesthesia. During the operation, we found the tumor masses occupied almost all of the abdominopelvic cavity about 310 mm× 230 mm×120 mm in size (**Figure 2**). The masses were nodular, rugged and cyst-solidary. They were closely connected with terminal mesoileum and adhered to the bladder, posterior peritoneum and descending colon. Local rupture and hemorrhage could be found in the capsule of the masses. There was totally about 2000 ml old hemoperitoneum and blood clot in the abdomen. We dissected the adhesion, controlled bleeding by ligation and resected intestine about 200 mm distal and proximal to the tumor separately which tightly connected to the tumors. After complete excision of the tumor, we did end to end anastomosis of ileum, and irrigated abdomen cavity for 10 minutes using distilled water in 43°C.

Postoperative histologic examination showed large spindle cell tumor with necrosis (**Figure 3A**). The immunohistochemical examination showed: VIM (+), CD34(-), CD117(+), S-100(-),

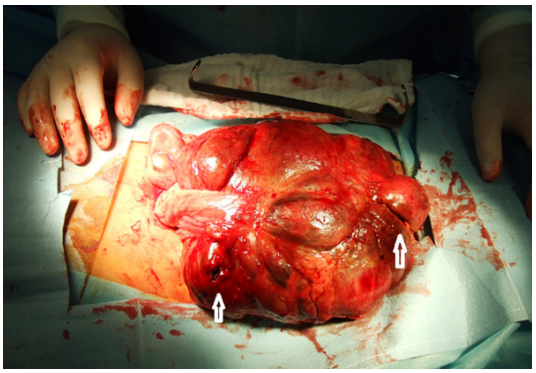

Figure 2. An image of tumor masses resected from the patientound after. The tumor is (310 rom the mm) in size. Multiple Rupture focus in the Tumor can be identified (white arrows).

CK(-), SE(+), Ki-67(+) 3% (**Figure 3B**). Pathologic examination confirmed that it was small intestinal stromal tumor with necrosis and hemorrhage, mitotic count <5/50 HPF (**Figure 3C**). No metastasis was found in the greater omentum and the surrounding fat tissue and the resected small intestine segment. C-kit/PDGFRα gene mutation examination showed C-kit gene exon 16: mutated type 550-554 absence and C-kit gene exon 9: wild type 4. The patient could not afford imatinib mesylate therapy because of economic factor. He took microsatellite instability (MSI) test which showed microsatellite stability (MSS) and received Tegafur therapy. He took Tegafur tablets 600 mg per day and one course lasted 3 months. After three months intervals we continued with the next course. After 10 courses of therapy, no bone marrow depression, leucocytopenia and thrombocytopenia occurred in the patient. No evidence of tumor recurrence or metastasis has been found by CT scan.

The patient was diagnosed with SIST and was stratificated as high risk of aggressive behavior [4, 5] by pathologic examination, immunohistochemical examination and gene mutation test. The patient was discharged with no complication. After 87 months follow-up, he received CT scan which revealed no tumor recurrence, metastasis and enlarged lymph node (**Figure 1C**, **1D**). The patient is now still alive and capable of physical labor.

Discussion

The main clinical manifestations of SIST include digestive tract hemorrhage, abdominal mass, anemia and abdominal pain. In our case, the patient was admitted on account of hemorrhage due to rupture of abdominal mass. GIST is a common type of digestive tract mesenchymal tumors which originate in submucosa and is hard to diagnose preoperatively. The diagnosis of GIST mainly relies on clinical manifestation, imaging findings and immunohistochemical examination. The positive expression of CD117 and CD34 is of importance to diagnose GIST but does not relate with prognosis [6]. NIH (the national institutes of health) risk classification of primary resection, which added two evaluation indicators including primary tumor site and tumor rupture to Fletcher classification, made SIST grading more explicit. It's a consensus that tumor size, mitotic Count, primary tumor site and tumor rupture are closely related with the prognosis of SIST and tumor rupture is a high risk fact for poor prognosis [3, 7, 8]. Our case is diagnosed with multiple and large tumors which is rare clinically. Tumor rupture due to local tissue necrosis caused hemorrhage which finally leaded to anemia. Postoperative pathologic examination showed large spindle cell tumor with necrosis and mitotic count <5/50 HPF. The immunohistochemical examination showed CD117(+). C-kit/PDGFRα gene mutation examination showed C-kit gene exon 16: mutated type 550-554 absence and C-kit gene exon 9: wild type. According to NIH risk classification of primary resection and Fletcher classification, our case is classified as high risk of aggressive behavior indicating high risk of recurrence and metastasis. SIST has a higher degree of malignancy than stromal tumor in stomach, colon, rectum and esophagus [7]. SIST is not sensitive to traditional radiotherapy and chemotherapy whose effective rate is lower than 4% [9]. SIST has a high risk of recurrence and metastasis (up to 50%-70.5%) in spite of complete resection of the tumor. It's the first choice to use TKI (Tyrosine Kinase Inhibitors) for treatment especially for patients with mutation of exon 11 [10].

