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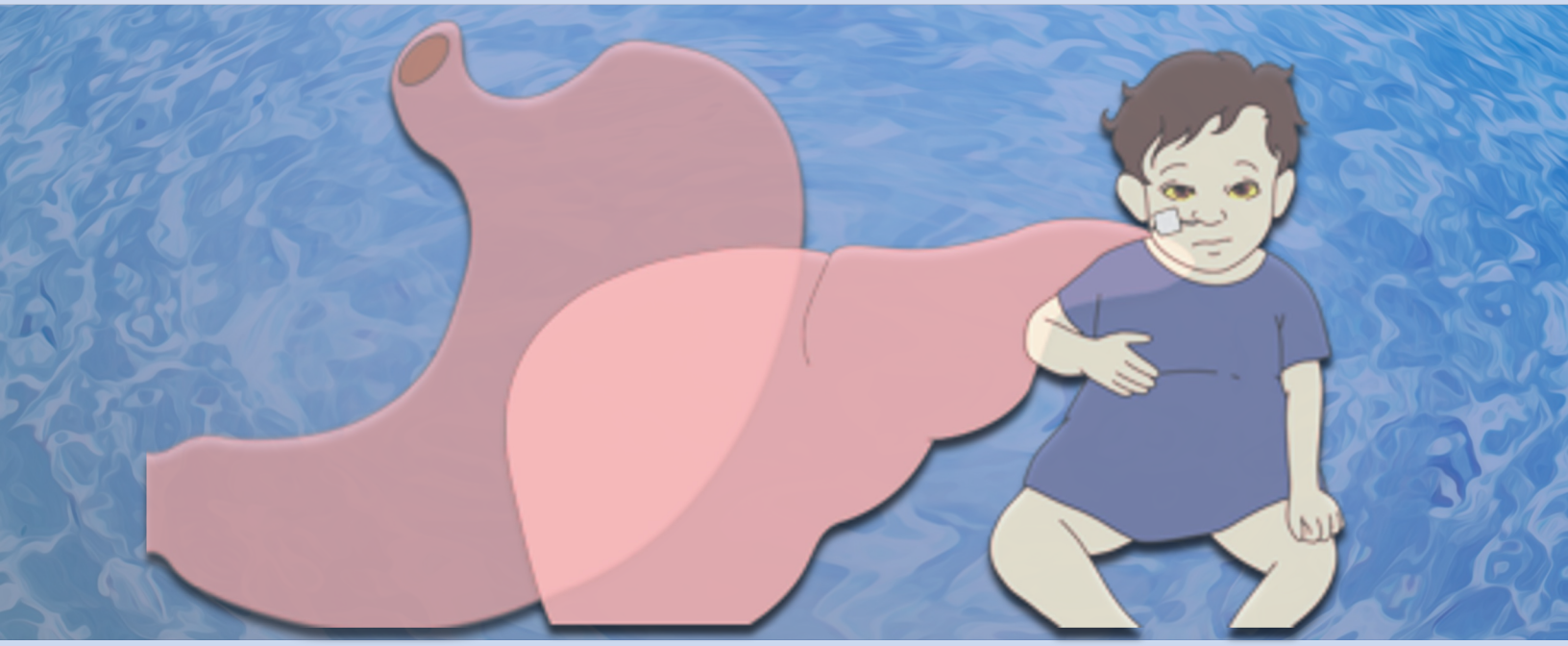

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Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Original Article

Risk Factors of Chronic Diarrhea in HIV-Infected Children

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Abstract:

Background. Chronic diarrhea increases mortality and other long-term morbidities in children. HIV-infected children are at higher risk of developing chronic diarrhea.

Objective. This study aimed to investigate the characteristics, prevalence, and risk factors of chronic diarrhea in HIV-infected children.

Methods. Data were obtained retrospectively from medical records of HIV-infected children at Dr. Cipto Mangunkusumo General Hospital (RSCM) from January 2014 until December 2016. The risk factors evaluated included age, nutritional status, dehydration status, HIV-infection phase, use of antiretroviral (ARV) drugs, and stool culture. All data that fulfilled the inclusion criteria were analyzed by bivariate followed by multivariate analysis, except for stool culture.

Results. The prevalence of chronic diarrhea in HIV-infected children in RSCM was 12.98%. Analysis of 132 data showed that chronic diarrhea was significantly associated with low nutritional status (p=0.037; adjusted OR=5.737) and dehydration (p=0.026; adjusted OR=6.891) among HIV-infected children.

Conclusion. Dehydration status and malnutrition are important risk factors for chronic diarrhea in HIV-infected children. These findings may also support that in managing HIV-infected children with diarrhea, one should first overcome dehydration and manage malnutrition to prevent the vicious circle of diarrhea – malnutrition – diarrhea.

Keywords: chronic diarrhea, HIV, infant, malnutrition, dehydration

Citation:
Fathurrahman SW and Gayatri P. Risk Factors of Chronic Diarrhea in HIV-Infected Children. *Arch Pediatr Gastr Hepatol Nutr*. 2022(1):1-8.

Introduction

Human Immunodeficiency Virus (HIV) infection remains one of the healthcare highlights in the current age of health. With an estimated global count of 2,100,000 newly infected with HIV, this disease causes morbidity and mortality not only in adults but also in the pediatric population.[1] In Indonesia, about 25,000 children are living with HIV.[1,2]

Children living with HIV are at a higher risk of infection and illness, including diarrhea, compared to healthy children of their age. Even in HIV-negative children, diarrhea is a prevalent disease as well as one of the leading causes of death in toddlers in developing countries, with an estimated number of annual global death of up to

800,000.[2-5] Thirty-five percent of this death is attributed to chronic diarrhea.[6] Chronic diarrhea often occurs in HIV-positive children. One study pointed out that chronic diarrhea, specific skin lesions, and failure to thrive are conditions that highly indicate the presence of HIV infection in children.[7] Other than death, chronic diarrhea causes an array of conditions, including growth and development problems as well as cognition impairment.[8-11]

Method

This study is a cross-sectional study aimed to find out the correlation between age, nutritional status, dehydration status, HIV infection phase, antiretroviral (ARV) drug usage, and chronic diarrhea incidence in HIV-positive children. Data were obtained from medical records of pediatric patients with HIV infection at Dr. Cipto Mangunkusumo General Hospital (RSCM), Jakarta, Indonesia from January 2014 until December 2016. Data were excluded if they did not contain all the factors included in the study (diarrhea status, age, nutritional status, dehydration status, HIV infection phase based on T-CD4$^+$ cell count, and ARV drug usage).

