Hemolytic Anemia after Acute Hepatitis B Virus Infection: A Case Report and Systematic Review

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Abstract:
Hemolytic anemia and pure red cell aplasia are rare hematological complications of hepatitis B virus infection. We herein report a 24-year-old man who was diagnosed with hemolytic anemia and possible transient pure red cell anemia eight weeks after a severe episode of acute hepatitis B virus infection. Rapid recovery was observed with conservative management. Hemoglobin returned to baseline within three months. As the clinical features of hemolytic anemia associated with hepatitis B virus have not yet been elucidated, we conducted a systematic review and present an analysis of the 20 reported cases, including our present case.

Key words: hepatitis B virus, liver failure; hemolytic anemia, pure red cell aplasia, case report, systematic review

Introduction
Hepatitis B virus (HBV) infection affects about 400 million individuals worldwide (1, 2). HBV is a partially double-stranded DNA hepadnavirus that can be transmitted by blood or other bodily fluids (3). In addition to liver diseases, such as hepatitis, cirrhosis, and hepatocellular carcinoma, HBV infection can lead to extrahepatic manifestations, including polyarthritis, polyarteritis nodosa, glomerulonephritis, and hematological disorders, in 20% of affected individuals (4-7).

Anemia is a well-known hematological complication of viral infections, including hepatitis viruses (8). Hemolytic anemia is a type of anemia characterized by the destruction of red blood cells before their normal 120-day life span, which results in jaundice and hemoglobinuria derived from free hemoglobin (9). Hemolytic anemia as an extrahepatic manifestation of acute hepatitis is rare, particularly after HBV infection (10). HBV-related pure red cell aplasia (PRCA), another cause of anemia that results from a sharp reduction in erythroid precursors in the bone marrow, is exceedingly rare (11).

We herein report a case of severe hemolytic anemia after HBV infection that was successfully treated conservatively. The extremely low reticulocyte count prompted us to suspect co-existing transient PRCA. We also present a systematic review of hemolytic anemia after HBV infection.

Case Report
A 24-year-old man was admitted for gradual-onset dyspnea and weakness. His medical history was only significant for childhood asthma. He was a social drinker but had no history of smoking. He denied any history of blood transfusions, overseas travel, intravenous drug use, tattoos, ingestion of raw meats, or family history of hepatitis. However, he admitted to sexual intercourse with a commercial sex worker without protection one month earlier.

On admission, the patient was afebrile and vital signs were normal. No altered mental status was noted. A physical examination was only remarkable for severe jaundice. Initial laboratory values were significant for total bilirubin (TB) of 13 mg/dL, direct bilirubin (DB) of 9.9 mg/dL, alanine transaminase (ALT) of 4,191 IU/L, aspartate aminotransferase (AST) of 1,795 IU/L, alkaline phosphatase of 465 IU/L, lactate dehydrogenase (LDH) of 564 IU/L, prothrombin time (PT) of 16.6 seconds (57%), and an international normalized ratio

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The patient returned five weeks later due to new-onset cough, dyspnea, and malaise that had started two weeks earlier. The patient denied any new medications or supplements, alcohol consumption, contact with sick individuals, travel, or sexual contact after his discharge. His hemoglobin level had decreased markedly, from 13.9 (at discharge) to 5.9 g/dL. Curiously, the reticulocyte count had also decreased sharply, to 5,200/μL (0.25%). White blood cells and platelets were within the normal range. Bilirubin remained elevated (TB of 31.3 mg/dL and DB of 24.5 mg/dL), while transaminases and INR had improved. LDH had increased to 756 U/L, with an increase in LDH isozyme 1. Haptoglobin was undetectable (<10 mg/dL). Direct and indirect Coombs tests were negative. Parvovirus B19 serologies were consistent with past infection. Red blood cell-associated IgG was within the normal range, making Coombs-negative autoimmune hemolytic anemia (AIHA) unlikely. Antinuclear and anti-SSA/Ro antibodies were negative. Hepatitis envelope antigen seroconversion was confirmed. A urinalysis was positive for hemoglobin and urobilinogen. Small amounts of schistocytes were observed in the peripheral blood smear. Contrast-enhanced computed tomography showed no significant interval change, notable only for mild splenomegaly.

