

Primary gastrointestinal stromal tumor of the liver treated with sequential therapy

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The tumor was microscopically composed of spindle cells and epithelioid cells, and immunohistochemistry results showed positive staining for CD117 and CD34 expression. A genetic analysis revealed a heterozygous point mutation and deletion in exon 11 of c-KIT. After an R0 resection, imatinib mesylate was administered for 1 year until its use was discontinued due to severe side effects. Two years after the original operation, the tumor recurred in the residual liver and was completely resected again. Imatinib mesylate was administered for 2 years until it was replaced by sunitinib malate because of disease progression. The patient has survived for 53 mo after undergoing a sequential therapy consisting of surgical excision, imatinib and sunitinib.

Key words: Gastrointestinal stromal tumor; Diagnosis and treatment; Tyrosine kinase inhibitor; Sequential therapy; Liver

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Core tip: The tumor was detected by computed tomography and diagnosed based on histopathological and genetic analyses. Metastases from gastrointestinal stromal tumors were excluded using computed tomography, ultrasound, esophagogastroduodenoscopy and colonoscopy. The patient was treated with an extended sequential therapy consisting of surgery, imatinib mesylate, and sunitinib malate. The patient has survived for 53 mo after the start of therapy.

Abstract

A 67-year-old female presented with a primary hepatic gastrointestinal stromal tumor that was detected by computed tomography and diagnosed based on histopathological and genetic analyses.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common abdominal tumors of mesenchymal origin. GISTs primarily occur in the gastrointestinal tract and frequently contain a gain-of-function mutation of the *KIT* or *PDGFRA* genes^[1]. Currently, diagnosis of GISTs is based on histopathological features, including the immunohistochemical staining of CD117, DOG-1, CD34, SMA, desmin and S-100. A minor subset of GISTs occur in other areas of the body, such as the mesentery, omentum, retroperitoneum, pancreas, uterus, gallbladder and liver^[2-5], and are referred to as "extra-gastrointestinal stromal tumors". Here, we report a case of primary GIST of the liver.

CASE REPORT

A 67-year-old female complained of fatigue for 6 mo without any abdominal symptoms. The patient had a history of hypertension, gastritis, and hysteromyoma. Additionally, she had undergone a cholecystectomy at the age of 55 years. The abdominal physical examination was unremarkable. The levels of tumor markers, such as carbohydrate antigen 199, carbohydrate antigen 125, carcinoembryonic antigen and α -fetoprotein (AFP), were all normal. Liver function tests were normal. An enhanced abdominal computed tomography (CT) scan showed a 7.4 cm \times 6.2 cm solid-cystic mass in the right hepatic lobe. However, no other abdominal neoplasm was evident (Figure 1A). Esophagogastroduodenoscopy (EGD) and colonoscopy were performed before resection; however, no tumor was found.

The hepatic mass was excised in August 2009. No other masses were found during the operation. A postoperative abdomen ultrasound (US) revealed no other lesions in the liver. Pathologically, the margins of resection were negative, and the tumor was composed of spindle cells and epithelioid cells with high mitotic activity (8/50 HPF) (Figure 2A). Immunohistochemical staining for CD117, CD34, desmin, SMA, CK19, HMB45, and AFP revealed positive results for CD117 and CD34 (Figure 2B and C). A heterozygous mutation was detected in a hot spot region of c-*KIT* exon 11. Specifically, codon 550 was mutated (AAA \rightarrow ATA), and codons 551-555 were deleted (CCC-ATG-TAT-GAA-GTA).

Imatinib mesylate was administered at 400 mg per day for 2 mo, beginning 1 mo after surgery. However, the patient experienced severe musculoskeletal pain from the medication, and the dosage was reduced to 200 mg per day for 1 year. In September 2011, a 6 cm \times 5 cm lesion was detected in the residual right liver after a routine CT examination. The tumor was completely resected again (Figure 1B). The results of immunohistochemical staining and genetic analysis of the specimen were consistent with the initial mass. Thus, recurrent hepatic neoplasia was diagnosed, and 200 mg of imatinib mesylate per day was administered beginning in October 2011.

