

Hepatitis B Viral Reactivation Secondary to Imatinib Treatment in a Patient with Gastrointestinal Stromal Tumor

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Abstract. *Hepatitis B virus (HBV) reactivation is a known risk in cancer patients receiving cytotoxic or immunosuppressive therapy; however, the risk associated with newer molecularly-targeted agents has not been well-quantified. Imatinib, a small molecule inhibitor directed against BCR-ABL, CKIT, and other tyrosine kinases, has been associated with HBV reactivation primarily in patients treated for chronic myelogenous leukemia. Herein we present the first reported case of a patient who developed HBV reactivation while receiving imatinib therapy for a gastrointestinal stromal tumor (GIST) in the adjuvant setting. This eventually resulted in fulminant liver failure and was effectively treated with living-related donor liver transplant and anti-viral medication. Currently, no guidelines exist for HBV screening prior to imatinib therapy. This report emphasizes the need for such guidelines and supports the idea that viral reactivation is a risk in all imatinib-treated patients, regardless of the underlying disease.*

Patients with chronic hepatitis B virus (HBV) infection who receive cytotoxic or immunosuppressive therapies are at risk of viral reactivation that can potentially result in fulminant hepatic failure (1, 2). The Centers for Disease Control updated their recommendations in 2008 regarding serological testing of HBV for select individuals undergoing such cancer treatment; specifically, routine testing was recommended for persons born in countries with an HBV surface antigen (HBsAg) prevalence of $\geq 2\%$, injection drug users, and HIV-infected individuals (3). Those who test

positive for HBsAg should then receive prophylactic anti-viral therapy to prevent reactivation.

However, cancer therapies vary widely in their degree of associated immunosuppression, and little is known about the risk of HBV reactivation associated with targeted agents such as oral tyrosine kinase inhibitors (TKI). We herein report the case of a patient who underwent resection of a primary gastrointestinal stromal cell tumor (GIST) of the stomach followed by adjuvant treatment with imatinib, who developed HBV reactivation and fulminant liver failure rescued by liver transplant.

Case Report

A 62-year-old man with no significant past medical history presented in March 2009 with epigastric discomfort. Diagnostic workup at that time included esophago-gastroduodenoscopy and computed tomography of the abdomen, which identified a mass in the greater curvature of the stomach (Figure 1). Fine needle aspiration revealed GIST, and he underwent laparoscopic wedge resection of the tumor with an uncomplicated post-operative course. Pathological examination demonstrated a 5.2×4.4 cm tumor with negative margins, 2 mitotic figures per 100 high-powered fields, and strong immunohistochemical staining for CD117 (C-KIT) and CD34. Recurrence risk was classified as low-intermediate, based on the Armed Forces Institute of Pathology guidelines (4).

The patient began adjuvant imatinib 400 mg per os daily in May 2009. At the time of treatment initiation, his hepatitis B status was unknown. Of note, he was of Chinese descent, was born in southeast Asia, and came to the United States in 2000. Laboratory tests two months into treatment revealed normal liver function, with AST 33 U/L (normal range 16-41 U/L) and ALT 30 U/L (normal range 12-59 U/L). However, follow-up labs in November showed new transaminase elevation (AST 163 U/L, ALT 252 U/L). Imatinib was held

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Key Words: Gastrointestinal stromal cell tumor (GIST), hepatitis B, reactivation, imatinib.

and the patient was subsequently confirmed to be positive for HBsAg, at which time entecavir was initiated. Repeat blood tests one week later showed a continued upward trend of his transaminases, with an AST now measuring 666 U/L and ALT 942 U/L, accompanied by increasing nausea, intermittent emesis, and confusion. He was admitted to his local Hospital on 12/5/09, at which time liver function testing revealed AST 994 U/L, ALT 2121 U/L, INR 3.6 (normal range=0.9-1.2), alkaline phosphatase 202 U/L (normal range=29-111 U/L), and total bilirubin 19.4 mg/dL (normal range=0.3-1.3 mg/dL). Ultrasound exam demonstrated no biliary dilatation. He was diagnosed with fulminant hepatic failure and subsequently transferred to our institution for consideration of emergency liver transplant.