However, in our report, the patient can't afford it for economic reasons. It was reported that Fluorouracil-based adjuvant chemotherapy benefited patients with stage II or stage III colon cancer with microsatellite-stable tumors or tumors exhibiting low-frequency microsatellite instability [11]. However, there was no related research about SIST. Regardless of low efficiency of traditional chemotherapy, we chose

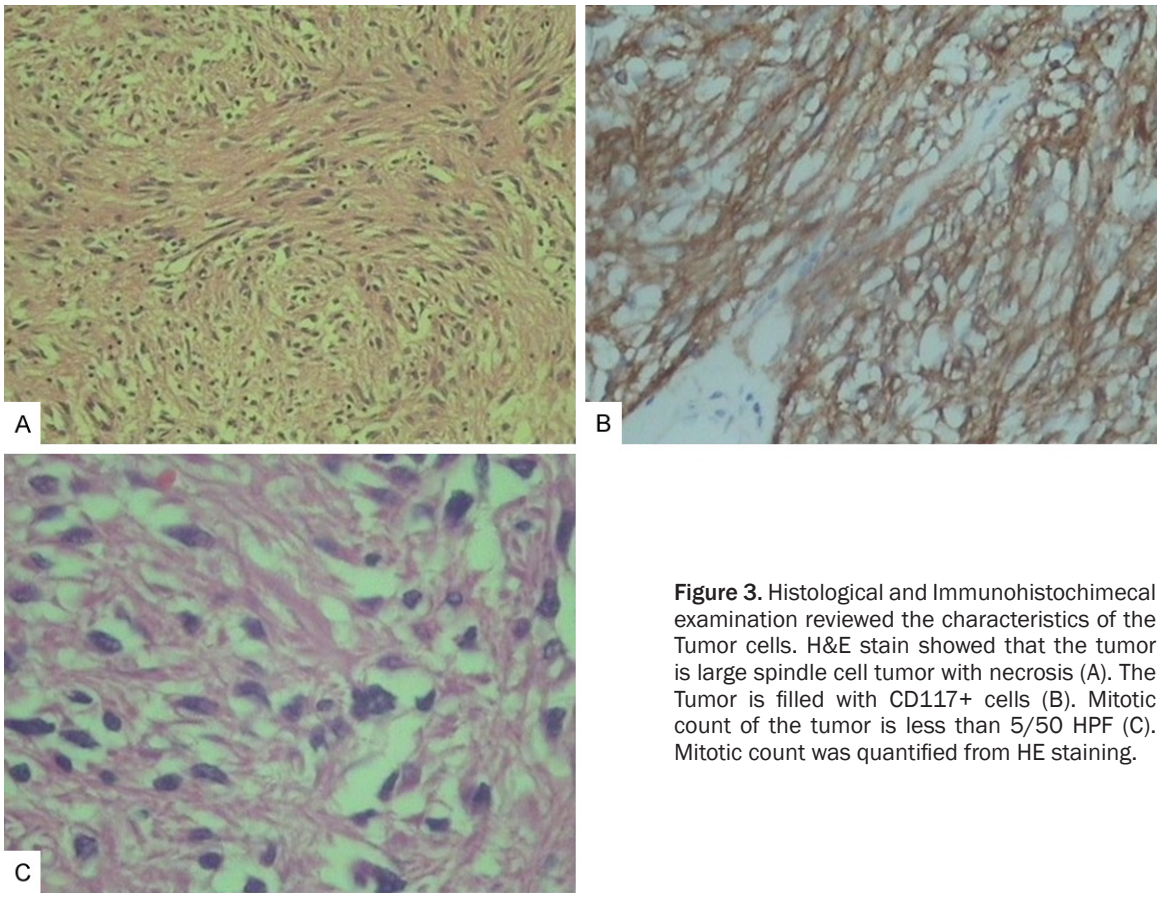

Figure 3. Histological and Immunohistochimecal examination reviewed the characteristics of the Tumor cells. H&E stain showed that the tumor is large spindle cell tumor with necrosis (A). The Tumor is filled with CD117+ cells (B). Mitotic count of the tumor is less than 5/50 HPF (C). Mitotic count was quantified from HE staining.

individual therapy according to the MSS result. The patient took Tegafur, a cell cycle specific drug, 200 mg three times a day. One course lasted 3 months. After three months intervals we continued with the next course. After 10 courses of therapy, no bone marrow depression, leucocytopenia and thrombocytopenia can be detected by laboratory examination. No evidence of tumor recurrence or metastasis has been found by CT scan.

Based on the reported case, in addition to routine pathological examination, MSI test is recommended for SIST. For those with MSS, Tegafur therapy could be considered. To our knowledge, this is the first report on treating large small intestinal using Tegafur with promising clinical efficacy, and further research is needed.

Disclosure of conflict of interest

None.

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