In October 2013, a 6 cm \times 5 cm mass was detected

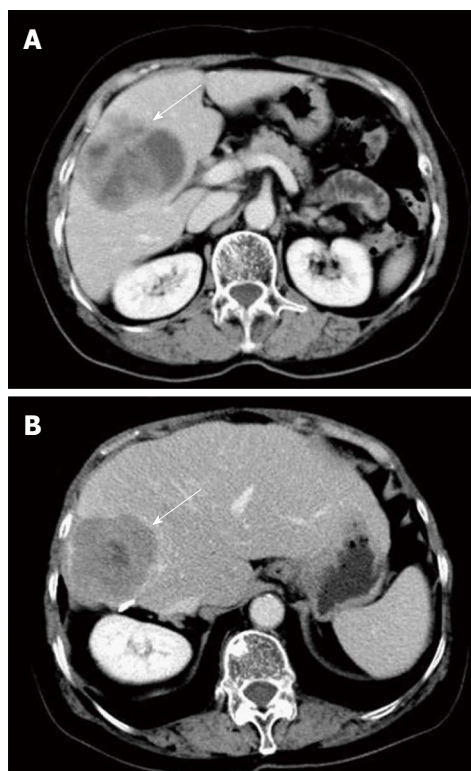


Figure 1 Computed tomography images of the tumor. A: An enhanced abdominal computed tomography (CT) scan from August 2009 showed a 7.4 cm \times 6.2 cm solid-cystic mass in the right hepatic lobe (venous phases in the axial plane). The central portion was of low-density with thickened irregular peripheral margins; B: An enhanced abdominal CT scan in September 2011 showed a 6 cm \times 5 cm solid-cystic mass in the residual right liver (venous phases in the axial plane).

in the right iliac fossa using CT. An emission CT revealed several bony metastases in the thoracic vertebrae, lumbar vertebrae and sacrum. Based on the disease progression while undergoing 2 years of imatinib mesylate therapy, the patient was switched to 37.5 mg of sunitinib malate per day.

DISCUSSION

GISTs are the most common gastrointestinal mesenchymal tumors and often occur due to a *KIT* or *PDGFRA* gene mutation. GISTs are similar to interstitial cells of Cajal (ICC) pacemaker cells in the gut musculature; thus, GISTs are considered to originate from ICCs^[6]. Furthermore, some researchers have observed "ICC-like" interstitial cells with a similar structure and function to ICCs in organs outside of the gastrointestinal tract^[7]. Other studies have suggested that GISTs originate from a group of undifferentiated cells, such as stem cells or primitive ancestor cells, and then differentiate into ICCs^[8]. It has been recently reported that ICCs, ICC-like cells and primitive ancestor cells are present in the gallbladder wall, myometrium, and pancreas, respectively^[3,4,9]. Rusu *et al*^[10] discovered the existence of portal interstitial cells of Cajal in the portal space, portal septa and periphery of the hepatic lobules based on immunohistochemical staining of