At the time of transfer, he was noted to have grade III hepatic encephalopathy. He was intubated, started on continuous veno-venous hemodialysis, and received infusions of fresh-frozen plasma, factor VII, and prophylactic broad-spectrum antibiotics. Serologies were obtained and returned positive for HBV core antibody (anti-HBc) but negative for the IgM fraction of anti-HBc, and negative for HBV surface antibody (HBsAb). HBV DNA level was 56,600 IU/mL. On 12/10/09, the patient underwent orthotopic liver transplant (OLT), with his 43 year-old wife serving as donor. Pathologic analysis of the explant liver revealed massive necrosis (>60% hepatic parenchyma loss) with positive HBsAg staining in hepatocytes, consistent with HBV reactivation (Figure 2).

The patient's postoperative course was complicated by transient renal insufficiency and biliary stricture which resolved after endoscopic retrograde cholangiopancreatogram (ERCP) with endobiliary stent placement. His initial immunosuppression regimen consisted of tapering doses of prednisone together with mycophenolic acid and tacrolimus. For hepatitis prophylaxis, he was continued on entecavir and received a 6-day course of HBV immunoglobulin (HBIG). He was discharged on 12/16/09. The risks of additional imatinib therapy were weighed with regard to GIST recurrence *versus* HBV reactivation, and the decision was made not to resume imatinib.

In February 2010, the patient experienced HBV viral breakthrough, which was effectively treated with HBIG and upward titration of his entecavir dose. He has since been maintained on mycophenolic acid, entecavir, and HBIG every 14 weeks and has developed no subsequent viral breakthrough. Moreover, he has demonstrated no evidence of GIST recurrence on most recent surveillance imaging obtained 53 months after initial resection.

Discussion

Reactivation of hepatitis B viral replication (defined as an increase in HBV DNA levels ≥ 10 -fold compared to baseline, or an absolute increase of HBV DNA level exceeding

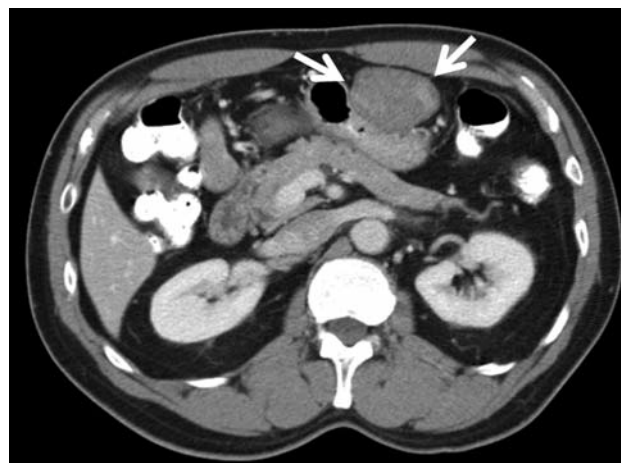


Figure 1. Abdominal CT imaging showing a rounded soft tissue lesion associated with the anterior greater curvature of the stomach (white arrows), biopsy-confirmed to represent GIST.

1,000 $\times 10^6$ genome equivalents/mL) (2) is a well-known consequence of immunosuppressive or cytotoxic therapy, and has been reported in 20-50% of viral carriers receiving such regimens without HBV prophylaxis (1, 2, 5). In such patients, the suppression of a chronic anti-viral immune response leads to unrestricted viral replication and extensive hepatocyte infection. Cessation of immunosuppression then leads to a vigorous immune response and destruction of infected hepatocytes (6), in some cases resulting in massive hepatic necrosis and fulminant liver failure.

In patients receiving targeted-therapies such as oral tyrosine kinase inhibitors (TKI), rates of HBV reactivation may be lower, due to this class of agents generally being associated with a less severe degree of immunosuppression. Imatinib (Gleevec, Novartis; Basel, Switzerland), a TKI with activity against the BCR-ABL fusion protein, C-KIT, and platelet-derived growth factor receptor (7-9), was initially approved by the FDA in 2001 for Philadelphia chromosome-positive chronic myelogenous leukemia (CML). It was subsequently shown to be effective in the treatment of C-KIT-positive advanced or metastatic GIST (10, 11) and was approved for this indication the following year. Later studies of GIST further established efficacy of imatinib in the adjuvant setting (12, 13), providing the rationale for our patient receiving treatment with this agent following resection of his primary tumor (14).

