Acute hepatitis A infection-associated hemophagocytic lymphohistiocytosis in adult presenting as impending acute liver failure: A case report and literature review

Panotpol Termsinsuk | Piyaporn Sirisanthiti

1Gastroenterology unit, School of Medicine, Institute of Medicine, Suranaree University of Technology, Nakhon Ratchasima, Thailand
2Division of Hematology, Department of Internal Medicine, Maharat Nakhon Ratchasima hospital, Nakhon Ratchasima, Thailand

Abstract
Hemophagocytic lymphohistiocytosis has been reported as a severe complication of various viral infections but unusual for the hepatitis A virus. We report a case of 25-year-old man with hepatitis A infection-associated hemophagocytic lymphohistiocytosis and impending acute liver failure to emphasize the importance of early diagnosis and treatment of this condition.

KEYWORDS
case report, hemophagocytic lymphohistiocytosis, hemophagocytic syndrome, hepatitis A, hepatitis A virus, infection-associated hemophagocytic syndrome

1 | INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening condition characterized by clinical and laboratory evidence of extreme systemic inflammation resulting from uncontrolled immune activation. Diagnosis of HLH required any five of eight criteria based on the HLH-2004 guidelines, which consist of fever, splenomegaly, at least two lineages of cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, elevated ferritin, low or absent NK cell activity, elevated soluble CD25, and hemophagocytosis in bone marrow, spleen, or lymph nodes. HLH was categorized into familial and acquired. Acquired HLH usually arises in association with malignancy, infection, and autoimmune disease. Among infectious etiology, virus is the major contributor including the Epstein–Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus (HHV). Nevertheless, HLH has been rarely reported as the consequence of acute hepatitis A infection. Delayed diagnosis and treatment in unrecognized cases has resulted in high mortality. Herein, we present a case of 25-year-old man with acute high-grade fever, hepatomegaly, thrombocytopenia, and rapidly progressive hepatic dysfunction. Acute hepatitis A infection-associated HLH with impending acute liver failure was diagnosed and treated successfully with corticosteroid and intravenous immunoglobulin.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
© 2022 The Authors. Clinical Case Reports published by John Wiley & Sons Ltd.
2 | CASE REPORT

A 25-year-old man presented with high-grade fever for one day without any significant organ-specific symptoms. His past medical history was unremarkable. He denied alcohol consumption, herbal intake, and illicit drug use. A physical examination revealed body temperature (BT) of 39.5°C, non-tender hepatomegaly (liver span of 14 cm) without icterus, signs of chronic liver stigmata, ascites, and splenomegaly.

On admission, laboratory tests were significant for aspartate aminotransferase (AST) 303 unit/L (normal range 5–34), and alanine aminotransferase (ALT) 374 unit/L (normal range 0–55). The bilirubin level, alkaline phosphatase, complete blood count (CBC), and coagulogram were unremarkable (Table 1). The hepatitis panel was positive for hepatitis A IgM. Whereas hepatitis A IgG, hepatitis E IgM/IgG, dengue NS1 antigen, dengue IgM/IgG, EBV IgM/IgG, hepatitis B surface antigen, hepatitis B core IgM/IgG, hepatitis C antibody, anti-nuclear antibody (ANA), and HIV antibody were negative. An abdominal ultrasoundography showed hepatomegaly without space-occupying lesions. The visualized hepatic vein, portal vein, and biliary system were also unremarkable. Therefore, acute hepatitis A infection became the diagnosis based on his clinical presentation and initial laboratory findings.

During admission, he had persistent high-grade fever (BT: 39–39.5°C) with rapid deterioration of the liver biochemistry (Table 1). Serial blood tests revealed mild thrombocytopenia along with international normalized ratio (INR) prolongation, elevated serum lactate dehydrogenase (LDH), and hyperferritinemia. Given the rapidly progressive hepatic dysfunction and severe systemic inflammation, impending acute liver failure due to acute hepatitis A infection-associated HLH was suspected. The differential diagnosis of this condition included severe sepsis due to complicated bacterial septicemia, severe leptospirosis and rickettsial infection. Thus, hemoculture for bacteria and indirect immunofluorescent (IFA) test for Leptospira and rickettsia were sent and became negative.