Data were analysed using bivariate analysis and continued with multivariate analysis of eligible factors. In addition, data on breastfeeding status in subjects with chronic diarrhea aged until 2 years and stool culture of subjects with chronic diarrhea were recorded.

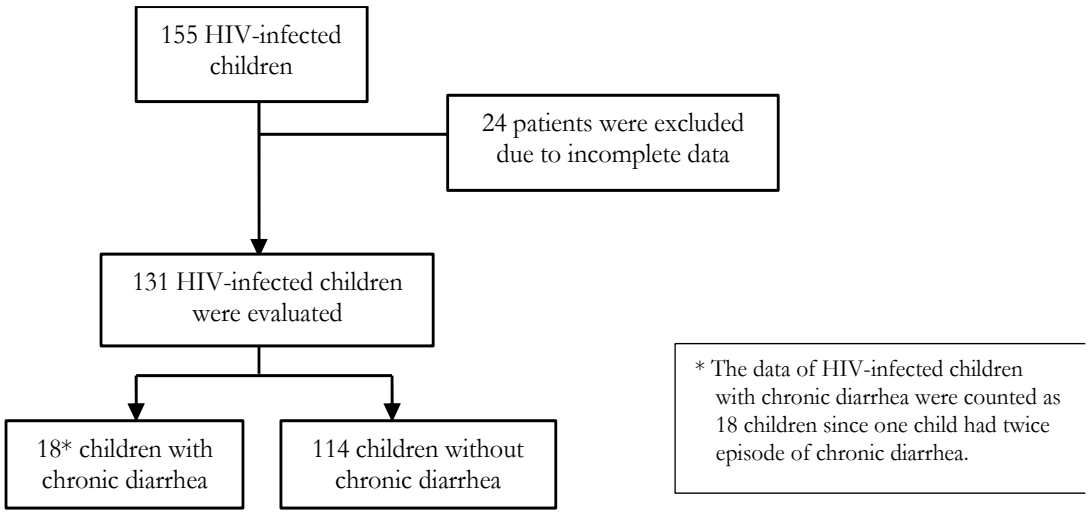

Figure 1. The research profile of subject participants.

Chronic diarrhea was defined as an increase in daily stool frequency (more than 3 times daily) with a change of stool consistency into watery or purely liquid stool for more than 14 days. Stool frequency depicts the stool volume. The cut-off to diagnose diarrhea was increased of more than 200 gram in stool volume. The diagnosis of diarrhea was obtained directly from the medical records made by the physician-in-

charge of the patient at admission. The subjects were divided into chronic diarrhea and no chronic diarrhea.[12] Age, ARV drug usage, and dehydration status were also retrieved from the medical records. The dehydration status was based on the clinical diagnosis made by the physician at admission and was categorized into dehydrated and not dehydrated. Age is categorized into one month to 5 years and >5 to 18 years. ARV drug usage was divided based on whether or not the subject had a regiment of ARV drugs before admission.

Nutritional status was determined using the World Health Organization Child Growth Standards graph for subjects aged one month to 2 years and using the Center for Disease Control and Prevention growth chart for subjects aged 2 to 18 years based on the subjects' weight, height, and age. The nutritional status was categorized into low and normal/high nutritional status. HIV infection phase was determined based on the T-CD4$^+$ cell count. The lower the cell count, the more advanced the infection phase. The HIV infection phase was divided into 3 groups (phase-1, phase-2, and phase-3) based on T CD4$^+$ cell count.[13]

Results

A total of 132 data from 131 subjects were obtained (one subject had two separate incidents of chronic diarrhea). From the data, the prevalence of chronic diarrhea in HIV-positive children between 2014 and 2016 was 13%. Most cases of chronic diarrhea in HIV-positive children occurred in those aged >5 – 10 years. No single HIV-positive child with chronic diarrhea had normal/high nutritional status. Other details of the study subject characteristic are shown in **Table 1**.

Table 1. Characteristic of HIV children with chronic diarrhea versus without chronic diarrhea (continued).

Variables	HIV with chronic diarrhea; n(%)	HIV without chronic diarrhea; n(%)	Total (n=131)
Age			
1-12 months	3(33)	6(67)	9
>12 months – 10 years	13(15)	75(85)	88
>10 – 18 years	1(3)	33(97)	34
Gender			
Male	9(14)	57(86)	66
Female	8(12)	57(88)	65
Nutritional Status			
Low	15(22)	52(78)	67
Normal / high	2(3)	62(97)	64

Table 1. Characteristic of HIV children with chronic diarrhea versus without chronic diarrhea (continued).

Variables	HIV with chronic diarrhea; n(%)	HIV without chronic diarrhea; n(%)	Total (n=131)
Dehydration Status			
Dehydration	4(57)	3(43)	7
No-dehydration	1310)	111(90)	124
ARV-drug Usage			
Use ARV	12(10)	104(90)	116
No ARV	5(33)	10(67)	15
Infection State of HIV			
Phase-1	6(8)	67(92)	73
Phase-2	3(15)	17(85)	20
Phase-3	8(21)	30(79)	38

Notes: ARV= antiretroviral; HIV = human immunodeficiency virus.

Bivariate analysis result of 132 data obtained were shown in **Table 2**. Variables with a p-value <0.2 were eligible for multivariate analysis. Significantly correlated variables with chronic diarrhea had a final multivariate analysis (**Table 3**) p-value <0.05.

