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CASE REPORT

ACUTE HEPATITIS OF UNKNOWN ORIGIN (AHUO) IN AN INFECTIOUS DISEASE REFERRAL HOSPITAL: A CASE REPORT

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Abstract

The World Health Organization (WHO) reported Acute Hepatitis of Unknown Aetiology (AHUA) occurred in children in several countries, including Indonesia. Before this study was conducted, the cause and treatment were unknown. The Ministry of Health reported 91 cases in less than 16 years old children which spread across 22 provinces in Indonesia. This is a case report which was part of a surveillance program at Sulianti Saroso Infectious Disease Hospital (SSIDH) in 2023. The treated probable AHUA case was 16 years and 10 months old, while other studies reported probable AHUA cases d"16 years old. Of the 17 patients suspected AHUA who were treated at SSIDH, one case was categorized as probable AHUA. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin levels were elevated. Tests for hepatitis B (HBsAg), hepatitis C virus (HCV) antibodies (Ab), hepatitis A IgM, and hepatitis E IgM were all negative. Length of Stay (LoS) hospitalisation was 12 days, and the patient has recovered. Adequate identification and management of cases were carried out by paediatricians so that severe conditions do not occur.

Keywords *AHUA, Probable, Surveillance, Case report*

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Introduction:

The World Health Organization (WHO) reported a mysterious case of Acute Hepatitis of Unknown Origin (AHUO) in children younger than 16 years in the United Kingdom and Northern Ireland on April 15, 2022[1,2]. Similar cases have been reported in Central Scotland, the United States, Israel, and Japan[2,3]. On July 8, 2022, the WHO reported 479 cases of mysterious acute hepatitis spread across Europe (23 countries), the American (eight countries), the Western Pacific Region (one country), Southeast Asia (two countries), and the Eastern Mediterranean (three countries). Meanwhile, as of August 26, 2022, the number of similar cases had increased dramatically to 1115 cases that spread across 35 countries worldwide. Most were female (52%) and aged six or older (76%)[4].

The agent of this hepatitis case is still unknown. Hepatitis A, B, C, D, and E tested negative[1], while some cases were confirmed for SARS CoV-2 or adenovirus[5]. The literature mentions the presence of adenovirus or SARS-CoV-2 in children with mysterious acute probable hepatitis, as well as the role of microorganism agents and other risk factors[6].

AHUO definition varies in several countries; however, the patient's clinical symptoms and age are the most important criteria, as well as the exclusion of hepatitis A, B, C, D and E infection[7]. Clinical signs are characterized by increased AST or ALT levels (>500 U/L)[8,9], along with jaundice[9] and sometimes with gastrointestinal symptoms[7] such as nausea, vomiting, abdominal pain, and diarrhea[9]. For cases with a poor prognosis, consultation with a pediatric hepatologist is required as some cases are treated with liver transplantation[5,10] and some others cause death[11]. Of there was no history of international travel[10].

The Ministry of Health reported 91 cases in less than 16 years old children which spread across 22 provinces in Indonesia. Jakarta Metropolitan Area was the province that contributed the most cases, with 12 cases[12]. SSIDH, an infectious disease referral hospital, reported there were 17 suspected cases of AHUO admitted to the hospital, one of them was included as probable AHUO. In this study, we described the case, its symptoms, clinical signs, laboratory, and findings management of AHUO in SSIDH.

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Case report:

A 16-year-old Javanese boy was referred from PHC with suspected AHUO. He was admitted due to persistent abdominal pain for 7 days. The Javanese boy also experienced jaundice for 4 days (Fig. 1), malaise, vomiting only once but felt nauseous, poor appetite, dark urine and acholic stool. He had a history of diarrhoea two days before admission and no history of fever. He was previously healthy and denied taking any prescription, over-the-counter or herbal medications. He had no exposure history to patients with COVID-19 and received the second dose of inactivated COVID-19 vaccine nine months before admission. He also had no history of hepatitis. He lives with his parents and an older sister. The other family members don't experience the same symptoms. The family consume bottled drinking water for drinking and cooking.

