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# Dasatinib-Induced CMV Hepatitis in an Immunocompetent Patient: A Rare Complication of a Common Drug[1]

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## Abstract

Dasatinib is a common anticancer drug used in the treatment of leukemia. Several side effects have been reported, the most common being myelosuppression, diarrhea, edema, and nausea. Three papers have been published reporting hepatic side effects of dasatinib treatment. A rare side effect of dasatinib treatment is reactivation of latent cytomegalovirus (CMV) infection. Never before has dasatinib therapy shown to be the cause of CMV hepatitis in an immunocompetent patient. We present a case of an immunocompetent patient who was treated with the standard dose of dasatinib therapy and subsequently developed CMV hepatitis. Well-known side effects of dasatinib therapy are understood and documented; unknown adverse drug reactions can occur and should be monitored for. This is a significant finding given the high rate of CMV seropositivity in the general population.

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## Introduction

Dasatinib is a common anticancer drug used in the treatment of leukemia, particularly Chronic Myelogenous Leukemia (CML). It is a relatively new tyrosine kinase inhibitor approved in 2006. Several side effects have been reported, the most common being myelosuppression, diarrhea, edema, and nausea, with diarrhea seen in 30% of patients and nausea reported in 20%. The first adverse hepatic effect of dasatinib therapy was reported in the literature in 2008. Since then, only three papers have been published that report hepatic side effects of dasatinib treatment. Another rare side effect of dasatinib treatment is reactivation of latent cytomegalovirus (CMV) infection in immunocompromised hosts. CMV hepatitis is often seen in the immunocompromised population; however, dasatinib has not yet been reported as a causative agent of CMV hepatitis. CMV reactivation has been documented as a side effect of dasatinib therapy in two cases. Neither of these cases reported hepatic involvement. Both reported cases of CMV reactivation resulted in hemorrhagic colitis. Never before has dasatinib therapy been reported to be the cause of CMV hepatitis in an immunocompetent patient.

## Case Report

A 42-year-old woman with a 5-year history of CML who was treated with dasatinib 100 mg q24h presented with a 12-day history of upper respiratory symptoms. She was seen in the emergency department and treated with a 5-day course of Tamiflu which failed to relieve her symptoms. The patient reported intermittent fevers accompanied by chills and body aches for which she took Motrin PRN. The patient stated that her children were sick at home with symptoms of an upper respiratory illness. She denied any cough or nasal congestion, sore throat, urinary symptoms, and abdominal pain. On initial examination, the lungs were clear to auscultation bilaterally. No lymph nodes were palpable on exam. S1 and S2 heart sounds were heard clearly with no murmurs. Abdominal examination revealed a soft, nontender abdomen with no guarding or rigidity in all quadrants. No rashes, cuts, bruises, or edema was noted on any exposed skin. The patient denied any muscle or joint pain. The patient had a history of diabetes mellitus and had a cholecystectomy 4 years before admission. On admission, she presented with a fever of 100.9°F. Her Point Of Care (POC) glucose was 161, white blood cell count was 4.0 K/μl, hemoglobin was 10.9 g/dl, hematocrit was 33.3 l, and platelet count was 472 K/μl. Aspartate aminotransferase was 200 U/l, alanine aminotransferase was 134 of U/l, alkaline phosphatase was 287 U/l, lactate

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[1] This case report highlights a rare and dangerous drug interaction of a common drug.