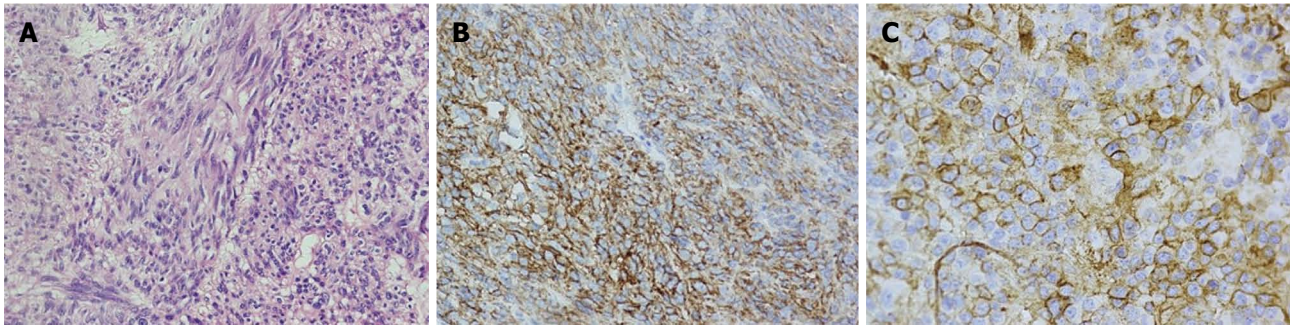


Figure 2 Microscopic and immunohistochemical findings of the resected specimen obtained in August 2009. A: Microscopically, the tumor was composed of spindle cells and epithelioid cells with high mitotic activity (8/50 HPF) (hematoxylin-eosin, original magnification $\times 400$); B, C: Immunohistochemical staining with antibodies against CD117 (B) and CD34 (C) showed diffuse cytoplasmic staining of almost all tumor cells when compared with the lack of staining in adjacent liver tissue (original magnification $\times 400$).

human hepatic tissue.

In cases of hepatic GISTs, metastases from GISTs and other primary hepatic tumors must be excluded. We believe the tumor in this case was a primary hepatic GIST because the intra-operative inspection and the imaging examinations, including CT, US, EGD and colonoscopy, revealed that the tumor was completely limited to the liver. Additionally, histopathological and genetic analyses strongly supported a GIST diagnosis. Finally, a lack of AFP, CK19, and HMB-45 expression distinguished the mass from a carcinoma, an epithelioid angiomylipoma, or a hepatic malignant melanoma.

The patient in our present case was treated with an extended sequential therapy consisting of surgery, imatinib mesylate, and sunitinib malate. According to the modified NIH consensus criteria in 2008, the patient was at high risk of tumor metastasis^[11]. Thus, 400 mg of imatinib mesylate per day was advised as a suitable therapy for at least 3 years after surgery^[12,13]. However, the dosage was reduced to 200 mg per day, and the treatment plan was interrupted one year later due to severe side effects of imatinib mesylate. Without blood concentration monitoring data, we cannot be sure whether a high enough dose was given to the patient. When the tumor metastasized after 2 years of continuous administration of imatinib mesylate, sunitinib malate therapy was initiated in accordance with the NCCN Clinical Practice Guidelines in Oncology^[14].

In conclusion, preoperative diagnosis of primary hepatic GISTs is difficult. Hepatic GISTs must be distinguished from other liver neoplasms or metastatic lesions in the gastrointestinal tract. Primary hepatic GISTs should be considered as highly aggressive. Following complete resection of the tumor, adjuvant therapy with imatinib mesylate for a minimum of 3 years is recommended.

COMMENTS

Case characteristics

A 67-year-old female complained of fatigue for 6 mo without any abdominal symptoms.

Clinical diagnosis

Abdominal physical examination was unremarkable.

Differential diagnosis

The differential diagnosis included hepatic carcinoma, hepatic hemangioma, hepatic cyst and metastases from gastrointestinal stromal tumors (GISTs).

Laboratory diagnosis

The results of routine blood tests, tumor markers and liver function tests were within normal limits.

Imaging diagnosis

An enhanced abdominal computed tomography (CT) scan showed a 7.4 cm \times 6.2 cm solid-cystic mass in the right hepatic lobe.

Pathological diagnosis

Postoperative pathology revealed a mixed-type gastrointestinal stromal tumor that was CD117- and CD34-positive.

Treatment

The patient was treated with a sequential therapy consisting of surgical excision, imatinib and sunitinib.

Related reports

Genetic analysis revealed a heterozygous point mutation and deletion in exon 11 of c-KIT.

Experiences and lessons

This case report excluded the diagnosis of metastases from GISTs using CT, ultrasound, esophagogastroduodenoscopy and colonoscopy. Additionally, a genetic analysis was used to confirm the tumor as a primary hepatic GIST.

Peer review

This case report verified the diagnosis using histological and genetic analyses. Furthermore, the patient underwent an extended sequential therapy consisting of surgery, imatinib mesylate, and sunitinib malate.

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