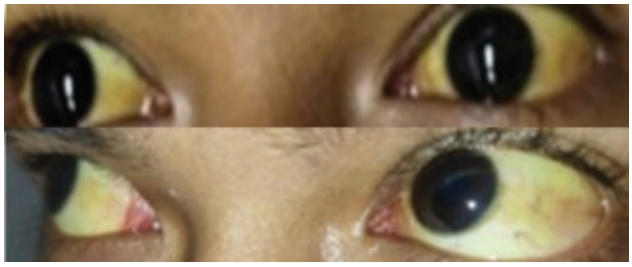

Fig.-1: *Jaundice and icteric sclera appearance*

Physical examination revealed that the teenager had normal vital signs, low weight-for-height, scleral icteric, jaundice, and hepatomegaly (2 cm below the rib edge). While the spleen was not palpable, he had upper abdominal tenderness. He was hospitalized for 10 days and discharge in good condition (Table 1).

Data was gathered from investigational forms of AHUO and electronic medical records. Laboratory supporting data, such as PCR EBV, ENT, CMV, ADV, leptospira, and whole genome sequencing (WGS) of Hepatitis E, were examined at the Research Laboratory for Infectious Diseases Prof. Dr. Sri Oemijati, Health Ministry of Indonesia.

The biochemical tests showed high levels of ALT (1005 U/L), AST (1276 U/L), gamma-glutamyl transferase [(GGT) 112 U/L], total bilirubin [(TB) 16.7 mg/dL] and direct bilirubin [(DB) 10.3 mg/dL). The coagulation function was within the normal range and the albumin level was slightly low (3.2 mg/dL). No abnormality was found in the blood routine and acute phase reactant (Table II). The patient underwent infectious pathogen screening. Evidence of hepatitis A, B, C, and E virus infection was not found. PCR examination on blood and nasopharynx specimens showed *Cytomegalovirus* (*CMV*), *Epstein-Barr* virus (*EBV*), adenovirus (*AdV*), enterovirus, and leptospiral infection were not found. *Klebsiella Oxytoca* and S*taphylococcus aureus* were detected in the blood.

Abnormal transaminase enzymes total and direct bilirubin, Gamma GT, INR and IgG Covid-19 were detected. Filmarray/Nested-Multiplex examination used Filmarray BioFire Gastrointestinal Panel 2.1 to detect *Campylobacter, Clostridium difficile toxin, A/B. Plesiomonas shigelloides, Salmonella, Vibrio, Vibrio Cholera, Yersinia enterocolitica, Enteroaggretative Escherichia coli (EAEC), Enteropathogenic E. coli (EPEC) lt/ st, Shiga-like-toxin-producing E.coli (STEC), E.coli O157, Shigella/ Enteroinvasive E.coli (EIEC), Cryptosporidium, Cyclospora cayetanensis, Entamoeba hystolytica, Giardia lamblia, and Adenovirus F40/41, Astrovirus, Norovirus GI/GII, Rotavirus A* and *Sapovirus*. The patient didn't undergo a liver biopsy due to parental rejection.

Abdominal ultrasound indicated hepatosplenomegaly with increased intrahepatic vascular (Fig.-2). Chest X-rays showed normal heart and lungs.