Esophagogastroduodenoscopy and colonoscopy showed no signs of gastrointestinal bleeding. The patient was diagnosed with hemolytic anemia. Concomitant PRCA was also suspected based on the sharp decrease in reticulocytes despite severe normocytic normochromic anemia.

The reticulocyte count had recovered markedly to 269,500/μL (9.26%) by two days later, when bone marrow aspiration was conducted and revealed slight hypercellularity with 272,500/μL nucleated cells. Erythroid hyperplasia was confirmed with an increase in CD71+ erythroid series (Fig. 1). The results of a chromosomal analysis were remarkable. While the erythroid hyperplasia could be attributed to a response to hemolytic anemia, hematologists believed it also reflected the recovery phase from transient PRCA.

The patient recovered rapidly with conservative management, including transfusion of four units of packed red blood cells. His hemoglobin level improved to 11.2 g/dL over four weeks (Fig. 2). No recurrence of liver failure or anemia was observed during 24 months of follow-up.

Discussion

Hemolytic anemia and HBV infection

Anemia after viral hepatitis has a relatively broad differential diagnosis, including gastrointestinal bleeding, splenomegaly due to portal hypertension, and vitamin B12 and folate deficiencies associated with alcohol consumption and nutritional deficits (8). Aplastic anemia (12), thrombocytopenia (7), leukopenia (13), hemolytic anemia (14), and PRCA (11) have all been reported in association with HBV.

Hemolytic anemia may be suspected based on clinical findings, such as anemia and jaundice, and diagnosed based on normocytic normochromic anemia, marked reticulocytosis, elevated indirect bilirubin, increased urinary urobilin, low urine urobilinogen, schistocytes on peripheral blood smear, and erythroid hyperplasia on bone marrow aspiration (9). Since the first report in 1976 (15), HBV infection
complicated with hemolytic anemia remains extremely rare. Hemolytic anemia is associated more frequently with hepatitis A virus (HAV), reported in up to 2.5% of affected patients (16, 17), and while rare, it has also been reported in the setting of hepatitis C virus (HCV) (18). Four mechanisms have been proposed for hemolytic anemia after viral hepatitis: weakened erythrocyte resistance due to direct viral action, rapid splenomegaly, erythrocyte fragility due to abnormal globulins, and increased hemolytic toxicants by decreased hepatic clearance (19). Hemolytic anemia may therefore occur immediately after HBV infection or during or after an episode of acute hepatitis.

There is some support for the use of antiviral agents in acute HBV infection, although data are limited (20). Entecavir may improve the clinical course of HBV-associated fulminant hepatitis and can reduce the risk of reinfection after liver transplantation (21, 22). In the present case, entecavir was started when the patient first met the criteria for fulminant hepatitis and the transplantation team was consulted.

While entecavir was briefly discontinued when severe anemia was first noted, recovery from hemolytic anemia and PRCA started the day after stopping entecavir. Recovery was too rapid for entecavir to have been the cause of hemolytic anemia and PRCA. We also found no reports of hemolytic anemia or PRCA associated with entecavir. Continued improvement was observed after carefully restarting the drug, ruling out entecavir-induced hemolytic anemia and PRCA.

We conducted a systematic review using MeSH terms and pre-defined criteria, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement (Fig. 3). Two researchers independently searched PubMed, EMBASE, and Ichushi from their inception to September 30, 2020, to review and extract data from relevant cases. Acute HBV was diagnosed based on the detection of hepatitis B surface antigen with elevated transaminases. Hemolytic anemia was diagnosed based on the presence of anemia, hemolysis evidenced by high LDH, high bilirubin, low haptoglobin, and/or increased reticulocyte count after the exclusion of other causes of anemia. Patients were only included if hemolytic anemia occurred concurrently with or within 10 years after the onset of HBV infection.

