Gastrointestinal Stromal Tumors (GISTs): Case Report And Review Of The Literature

A. M. Al-Amri¹, M.A. Shawarbi², A. Y. El-Hassan³, K. S. Al-Johi²

¹Department of Internal Medicine, ²Department of Pathology, ³Department of Radiology
King Fahd Hospital of the University, Eastern Province, Al-Khobar, Saudi Arabia

Abstract

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract, the majority of which is KIT (CD117) positive. In this case report, we describe a case of recurrent and metastatic GIST who presented with hepatic and brain metastases. Despite the patient's GISTs was negative for c-Kit (CD 117), he responded to imatinib mesylate (Glivec) treatment with complete resolution of his liver and brain lesions. The patient has been and still in complete remission for 18 months of follow-up.

Keywords

GIST, Gastrointestinal stromal tumors

Introduction

Gastrointestinal stromal tumors (GISTs) are currently defined as c-Kit-positive (CD117) mesenchymal tumors in conjunction with specific histological characteristics that occur in the gastrointestinal tract.(1,2) GISTs have been classified as either benign or malignant with the majority of tumours diagnosed as benign. However, many pathologists and clinicians currently believe that all GISTs have at least some malignant after potential(1). Until recently, GISTs treatment consisted of resection followed by surveillance for metastatic disease. Chemotherapy and radiotherapy have been ineffective and unresectable for metastatic GIST is a fatal disease(3, 4)

Case Report

A 56-year- old Filipino male patient was diagnosed with gastrointestinal stromal tumors in November 1999. He initially presented with clinical features of gastrointestinal obstruction in the form of nausea, vomiting, severe abdominal pain and constipation with clinical findings of diffuse abdominal tenderness and rigidity. The patient was treated with surgical excision of the mass with small intestinal resection and re-anastomosis and the patient’s post-operative course was uneventful.

Pathological findings

Macroscopic examination revealed a firm mesenteric mass measuring 12x11x8 cm attached to a 28 cm long loop of small bowel. The mucosal surface of the bowel overlying the mass was flattened but the rest of the mucosa appeared normal. The cut section of the mass showed a central cavity containing hemorrhage, measuring 6 cm in diameter. The cut surface was fleshy, tan-brown with grayish-white and yellowish areas of necrosis. The resection margins were clear.

Microscopic examination revealed a well circumscribed fairly cellular neoplasm arising...
from the bowel wall, made up of fascicles and whorls of proliferating spindly cells (Figure 1). This tumor showed mild nuclear pleomorphism, rare mitosis and foci of necrosis and hemorrhage (Figure 2). The neoplastic cells showed positive cytoplasmic immunoreactivity for S100 protein (Figure 3). There was no reactivity for actin, desmin, CD 34 or CD117.

The surgical margins were free and post-operative CAT scan of the brain, chest and abdomen did not show any evidence of metastatic lesions. The patient was seen at regular bases in the oncology clinic. 2 years latter, he was admitted with abdominal distention. CAT scan of the abdomen showed enlarged liver and liver biopsy proved recurrence of GISTs. He was treated with imatinib mesylate (Glivec) but the medication was not taken regularly. 5 months latter, he was admitted with abdominal distention, blurring of vision, dizziness, dysarthria and confusion. His other previous illness was hypertension which was controlled with atenolol and amlodipine. On examination, he was dizzy, dysarthric, and not able to walk. His pulse was 90/minute regular and blood pressure (BP) 170/90 mmhg. He had hepatomegaly (Liver span 20 cm) and ascitis. His investigations at the time of recurrence were as follows: Complete blood count, renal function test, carcinoembryonic antigen, calcium, magnesium, random blood sugar, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), total protein and albumin were normal. Lactate dehydrogenase (LDH) 238 (140-190 U/L), alkaline phosphatase 267 (50-140 mg/dl) and gamma-glutamyl transpeptidase (GGTP) 423 (5-85 U/L). Computed tomography revealed enlarged liver with smooth outline. There was 20x16x15 cm sized well defined cystic mass in the right lobe of the liver with nodular thick wall, measuring about 16-20 mm. In addition there were multiple, hypodense lesions seen in the rest of the liver, both right and left lobes. Some lesion show central necrosis and no evidence of intrahepatic biliary dilatation. The cranial magnetic resonance imaging (MRI) showed multiple small low intensity lesions on T1-weighted images and hyperintense on T2-weighted images mainly involving the right fronto-parietal, periventricular, centrum semiovale and the left cerebellar hemisphere.