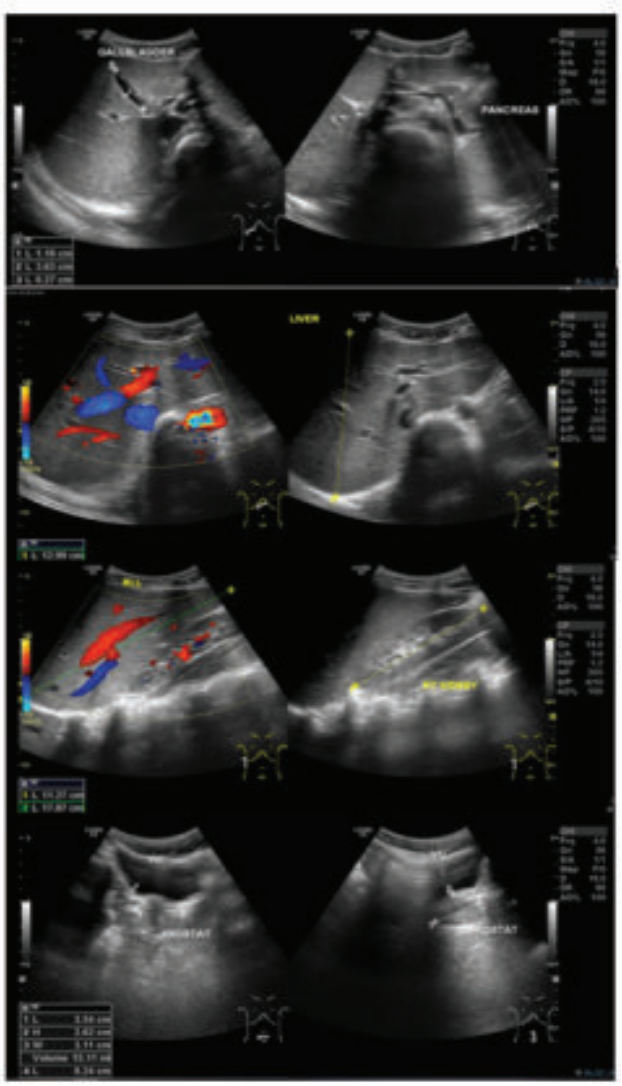

Fig. 2. *The Abdominal Ultrasound results show normal descriptions of the gallbladder, pancreas, kidney, and prostate. The liver's measurement shows a craniocaudal size of 17.87 cm, inhomogenous echostructure, and increasing intrahepatic vascularization, which indicates acute hepatitis.*

Table I

Clinical sign and symptoms

Day	Signs and Symptoms										
	Fever	Abdominal Pain	Nausea	Vomit	Diarrhoea	Acholic faeces	Urine color	Headache	Icteric	Jaundice	Hepatomegaly
Day -9	-	+	-	-	-	-	Clear-Yellow	-	-	-	N/A
Day-8	-	+	+	-	-	-	Clear-Yellow	-	-	-	N/A
Day -5	-	+	+	-	-	-	Clear-Yellow	-	+	+	N/A
Day-3	-	+	+	-	-	+	Clear-Yellow	-	+	+	N/A
Day-1	-	+	+	-	+	+	Clear-Yellow	-	+	+	N/A
Day 0*	-	+	+	+	+	+	Brown	-	+	+	+
Day 1	-	+	+---	+	+	+	Brown	+	+	+	+
Day 2	-	-	+	-	-	-	Brown	+	+	+	+
Day 3	-	-	-	-	-	-	Brown	-	+	+	+
Day 4	-	-	-	-	-	-	Dark yellow	-	+	+	+
Day 5	-	-	-	-	-	-	Dark yellow	-	+	+	+
Day 6	-	-	-	-	-	-	Dark yellow	-	+	+	+
Day 7	-	-	-	-	-	-	Dark yellow	-	+	+	+
Day 8	-	-	-	-	-	-	Clear-Yellow	-	+	+	+
Day 9	-	-	-	-	-	-	Clear-Yellow	-	+	+	+
Day 10	+	-	-	-	-	-	Clear-Yellow	-	+	+	+
Day 11	+	+	-	-	-	-	Clear-Yellow	-	-	+	+
Day 12	-	-	-	-	-	-	Clear-Yellow	-	-	-	+
Day 21	-	-	-	-	-	-	Clear-Yellow	-	-	-	-

*Day 0 marks hospital admission

Table II

Laboratory parameter

Date	Laboratory Parameter									
	Leucocyte (10^3/µL)	AST (U/L)	ALT (U/L)	Total bilirubin (mg/dL)	Direct Bilirubin (mg/dL)	Indirect Bilirubin (mg/dL)	Albumin (g/dL)	CRP (mg/L)	Procalcitonin (ng/mL)	Gamma GT
Day 0*	4.4	453	1005	16.7	-	-	-	-	--	
Day 1	4.8	556	1276	13.5	10.3	3.2	3.0	2.55	0.21	-
Day 6	-	59	506	4.9	4.2	0.7	-	-	-112	
Day 11	6.8	37	251	3.2	2.5	0.7	-	-	--	
Day 21	-	35	99	1.8	1.4	0.4	-	-	--	

