

Subcapsular Liver Hematoma in Metastatic GIST Complicating Imatinib (Gleevec) Therapy

Sridhar Shankar, M.D.

We report two patients with metastatic gastrointestinal stromal tumor (GIST) who had large subcapsular hepatic hematomas that developed while on imatinib mesylate (Gleevec) therapy. We describe the pertinent radiologic features of the subcapsular hematomas in these patients, and discuss possible etiologies for the bleeding in each patient.

Introduction

Imatinib mesylate (Gleevec, Novartis Pharmaceuticals Corp, East Hanover, NJ) has been used successfully to treat chronic myelogenous leukemia [1]. The drug, a tyrosine kinase inhibitor, has also shown significant promise in clinical trials for gastrointestinal stromal tumor (GIST) by arresting and sometimes reversing the progression of disease [2, 3]. We report two patients who had an unusual, and hitherto unreported response to the drug--large subcapsular hepatic hematomas. We describe the pertinent radiologic features of the subcapsular hematomas in these patients, and discuss possible etiologies for the bleeding in each patient.

Citation: Shankar S. Subcapsular liver hematoma in metastatic GIST complicating imatinib (Gleevec) therapy. *Radiology Case Reports*. [Online] 2007;2:53.

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Abbreviations: CT, computed tomography; GIST, gastrointestinal stromal tumor; IVC, inferior vena cava; WBC, white blood cell;

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Published: August 13, 2007

DOI: 10.2484/rcr.v2i4.53

Case Report 1

A 49-year-old man was diagnosed with GIST when he presented with symptoms of bloating, increased abdominal size, and decreased appetite. He underwent exploratory laparotomy and resection of a circumscribed, nodular, 17 cm intra-abdominal mass arising from the small intestine. Pathology confirmed the diagnosis of GIST, positive for the oncogene c-kit. At that time, no other sites of involvement were seen either on CT or during the exploratory laparotomy. Approximately one year later he was found to have multiple liver metastases on follow-up CT, the largest being 6 cm by 5 cm. The extent and number of these lesions rendered the patient unsuitable for surgery or percutaneous ablation.

The patient was treated with several chemotherapy regimens unsuccessfully: carboplatin and taxotere, taxotere alone, as well as several experimental chemotherapeutic phase 1 drugs. All of these chemotherapeutic drugs were found to have limited or no effect, as evidenced by the increasing size of the liver lesions on serial CT scans over 34 months. The patient was then placed on an experimental protocol using STI-571 (imatinib mesylate, marketed as Gleevec, Novartis, USA), nearly three years after his primary tumor was discovered. Before initiation of the drug, he had a hemoglobin level of 12.8 gm/dL and a normal WBC

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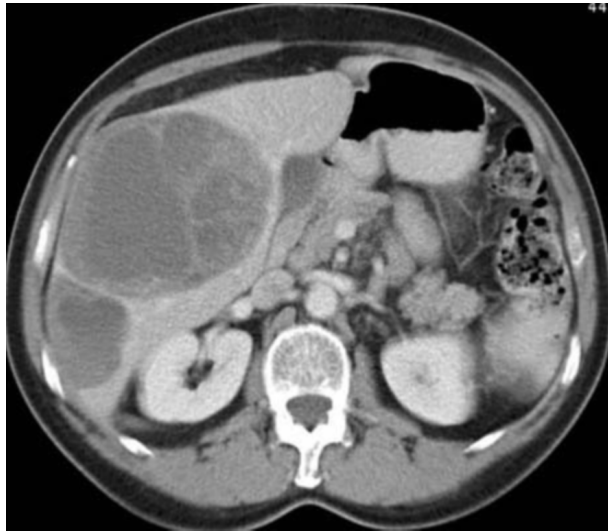


Figure 1A. 49-year-old man with metastatic GIST. Contrast enhanced axial CT scan through the liver 8 weeks after treatment with imatinib, shows two adjacent liver lesions that show cystic areas within them.



Figure 1B. Contrast enhanced axial CT scan through the liver at a higher level shows a tumor with internal fluid-fluid level (arrow) suggesting intratumoral hemorrhage.

count. He had no fever and liver function tests were within normal limits. The patient was started on the drug according to protocol requirements, at 600 mg by mouth daily. A pre-therapy CT guided percutaneous liver biopsy of the largest right lobe lesion revealed metastatic GIST.

A CT scan 8 weeks after initiation of therapy with imatinib showed that the liver metastases were reduced in size, and demonstrated cystic areas (Fig. 1A). One lesion, located immediately lateral to the inferior vena cava (IVC) had decreased the most—from a previous measurement of 5.2 cm x 4.3 cm, to 3.7 cm x 3.4 cm. This mass also demonstrated an intratumoral fluid-fluid level, suggesting hemorrhage (Fig. 1B).

