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# Suspected Drug-induced Liver Injury Due to 6-Mercaptopurine With a Superimposed SARS-CoV-2 Infection in a Patient With B-ALL

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**Summary:** 6-mercaptopurine is a chemotherapeutic drug that exhibits hepatotoxic effects due to its toxic metabolites. This report describes a case of suspected drug-induced liver injury exacerbated by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A 16-year-old male with very high risk B-cell acute lymphoblastic leukemia was admitted for hyperbilirubinemia 2 months after a 6-mercaptopurine dosage increase and found to have an active SARS-CoV-2 infection. Liver function improved throughout hospitalization and the patient was discharged on allopurinol. Following liver function after a dosage increase of hepatoxic chemotherapy and in a pediatric oncology patient with an active SARS-CoV-2 infection undergoing treatment is vital due to potential liver impact.

**Key Words:** acute lymphoblastic leukemia (B-ALL), severe acute respiratory syndrome coronavirus 2, 6-mercaptopurine

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Acute lymphoblastic leukemia is the most common cancer diagnosed in children, with ~85% of cases being B-cell acute lymphoblastic leukemia (B-ALL).[1] Maintenance therapy for B-ALL in the pediatric population consists of antimetabolite treatment that includes 6-mercaptopurine (6-MP) and methotrexate (MTX), both of which have well-studied side effect profiles.[1] 6-MP specifically has been shown to have thiopurine metabolites that exhibit hepatoxic properties. 6-MP is broken down into 6-thioguainine (6-TG) by hypoxanthine-guanine phosphoribosyl transferase and 6-methylmercaptopurine (6-MMP) by thiopurine S-methyltransferase.[2] Elevated levels of 6-MMP can lead to a nonobstructive intrahepatic cholestasis pattern of liver injury that presents with hyperbilirubinemia and elevated liver enzymes.[3,4] Drug-induced liver injury (DILI) due to 6-MMP occurs after a dosage increase with a delayed onset of symptoms and can occur regardless of any prior bouts of liver dysfunction.

In addition to DILI, viral infection has been known to exacerbate hepatic dysfunction leading to hyperbilirubinemia. The effects of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on patients undergoing chemotherapy for very high risk (VHR) B-ALL have not been elucidated to date. Jothimani et al[5] indicated up to 50% patients with SARS-CoV-2 infections exhibit liver dysfunction. Furthermore, data from a subset of patients at the beginning of the SARS-CoV-2 pandemic has shown infected patients with hematologic malignancies exhibited liver dysfunction comparable to those who did not have malignancies.[6] As result, we hypothesize that a SARS-CoV-2 infection could exacerbate liver dysfunction in those receiving hepatotoxic chemotherapy for hematologic malignancies. Herein, we present a case of suspected DILI in a patient on maintenance therapy for VHR B-ALL with a superimposed SARS-CoV-2 infection.

## CASE DESCRIPTION

A 16-year-old male with VHR B-ALL presented to the outpatient pediatric oncology clinic early December 2020 for maintenance cycle 4 per COG protocol AALL1131 with 15 mg intrathecal MTX and 2 mg intravenous (IV) vincristine (VCR). Chemotherapy at the beginning of cycle 4 included 6-MP 125 mg weekly and MTX 30 mg weekly. Of note, the patient's 6-MP dosage increased 25% per protocol late September 2020 due to 2 absolute neutrophil counts > 1500 at prior visits. The patient was not taking any additional medications outside of his chemotherapy regimen nor any supplements. There was no family history of hepatic disease, and the patient had no prior bouts of hepatotoxicity.

Labs drawn before IV VCR administration on day 1 revealed aspartate aminotransferase of 61, alanine aminotransferase of 81, total bilirubin of 3.8 mg/dL, and normal alkaline phosphatase. Physical examination was unremarkable. A blood test for fractionated bilirubin was subsequently obtained to determine the appropriate VCR dosage per protocol. However, this laboratory result was delayed, and the treating physician administered the full dose of 2 mg IV VCR. At home medications, day 1 of maintenance cycle 4 were 6-MP 150 mg daily, MTX 30 mg weekly, and prednisone 35 mg every morning and 30 mg every evening. On day 2, the direct bilirubin resulted at 3.3 mg/dL. The patient was notified to return for further laboratory work on day 3 which showed aspartate aminotransferase 140 IU/L, alanine aminotransferase 130 IU/L, total bilirubin 7.6 mg/dL (< 1.3 mg/dL), direct bilirubin 6.3 mg/dL (0.0 to 0.2 mg/dL), gamma-glutamyl transferase (GGT) 113 IU/L (8 to 55IU/L), prolonged prothrombin time 17.3 (1.6 to 12.5 s) and partial thromboplastin time 178.5 s (24 to 37 s).

The patient was therefore admitted for hydration and treatment of conjugated hyperbilirubinemia. Physical examination showed jaundice and scleral icterus. However, sore throat, loss of sense or smell, myalgias, congestion, nausea, vomiting, fever, abdominal pain, and fatigue were not endorsed. Oral trimethoprim-sulfamethoxazole and chemotherapy were held, while oral prednisone was continued for its 5-day course. Epstein-Barr virus, cytomegalovirus, and parvovirus B19 antibodies were ordered along with a SARS-CoV-2 polymerase chain reaction test and a hepatitis panel. Liver ultrasound revealed biliary sludge with no stones. IV vitamin K 5 mg every 24 hours for 3 days was started on day 3 to normalize coagulation values. Further workup revealed severely elevated 6-MMP at 35,302 pmol/8×10$^8$ red blood cell (RBC) (< 5700 pmol/8×10$^8$ RBC) and low 6-TG of 142 pmol/8×10$^8$ RBC (235 to 400 pmol/8×10$^8$ RBC) (Table 1). Natural killer cells and soluble CD25 values were found to be within normal limits.