A bone marrow study was urgently performed to establish the diagnosis. Increased histiocytes with multiple foci of hemophagocytosis were demonstrated on aspiration smears (Figure 1). Pulse intravenous dexamethasone at a dose of 40 mg/day was immediately started resulting in defervescence and marked improvement of the liver biochemistry, inflammatory markers, and thrombocytopenia within 72 h (Table 1). The bone marrow biopsy confirmed hemophagocytosis without any histologic and immunohistochemical evidence of lymphoma and EBV. Abdominal and chest computer tomography (CT) unrevealed lymphadenopathy that could suggest lymphoma. Intravenous immunoglobulin (IVIG) at a dose of 400 mg/kg/day for five days was then administered at Day 7 of the illness with a satisfactory result. Oral dexamethasone was tapered off over the next four weeks. There was no evidence of clinical and laboratory recurrence after a five-month follow-up.

### TABLE 1  Laboratory findings of patient in current report with acute hepatitis A infection-associated hemophagocytic lymphohistiocytosis

| Laboratory findings                  | Day 1 | Day 3 | Day 4† | Day 5 | Day 7‡ | Day 11 | Day 30 | Day 150 |
|-------------------------------------|-------|-------|--------|-------|--------|--------|--------|--------|
| Hemoglobin, g/dl                    | 16.1  | 14.9  | 15.0   | 16.0  | 13.1   | 13.3   | 13.5   | 14.8   |
| Leukocytes x109/L                   | 3.7   | 2.8   | 3.6    | 4.3   | 7.9    | 7.7    | 14.4   | 5700   |
| Platelet count x109/L               | 140   | 109   | 100    | 110   | 114    | 273    | 164    | 276    |
| Total bilirubin, mg/dl (normal 0–1.2) | 0.7   | –     | 3.5    | 4.4   | 7.3    | 2.8    | 1.2    | 0.7    |
| Direct bilirubin, mg/dl (normal 0–0.5) | 0.4   | –     | 2.8    | 3.5   | 4.6    | 1.3    | 0.4    | 0.1    |
| AST, IU/L (normal 5–34)             | 303   | 1486  | 5652   | 2872  | 526    | 74     | 43     | 25     |
| ALT, IU/L (normal 0–55)             | 374   | 1537  | 5397   | 5794  | 3560   | 838    | 134    | 45     |
| Alkaline phosphatase, IU/L (normal 40–150) | 98    | –     | 150    | 143   | 153    | 183    | 113    | 89     |
| INR                                 | –     | 1.07  | 1.34   | 1.29  | 1.24   | 1.02   | –      | 1.01   |
| Ferritin, ng/ml                     | –     | –     | 59332  | 53620 | 16272  | 1635   | 1308   | 756    |
| LDH, IU/L (normal 0–248)            | –     | –     | 6255   | 2541  | 688    | 154    | 243    | 252    |
| Triglyceride, mg/dl                 | –     | –     | 80     | 82    | –      | –      | –      | –      |
| Fibrinogen, mg/dL                   | –     | –     | 324    | 300   | –      | –      | –      | –      |

Abbreviations: AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; INR, International normalized ratio; LDH, Lactate dehydrogenase.

†Start high-dose dexamethasone
‡Start intravenous immunoglobulin (IVIG) 400 mg/kg/day for 5 days
3 | DISCUSSION

Hepatitis A virus (HAV), the RNA virus in the Picornaviridae family, is one of the most common causes of acute hepatitis worldwide. Primary transmission of HAV is the fecal-oral route via contaminated food and water. The incidence of HAV infection tends to be higher in low socio-economic and poor sanitation areas. Furthermore, the high-risk population includes males who have sex with males, HIV-infected patients, close contact of HAV-infected cases, and illicit drug users. Non-specific viral illness is the most common presenting symptom and usually self-limited. However, 0.5% of acute HAV-infected patients were complicated with acute fulminant hepatitis causing a high mortality rate up to 80%.