Nineteen cases from 10 studies were included (14, 15, 23-30). The clinical characteristics of the 20 cases including our case are summarized in Table. The median age was 28 years old, and 40% were men. Most cases were reported from Asia, with 75% originating in Japan. The average time between the HBV diagnosis and hemolytic anemia was 24.5 (range: 5-61) days. A fever was present at the onset of hemolytic anemia in 65% of cases. Eighty percent had acute HBV infection, and the remaining 20% had chronic infection; 2 cases in each group were treated with antiviral agents. Three out of five acute cases with INR data had acute liver failure, defined as INR ≥1.5 with no pre-existing cirrhosis or anticoagulant therapy, with or without encephalopathy. Both peak ALT (n=6, median: 2,112 U/L, range: 780-4,191 U/L) and peak TB levels (n=5, median: 29.0 mg/dL, range: 11.6-35.1 mg/dL) tended to be very high in acute HBV cases with a delayed onset of hemolytic anemia. Erythroid hyperplasia was the sole finding in all seven cases for which bone marrow findings were reported. Steroid therapy was introduced in 53% of cases. Anemia im-

Figure 2. Clinical course timeline. Hb: hemoglobin, Retic: reticulocytes, TB: total bilirubin, LDH: lactate dehydrogenase, HBeAg: hepatitis B envelope antigen, HBeAb: hepatitis B envelope antibody
proved within two months in 87.5% of cases, regardless of treatment. No mortality was reported.

The liver function had generally improved at the onset of the anemia, making an immunological mechanism more likely than direct hemolysis due to viral infection or liver damage. Reports of hemolytic anemia in chronic HBV infection also support this hypothesis (23, 28, 31).

The Coombs test positivity was low (23.5%), possibly due to Coombs-negative AIHA. AIHA is diagnosed based on evidence of a shortened erythrocyte survival in the setting of anti-red blood cell autoantibodies (32). Typical patients exhibit a positive direct antiglobulin test, but false-negatives occur in 5%-10% of cases (33). Such false-negatives can occur in severe hemolysis, causing rapid erythrocyte loss (34). In the present case, Coombs-negative AIHA was essentially ruled out using red blood cell-associated IgG. The association between hemolysis and specific HBV genotypes could not be investigated in our study, as none of the case reports mentioned genotypes.

The expected increase in indirect bilirubin at the onset of hemolytic anemia was not clear in our case. We believe this is due to the extremely high total bilirubin level, which lingered after the acute HBV episode and may have masked the increase in indirect bilirubin resulting from hemolytic anemia. Thus, total and direct bilirubin trends may not be reliable indicators of hemolytic anemia in patients with severe persistent hyperbilirubinemia.

While no risk factors for HBV-induced hemolytic anemia could be identified, the prognosis appears favorable. HBV-associated hemolytic anemia should be suspected when anemia develops approximately one month after the HBV onset.

**PRCA and HBV infection**

PRCA is characterized by severe normocytic anemia, reticulocytopenia, and the absence of erythroblasts in otherwise normal bone marrow (35). Most acute cases are acquired, induced by either viruses or medications (35, 36). Parvovirus is the most common viral cause (37). Approximately 30 cases of hepatitis-related PRCA have been reported, mostly in connection with HAV (38-51) but also with HBV (52), HCV (53), and hepatitis E virus (54). HCV cases are generally iatrogenic, resulting from treatment with...
### Table. Reports of Hemolytic Anemia in Patients with Hepatitis B Virus Infection.