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**TABLE 1.** Table Demonstrating Laboratory Values Over Time

| | Day 1 | Day 2 | Day 3 | Day 9 |
|---|---|---|---|---|
| AST (10-42 IU/L) | 61 | | 140 | 76 |
| ALT (10-60 IU/L) | 81 | | 130 | 161 |
| Alkaline phosphatase (67-372 IU/L) | 126 | | 126 | 122 |
| Total bilirubin (< 1.3 mg/dL) | 3.8 | | 7.6 | 1.7 |
| Direct bilirubin (0.0-0.2 mg/dL) | | 3.3 | 6.3 | 1.2 |
| GGT (8-55 IU/L) | | | 113 | 97 |
| PT (1.6-12.5 s) | | | 17.3 | 12.6 |
| INR | | | 1.5 | 1 |
| PTT (24-37 s) | | | 178.5 | 23.7 |
| 6-MMP (< 5700 pmol/ $8\times10^8$ RBC) | | | 35,302 | |
| 6-TG (235-400 pmol// $8\times10^8$RBC) | | | 142 | |

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; 6-MMP, 6- methylmercaptopurine; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; 6-TG, 6-thioguanine.

Liver function tests plateaued throughout days 3 and 4, and the patient continued to do well with no additional symptoms. The patient was discharged day 5 with pending viral labs, along with close follow-up in the outpatient clinic. Results on day 7 revealed a positive SARS-CoV-2 polymerase chain reaction test, while all other viral labs indicated no active infection. Labs drawn day 9 continued to trend towards baseline with decreased liver enzymes, direct bilirubin, GGT, and normal prothrombin time and partial thromboplastin time. Oral MTX 30 mg weekly and 6-MP 50 mg daily were restarted along with allopurinol 100 mg daily on day 29. The patient continued with treatment according to AALL1131, while 6-MP dosages were titrated back to 125 mg based on absolute neutrophil counts, thiopurine metabolite levels, and liver function tests.

## DISCUSSION

This case represents a report of a viral and DILI in a pediatric patient with VHR B-ALL in the setting of a concurrent a SARS-CoV-2 infection. Approximately 2 months post-6-MP dosage escalation, the patient was admitted for hyperbilirubinemia and labs indicative of nonobstructive intrahepatic cholestasis. Subsequent viral labs were positive for SARS-CoV-2 infection.

Publications from the SARS-CoV-2 pandemic have indicated varying levels of hepatic impacts due to infection. It has been established that elevations in GGT in the setting of cholestasis is caused by damage to the apical membrane of bile ducts and disruption of intracellular junctions due to high concentrations of biliary acids.[7] Cholangiocytes, which line the apical membrane of bile ducts, express Angiotensin-converting enzyme 2 receptors in a similar manner to that of type 2 alveolar cells, thus making itself a potential target of the SARS-CoV-2virus.[5] Li and Fan[8] reviewed patterns of liver injury in patients with SARS-CoV-2 and hypothesized injury was due to either direct cytotoxicity of the virus, uncontrolled immune reaction, sepsis, or DILI. This could represent a second-hit phenomenon, in which damage to cholangiocytes that line bile ducts from a SARS-CoV-2 infection could exacerbate the toxicity of hepatotoxic medication such as 6-MP. In addition, our patient received the full VCR dose of 2 mg with a total bilirubin of 3.8 mg/mL on day 1. Per protocol, this patient should have received 1.0 mg or half of the scheduled VCR dose. Multiple case reports have described transient elevations in transaminase values after administration VCR when administered with hepatotoxic chemotherapy.[9,10] It is possible this also could have exacerbated the preexisting hyperbilirubinemia observed in our patient.

6-MP is known to cause hepatotoxicity due to its metabolites, of which 6-MMP is the most hepatotoxic.[2,3,11,12] This typically presents with elevated liver enzymes, GGT, and hyperbilirubinemia with normal alkaline phosphatase, as seen in our patient.[4] Thiopurine S-methyltransferase genotyping completed at the time of diagnosis was negative for any poor metabolism genetic alterations. Yet labs during hospitalization indicated the metabolism of 6-MP to its metabolites had been shunted towards 6-MMP, in which allopurinol was started to balance metabolite levels of 6-TG and 6-MMP by increasing hypoxanthine-guanine phosphoribosyl transferase activity.[12] In addition, Bjornsson and colleagues indicated there is a delayed onset of DILI due to 6-MP after a dosage increase, specifically 3 weeks to 6 months between dosage increase and toxicity. Our patient's 6-MP was increased in 2 months before presenting with hyperbilirubinemia, thus falling into this reported time frame.

As a result, the liver injury observed in this patient is most likely primarily due to the dosage increase of 6-MP exacerbated by acute SARS-CoV-2 infection and full VCR dose that was administered in the setting of hyperbilirubinemia. Current COG protocols indicate that comprehensive metabolic panels should be completed once every 12 weeks regardless of dosage escalation or coexisting viral injection. Due to experience with this case, our institution now monitors bilirubin levels and liver function by ordering a comprehensive metabolic panel at every visit. Further, we encourage practitioners to withhold chemotherapy dosage increases and to monitor liver function closely in pediatric oncology patients who have a positive SARS-CoV-2 infection.

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