In addition to acute fulminant hepatitis, hemophagocytic lymphohistiocytosis (HLH) has been reported as a rare complication of acute HAV infection. HLH is the catastrophic hyperinflammatory condition caused by overstimulation of hemophagocytic activity of the macrophage in reticuloendothelial organs. For HAV-associated HLH, the virus triggers T-lymphocytes to release the inflammatory cytokines and stimulate massive hemophagocytosis. Delayed diagnosis and treatment of acute HAV infection-associated HLH result from the rarity of the disease entity and non-specific clinical presentation. Thus, the authors conducted a literature review from the PubMed, Google Scholar, and Cochrane databases till September 2021, using the following terms: "hepatitis A"; "hepatitis A virus"; "HAV"; "hemophagocytosis"; "hemophagocytic lymphohistiocytosis"; "haemophagocytic lymphohistiocytosis"; and "HLH". The publications were extracted only for the case report in adults (aged over 15 years at diagnosis). A total of 20 case reports (including the current patient) were reviewed, and the clinical data comprising the baseline characteristics, laboratory findings, clinical progression, treatment, and outcomes were obtained (Table 2).

The clinical characteristics of the reported cases from the literature review were analyzed using SPSS software for Windows, version 18 (SPSS, Inc.,) and delineated in Table 3. The mean age at diagnosis was 30.5 ± 11.2 years (range from 15 to 50 years), and 12 patients (60%) were male. The most common presenting symptoms were fever (95%) and jaundice (50%). On physical examination, hepatomegaly and splenomegaly accounted for 91.6% and 81.3%, respectively. In comparison with the study of MacKinney-Novelo et al., the presenting symptoms among uncomplicated acute HAV infection and HAV-associated HLH based on the reviewed data were comparable. However, hepatosplenomegaly was the predominant physical sign in HAV-associated HLH compared to those without HLH (81.3%–91.6% vs. 7%–78%).

Acute hepatitis A infection was diagnosed by HAV IgM in all reported cases. The test usually positive at the onset of the symptoms gave a high diagnostic sensitivity and specificity of more than 99%. Therefore, delayed diagnosis for acute uncomplicated HAV infection was not observed, and the diagnosis was usually made on their first admission of viral illness in the reviewed data. In contrast to HAV-associated HLH, four cases were diagnosed at 15–30 days after the improvement of their first episode of acute hepatitis A infection causing a delay in treatment and high mortality. The explanation for the delayed onset of HLH in these four cases was unclear. Nonetheless, it could be a result of delayed immune activation or a relapse of acute HAV infection ("relapsing hepatitis") causing an immunologic rebound and trigger more severe systemic inflammation.

Thrombocytopenia was the initial hematologic abnormality in HAV-associated HLH based on the reviewed data (Table 3). In childhood HAV infection, thrombocytopenia is usually caused by immune thrombocytopenia (ITP). However, in adult HAV infection, thrombocytopenia could be the early sign of HLH and usually progress to pancytopenia at the maximal disease activity. Thus, the superimposed HLH should be considered in acute HAV-infected patients who have thrombocytopenia on the initial presentation. Moreover, cytopenia of at least two lineages was required to complete the diagnostic criterion according to the HLH-2004 guidelines. Nevertheless, only 45% of HAV-associated HLH patients exhibited two lineages of cytopenia based on the reviewed data (Table 3). Thus, this criterion was ineligible to contribute to the early HLH diagnosis since more than two cytopenia usually occurred in the latter course of HLH.