| Author       | n | Age | Sex | Symptoms                                                                 | Days from symptoms to admission | Days from HBV to anemia | Peak ALT (U/L) | Peak TB (g/dL) | Hb (g/dL) | ALT (U/L) | LDH (U/L) | TB (mg/dL) | Reticulocytes | Haptoglobin (mg/dL) | Bone marrow aspiration | Coombs test | Type of HBV infection | Acute liver failure | Treatment for HBV | Treatment for anemia | Outcome | Days to recovery from anemia |
|--------------|---|-----|-----|--------------------------------------------------------------------------|---------------------------------|--------------------------|---------------------|---------------|-----------|-----------|-----------|-----------|-------------|---------------------|-------------------------|-------------|------------------------|----------------------|----------------------|-----------------------|----------|--------------------------|
| Vanderhoof¹⁵ | 1 | 17  | F   | jaundice, fever, chills, nausea, vomiting                               | 21                              | 9                        | 780                 | 29            | 9.9       | 160       | NA        | 29        | 27%         | 0                   | Erythroid hyperplasia  | -           | Acute                 | NA                   | NA                   | Transfusion           | Cure     | 18                       |
| Yoshioka²⁰  | 1 | 2   | M   | jaundice, fever, pallor                                                 | 21                              | 0                        | NA                  | NA            | NA        | 7.6       | 43        | 360       | 0.3        | 6%         | 0                   | NA                     | +(direct)   | Chronic               | Observation          | Observation          | Supportive            | Cure     | 21                       |
| Okafuji²¹   | 1 | 33  | M   | fever, abdominal pain                                                    | 14                              | 27                       | 2,615               | 11            | 6.2       | 143       | 1,704     | 11.7      | 66%        | ≤5                  | Erythroid hyperplasia | -           | Acute                 | No                   | Supportive           | Steroids              | NA       | Several                 |
| Ishiyama²²  | 1 | 25  | F   | fever, jaundice, abdominal pain                                          | 21                              | 48                       | 1,608               | 25.7          | 5         | 120       | 3,350     | 25.7      | 16%        | ≤20                 | Erythroid hyperplasia | -           | Acute                 | No                   | NA                   | Steroids              | NA       | NA                       |
| Nakayama²³  | 1 | 19  | F   | fever, malaise, jaundice, abdominal pain                                 | 14                              | 37                       | 1,035               | 32            | 4.9       | NA        | NA        | 32        | 172%       | ≤10                 | Erythroid hyperplasia | -           | Acute                 | Yes                  | Supportive           | NA                    | Cure     | 58                       |
| Kanematsu¹⁴ | 10| Mean |     | M:F 4:6                                                                  | NA                              | Mean 18.6               | NA                  | NA            | NA        | NA        | NA        | NA        | NA         | - (7 of 7)          | Acute                 | NA          | NA                     | NA                   | NA                   | NA                    | NA       | NA                       |
| Kaluyci²⁴   | 1 | 3   | M   | pallor, petechiae, ecchymoses                                            | NA                              | 0                        | NA                  | 5.3           | 144       | NA        | 14%       | NA        | +(direct)  | Chronic             | Antiviral            | Steroids   | NA                     | Cure                 | NA                   | NA                    | NA       | NA                       |
| Khawaja²⁵   | 1 | 10  | F   | pallor, malaise                                                           | NA                              | 0                        | NA                  | 2.7           | 121       | 975       | 3.8       | 41%       | NA         | +(direct)            | Chronic             | NA         | NA                     | Steroids              | NA                   | Transfusion           | Cure     | 37                       |
| Zhang²⁶     | 1 | 66  | F   | jaundice, loss of appetite, dizziness, palpitations, fatigue, nausea     | 28                              | 0                        | NA                  | 11.6          | 5.3       | 528       | 6.62      | 19%       | 0.3        | +(direct, indirect) | Antiviral            | Steroids   | Transfusion             | Steroids, rituximab | Cure                 | NA                    | NA       | 33                       |
| Furtado²⁷   | 1 | 41  | F   | nausea, jaundice, abdominal pain                                         | 7                               | 0                        | 2,889               | 6.2           | 2,889     | 1,163     | 22.9      | NA        | <0.24      | NA                  | -                     | Acute                 | Yes                    | Antiviral            | Supportive           | Cure 120               | <120     | NA                       |
| Our case    | 1 | 24  | M   | jaundice, fever, cough, dyspnea                                           | 5                               | 61                       | 4,191               | 5.9           | 62        | 756       | 31.3      | 0.25%     | ≤10        | Erythroid hyperplasia | -                     | Acute                 | Yes                    | Antiviral            | Transfusion           | Cure     | 28                       |