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dehydrogenase was 274 U/l, and total protein was 7.4 g/dl with an albumin of 3.2 g/dl. Anion gap was 11.3 mM, estimated glomerular filtration rate was >90.00 ml/min, magnesium was 1.9 mg/dl, mean corpuscular hemoglobin was 28.1 pg, mean corpuscular hemoglobin concentration was 32.0 g/dl, mean platelet volume was 7.5 fl, international ratio was 1.20, prothrombin time was 12.5 seconds, activated partial thromboplastin time was 22.8 seconds, red blood count was 3.20 m/μl, red cell distribution width was 20.4%, and mean corpuscular volume was 87.3 fl. Patient was started on levofloxacin for possible urinary tract infection or pneumonia given the unclear etiology of her unremitting fever. She remained on the drug for 5 days until it was discontinued despite the cause of the fever remaining unclear. Two-dimensional echocardiogram, and chest and lateral spine X-ray computed tomography of the chest, abdomen, and pelvis showed no significant findings. Given her episodic fever and elevated liver function tests, cultures were drawn for malaria and CMV, along with a malarial smear, fungal culture, Epstein-Barr virus (EBV), immunoglobulin (Ig) M, and *Clostridium difficile*. Results of malarial smear, fungal culture, EBV IgM, and *C. difficile* all were negative. CMV IgG showed positive IgG levels of CMV infection at 4.60 with a reference range of <0.91 being negative for infection and >1.10 being a positive result. CMV IgM for our patient showed a level of 4.0 with >1.1 being a positive result. Given the positive CMV IgM and IgG titers in conjunction with the elevation in liver function tests, a diagnosis was made of CMV hepatitis. The patient was subsequently started on gangciclovir at 5 mg/kg q12h IV for 14 days for induction therapy. Desatinib therapy was stopped during the treatment for CMV hepatitis. Ophthalmology examination was performed and showed a retinal hemorrhage of left eye not consistent with CMV retinitis, with no diabetic retinopathy. The patient was monitored until liver function tests returned to normal and her fever subsided. Dasatanib therapy was restarted, and a Peripherally Inserted Central Catheter (PICC) line was placed following the remission of her symptoms. The patient was subsequently discharged with gangciclovir and was given an outpatient appointment to monitor subsequent CMV levels.

## Discussion

CMV is a member of the herpesvirdae family. It is a double-stranded DNA virus that often affects immunosuppressed patients [1]. Active infection with CMV virus is rarely seen in immunocompetent hosts. Rather, it is usually the result of a reactivation of a latent infection caused by immunosuppression. For CMV to result in end-organ damage, CD4 count of less than 50 is expected, as often seen in AIDS patients [2]. The severity of CMV infection is positively correlated to viral load, with the highest viral load being responsible for end-organ damage. In particular cases, such as immunocompetent hosts and pregnant woman, CMV infection often mimics the signs and symptoms of an infection with EBV. The second most common presenting signs in immunocompromised host are central nervous system manifestations mimicking the presentation of influenza. Dasatinib is a tyrosine kinase inhibitor that is metabolized by CYP3A4. In addition to being metabolized by this cytokine, it also inhibits this same enzyme. The exact mechanism of the adverse effects of dasatinib therapy is unknown. It is postulated that the side effects may be the result of tyrosine kinase inhibitory effects in unintended locations [3]. There may also be specific inhibitor effects on PDGF, c-KIT, BCR-ABL, and SRC-family kinases. Induction of the SRC-family kinases may specifically inhibit T-cell and NK-cell function leading to reactivation of a latent infection in an immunocompetent host [3,4]. Dasatinib has been reported to inhibit platelet aggregation in 85% of patients being treated for CML. Therefore, bleeding is an expected complication [5,6]. There have been reported cases of CMV hemorrhagic colitis secondary to dasatinib treatment and even documented cases of pulmonary damage [2,7–9]. To date, there is only one documented case of dasatinib-induced hepatitis in which the patient had no evidence of an active CMV infection [10]. Detection of the CMV virus in host patients can be determined in several ways. The more popular methods are PCR, viral antigen, viral culture, and immunohistochemical staining. In our patient, the CMV virus was detected using levels of serum IgM and IgG antibodies. In the event of an acute flare-up, CMV infection can be detected by evaluating the concentration of IgG anti-CMV antibodies. Several imatinib-related cases of hepatic damage have been reported in the literature [5]. Imatinib-induced hepatic damage has been reported as soon as 2 months after initiation of treatment and as late as 2 years after initial treatment. The timeline of this adverse effect is not yet understood for dasatinib. An appropriate timeline for this side effect could provide a better guide to hepatic monitoring in patients being treated with dasatinib. Dasatinib therapy is aimed at creating a complete cytogenetic response within 12 months [10]. This response in patients correlates to a good prognosis and is currently the best hope for halting disease progression. This positive correlation between dasatinib treatment and disease regression occurs at the standard dose of 100 mg once daily. Our patient was on this regimen. Serious side effects noted at this dosage are of particular interest. This treatment modality is still fairly new, which makes awareness of rare side effects essential. Additional importance of this case lies in the possible use of imatinib as an alternative for treatment in patients with hepatic damage or increased risk factors for hepatitis. According to the CDC, 50% to 80% of US adults will be infected with CMV by the time they reach 40 years of age [1]. Given this high rate of infection with CMV, the dangers of reactivation of a latent infection as a result of drug therapy should be noted. This is of particular interest given the possibility of CMV-induced end-organ damage such as seen in our patient. We suggest that CML patients being treated with dasatinib therapy undergo testing for CMV infection before initiation of therapy. Once dasatinib therapy has been initiated in a CMV-positive patient, routine testing of CMV antibodies may help guide the course of treatment. In the event of a CMV reactivation, an alternative treatment may be a safer option to avoid complications. If dasatinib does induce CMV hepatitis as shown in our patient, treatment should be guided based on CMV seropositivity. In a CMV-positive patient, imatinib may be a safer alternative to dasatinib [11].