Among uncomplicated HAV-infected patients, liver biochemical changes usually manifested as a mixed...
| Case | Authors | Year | Age | Sex | Presenting symptoms | Clinical progression | Treatment | Outcome | Remarks |
|------|---------|------|-----|-----|---------------------|--------------------|----------|---------|---------|
| 1    | McPeake JR²⁸ | 1993 | 20  | F   | Fever, headache, vomiting | Confusion, pancytopenia, jaundice | Hydrocortisone 50 mg IV every 6 h and IVIG | Alive | Still's disease |
| 2    | Kondo H²¹ | 1995 | 49  | F   | Fever, jaundice | Persistent fever, rash, pancytopenia | 1.5 g pulse IVMP and 250 mcg rhG-CSF | Alive |
| 3    | Wu CS²⁴ | 1995 | 23  | M   | Fever, jaundice for 3 weeks | Progressive pancytopenia, and hepatosplenomegaly | IV steroid | Died | HCV carrier ALF, DIC, GIB |
| 4    | Kyoda K²⁹ | 1998 | 40  | M   | Fever, anorexia | Self-limited | No specific treatment | Alive |
| 5    | Onaga M³⁰ | 2000 | 19  | F   | Fever, malaise, nausea, vomiting | Rapidly progressive thrombocytopenia | 1000 mg IVMP then tapered dose | Alive |
| 6    | Watanabe M²¹ | 2002 | 45  | M   | Headache, fatique, fever | Self-limited | No specific treatment | Alive |
| 7    | Watanabe M²¹ | 2002 | 41  | M   | Fever, hepatitis | Self-limited | No specific treatment | Alive | HCV carrier |
| 8    | Ishii H¹⁶ | 2003 | 37  | M   | Fever, fulminant hepatitis with partial clinical improvement | Died on Day 66 of admission. Autopsy confirmed HLH. | IVMP, vincristine cyclophosphamid, plasma exchange | Died | Aspergillosis abscess |
| 9    | Tai CM³¹ | 2005 | 32  | M   | Fever, malaise, splenomegaly | – | IVIG | Alive |
| 10   | Lee HJ³² | 2007 | 26  | F   | Fever, pancytopenia | – | Cyclosporine, dexamethasone, and IVIG | Alive |
| 11   | Tuon FF⁵ | 2008 | 24  | F   | Nausea, vomiting, myalgia, jaundice, fever (improved) | Persistent jaundice at Day 30 after onset with anemia, fever, and hepatosplenomegaly | IVIG 400 mg/kg/day for 5 days and G-CSF for 3 days | Alive |
| 12   | Cho E²³ | 2010 | 48  | M   | Fatigue, jaundice | Progressive jaundice with fever, rash, and acute kidney injury | IV steroid, G-CSF | Alive |
| 13   | Seo JY¹⁷ | 2010 | 22  | F   | Nausea, anorexia (improved) | Day 16 after onset, she developed fever, jaundice, pancytopenia, and hepatosplenomegaly | IVIG 400 mg/kg/day | Died | ALF, DIC, intraperitoneal bleeding |
| 14   | Park YH³³ | 2011 | 24  | F   | Fever, anorexia | Progressive jaundice, anemia, and thrombocytopenia | Dexamethasone 10 mg/m²/day IV and cyclosporin 3 mg/kg IV | Alive |
| 15   | Park HS²⁵ | 2012 | 28  | F   | Fever, cytopenia | – | Not available data | Died |
hepatocellular and cholestatic pattern. The average peak of total bilirubin (TB) was 7–9 mg/dL, whereas the mean AST and ALT levels could be higher than 1000 IU/L, which were similar to those with HAV-associated HLH based on the reviewed data.\(^7,12\) However, the patient of the current report had rapidly progressive hepatic dysfunction characterized by the increase of the AST and ALT levels above twentyfold of the upper normal limit within 48 h along with the INR prolongation (Table 1). All of these findings postulated the impending acute liver failure and raised suspicion of superimposed HLH.

Liver injury in HLH typically occurs in the early phase as a result of a cytokines storm and could rapidly progress to acute liver failure and death.\(^2\) Hepatic dysfunction would lead to various biochemical alterations, including hypertriglyceridemia (due to impaired lipoprotein lipase activity), hypofibrinogenemia causing subsequent coagulopathy, disseminated intravascular coagulation (DIC), and multiorgan dysfunction.\(^2\) The elevation of the LDH and serum ferritin was a result of cellular injury and severe systemic inflammation. Nonetheless, hypofibrinogenemia and hypertriglyceridemia were not observed in the patient of the current report, as the HLH was diagnosed in the early course.

Bone marrow aspiration and/or biopsy usually demonstrates hemophagocytosis in most reported cases. Bedside microscopic evaluation of aspiration smears provided prompt HLH diagnosis in the patient of the current report even though there were only three compatible diagnostic criteria including fever, hyperferritinemia, and bone marrow hemophagocytosis. The presence of at least five of eight criteria for the HLH diagnosis was observed only in seven patients (36.8%) based on the reviewed data (Table 3). Thus, the combination of the clinical findings, laboratory evidence of systemic inflammation, organ damage, and bone marrow hemophagocytosis was crucial for the HLH diagnosis even though there were incomplete HLH-2004 criteria. The HLH diagnostic criteria were usually fulfilled in the later course of the disease and could delay the diagnosis and treatment.