ALT: alanine transaminase, TB: total bilirubin, Hb: hemoglobin, LDH: lactate dehydrogenase, HBV: hepatitis B virus, NA: not available
interferon, ribavirin, mycophenolate mofetil, and epoetin alfa (55-58). Multiple pathological mechanisms of drug-induced PRCA have been suggested, including direct toxic effects on DNA synthesis by erythroid cells and indirect effects on accessory cells required for erythroid progenitor cells to differentiate into mature erythroblasts (59, 60). Reports of HBV-related PRCA (11, 52, 61, 62) suggest possible mechanisms, such as direct viral effects on hematopoietic cells, production of toxic substances by injured hepatocytes, an inability to inactivate erythropoietic toxins due to an impaired liver function, and autoimmune suppression of red blood cell production. However, the precise mechanism remains unknown. As many cases recover rapidly, the disease process may be transient and self-limiting in nature, possibly resulting from the reversible cell-mediated suppression of erythroid colony formation. Interestingly, the time interval of four to nine weeks from hepatitis to PRCA in published cases is similar to that of aplastic anemia, pancytopenia, and hemolytic anemia after HBV (11, 49, 63-66). Similar mechanisms may be involved in the viral inhibition of bone marrow hematopoiesis and selective targeting of immature bone marrow cells (67). As the mechanism underlying hepatitis-induced PRCA is not well understood, previous reports support the use of immunosuppressive agents in severe cases.

Although the delay in the bone marrow aspiration precluded a definite diagnosis of PRCA, transient HBV-associated PRCA was suspected in the present case. The time interval and transient, self-limiting nature were both consistent with previous reports.

**Hemolytic anemia and PRCA**

Hemolytic anemia and PRCA can occur in the same patient, either synchronously or metachronously (68). Synchronous autoimmune hemolytic anemia and PRCA have been reported in systemic lupus erythematosus (SLE), Sjögren’s syndrome, HAV, human parvovirus B19, and Epstein-Barr virus (35, 69-72).

There have been four reports of synchronous hemolytic anemia and PRCA associated with hepatitis viruses, all in the setting of HAV (38, 42, 50, 71). The average time from the diagnosis of hepatitis to the onset of anemia was about three weeks. All cases responded well to treatment with steroids (1-1.5 mg/kg/day) and blood transfusions. There have been no reports of both occurring after HBV infection.

The simultaneous development of hemolytic anemia and PRCA could only be explained by direct damage to erythroid progenitor cells and the presence of peripheral destruction of mature red blood cells (73). Given the reported association between hepatitis viruses and myelosuppression (74) and the presence of antibody-related collagen diseases, such as SLE and Sjögren’s syndrome, the possibility of antibody-induced hemolysis and myelosuppression should be considered (69, 70). As anemia resulting from autoantibodies against the erythroid system and effective control with immunosuppressants have been reported, steroids should be considered if the clinical course is not favorable (75, 76).

In our case, the marked decrease in the reticulocyte count could not be explained by hemolytic anemia alone, which usually triggers an increase in reticulocytes. The two disease processes may have both contributed to the rapid progression of anemia in our patient.

In conclusion, we herein report a case of acute HBV infection complicated by hemolytic anemia and possible PRCA that improved with conservative treatment. Further research should be conducted to determine the risk factors for hematological complications after acute viral hepatitis.

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

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