Four months after initiation of therapy, the patient complained of acute right upper quadrant pain. Hemoglobin was 7.6 gm/dL, compared to the baseline of 12.8 gm/dL. The patient initially refused a blood transfusion. However, one week after the acute episode, his hemoglobin was 8.5 gm/dL and he was now lethargic, easily fatigued, pale, and short of breath. A CT scan performed at that time revealed a large hepatic subcapsular fluid collection around the right lobe, with layering of high-density material, consistent with a hematoma (Fig. 1C). The lesion lateral to the IVC (the lesion that had decreased most in size from baseline) was contiguous with the bleed.

His anemia was treated with a transfusion of 2 units of

packed red blood cells, following which the hemoglobin rose to 11.5 gm/dL. The daily dosage of imatinib was decreased to 400 mg, as per the study protocol. The patient was not hospitalized. Over the next three weeks, the patient progressively improved, with significant decrease in his right upper quadrant pain and flank tenderness. The patient's blood count was monitored on a weekly basis for several weeks. The patient became asymptomatic six weeks after the transfusion. A follow-up CT scan 3 months later (7 months after initiation of therapy) showed that the hematoma had nearly completely resolved (Fig. 1D). The size of the liver metastases continued to show significant improvement; the lesion lateral to the IVC had become imperceptible.

Case Report 2

A 57-year-old woman presented four years prior to the bleeding incident with vomiting and abdominal pain. At that time she had been diagnosed with a 20 cm mass in the pelvis, adherent to the small intestine. The tumor was resected, and pathology confirmed the diagnosis of c-kit positive GIST. Two years later, a CT scan revealed three abdominal masses in the right upper quadrant; a second surgical procedure was performed to remove these lesions. The patient was started on ET-743 and then CT-2584 ex-

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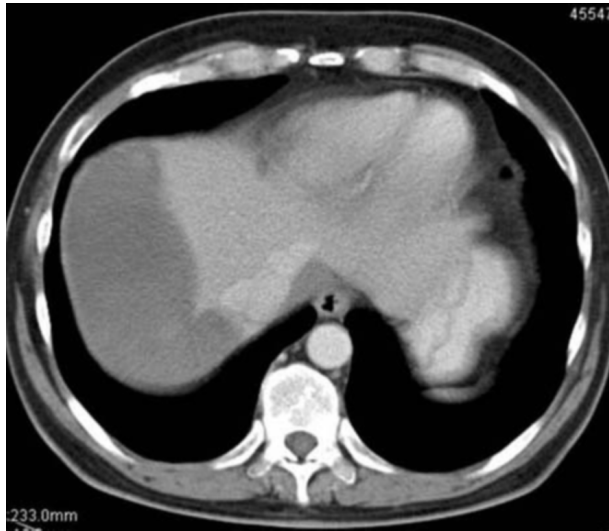


Figure 1C. Contrast enhanced axial CT scan through the liver 4 months after initiation of imatinib therapy, demonstrates a large variable density subcapsular liver collection, likely hematoma.



Figure 1D. Follow up contrast enhanced axial CT scan through the liver 7 months following initiation of imatinib therapy demonstrates near complete resolution of subcapsular liver hematoma.

perimental chemotherapy protocols; these failed to control disease progression. A third operation was performed six months later as a palliative measure, during which several large intra-abdominal masses were resected. Numerous liver lesions were noted intraoperatively. Intraoperative biopsy proved these to be metastases as well.

Approximately 3 years after the initial diagnosis, the patient began treatment with imatinib. A baseline CT scan showed multiple metastatic lesions in the liver (Fig. 2A). The patient presented to the emergency department with nausea, vomiting, and abdominal pain five days after initiating treatment. She was found to have a fever of 101.1 and a hematocrit of 24.4%, compared to 38% five days earlier. A CT scan at this time revealed new high attenuation fluid in the abdomen and pelvis, and around the liver. The patient was admitted urgently and a blood transfusion (4 units of packed cells) was given to correct her anemia. The patient was taken off imatinib for 3 days, but restarted after 2 weeks after she had stabilized.

A CT scan two months later continued to show high attenuation density in the abdomen and pelvis. A repeat scan five months later revealed a subcapsular hepatic hematoma (Fig. 2B) that was not as well-appreciated in the earlier scans, possibly owing to generalized intraperitoneal fluid; the hematoma was likely present the whole time. The liver lesions were decreased in size, as in the first case.

Discussion

These patients illustrate that hepatic subcapsular hematoma is a potential complication when imatinib is used to treat metastatic GIST. Both of our patients developed the subcapsular hematomas in the liver within four months of initiation of treatment with imatinib. They both lost substantial amounts of blood for which transfusions clinically were necessary to stabilize the patients.

