A Hemodialysis Patient with Primary Extra-gastrointestinal Stromal Tumor: Favorable Outcome with Imatinib Mesylate

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Abstract

Extra-gastrointestinal stromal tumors (EGISTs) are rare. We describe a 69-year-old man with a 9-year history of hemodialysis. This patient was diagnosed as having peritoneal tumors measuring over 10 cm in length. Histologically, the tumors were composed of monomorphic spindle cells. The number of mitotic figures was 5 per 50 high-power fields. Immunohistochemical analysis revealed strong positivity for c-KIT and MIB-1. He was treated with imatinib mesylate with no recurrences 20 months later. We present this first case of EGIST in a hemodialysis patient in which imatinib mesylate had a favorable outcome and also discuss the rarity of this case.

Key words: hemodialysis, EGIST, GIST, c-KIT, imatinib mesylate

Introduction

Gastrointestinal stromal tumors (GISTs) are one of the common mesenchymal tumors of the gastrointestinal tract. GISTs are estimated to occur in 0.001% to 0.002% of the population (1). These tumors are usually positive for CD117 (c-KIT), which is the specific defining immunohistochemical feature indicating c-kit proto-oncogene mutations for these groups of tumors (2). Extra-gastrointestinal stromal tumors (EGISTs) are neoplasms with immunohistological features overlapping those of GISTs and they occur in the abdomen outside the gastrointestinal tract with no connection to the gastric or intestinal wall (3). GISTs are mostly found in the stomach (40 to 70%), small intestine (20 to 50%), and colorectum (5 to 15%) (4). However, EGISTs are rare (5).

Accurate surgical resection and postoperative therapy with the single-agent KIT inhibitor imatinib mesylate (GLIVEC, STI571) is the gold standard treatment for GISTs (6). Imatinib mesylate is a break-through targeted therapeutic with three well-characterized molecular targets: BCR-ABL, c-KIT, and PDGFR (7, 8).

Case Report

A 69-year-old man was admitted to our hospital in September 2009 because of general fatigue and anemia. Eleven years previously, the patient was diagnosed as having diabetic nephropathy. Two years later, the patient eventually reached end-stage renal disease and was started on hemodialysis. His medical history included hypertension and ischemic heart disease in 2008. He did not have a history of alcohol consumption, smoking, or surgery. His family medical history was unremarkable.

His blood pressure was 121/42 mmHg, his pulse rate was 79 beats/min, and his temperature was 36.6°C. Physical examination revealed anemia in the palpebral conjunctiva, obvious abdominal distension, and microscopic blood in the stools. No icterus, swelling of lymph nodes, abdominal tenderness, peritoneal sign, or edema was observed. There was no complaint of appetite loss, weight loss, bowel habit...
Laboratory tests revealed the following results: white blood cell count, 6,530/mm$^3$; erythrocyte count, 232×10$^4$/mm$^3$; hemoglobin level, 6.7 g/dL; hematocrit, 21.0%; platelet count, 29.0×10$^4$/mm$^3$; total protein level, 6.7 g/dL; albumin level, 3.3 g/dL; blood urea nitrogen level, 33.8 mg/dL; creatinine level, 5.7 mg/dL; C-reactive protein level, 1.2 mg/dL; and ferritin level, 118.5 ng/mL. The levels of tumor markers drawn for CEA, CA-19-9, CA-72-4, STN, and alpha-fetoprotein were all within the normal range.

Upper gastrointestinal endoscopy revealed an ulcerative lesion in an irregular wall of the gastric antrum. Gastric biopsy showed a well-differentiated adenocarcinoma. Computed tomography (CT) of the abdomen showed ascites and multiple peritoneal nodules without connection with the gastrointestinal tract (Fig. 1). Abdominal ultrasonography also revealed peritoneal tumors measuring over 10 cm in length (Fig. 2). However, peritoneal fluid cytology revealed no malignancy. Whole-body CT was negative for lung parenchyma, liver lesions, and bone lesions.

Multiple biopsy samples were taken from a portion of a peritoneal tumor mass by surgical resection on the 26th day of hospitalization. The maximum diameter of the tumor mass that was resected for the biopsy was 11.2 cm. On sectioning the neoplasms consisted of whitish-grey and relatively firm areas (Fig. 3). Histological examination of the tumor tissue demonstrated the typical appearance of the GIST composed of cells with spindle-shaped nuclei (Fig. 4A). The number of mitotic figures was 5 mitosis per 50 high-power fields. Focal necrosis (Fig. 4B) and foci of mixoid degeneration were present (Fig. 4C). Immunohistochemical studies showed strongly positive staining of tumor cells for CD117 (Fig. 5A). The MIB-1 labeling index was approximately 13% (Fig. 5B). However, the tumor was negative for CD34, desmin, smooth muscle actin, and the S-100 protein. These findings strongly supported a diagnosis of high-risk EGIST of the peritoneum. A molecular genetic analysis for KIT protein mutation was not performed due to its unavailability in our institute.

The patient started treatment with oral imatinib at 400 mg daily on the 41st day of hospitalization. Endoscopic submucosal dissection (ESD) of gastric cancer was performed on the 71st day of hospitalization. The histopathological diagnosis of the gastric cancer was as follows: early gastric cancer resected by ESD, type 0, IIa + IIc, 40×24 mm, adenocarcinoma (tub1), T1 (M), ly0, v0, LM (-), VM (-). After these surgical and medical treatments, the patient had an uneventful hospital stay and he was discharged. An abdominal CT showed a marked tumor regression and ascites disappeared (Fig. 6). Presently, 20 months later, the patient remains in good condition on hemodialysis and is receiving 400 mg of oral imatinib on a daily basis. Furthermore no signs of tumor recurrence were observed.