Table 2. Bivariate Analysis Results

Variables	Diarrhea Status		*p* value
	Chronic Diarrhea	No Chronic Diarrhea	
Age			
0 – 5 years old	11 (26.2)	31 (73.8)	0.004[a]*
>5 – 18 years old	7 (7.8)	83 (92.2)	
Nutritional status			
Low	16 (23.5)	52 (76.5)	0.001[a]*
Normal / High	2 (3.1)	62 (96.9)	
Dehydration status			
Dehydrated	5 (62.5)	3 (37.5)	0.001[b]*
Not dehydrated	13 (10.5)	111 (89.5)	
HIV infection phase			
Phase 3	8 (21.1)	30 (78.9)	
Phase 2	4 (19.0)	17 (81.0)	0.128[a]
Phase 1	6 (8.2)	67 (91.8)	
ARV drug usage			
Does not use ARV drug	5 (33.3)	10 (66.7)	0.034[b]
Uses ARV drug	13 (11.1)	104 (88.9)	

Notes: HIV = human immunodeficiency virus; ARV= antiretroviral. [a]Analysed using *Pearson Chi Square Test*, [b]Analysed using *Fisher's Exact Test*. *Significant result.

Data on stool culture (**Table 4**) and breastfeeding status showed further detail of the chronic diarrhea condition. Out of the 18 data with chronic diarrhea, stool culture was available on 10 subjects. The most prevalent pathogen was *Klebsiella pneumoniae*, found on 4 cultures. Other identified pathogens were *Escherechia coli* (1 culture), *Pseudomonas aeruginosa* (1 culture), and the presence of pseudohyphae (2 culture).

Table 3. Multivariate analysis results

Variables	*p* value	Adjusted OR	Confidence Interval 95%
Dehydration	0.026*	6.891	1.258-37.739
Does not use ARV drugs	0.109	3.282	0.768-14.022
HIV infection phase 2	0.776	0.79	0.155-4.013
HIV infection phase 3	0.767	1.229	0.315-4.797
Low nutritional score	0.037*	5.737	1.108-29.698
Age	0.065	2.987	0.935-9.543

Notes: HIV = human immunodeficiency virus; ARV= antiretroviral. *Significant results.

Table 4. Positive culture in patient with chronic diarrhea

Organisms	Number of identified organism(s)
Klebsiela pneumoniae	4
Escherechia coli	1
Pseudomonas aeruginosa	1
Fungi	2
None	8

Discussion

1. Correlation Between Dehydration Status and Diarrhea.

In this study, dehydration and nutritional status were significantly correlated with the incidence of chronic diarrhea among HIV-positive children. Dehydration is a well-known clinical condition caused by the water loss in diarrhea and is now instated the main pillars of diarrhea treatment. However, the relationship may go both ways. Dehydration observed among judo athletes by Chishaki et al. indicated that dehydration causes immunosuppression, causing changes in the IgA, IgM, and IgG ratios in the body and decreasing the phagocytic activity of neutrophils. However, the cell count is actually increased.[17] Fortes et al. studied in more detail the relationship between dehydration and immune system function in the saliva and revealed that dehydration is associated with a lower secretion rate of α-amylase and lysozyme.[18]

2. Correlation Between Nutritional Status and Diarrhea

Similar to dehydration, diarrhea causes suboptimal processing of ingested nutrients that ultimately leads to decreased nutritional status in the long run. A study by Palupi et al. in Yogyakarta showed similar results to this study, with low nutritional status and days of hospitalization in children with acute diarrhea having a significant positive correlation.[19] A condition of low nutritional status causes further worsening of the infectious process through alterations of various immune functions, such as the decrease in the cytotoxic activity of Natural Killer (NK) cells and neutrophils. These alterations occur as a direct effect of micronutrient deficiency, namely zinc and vitamin A.[20] It is not yet known, however, the actual level of micronutrients in these patients and which micronutrients are the exact cause for this immunodeficiency. A study in Kenya showed that the daily consumption of HIV-positive people is similar in quantity and quality to others of the same background that are HIV-negative. This study proved that the low nutritional score that happens in HIV-positive children with chronic diarrhea was more greatly attributed to the diarrhea than to the HIV infection.

3. Correlation Between Age, HIV Infection Phase, and ARV Usage

Age is associated with immunological maturity. The most common etiology of diarrhea varies with age group, like in infants and children under three years old who usually suffer viral diarrhea. Behavioral factors may also contribute to the infection, usually by creating opportunities for infection by oral manipulation of unclean hands. Although subjects with chronic diarrhea in this study are mostly under 10 years old, the statistical analysis was insignificant. The infection phase of HIV also correlates with immunological capability and is theoretically impaired as infection phase rises. Findings from this study contradict a study by Nsagha and colleagues in Cameroon.[21] In their study, intestinal infections in HIV-positive cases are correlated with the T $CD4^+$ cell count.[21]

The gastrointestinal system contains an abundant amount of lymphoid tissues near the mucosa as protection against the microbes in the gut.[22-26] This anatomical placement of lymphocytes further highlights the hypothesis that a decrease in the T $CD4^+$ cell would cause the body to be more susceptible to infections, especially in the intestine. Usage of ARV drugs counters the reduction in T $CD4^+$ cells, increasing immunity against infectious diarrhea. In this study, the T $CD4^+$ cell and ARV usage did not yield a significant result. The insignificant resut may be because the etiology of diarrhea is not always an infection. A decrease in T $CD4^+$ cell count may also alleviate inflammation in the intestinal mucosa caused by direct infection of the lymphoid tissue, hence explaining the unclear correlation between HIV infection phase and the incidence of chronic diarrhea.[22-26] The same logic may apply to the usage of ARV drugs, as some drugs cause diarrhea by unknown mechanisms.[15]

Conclusion

Dehydration status and malnutrition are important risk factors for chronic diarrhea in HIV-infected children. These findings may additionally support that in dealing with HIV-infected children with diarrhea, one should overcome dehydration first and manage the malnutrition to prevent the vicious circle of diarrhea – malnutrition – diarrhea.

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Original Report

Clinical Characteristic of Bloody Diarrhea in Under-Five Pediatric Inpatients

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Susianto SC, Atthiyah AF, Paramitha AA, Koendhori EB, Sumitro KR, Darma A, et al. Clinical Characteristic of Bloody Diarrhea in Under-five Pediatric Inpatients. *Arch Pediatr Gastr Hepatol Nutr.* 2022(1):9-16.

Abstract:

Background: Diarrhea is the most common cause of death in under-five children. Bloody diarrhea comprises around 10% of all cases of diarrhea and may lead to severe complications until death. This study examined the characteristics of bloody diarrhea in children under five years old in Dr. Soetomo General Hospital Surabaya from 2013 to 2017.