Standard treatment protocol for acute HAV-associated HLH was not well-established. Various treatment regimens for HAV-associated HLH have been reported, including corticosteroid, intravenous immunoglobulin (IVIG), and chemotherapeutic agent either single or combination therapy (Table 2). Twelve patients (63.2%) and eight patients (42.1%) in the reviewed data were treated with corticosteroid and IVIG, respectively. A chemotherapeutic agent was prescribed in three patients (15.8%) and usually combined with corticosteroid and/or IVIG. A granulocyte colony-stimulating factor (G-CSF) was used as an adjunctive treatment in three reported cases.\(^5,22,23\)

| Case | Authors | Year | Age | Sex | Presenting symptoms | Clinical progression | Treatment | Outcome |
|------|---------|------|-----|-----|---------------------|---------------------|-----------|---------|
| 16   | Saxena P\(^1\) | 2014 | 15  | M   | Fever, anorexia, nausea, vomiting (improved) | Progressive jaundice and pancytopenia | Oral prednisolone 25 mg/day then tapered-off within 10 days | Alive |
| 17   | Alhaddad OM\(^4\) | 2016 | 19  | F   | Jaundice and fatigue | Progressive pancytopenia | 1 g IVMP for 3 days, oral prednisolone 60 mg/day | Alive |
| 18   | Mallick B\(^15\) | 2019 | 21  | M   | Fever, jaundice, nausea, vomiting | Progressive jaundice and pancytopenia | IVIG 400 mg/kg/day for 5 days | Alive |
| 19   | Dogan A\(^6\) | 2021 | 50  | M   | Nausea, vomiting, fever, fatigue, and jaundice | Persistent fever, rapidly progressive hepatitis, and thrombocytopenia | IVIG 0.5 g/kg/day for 2 days and dexamethasone 10 mg/m\(^2\)/day IV | Alive |
| 20   | Our case | 2021 | 25  | M   | High-grade fever, hepatic encephalopathy, and thrombocytopenia | Persistent fever, rapidly progressive hepatitis, and impending ALF | Dexamethasone 10 mg IV every 6 h (tapered-off within 4 days), IVIG 400 mg/kg/day for 5 days | Alive |

Abbreviations: ALF, Acute liver failure; DIC, Disseminated intravascular coagulation; G-6-PD, Glucose-6-phosphate dehydrogenase; GIB, Gastrointestinal bleeding; HCV, Hepatitis C virus; HLH, Hemophagocytic lymphohistiocytosis; IV, Intravenous; IVIG, Intravenous immunoglobulin; IVMP, Intravenous methylprednisolone; rhG-CSF, Recombinant human granulocyte colony-stimulating factor.
Nonetheless, three patients (15.8%) were spontaneously resolved without treatment.

The patient of the current report was successfully treated with intravenous high-dose dexamethasone and IVIG without any evidence of clinical and laboratory recurrence at a 5 months follow-up. However, three reported cases of HAV-associated HLH died upon corticosteroid and/or IVIG treatment due to acute liver failure and superimposed infection.16,17,24 Although corticosteroid and IVIG seemed to be the effective treatment options in HAV-associated HLH, treatment initiation in the latter disease course eventually contributed to the poor treatment

### TABLE 3 Clinical characteristics of the reported cases of acute hepatitis A infection-associated hemophagocytic lymphohistiocytosis