## References

[1] Cdc.gov (2015). CMV|overview|cytomegalovirus and congenital CMV infection|CDC; 2015 [N.p., 2015. Web. 13 Oct. 2015].

[2] Yassin, et al (2015). Cytomegalovirus-induced hemorrhagic colitis in a patient with chronic myeloid leukemia (chronic phase) on dasatinib as an upfront therapy. *Clin Med Insights Case Rep* , 77–81 [Web].

[3] Shimokaze Tomoyuki, et al (2009). Severe hemorrhagic colitis caused by dasatinib in Philadelphia chromosome–positive acute lymphoblastic leukemia. *Pediatr Hematol Oncol* **26**(6), 448–453 [Web].

[4] Kreutzman A, et al (2011). Expansion of highly differentiated CD8+ T-cells or NK-cells in patients treated with dasatinib is associated with cytomegalovirus reactivation. *Leukemia* **25**(10), 1587–1597 [Web].

[5] Quintás-Cardama A, Kantarjian H, Ravandi F, O'Brien S, Thomas D, Vidal-Senmache G, Wierda W, Kornblau S, and Cortes J (2009). Bleeding diathesis in patients with chronic myelogenous leukemia receiving dasatinib therapy'. *Cancer* **115**(11), 2482–2490 [Web].

[6] Erkut M, Erkut N, Ersoz S, Arslan M, and Sonmez M (2010). A case of acute colitis with severe rectal bleeding in a patient with chronic myeloid leukemia after dasatinib use. *Acta Haematol* **123**(4), 205–206 [Web].

[7] Yangzhen S, Liu K, Xu T, Yang Y, and Zhang Y (2015). Synchronous onset of CMV colitis and ulcerative colitis in an immunocompetent patient: a case report. *West Indian Med J* [n. pag. Web].

[8] Uslu U, Agaimy A, Hundorfean G, Harrer T, Schuler G, and Heinzerling L (2015). Autoimmune colitis and subsequent CMV-induced hepatitis after treatment with ipilimumab. *J Immunother* **38**(5), 212–215 [Web].

[9] Sillaber C, et al (2009). Immunosuppression and atypical infections in CML patients treated with dasatinib at 140 mg daily. *Eur J Clin Investig* **39**(12), 1098–1109 [Web].

[10] Bonvin A, Mesnil A, Nicolini FE, Cotte L, Michallet M, Descotes J, and Vial T, et al (2008). Dasatinib-induced acute hepatitis. *Leuk Lymphoma* **49**(8), 1630–1632 [Web].

[11] Hochhaus A, et al (2008). Dasatinib induces durable cytogenetic responses in patients with chronic myelogenous leukemia in chronic phase with resistance or intolerance to imatinib. *Leukemia* **22**(6), 1200–1206 [Web].