Although its long term efficacy, susceptibility to recurrence, and safety are still being evaluated, imatinib has shown significant promise in treating GIST [2]. In past studies, the most commonly reported side effects included nausea, vomiting, diarrhea, and headache [2, 5]. In these studies, some patients showed internal bleeding, elevated liver function tests, and severe abdominal pain. These studies have shown a low number of such occurrences (less than 20%), and the potential risk in using the drug was outweighed by the invariably lethal consequences of metastatic GIST when left untreated, or when treated with other currently available chemotherapeutic regimens.

The subcapsular liver hematomas in our two patients were likely caused by some element of the tumor's response to imatinib versus other more common causes. One common cause of subcapsular hematoma is iatrogenic injury. The most common etiology for iatrogenic hepatic subcapsular hematoma is percutaneous liver biopsy [6]. These

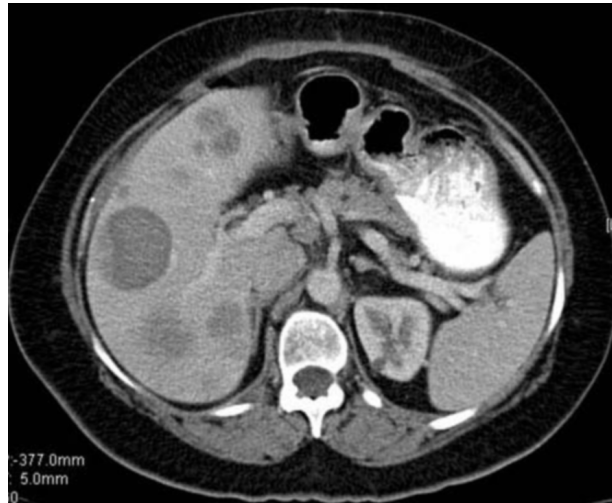


Figure 2A. 59-year-old woman with metastatic GIST. Baseline contrast-enhanced CT scan demonstrates multiple liver masses.

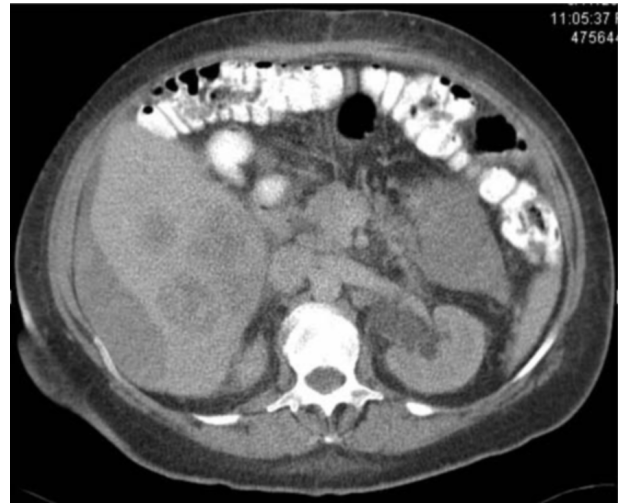


Figure 2B. Follow up contrast enhanced CT scan through the liver several months following the acute episode within a week of therapy clearly shows the subcapsular liver hematoma. The previously present masses are smaller.

bleeds have always been found to occur within two weeks of the procedure [7]. The patient in the first case report did have a liver biopsy; however, a CT scan performed two months later showed no signs of hemorrhage, and the lesion biopsied was likely not the tumor that bled. In addition, the patient had no symptoms immediately after this biopsy. The absence of CT or physical findings following the biopsy make it unlikely to have been the cause for this patient's hemorrhage.

Another possible cause of subcapsular hematoma is that it was secondary to a spontaneously hemorrhaging lesion. This cannot be fully excluded in our patients, but it is unlikely due to the close association between the treatment and the hemorrhagic episode. Bleeding into a liver tumor is not, in and of itself, uncommon. The commonest underlying tumors are hepatocellular carcinoma or hepatic adenoma [8].

It is likely that the subcapsular liver hematoma in our patient was caused by the tumor's response to imatinib. The mechanism of the bleeding could be from rupturing of vessels secondary to a rapidly retracting and shrinking tumor. In the first case, the lesion that responded the most to imatinib was shown radiographically to be contiguous communicate with the hemorrhagic collection. The second case also supports the association between response of liver metastatic GIST to imatinib and the resulting subcapsular liver hematoma although it is not possible to be certain

regarding the lesion that caused the hemorrhage.

As the indications for imatinib increase and its efficacy in treating GIST is further established, it is important for radiologists not to misread the occurrence of subcapsular hematoma as being a sign of progression of disease. Although the development of a liver subcapsular hematoma is apparently a sign of improvement, these findings, i.e., the hematoma itself, and possibly intraperitoneal hemorrhage (secondary to bleeding from intraperitoneal metastases) should be considered potentially life threatening. This fact should be kept in mind when evaluating images of patients with GIST being treated with imatinib. Awareness of this potential complication should result in earlier diagnosis and treatment of blood loss and anemia, and could thus decrease overall morbidity and mortality.

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