| Characteristics                                      | Value                   | Data available |
|------------------------------------------------------|-------------------------|----------------|
| Age at diagnosis, years                             | 30.5 ± 11.2             | 20/20          |
| Male gender, n (%)                                  | 12 (60.0%)              | 20/20          |
| Clinical manifestation                              |                         |                |
| Fever                                                | 19 (95.0%)              | 20/20          |
| Jaundice                                             | 10 (50.0%)              | 20/20          |
| Nausea, vomiting                                    | 7 (35%)                 | 20/20          |
| Anorexia                                             | 4 (20%)                 | 20/20          |
| Hepatomegaly                                         | 11 (91.6%)              | 12/20          |
| Splenomegaly                                         | 13 (81.3%)              | 16/20          |
| Hemoglobin, g/dl                                     | 11.8 ± 4.2†, 6.6 ± 3.5‡ | 19/20†, 8/20‡  |
| Leukocytes x10⁹/L                                   | 3.7 (2.1–7.8)†, 3.0 (2.5–3.9)‡ | 19/20†, 8/20‡ |
| Platelet x10⁹/L                                     | 85 (37–147)‡, 80 (15–108)‡ | 19/20‡, 11/20‡ |
| At least two lineages of cytopenia                   | 9 (45.0%)               | 20/20          |
| Total bilirubin, mg/dl                              | 7.8 (2.0–30.0)†, 22.0 (6.5–30.0)‡ | 19/20†, 13/20‡ |
| AST, IU/L                                            | 1212 (351–2982)†, 906 (351–5652)‡ | 15/20†, 10/20‡ |
| ALT, IU/L                                            | 731 (350–2456)†, 1797 (400–5794)‡ | 18/20†, 10/20‡ |
| Alkaline phosphatase, IU/L                           | 299.5 (162.0–411.5)†, 150 (119–321)‡ | 12/20†, 3/20‡ |
| Ferritin, ng/ml                                      | 3558.3 (1499.7–59332.0)†, 34051 (5724–61466)‡ | 13/20†, 4/20‡ |
| LDH, IU/L                                            | 3071 (1447–5679)†, 5439 (2938–6255)‡ | 14/20†, 6/20‡ |
| Triglyceride, mg/dl                                 | 386 (138–579)‡, 493 (212–520)‡ | 11/20†, 5/20‡ |
| Fibrinogen, mg/dl                                    | 267 (218–462)‡, 296.7 (171.2–440.5)‡ | 7/20†, 3/20‡ |
| NK cell activity, %                                  | 7‡                      | 1/20†          |
| Soluble CD25 (sIL2R), IU/ml                          | 2590 (1920–4870)†       | 3/20†          |
| Hemophagocytosis in bone marrow                     | 13 (100.0%)             | 13/20          |
| Bone marrow aspiration                               | 13 (100.0%)             | 13/20          |
| Bone marrow biopsy                                   | 10 (100.0%)             | 10/20          |
| Complete five of eight diagnostic criteria§         | 7 (36.8%)               | 19/20          |
| Treatment                                            |                         |                |
| Steroid                                             | 12 (63.2%)              | 19/20          |
| Chemotherapeutic agent                               | 3 (15.8%)               | 19/20          |
| IVIG                                                 | 8 (42.1%)               | 19/20          |
| Spontaneous resolution without treatment             | 3 (15.8%)               | 19/20          |
| Mortality rate                                       | 4 (20%)                 | 20/20          |

Data are presented as mean ± standard deviation or median (interquartile range) and number (proportion) of patients with a condition according to the available data.

Abbreviation: AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; LDH, Lactate dehydrogenase; IVIG, Intravenous immunoglobulin; sIL2R, Soluble interleukin-2 receptor.

†Value at diagnosis.

‡Value at maximal disease activity.

§Based on HLH-2004 guideline.
outcomes, especially in those who already had significant organ failure. A chemotherapeutic agent was not initiated in the patient of the current report, as he was in clinical and laboratory remission after corticosteroid and IVIG treatment.

The overall mortality rate of HAV-associated HLH was 20%, whereas the 30 days mortality and overall mortality of adult HLH were 20%–44% and 50%–75%, respectively.25–27 The cause of death in the reported cases of HAV-associated HLH was acute liver failure and superimposed disseminated fungal infection.16,17,24 Delayed immunosuppressive therapy and presence of acute liver failure at treatment initiation might be associated with death according to the reviewed data (Table 2).

In conclusion, this case report emphasized the importance of early diagnosis and treatment of HAV-associated HLH. Thus, clinical, laboratory, and hemophagocytic evidence is crucial for diagnosis and would encourage prompt treatment even with incomplete HLH diagnostic criteria. Although the standard treatment approach in adult HAV-associated HLH is not well-defined, early immunosuppressive therapy would be the cornerstone for improving survival and evading fatal complications. Hence, further clinical studies could elaborate a more effective treatment paradigm for HAV-associated HLH.