Material and Methods: A retrospective, cross-sectional study was conducted using secondary data from Dr. Soetomo General Hospital's inpatients with bloody diarrhea from 2013 to 2017. Gender, age, nutritional status, clinical symptoms, degree of dehydration, and laboratory results were assessed, and the data were presented in percentage (%)

Results: Fifty-six samples were included in this study. The main demographics were male (58,9%), aged 7-24 months (44,6%), and normal nutritional status (66,1%). Meanwhile, the most notable manifestations were stool mucous (55,3%), mild to moderate degree of dehydration (60,7%), and leukocytosis (62%). Eleven patients (39,2%) had temperatures ≥38^{0}C. Leukocytes were positive in 93.7% of the stools. Furthermore, amoeba was found in 46,8% of samples. The serum electrolyte result showed hyponatremia (18%) and hypokalaemia (15%).

Conclusion: The primary demographics of bloody diarrhea in under-five children admitted to Dr. Soetomo General Hospital were males, 7-24 months of age, and with normal nutritional status. The most frequent manifestations were mucous in stool, mild to moderate dehydration, leucocytosis, as well as positive leucocytes and amoeba in the stool.

Keywords: characteristics, diarrhea, bloody diarrhea, children, amoeba

Introduction

Diarrhea is the second leading cause of death in children under five years old after pneumonia. It accounts for 9% of all deaths in the under-five population and is estimated to kill more than 1.400 children worldwide every day.[1,2]A study conducted by RISKESDAS (*Riset kesehatan Dasar*) 2011 in Indonesia found that the number of deaths due to diarrhea in infants and toddlers from 15 districts and cities were 17.4% and 13.3%, respectively. Furthermore, the results of a morbidity study conducted by Ministry of Health showed that the mortality rate caused by diarrhea in children under five was 75.3 per 100,000, with a morbidity rate of 900 per 1,000 for children under five years old and 23.2 per 100,000 population for all ages in 2012.[3,4]

Bloody diarrhea contributes to nearly 10% of all diarrheal episodes globally and accounts for 5-15% of all deaths due to diarrhea in children under five.[5,6] Bloody diarrhea in children is still becoming a concern in developing countries. This type of diarrhea is characterized by blood in runny stools that occur three or more times in one day. The blood should originate from the gastrointestinal tract. However, it is necessary to distinguish whether the etiology of the bloody stool is bloody diarrhea or intestinal inflammation.[7] Bloody diarrhea is mainly caused by food or drinks contaminated by stool containing bacteria (*Shigella, Salmonella, Campylobacter, Enterohemorrhagic Escherichia coli*), virus, or parasite (*Entamoeba histolytica*).[8] Previous studies showed various characteristics, clinical symptoms, laboratories profile, and parasite stool profiles. Varying clinical symptoms of bloody diarrhea can delay the diagnosis and determination of appropriate therapy. Thus, the success of bloody diarrhea management in children under five requires effective and efficient health service strategies.

This study examined the clinical characteristics and laboratory profile of bloody diarrhea in under-five children, which can be used as additional information on determining the proper diagnosis and therapy to reduce the mortality rate of bloody diarrhea.

Material and Methods

This was a retrospective, descriptive, cross-sectional study conducted in Dr. Soetomo General Hospital Surabaya. Medical records of the pediatric inpatients under-five children with bloody diarrhea were obtained from January 2013 to December 2017. This study had been approved by The Health Research Ethical Committee at Dr. Soetomo General Hospital, Surabaya, Indonesia. Data on age, gender, nutritional status, exclusive breastfeeding, clinical sign and symptoms such as vomiting, abdominal pain, mucous in stool, dehydration state, temperature, complete blood count, complete stool examination, and serum electrolytes were recorded. Incomplete medical records were excluded from the study.

The dehydration status was assessed using the World Health Organization (WHO) standard and divided into no dehydration, mild to moderate dehydration, and severe dehydration.[9] The nutritional status was measured and classified into severely wasted (weight for length/height <-3 SD), wasted (-3 SD ≤ weight for length/height <-2 SD), normal nutrition (-2 SD ≤ weight for length/height ≤ 2 SD, overweight (2 SD < weight for length ≤3 SD) and obese (weight for length >3 SD) using the WHO weight for length/ height chart.[10] Complete blood counts were assessed for hemoglobin, hematocrit, leukocyte, and thrombocyte. A complete stool examination was conducted to assess the presence of erythrocytes and leukocytes and determine the stool's parasite profile. Serum electrolyte was measured to identify the potassium, sodium, and chloride levels. All data were presented in numbers and percentages and analysed using IBM SPSS Statistics 20.0 for Windows.

Result

Fifty-six subjects were included in the final analyses. Most of the study participants was male (58.9%), aged 7-24 months old (39.3%), and had normal nutritional status (66.1%). Mucous in stool was found in 55.3% of subjects, while vomiting occurred in 39.3% of subjects. Thirty-six subjects had mild-moderate dehydration. Other characteristics are described in **Table 1**.

Table 1. Subject demographics and clinical characteristics (continued).

Characteristics	Number (%)
Gender	
Male	33 (58.9)
Female	23 (41.1)
Age group	
0-6 months	15 (26.8)
7-24 months	22 (39.3)
>24 months	19 (33.9)
Nutritional Status	
Severely wasted	6 (10.7)
Wasted	11 (19.6)
Normal	37 (66.1)
Overweight	2 (3.6)
Obesity	0 (0.0)
Vomiting	
Yes	22 (39.3)
No	34 (60.7)
Form of stool	
Watery	19 (33.9)
Watery and dregs	32 (57.1)
Mushy	5 (9.0)
Mucous in stool	
Yes	31 (55.3)
No	25 (44.7)

Table 1. Subject demographics and clinical characteristics (continued).

Characteristics	Number (%)
Dehydration status	
No dehydration	20 (35.7)
Mild-moderate	34 (60.7)
Severe	2 (3.6)
Temperature (n=49)	
36-36.9	19 (33.9)
37-37.9	19 (33.9)
38-38.9	9 (28.6)
39-40.0	2 (3.6)

The laboratory result showed that 29 subjects had leucocytes count >10,000/mm^3, while 30 subjects had a normal range of thrombocytes (Table 1). From the complete stool examination, 93.7% of the stools were positive for leukocytes. Furthermore, some of the stool specimens exhibited the presence of amoeba (43,8%). Further findings are described in **Table 2 and 3**.