*Day 0 marks hospital admission

Treatment:

During hospitalisation, the patient received supportive treatment. Ranitidine, a lipid-soluble vitamin, compound glycyrrhizin injection, and ursidoxycholic acid were given. Treatments were intravenous fluids that contained electrolytes and carbohydrates based on body weight, regular diet 1700 kcal, and supplementary milk; enteral nutrition specifically for liver dysfunction has a tailored composition, with carbohydrates contributing 62%, protein 13%, and fat 35%. It is also supplemented with specific nutrients such as BCAAs (Branched-Chain Amino Acids) to improve the Fischer ratio and support muscle protein recovery processes. Additionally, it contains MCTs (Medium-Chain Triglycerides), a type of fat that is easily digested and metabolized, serving as an alternative energy source 1 × 200 cc. Hepatoprotector drugs were given two times one ampule per day, ranitidine injection two times per day, antipyretic three times one tablet a day, vitamin E 400 IU per day, and ursodeoxycholic acid 2 times 500 mg were given to treat. On day 12, the patient was discharged. Post-discharge follow-up was done seven days after discharge, there was no complaint.

Discussion:

More than 30 countries reported a new disease that infects children aged < 16 years with AHUO. After a cluster of unexpected cases of pediatric AHUO was identified in Scotland in March 2022[1], WHO announced an outbreak alert with more than 1010 probable cases of mysterious acute hepatitis spread across 35 countries (1 October 2021 to 18 July 2022)[1,13].

Gastrointestinal complaint was the most common symptom. Icteric sclera and jaundice were seen, and laboratory tests showed an increase in liver enzymes. Some patients experience complications of acute liver failure that require liver transplantation. Between March and August 2022, 17 patients were referred with a suspected diagnosis of acute hepatitis of unknown cause in SSIDH.

Seventeen of these suspected referral cases of acute hepatitis were characterised by elevated liver enzyme levels (more than 500 U/L), and the majority were icteric. Most patients experience other intestinal symptoms. All patients receive the same treatment, SARS CoV-2 examination is always carried out on in-patients as a strategy to identify COVID-19 cases[14,15]. In addition, other laboratory tests, such as adenovirus[16], immune-serology hepatitis virus test, AST-ALT, total bilirubin, rapid dengue/NS-1, and leptospirosis, were performed. Of 17 cases, 16 were discarded, and one case was probable cases of AHUA.

Our case was experienced by a 16 year 10 months-old boy. According to some investigations, infection occurs in all sexes[1,17]. However, there is a difference with cases reported in Europe where most cases occur in younger children, less than 5 years old[1,18]. The research of Chen et al, 2022 stated that there is no relationship between hepatitis of unknown cause and travel history[19]. The patient experienced jaundice symptoms, nausea, vomiting, lower abdominal pain, diarrhoea and no history of fever[20]. Laboratory tests revealed AST or ALT levels >500 IU/L, negative hepatitis tests, and adenovirus-negative results[1]. Several research stated one of the possible causes of AHUO is adenovirus. Adenovirus infection is a cause of fulminant hepatitis but is rare in immunocompetent children in only a few cases[4] in a few countries[1,18,21–24], which states the possible cause of AHUO is adenovirus.

Some other hypothesis mentioned involvement of Covid-19 mRNA vaccine as the cause of AHUA. However, this theory was easily ruled out as most children with AHUO were too young to receive the vaccine at the time they were sick[25]. In July 2022, covid-19 immunization rate in China was 92.1% for the first dose, 89.7% for the full course and 71.7% for the booster. However, the reported AHUO was 0[26].