ACKNOWLEDGMENT
Not applicable.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS
PT provided clinical and pathological diagnosis, performed literature review, images acquisition, and wrote the manuscript. PS acquired information of the patient, provided pathological diagnosis, supervised for the treatment and followed up. All authors have read and approved the final manuscript.

ETHICAL APPROVAL
Not applicable.

CONSENT
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no datasets were generated.

ORCID
Panotpol Termsinsuk @ https://orcid.org/0000-0002-7011-5060

REFERENCES
1. Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood. 2015;125(19):2908-2914.
2. Henter J-I, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124-131.
3. Fisman D. Hemophagocytic Syndromes and Infection. Emerg Infect Dis. 2000;6(6):601-608.
4. Ansuini V, Rigante D, Esposito S. Debate around infection-dependent hemophagocytic syndrome in paediatrics. BMC Infect Dis. 2013;13(1):15.
5. Tuon FF, Gomes VS, Amato VS, et al. Hemophagocytic syndrome associated with hepatitis A: case report and literature review. Rev Inst Med Trop São Paulo. 2008;50(2):123-127.
6. Lemon SM, Ott JJ, Van Damme P, et al. Type A viral hepatitis: a summary and update on the molecular virology, epidemiology, pathogenesis and prevention. J Hepatol. 2018;68(1):167-184.
7. MacKinney-Novelo I, Barahona-Garrido J, Castillo-Albarran F, et al. Clinical course and management of acute hepatitis A infection in adults. Ann Hepatol. 2012;11(3):652-657.
8. Lin KY, Chen GJ, Lee YL, et al. Hepatitis A virus infection and hepatitis A vaccination in human immunodeficiency virus-positive patients: a review. World J Gastroenterol. 2017;23(20):3589.
9. Radha Krishna Y, Saraswat VA, Das K, et al. Clinical features and predictors of outcome in acute hepatitis A and hepatitis E virus hepatitis on cirrhosis. Liver Int. 2009;29(3):392-398.
10. Murohashi I, Yoshida K, Ihara N, et al. Serum levels of Th1/Th2 cytokines, angiongenic growth factors, and other prognostic factors in young adult patients with hemophagocytic syndrome. Lab Hematol. 2006;12(2):71-74.
11. Watanabe M, Shibuya A, Okuno J, et al. Hepatitis A virus infection associated with hemophagocytic syndrome: report of two cases. Intern Med. 2002;41(12):1188-1192.
12. Tong MJ, El-Farra NS, Grew MI. Clinical manifestations of hepatitis a: recent experience in a community teaching hospital. J Infect Dis. 1995;171(Supplement. 1):S15-S18.
13. Routenberg JA, Dienstag JL, Harrison WO, et al. Foodborne outbreak of hepatitis A: clinical and laboratory features of acute and protracted illness. Am J Med Sci. 1979;278(2):123-137.
14. Liaw YF, Yang CY, Chu CM, et al. Appearance and persistence of hepatitis A IgM antibody in acute clinical hepatitis A observed in an outbreak. Infection. 1986;14(4):156-158.
15. Lemon SM. Type A viral hepatitis: epidemiology, diagnosis, and prevention. Clin Chem. 1997;43:1494-1499.
16. Ishii H, Yamagishi Y, Okamoto S, et al. Hemophagocytic syndrome associated with fulminant hepatitis A: a case report. Keio J Med. 2003;52(1):38-51.
17. Seo JY, Seo DD, Jeon TJ, et al. A case of hemophagocytic syndrome complicated by acute viral hepatitis A infection. Korean J Hepatol. 2010;16(1):79.
18. Saxena P. Hepatitis A induced hemophagocytic syndrome. Trop Gastroenterol. 2014;35(2):122-124.
19. Shenoy R. Thrombocytopenia in hepatitis A-An atypical presentation. *J Trop Pediatr*. 2004;50(4):241-244.

20. Biswas B, Mondal M, Thapa R, Mallick D. Childhood hepatitis A virus infection associated with immune thrombocytopenic purpura: report of two cases. *Med J Dr Patil Univ*. 2015;8(4):547.