Table 2. Complete blood count and serum electrolyte findings

Laboratory findings	Number (%)
Complete blood count (n=47)	
Leucocyte (/mm^3)	
<4,000	1 (2.1)
4,000-10,000	17 (36.2)
>10,000	29 (61.7)
Hemoglobin (g/dl)	
<11	21 (44.7)
≥11	26 (55.3)
Hematocrit (%)	
<33	19 (40.4)
33-49	27 (57.5)
>49	1 (2.1)
Thrombocyte (/mm^3)	
<150,000	2 (4.3)
150,000-450,000	30 (63.8)
>450,000	15 (31.9)
Serum Electrolyte (n=33)	
Natrium (mEq/L)	
<135	6 (18.2)
135-144	26 (79.8)
>144	1 (3.0)
Potassium (mEq/L)	
<3.6	5 (15.2)
3.6-5.2	25 (75.7)
>5.2	3 (9.1)
Chloride (mEq/L)	
<97	1 (3.0)
97-106	13 (39.4)
>106	19 (57.6)

Table 3. Complete stool examination

Laboratory findings	Number (%)
Complete stool examination (n=16)	
Stool erythrocytes	
Positive	14 (87.5)
Negative	2 (12.5)
Stool leukocytes	
Positive	15 (93.7)
Negative	1 (6.3)
Parasite stool examination (n=16)	
Amoeba	7 (43.8)
Helminth Eggs	0 (0.0)

Discussion

Our study found that males gender and aged 7-24 months old had a higher rate of bloody diarrhea in Dr. Soetomo General Hospital Surabaya. A previous study in Baghdad, Iraq, showed that prevalence of blood diarrhea in males was higher than in females.[5] The difference in activity patterns between males and females might the reason as boys tend to play in the outdoor environment, putting them in high exposure to microbial agents. This results in increased susceptibility to diarrhea compared to females.[11] Children aged 6-11 months old have started getting complimentary food. Thus, they tend to be more active and have direct contact with the environment, which can be the source of pathogens transmission. Meanwhile, the 0-5 months age group still received immunity directly from breastfeeding, lowering the risk of diarrhea.[12,13]

This study showed that patients with bloody diarrhea in our centre mostly had normal nutritional status. Children with normal nutritional status were usually more active and at higher risk of suffering bloody diarrhea than undernourished or overnourished children. Ticket et al. found no difference in the prevalence of pathogens within the nutritional status group, however, wasted children presented with more severe disease.[14] Our subjects mostly came with the chief complaint of diarrhea. Twenty-two subjects also had symptoms of vomiting, and 55.3% of subjects experienced mucous in stool. The previous study on bloody and watery diarrhea demonstrated that the diarrhea frequency and presence of mucous in stool were more prevalent in bloody diarrhea. The study also reported lower vomiting incidents in the bloody diarrhea group.[7]

Bloody diarrhea involves the large bowel, which produces frequent and small volume stools. Mucous in the stool is caused by hypersecretion of mucous in the colonic mucosal wall due to infection, inflammation, or an anatomical abnormality. Vomiting is considered a natural circumstance for protecting the body against stimulants and toxins in food. It is stimulated by certain conditions, particularly the involvement of the small bowel.[15,16] Our result showed that more than half of the patients (60.4%)

experienced mild-moderate dehydration. Dehydration often accompanies diarrhea and causes deaths due to water loss and electrolytes. Bloody diarrhea is mainly caused by parasitic agents and *Shigella sp*., which damage the colonic mucosa that only absorbs approximately 10% of water. Diarrhea resulting from large intestine mucosa damage is more often and probably causes mild to moderate dehydration in smaller volumes.[17,18] Our study found 11 patients with temperatures ≥38^{0}C. Based on a previous study, higher temperatures suggest Shigella infections, whereas the absence of fever is more likely to indicate *Escherichia coli* or parasite infection.[19]

More than half (61.7%) of the subjects showed a high level of leukocytes (> 10,000 cells/mm^3). Meanwhile, most participants exhibited normal hemoglobin, hematocrit, and thrombocyte level. Leukocytosis indicates an infectious process in the body related to diarrhea, which is often a marker of bacterial infections.[20] However, in the case where bacterial and non-bacterial infections overlap, some research suggests using CRP and procalcitonin as markers.[21] Both stool leukocytes and erythrocytes were found in patients under five with bloody diarrhea. However, the diagnostic performance of fecal leukocytes on bloody diarrhea due to bacteria is suboptimal, particularly in the condition of mild inflammatory response. Confirmation using stool culture is still the gold standard for identifying the bacterial species that cause bloody diarrhea.[22,23]

The stool examination results showed positive amoeba in 43,8% of subject. Northern Jordan study found visible blood in stool was higher in *Shigella* spp, (60%) *Salmonella,* spp. (20%) as bacterial cause and *Entamoeba histolytica* in 25% of patients as parasite infection cause.[24] In Iraq Study, 92,9% of childhood bloody diarrhea distribution originated from *E. histolytica,* particularly in children aged 0-3 years. Parasites had been the common cause of childhood bloody diarrhea and varied symptoms, treatment, and prognosis. A higher prevalence of parasite infection in the country is strongly associated with unhealthy behavior, poor sanitation, and an unhygienic environment.[5,25] However, this study did not differ on the bacterial cause of bloody diarrhea. The limitation of this study is that there are no results of bacterial culture and PCR data to determine the appropriate etiology of each cause of bloody diarrhea.

Our study exhibited normal serum electrolytes in patients; however, 18,2% of patients were hyponatremic. Electrolyte imbalance is common in those under five years. It is related to the severity of dehydration, which increases mortality and length of stay that need urgent active oral or intravenous rehydration. The etiologic cause of bloody diarrhea rarely causes dehydration and electrolyte imbalance in patients under five years.[26,27]

Conclusion

The main characteristics of under-five children with bloody diarrhea in the pediatric ward of Dr. Soetomo General Hospital, Surabaya, Indonesia from 2013 to 2017 were male, 7-24 months of age, and normal nutritional status. The most frequent clinical symptoms were mucous in stool, mild to moderate dehydration, leukocytosis, positive stool leukocytes, and the presence of amoeba in the complete stool analysis. This study could become the primary data for the enforcement of diagnosis and therapy for pediatric patients under five years of age with bloody diarrhea in tertiary hospitals. Further research is needed to evaluate the therapy and long-term follow-up of the patient.