To our knowledge, this is the first case of HBV viral reactivation in a patient with GIST receiving imatinib monotherapy, although isolated cases have previously been reported in patients treated with imatinib for CML (15-20) and desmoid tumor (21). Interestingly, the immunosuppressive

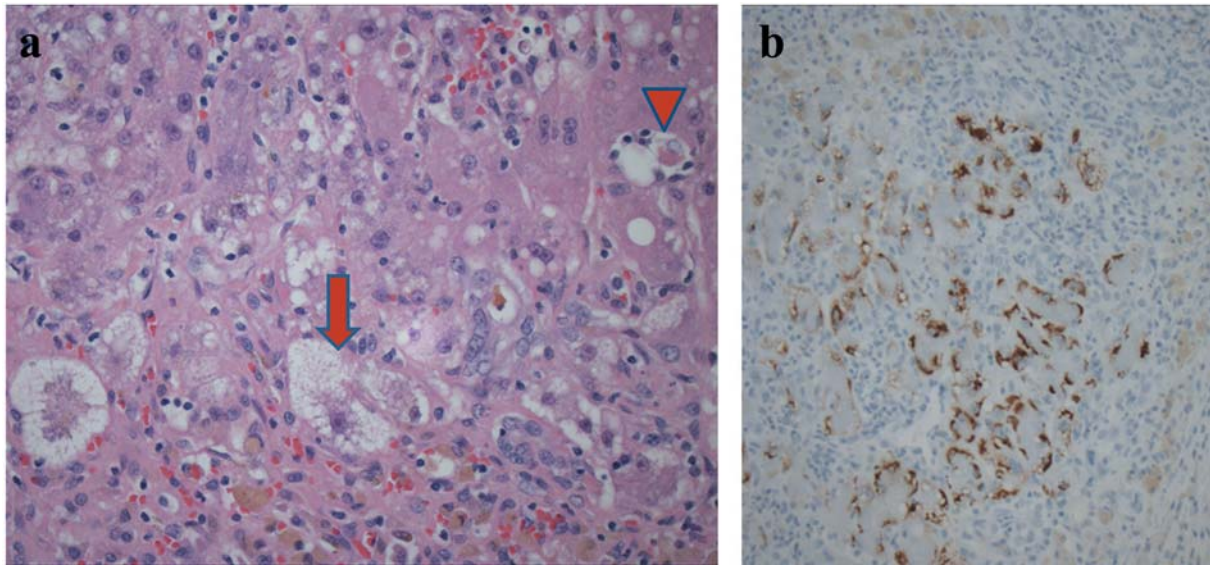


Figure 2. a: Liver explant, showing ballooned (arrow) and necrotic (arrowhead) hepatocytes (original magnification, $\times 400$). b: Liver explant showing positive staining for Hepatitis B surface antigen (original magnification, $\times 200$).

profile of imatinib may differ between patients treated for CML *versus* solid tumors such as GIST. In independent phase II studies of imatinib 400 mg daily, grade 3-4 neutropenia was observed in 35.1% of CML patients (22) and only 6.8% of GIST patients (10), suggesting that the severity of myelosuppression in CML may be related to the pathophysiology of the leukemic bone marrow. However, mounting evidence supports that imatinib may also affect the immune system in a clinically significant manner through a variety of other mechanisms, independent of underlying disease type. Imatinib inhibits the Src-family tyrosine kinase Lck (23), which regulates T-cell development, and has been shown to interfere with T-cell activation and proliferation *in vitro* and *in vivo* (24-27). It also inhibits the differentiation and function of CD34⁺ dendritic cells *in vitro* (28). In addition to hepatitis B reactivation, reported infectious complications of imatinib-related immunosuppression include cases of tuberculosis (29), candidal pneumonia (30), Epstein Barr Virus-positive lymphoproliferative disease (31, 32), and herpes zoster infection (33, 34).