Discussion

GISTs are currently considered to be derived from the interstitial Cajal cells (ICCs). Cajal cells are intermediates between the gastrointestinal (GI) autonomic nervous system and the smooth muscle cells regulating GI motility and autonomic nerve function (9). GISTs arise because of a mu-
EGISTs are mesenchymal tumors with clinicopathologic and genetic profiles similar to GIST. EGISTs arise outside the gastrointestinal tract and are usually localized in the omentum, mesentery, and retroperitoneum (3). Agaimy and Wünsch suggest that true EGISTs are extremely rare, comprising less than 1.5% of GISTs (5). The immunohistochemical features of EGISTs (13 omental and 10 mesenteric) were reported by Miettinen et al. (15). They showed that EGISTs are typically positive for CD117 and sometimes positive for alpha smooth muscle actin. However, similar to the present case, these EGISTs are all negative for CD34, desmin, and the S-100 protein. The prognosis of EGIST, similar to GISTs, mainly depends on mitotic activity and tumor size. Mitotic activity, cellularity, and the presence of necrosis have been found to be associated with poor outcomes (3, 4, 11, 16). Reith et al. found that a mitotic rate of >2/50 HPFs, the presence of necrosis, and high cellularity are useful in predicting the aggressive clinical behavior of EGISTs (17). Moreover, Yamamoto et al. showed that a high mitotic rate (>5/50 HPFs) and a high Ki-67 labeling index (>10%) indicate a significantly poor outcome (18). On the other hand, Yamamoto et al. also found that C-kit gene mutations do not correlate with the prognosis in patients with EGIST (18). In the present case, the tumor mass exceeded 10 cm in diameter. The Ki67 labeling index was approximately 13%. Histopathological examination revealed a rate of 5 mitoses per 50 HPFs and the presence of necrosis. On the basis of these observations our patient fulfilled the criteria of a malignant EGIST with high probability for poor outcomes. Furthermore, to the best of our knowledge, this is the first case of primary peritoneal EGIST and early gastric cancer occurring simultaneously. This simultaneous occurrence is unknown, thus this case is extremely rare.
Generally, patients with end-stage renal disease who require chronic dialysis are at a high risk of developing malignancy. There are many cases of gastroenterology cancer in such patients (19). After performing a literature search using MEDLINE from 1990 to 2011 using the search terms “gastrointestinal stromal tumor, extra-gastrointestinal stromal tumor, chronic kidney disease, and hemodialysis” we found one other case of GIST metastatic to the liver while on hemodialysis (20). However, no case of EGIST in hemodialysis patient existed. Therefore, to the best of our knowledge, we report the first case of EGIST in a hemodialysis patient.

Next, we will discuss imatinib mesylate. Imatinib is the first marketed “molecularly targeted therapy” for cancer. This means that the drug affects only those cells that express highly specific targets, in contrast to conventional cancer chemotherapies that affect all fast-growing cells in the body. The targets of imatinib in GIST patients are mainly two growth-factor receptors named c-KIT and PDGFR, and a corollary of this finding that the inhibition of these dysregulated tyrosine kinase signals is known to be therapeutically useful for the patients with GIST (7, 8). Thus, the introduction of imatinib mesylate, a tyrosine kinase inhibitor targeting c-KIT, has provided a much needed chemotherapeutical option for patients with both resectable and unresectable GISTS (21). In general, conventional chemotherapy has proven ineffective against GISTS (less than 10% response) and postoperative recurrence is observed in 40-90% of the patients treated with surgery alone (6, 22). On the other hand, imatinib mesylate has demonstrated a favorable response in more than one half of patients with advanced and unresectable or metastatic GISTS (23). Therefore, imatinib mesylate is considered to be the only therapeutic option for patients, such as ours, with unresectable EGISTS. In addition, Yamamoto et al. suggested that the application of imatinib mesylate could be a therapeutic strategy for EGISTS because they have kit alterations (18).

Imatinib mesylate is predominantly metabolized in the liver and is eliminated through the biliary route (24). However, data in patients with impaired renal function is not sufficient to guide the dosage in such cases. Pappas et al. evaluated the pharmacokinetics of imatinib mesylate and its main metabolite (CGP74588) in a hemodialysis patient who was receiving daily 400 mg of oral imatinib mesylate for the treatment of GIST metastatic to the liver, and they compared them with published data from subjects with normal renal function (20). Their results demonstrated that the pharmacokinetic values for imatinib and CGP74588 were respectively as follows: maximum concentrations, 3,340 and 781 ng/mL; time to maximum concentrations, 2 hours; half-lives, 18.2 and 34.0 hours; areas under the curve, 53.9 and 14.8 lg.h/mL; and trough concentrations, 1,540 and 508 ng/mL for at least 24 hours. In addition, all the obtained values showed that the pharmacokinetics of imatinib and CGP74588 do not change by hemodialysis and fall within the range of pharmacokinetics values expected from patients with a normal renal function (25). Furthermore, similar to our case, oral imatinib mesylate at 400 mg daily, the same dosage in subjects with normal renal function, was effective and safe for their patient. Thus, they concluded that the standard dosage of imatinib can be safely administered to...
patients on hemodialysis, and probably with renal failure, at any stage.

In conclusion, we report the first case of primary peritoneal EGIST in a hemodialysis patient. The prognosis of our patient was considered very severe. However, our patient was managed successfully with a standard dose of imatinib mesylate. At the time of his recent follow-up examination our patient showed no evidence of recurrent disease, but a close follow-up will be necessary because of the recent history of his high-risk EGIST.

The authors state that they have no Conflict of Interest (COI).

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References