Acknowledgement

The authors declare that there is no potential conflict of interests.

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Literature Review

Autoimmune Hepatitis

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Abstract: Autoimmune hepatitis (AIH) is a condition caused by self-perpetuating immune response towards hepatocytes in liver. In children, AIH may progressed more rapidly compared to adults. Thus, early diagnosis and prompt treatment are the key for successful management of AIH. Five main characteristics of AIH include female predominance, increased IgG or hypergammaglobulinemia, circulatory auto-antibody seropositivity, and hepatitis interface from the histological finding. Liver biopsy is needed to evaluate the degree of damage and to confirm the diagnosis. The standard regiment for AIH include prednisone (or prednisolone) and azathioprine. Other alternative treatments available for non-responder, such as mycophenolate mofetil, tacrolimus, cyclosporine, budesonide, rituximab, and infliximab. AIH treatment is recommended to be taken minimally for 2-3 years before attempting treatment termination.

Keywords: autoimmune hepatitis, children, genetic disorder, diagnosis

Introduction

Autoimmune hepatitis (AIH) is a condition that could occur in children and adults of all ages. AIH is a hepatopathy caused by self-perpetuating immunity toward the liver cells. This condition leads to chronic and progressive inflammation and may eventually lead to irreversible liver damage. The main characteristics of AIH include the histological appearance of hepatitis, female predominance, positive circulatory antibody, presence of hypergammaglobulinemia or increased IgG, and family history of autoimmune disease. The occurrence of AIH in children has been seen to cause a worse impact on children than on adults.[1,2]

Early treatment is the key to preventing the progression of AIH into end-stage liver disease and increasing demand for liver transplantation. Treatment using immunosuppressants in AIH patients without acute and serious manifestation accompanied by encephalopathy has shown satisfactory results. However, there is still no diagnostic test or eligible and reliable criteria to be used as the gold standard

for diagnosing AIH in pediatric patients. Currently, the only diagnostic criteria available are only applicable to adults.[1,2] Thus, through this literature, we aim to summarize the important findings and current knowledge on AIH in children for better understanding and clinical judgment in diagnosing and treating AIH patients.

Epidemiology

AIH can occur at any age and ethnicity, with varying manifestations. The prevalence of AIH in Asia is 12.99 per 100,000 people.[3] Meanwhile, in the United States, the prevalence reached up to 31.2 per 100,000 people.[4] AIH can occur in both adults and children. The prevalence of AIH in females is high[3], with 71%-95% occurring in adults and 60-76% in children. AIH often occurs at the age of 10-30 years and 40-60 years.[2] The ratio of vulnerable sex and age may vary depending on the region.

Genetic Predisposition

AIH is a complex genetic disease. It was influenced by epigenetic, immunological, and environmental. Currently, genetic factor is suspected to be important in determining a person's susceptibility to AIH. Human leukocyte antigen (HLA) has been proposed as the most important genetic factor in AIH. HLA is the main molecule in antigen presentation and is associated with the onset of AIH.[2,3]

In addition, AIH is also proposedly related to non-HLA genetics. It associates with genetic polymorphisms that encode cytotoxic T lymphocyte antigen-4, TNF alpha, Fas, vitamin D receptors, signal transducers, transcription activators 4, TGF beta, IL-23, etc. Dysfunction of genetic products or abnormalities at the genetic level can affect the proliferation and resistance of B cells and auto-reactive T cells. It may affect the regulation of cytokine production, modulation of inflammation, and immune response control.[2]

Pathogenesis

The pathogenesis of AIH is a complex cascade triggered by multifactorial factors. The failure of the immune system to inhibit the T cells' autoreactivity towards autoantigens in the liver is proposedly affected by environmental and genetic factors. In general, AIH is primarily caused by three main impairments; the disruption of regulatory cells (particularly Tregs), the inability of the immune system to recognize self-antigen, and the inadequate control of inflammation.[2]

During the conditions requiring hepatic or systemic immune response (consumption of hepatotoxic drugs or viral infections), the dysfunction of T regulatory cells (Tregs) in tolerating the hepatic autoantigens causes the antigen-presenting cells (APC) to be able to present the autoantigens to the T cell receptors (TRC) on naive CD4-positive and CD8-positive T lymphocytes.[2] The activation of CD4-positive and CD8-positive

T cells leads to the series of cytokines productions, which contributes to the development of both CD4 and CD8 into their differentiated and mature forms, particularly CD4 Th1, Th2, Th9, Th17, Tfh, iTreg, as well as CD8 Tregs and CD8 CTLs. CD4 Th1 and CD4 Th9 are known to initiate macrophage activation, while CD Th2 and CD4 Tfh play an important role in the generation and activation of B cells autoantibodies into antibody-secreting plasma cells that produce immunoglobulin G (IgG). Furthermore, CD4 Th17 is seen to generate cytotoxic effect, which also increases the degree of hepatocytes injury due to inflammation.[2]

Normally, the function of CD4 induced Treg (iTreg) alongside other Tregs and Breg is to regulate the inflammation caused by the CD4 Th subsets. However, the defect of CD4 iTregs due to the exposure to specific cytokines may lead to the differentiation of CD4 iTregs to CD4 Th17, which further aggravates the inflammation occurring in the hepatocytes. The presence of CD4 subtypes, and the inability of both CD4-positive and CD8-positive Tregs and Bregs to control the autoreactivity of immune system towards hepatic autoantigen, leads to the prolonged incidence of AIH. Besides the generation of CD4-positive and CD8-positive subtypes, APC also triggers mucosal invariant T (MAIT) cell activation, which also contributes to CD4 iTregs alteration to CD4 Th17. Furthermore, MAIT cells have been seen to exhibit similar trait possessed by CD4 Th1 and Th17.[2]