The patient had positive blood cultures of klebsiella and staphylococcus. Klebsiella, as it a common bacteria found in hospital, and staphylococcus, as it a common bacteria of skin, both could cause jaundice in patients with sepsis[27]. Given the high morbidity and mortality linked to *Staphylococcus aureus* bacteremia (SAB), the presence of even a single *S. aureus*–positive blood culture bottle (SPBCB) in blood culture sets is often regarded as clinically significant. Notably, there have been no studies to date examining the clinical significance of a single *S. aureus*–positive blood culture bottle (SPBCB) in patients with SAB, despite its frequent recognition in clinical microbiology. Local anecdotal experience shows that antibiotic therapy is often initiated, even though it is recognized that *S. aureus*, like other commensal bacteria, can colonize the skin and lead to contamination in blood cultures[28]. It is noteworthy that coagulase-negative staphylococci are well-known as skin flora and a frequent source of blood culture contamination, often appearing in only a single blood culture bottle[29].

The probability of bacterial infection in this case could be ruled out because clinical signs did not indicate infection, and the patient had a borderline procalcitonin level; therefore, he did not receive any antibiotics.

Study strength: This study describes that examinations of all suspected AHUO cases were

performed during treatment. One of the unique features of this case is that the patient was 16 years and 10 months old. While other studies reported probable AHUO cases d"16 years old[30,31]. The clinical symptoms (experienced jaundice symptoms, nausea, vomiting, lower abdominal pain, diarrhoea and no history of fever) were consistent with the results of the supporting examination of ALT 1276 and AST 556 and this indicated symptoms of acute hepatitis. Supportive examinations up to genomic sequencing were performed on all AHUO suspect patients.

The working definition of probable is established after all the results of the supporting examination are negative / no specific microorganism agent is identified that causes AST, ALT, and bilirubin to increase[31,32]. So that the diagnosis of the disease in this case cannot be established. The contribution of this study is the recommendation of adequate treatment (Hepatoprotector drugs) immediately given to patients with impaired liver function. This study also confirms that there is no link to the administration of the COVID-19 mRNA vaccine as a cause of AHUO because in this study the history of the COVID vaccine was 1 year before this case was reported.

There are some limitations to the exploration of aetiology in this study. Some investigations, such as multiplex PCR for respiratory virus and faecal cultures for common bacterial entero-pathogens were not performed. Also, pathology and histology examinations were carried out after stable conditions, which is not proper for aetiology investigation. The patient underwent infectious pathogen screening. Evidence of hepatitis A, B, C, and E virus infection were not found. PCR from blood and nasopharynx swabs showed Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Adenovirus (AdV), Enterovirus, and leptospiral infection were not found. Abdominal ultrasound indicated hepatosplenomegaly with increased intrahepatic vascular. Any manifestations of the acute phase in the liver biopsy also were not found. Comprehensive follow-up is needed for further clarification of clinical characteristics and aetiology of AHUO in children.

A history of risk factors and transmission was not obtained from anamnesis. Therefore, the authors could not determine the source of the transmission. Case identification was easily screened based on clinical symptoms and ALT and AST levels of >500 U/L. Adequate management by treated with hepato-protector was done in this case.

Conclusion:

We identified one probable case of mysterious acute hepatitis out of the 17 cases we observed at SSIDH. The case was a 16-year 10-month-old boy, AHUO. We recommend liver biopsy for patients with severe acute hepatitis of unknown origin and trial steroid therapy when liver damage is similar to autoimmune hepatitis. With this case report, we hope to add information that immune dysfunction may be the leading cause of liver damage in children with acute hepatitis of an unknown origin.

Declaration:

Ethics approval and consent to participate

Ethics approval:

This study was reviewed and approved by the Health Research Ethics Committee of Sulianti Saroso Hospital, Number. 13/XXXVIII.10/II/2023.

Consent for publication:

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-in-Chief of this journal.

Conflict of Interest:

The authors declare that they have no conflict of interest

Funding:

None.

Author's contributions:

S.M. was responsible for data collection, data analysis and research conceptualisation. E.S. and N.A. were responsible for data collection. A.D.W. and V.S. were responsible for overseeing the write-up. L.D.R. was refining the methodology.

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