Fig. 2 : GISTs showing focal necrosis (Hematoxylin & Eosin x 250).

Fig. 3 : S-100 protein positive immunoreactivity in GISTs (IHC x 400).

Fig. 4 : MRI axial flair film showing multiple areas of increased signal intensities in the parietal and periventricular areas.
(Figure 4). These lesions were not contrast-enhancing and were not associated with edema or mass effect. The cerebrospinal fluid analysis were normal apart from protein 57.5 (15-45 mg/dl) The differential causes of these lesions included demyelinating diseases like multiple sclerosis, brain infarcts or vasculitis.

Imatinib mesylate (Glivec) treatment of 200 mg p.o twice a day was restarted. After 3 months of treatment the patient improved. The ascitis disappeared, the liver normalized in size and functions. The neurological symptoms disappeared completely and the abnormal findings seen in the MRI cleared as shown (Figure 5). Since the brain lesions were multiple, low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, improved simultaneously with liver lesions and cleared without residuals after the treatment, make gastrointestinal stromal tumors metastases more likely rather than multiple sclerosis, infarcts or vasculitis.

Discussion

The definition of the term “GISTs” has evolved rapidly in the past few years, as the pathophysiology of this disease was better understood. Tumours are now recognized as mesenchymal neoplasms that appear to be related to the intestinal cells of cajal of the myenteric plexus(5,6) Gastrointestinal stromal tumours express the cell-surface transmembrane receptor KIT that has tyrosine kinase activity and is the protein product of the KIT proto-oncogene(7) The presence of the c-kit protein also known as CD117 cell surface antigen in conjunction with specific histological criteria currently defines GISTs.(1) The acceptance of the c-Kit as a primary diagnostic marker has clarified the classification of these tumors. It has recently been reported that KIT activation occurs in all cases of gastrointestinal stromal tumors, regardless of the mutational status of KIT.

The symptoms and signs of GISTs vary according to tumour location, size of the tumour and rate of the growth. The most frequent clinical presentation is a palpable abdominal mass associated with vague gastrointestinal symptoms, which occur in 50% to 75% of patients. About one third of patients had gastrointestinal hemorrhage. Less frequent symptoms include anorexia, weight loss, jaundice and nausea(2, 6, 8)

GISTs rarely spread to regional lymphnodes (<10%) and metastases occur primarily within the abdomen. Distant metastases of GISTs most commonly involve liver (50-65%) and peritoneum (21-34%). Only 10% of metastatic lesions occur in the lungs or bones(2, 8, 9, 10, 11) Up to our knowledge, this is the first reported case of c-KIT negative gastrointestinal stromal tumors with brain metastases that respond completely to the non-chemotherapy treatment (Imatinib mesylate).

Until now, patients with unresectable or metastatic gastrointestinal stromal tumors have limited options of treatment and the disease is fatal. With the lack of response achieved with radiotherapy or chemotherapy, advanced malignant GISTs have been uniformly lethal. The median duration of survival for patient with metastatic gastrointestinal stromal tumors is approximately 20 months, and for patients with local recurrence is 9 to 12 after months(3). The bleak prognostic picture for patients with
malignant GISTs has recently changed with the availability of Imatinib mesylate, now referred to as Gleevec in the U.S.A. and Glivec in Europe. It is a small molecule with activity against a select number of related protein tyrosine kinase, including c-Kit, PDGF receptor, Abl and Bcr-Abl. Imatinib mesylate (Glivec) was approved for the treatment of adult patient with c-Kit (CD117)-positive unresectable and/or metastatic malignant gastrointestinal tumors (GISTs). The gastrointestinal stromal tumor of our patient, however, was c-Kit (CD117)-negative and the patient had multiple brain metastases. Irrespective of the above mentioned factors, imatinib mesylate (Glivec) induced effective response, excellent outcome and without adverse effects. The patient’s massive hepatomegaly normalized clinically and radiologically, liver function test become normal, neurological symptoms disappeared and the brain lesions seen in the MRI cleared. Since the institution of the treatment, the patient is in complete remission for 18 months.

In summary, by month 3 of treatment with imatinib mesylate (Glivec) our patient was in complete remission and free of symptoms with normal function status (an ECOG performance status of 0).

References