The increased amount of both humoral and cellular inflammatory components leads to hepatocytes injury as well as the build-up in hepatic portal. Further activation of chemokines and adhesion molecules initiate diapedesis, which causes inflammation in the periportal and lobules. The initiation of the whole cascades results in cytotoxic injury and necroinflammation. Continuous activation of the immune response will induce portal fibrosis, eventually resulting in the end stage liver disease.[2]

Classification

AIH is generally a progressive inflammatory hepatopathy that can develop into end-stage liver disease. There are two types of AIH subtypes depending on the serological profile. People with AIH Type 1 are positive for anti-nuclear antibody (ANA) or anti-smooth muscle antibody (SMA). Meanwhile, those who are classified with AIH Type 2 are positive for anti-liver kidney microsomal type 1 antibody (anti-LKM-1) and/or anti-liver cytosol type 1 antibody (anti-LC-1).[1]

Diagnosis Criteria

AIH is diagnosed based on clinical, biochemical, immunological, and histology features and must not be caused by another liver disease. Typical AIH findings include:[1]

- Higher prevalence in women.

- Increased immunoglobulin G (IgG)/ hypergammaglobulinemia.
- Circulatory auto-antibody seropositivity.
- Hepatitis interface in histological finding.

There is still no gold standard to establish AIH diagnosis. The International Autoimmune Hepatitis Group has reviewed the scoring system to determine probable or definitive AIH. However, the scoring system is found to be applicable to pediatric cases of AIH. A liver biopsy is needed to confirm the diagnosis and evaluation of the degree of liver damage.[1]

Clinical Manifestation

In general, the clinical manifestation of AIH is divided into five features, including:[1]

1. Manifestations are similar to acute viral hepatitis symptoms include malaise, nausea/vomiting, anorexia, joint and abdominal pain, followed by symptoms of bile duct obstruction (jaundice, dark urine, and pale stools).
2. Acute liver failure with hepatic encephalopathy (grade II to IV) occurred within 26 weeks after the symptoms first appeared; INR≥2; with no history of liver disease before.
3. Non-specific symptoms that indicate dangerous onset (progressive fatigue, relapsing jaundice, amenorrhea, headache, anorexia, joint and abdominal pain, diarrhea, weight loss) appeared for six months until several years before diagnosis.
4. Complications of cirrhosis and port hypertension (hematemesis of esophageal/ gastric varicose veins, diathesis bleeding, splenomegaly), without a history of jaundice or liver disease
5. Hepatic aminotransferases increase with no signs or symptoms.

Additional/Pathological Examination

- *Autoantibodies*

  A positive autoantibody must be present in the diagnosis of AIH. Autoantibodies associated with AIH include ANA, SMA, anti-MFI1, anti-LC-1, and anti-mitochondrial antibody (AMA). In adults, the autoantibodies test result is positive when the autoantibodies are found after ≥1:40 dilution. Meanwhile, the positive result in children is concluded with the presence of autoantibody after a dilution of ≥1:20 for ANA and SMA or ≥1:10 for anti-LKM1.[1]
- *Histological features*

  Enforcement of the diagnosis of AIH should be accompanied by an additional examination of liver biopsy and compatible histological findings. However, there are still no specific histological findings for AIH. AIH should be considered if there are some of the following histological findings below:[2]

a. The histological finding of the hepatitis interface. It is usually accompanied by infiltration of plasma cells and lobular hepatitis.
b. Emperipolesis. Emperipolesis can be found in 65% of patients with AIH. Emperipolesis is the penetration of the whole cell into another cell, with both cells retaining their viability. Besides emperipolesis, hepatocyte rosette also can be found in 33% of patients.
c. Cirrhosis features. The features are found in 28-33% of adult patients and 38% of pediatric patients. The description of cirrhosis with multilobular necrosis or bridging necrosis is important to rule out differential diagnoses and determine the severity of inflammation or indicate fibrosis.
d. In AIH with ALF, the hallmark consists of 4 important features: central perivenulitis, plasma cell-enriched inflammatory infiltrate, massive hepatic necrosis, and lymphoid follicles. It primarily occurs in the centrilobular zone.

Table 1. The comparison of clinical features between the two types of AIH[1,2]

	AIH 1	AIH 2
Age distribution	Occurring at all age, peaks during childhood/adolescence and adulthood.	Present at younger age, including infant. Mainly in children and young adults.
Symptoms	Chronic symptoms Rare sign of portal hypertension	Acute onset Higher tendency to present as ALF Frequent relapse Rare presentation of cirrhosis
Laboratories	IgG usually elevated (hypergammaglobulinemia)	Partial IgA deficiency (40%)
Autoantibodies	ANA, SMA, anti-actin, SLA	Anti-LKM1, Anti-LC1, Anti-LKM3
Comorbid immune disease	Autoimmune thyroiditis Rheumatic disease IBD	Comorbid immune disease Diabetes Mellitus Vitiligo Adisson disease
Response towards therapy	Possible remission after drug withdrawal	More refractory to eventual treatment, need long-term immunosuppressive

Management of Autoimmune Hepatitis

The aims of AIH management are to achieve remission, reduce liver inflammation, improve symptoms, and prolong life expectancy.[1,6] According to ESPGHAN 2018, remission among the pediatric population is defined as clinical recovery marked by normalization of transaminase and IgG levels, negative or very low titer for autoantibodies including ANA or SMA (<1:20) and anti-LKM-1 and anti-LC-1 (<1:10), and histological resolution of the inflammation.[1] Although improvement of

histological findings can be found in 95% of patients after approximately 4 years of effective treatment. This resolution succeeds late after the clinical, biochemical, and immunological remission.[1] Clinical remission may be assumed if biopsy could not be conducted.