When our patient developed transaminitis, it was reasonable first to consider that this was due to imatinib-related hepatotoxicity, a well-characterized adverse event associated with this drug (rates of grade ≥ 3 hepatotoxicity were roughly 5% for imatinib-treated patients in randomized phase III trials of both GIST (11) and CML (35)). However, his positive hepatitis B serology studies and the progression of hepatic dysfunction even after drug withdrawal made direct drug-induced liver injury less likely. Acute HBV infection was another possibility on the differential diagnosis, but the patient did not describe any recent

exposure risks. Furthermore, the patient's HBV serological profile was suggestive of reactivation of chronic disease rather than incident acute hepatitis. In a retrospective study by Kumar *et al.*, the combination of high levels of HBV DNA (>0.5 pg/mL or $\sim 28,600$ IU/mL) with low titers of IgM anti-HBc ($<1:1,000$, including reported negative IgM anti-HBc) yielded positive and negative predictive values of 96.3% and 100%, respectively, for diagnosing an exacerbation of chronic hepatitis as opposed to acute hepatitis (36). Thus, medical history, serological data, and pathologic examination of the explant liver all supported the diagnosis of reactivated HBV leading to fulminant liver failure in this patient.

When HBV reactivation occurs, it should be treated with anti-viral therapy and urgent referral to a transplant center if the clinical course is progressive. Several anti-viral options exist: use of lamivudine is well established and most extensively studied, while newer drugs like entecavir and tenofovir are more potent and have lower rates of drug resistance. Even with treatment, however, the mortality of chemotherapy-related HBV reactivation is roughly 20% (37). Thus, anti-viral treatment should be given prophylactically whenever possible, as benefits of treatment are greater when administered prior to a reactivation flare. In one study, prophylactic lamivudine administration was shown to reduce risk of viral reactivation and HBV-related hepatitis by $\geq 79\%$ (38). In the provisional clinical opinion on HBV screening for patients receiving chemotherapy, however, the American Society of Clinical Oncology found insufficient evidence to determine the net benefits and harms of routine screening

(39). The decision to screen is currently left to the discretion of treating physicians, with testing encouraged for those at heightened risk for chronic HBV infection or receiving highly immunosuppressive therapy, including hematopoietic cell transplantation and regimens containing rituximab. The most recent National Comprehensive Cancer Network guidelines for GIST (40) or CML (41) do not address routine HBV screening when starting imatinib therapy. Furthermore, even had our patient's HBV status been checked prior to initiating imatinib, prophylactic use of lamivudine or another antiviral agent may not necessarily have been recommended given the perceived low risk of clinically significant immunosuppression.

As demonstrated in this case report, hepatitis B reactivation can occur in previously asymptomatic patients at any point in the course of anticancer treatment. When fulminant hepatitis develops, the decision to proceed with OLT is complicated for cancer patients in whom prognosis may already be limited. However, since the presented patient had undergone complete surgical resection of his GIST and was categorized as low-to-intermediate risk of recurrence, and his wife was a compatible and willing donor, he was felt to be a suitable candidate for transplantation. While the currently accepted duration of adjuvant imatinib for resected GIST is one or three years (depending on tumor size and mitotic count) (13, 14) the patient received only 6 months of treatment prior to discontinuation. Imatinib was not restarted post-transplant, as the risk of recurrent viral reactivation due to prolonged immunosuppression was deemed greater than the marginally increased risk of GIST recurrence with suboptimal duration of treatment with imatinib. Gratifyingly, the patient remains disease free at most recent follow up, nearly 5 years after initial resection.

In summary, this is the first reported case of imatinib-related hepatitis B reactivation in a patient treated for GIST. This phenomenon has been previously reported on several occasions in patients with CML, in which viral reactivation poses a higher risk compared to GIST patients given the greater severity of imatinib-related immunosuppression. However, the presented case supports the hypothesis that HBV reactivation represents a potential risk in all imatinib-treated patients, regardless of underlying disease. A greater understanding of this conferred risk may lead to modified screening and treatment guidelines for imatinib-treated patients deemed to be at high risk for HBV infection.

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Received May 7, 2014

Revised May 23, 2014

Accepted May 26, 2014