21. Padhi S, Sarangi R, Patra S, et al. Hepatic Involvement in Hemophagocytic Lymphohistiocytosis. In Teodor Streba C, Constantin Vere C, Rogoveanu I, Tripodi V, Lucangioli S, Eds. *Hepatitis A and Other Associated Hepatobiliary Diseases* [Internet]. IntechOpen; 2020. [cited 2021 Sep 24]. Available from: https://www.intechopen.com/books/hepatitis-a-and-other-associated-hepatobiliary-diseases/hepatic-involvement-in-hemophagocytic-lymphohistiocytosis

22. Kondo H, Date Y. Effects of simultaneous rhG-CSF and methylprednisolone “pulse” therapy on hepatitis A virus-associated haemophagocytic syndrome. *Eur J Haematol*. 2009;54(4):271-273.

23. Cho E, Cha I, Yoon K, et al. Hemophagocytic syndrome in a patient with acute tubulointerstitial nephritis secondary to hepatitis A virus infection. *J Korean Med Sci*. 2010;25(10):1529.

24. Wu CS, Chang KY, Dunn P, et al. Acute hepatitis A with coexistent hepatitis C virus infection presenting as a virus-associated haemophagocytic syndrome: a case report. *Am J Gastroenterol*. 1995;90(6):1002-1005.

25. Park HS, Kim DY, Lee JH, et al. Clinical features of adult patients with secondary hemophagocytic lymphohistiocytosis from causes other than lymphoma: an analysis of treatment outcome and prognostic factors. *Ann Hematol*. 2012;91(6):897-904.

26. Parikh SA, Kapoor P, Letendre L, Kumar S, Wolanskyj AP. Prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis. *Mayo Clin Proc*. 2014;89(4):484-492.

27. Li J, Wang Q, Zheng W, Wang W, Tian X. Hemophagocytic lymphohistiocytosis: clinical analysis of 103 adult patients. *Medicine (Baltimore)*. 2014;93(2):100-105.

28. McPeake JR, Hirst WJR, Brind AM, Williams R. Hepatitis A causing a second episode of virus-associated haemophagocytic lymphohistiocytosis in a patient with Still's disease. *J Med Virol*. 1993;39(2):173-175.

29. Kyoda K, Nakamura S, Machi T, Kitagawa S, Ohtake S, Matsuda T. acute hepatitis A virus infection-associated hemophagocytic syndrome. *Am J Gastroenterol*. 1998;93(7):1187-1188.

30. Onaga M. A case of acute hepatitis A with marked hemophagocytosis in bone marrow. *Hepatol Res*. 2000;17(3):205-211.

31. Tai CM, Liu CJ, Yao M. Successful treatment of acute hepatitis A-associated hemophagocytic syndrome by intravenous immunoglobulin. *J Formos Med Assoc Taiwan Yi Zhi*. 2005;104(7):507-510.

32. Lee HJ, Chung JS, Shin HJ, et al. A case of hemophagocytic lymphohistiocytosis accompanied by acute hepatitis A: review of the literature. *Korean J Hematol*. 2007;42(1):62.

33. Park YH, Kim DY, Kim SD, et al. A case of hemophagocytic syndrome as a complication of acute hepatitis A. *Korean J Med*. 2011;80(2):278-282.

34. Maha ME. Complicated hepatitis A virus infection: a report of three cases from single tertiary referral center. *J Clin Intensive Care Med*. 2016;014-20.

35. Mallick B, Daniel P, Dutta U. Hepatitis A infection related hemophagocytic syndrome: a case report and systematic review. *Trop Doct*. 2019;49(3):234-238.

36. Dogan A, Demircioglu S, Ekinci O. Acute hepatitis-A virus infection as a rare cause of hemophagocytic lymphohistiocytosis. *J Coll Physicians Surg Pak*. 2021;31(02):232-234.

How to cite this article: Termsinsuk P, Sirisanthiti P. Acute hepatitis A infection-associated hemophagocytic lymphohistiocytosis in adult presenting as impending acute liver failure: A case report and literature review. *Clin Case Rep*. 2022;10:e05334. doi:10.1002/ccr3.5334