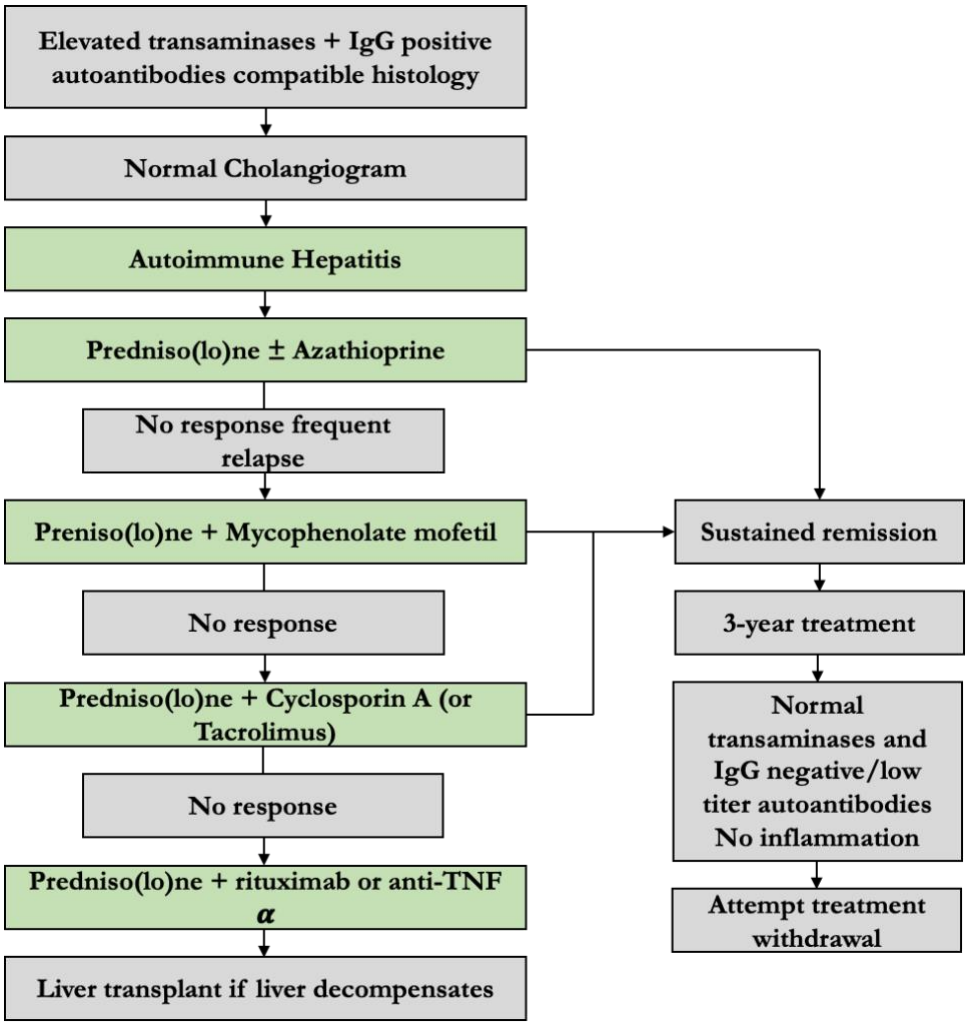

Figure 2. Flow chart for treatment for autoimmune hepatitis (Modified from Mieli-Vergani et al).[1]

As the treatment begins, patient with the sudden increase in serum aminotransferase levels following remission is categorized as relapse. This is a common occurrence in approximately 40% of patients, especially adolescents. The treatment for AIH should be given promptly in all children to prevent progression to end-stage liver disease. AIH usually responds well to immunosuppressive therapy in all degrees of liver impairment, with a remission rate of 90%. The flowchart for treatment for AIH could be seen in **Figure 2**.

The standard treatment usually consists of corticosteroids (usually prednisone or prednisolone and azathioprine (**Table 1**). Some of the roles of corticosteroid in AIH is (1) binding with the cytoplasmic receptor, translocation to the nucleus, and interacting with the specific DNA sequences present at regulatory sites in some genes; (2) inhibiting T-lymphocyte activation and proliferation, and (3) inhibits the synthesis of proinflammatory cytokines (e.g., IL-2 and IL-6). Conventionally, the treatment for AIH consists of predniso(lo)ne with starting dose of 2 mg/kg/day, maximum dose of 60 mg/day, gradually decreasing after 4-8 weeks with the resolution of the serum transaminases. The maintenance dose is 2.5 to 5 mg/day.[1,6]

Table 2. Standard regimen for autoimmune hepatitis.[1,2,6-10]

Drug	Recommended dose	Mechanism of action	Side effects
Predniso(lo)ne	**Initial dose:** 2 mg/kg/day Max dose: 60 mg/day **Maintenance dose:** 0.1-0.2 mg/kg/day or 2.5 – 5 mg/day	• Binds to cytoplasmic receptors, translocates to the nucleus, and interacts with specific DNA sequences that are present at regulatory sites in certain genes. • Inhibits T-lymphocyte activation and proliferation • Inhibits the synthesis of pro-inflammatory cytokines such as IL-2 and IL-6	• Cosmetic (moon face, Cosmetic (moon face, hirsutism, alopecia, dorsal hump, striae) • Systemic (weight gain, glucose intolerance, hypertension, fatty liver, osteoporosis, vertebral compression, cataract, glaucoma, opportunistic infection) • Quality of life (emotional instability, psychosis, depression, and anxiety)
Azathioprine (AZA)	**Initial dose:** 1-2 mg/kg/day **Maintenance dose:** 1-2 mg/kg/day if required OR **Maintenance dose for azathioprine monotherapy (AIH-1):** 1.2-1.6 mg/kg/day	• The exact mechanism is unclear • Might be linked to nucleic acid synthesis supression	• Hematology (mild cytopenia, severe leukopenia or bone marrow failure) • Gastrointestinal (nausea, vomiting, pancreatitis) • Neoplastic (non-melanoma skin cancer) • Cholestatic liver damage (rare)

Azathioprine is needed in about 85% of AIH children. However, the exact timing to start azathioprine may differ according to the center. Some centers start azathioprine only when corticosteroid monotherapy fails to induce remission or if a serious side effect occurs while others might start after 2 weeks of corticosteroid therapy or even begin the azathioprine regimen with corticosteroid therapy. The starting dose of azathioprine is 1-2 mg/kg/day, increased gradually if the decline of serum aminotransferase reaches plateau.

Alternative Treatment

Some patients who are non-responder to the conventional treatment may be given alternative AIH treatments to induce remission. In addition, some physicians choose this alternative treatment in an attempt to reduce steroid side effects or intolerant to conventional therapy. **Table 3** shows some of the alternative treatments that can be used in treating children with AIH.

Mycophenolate mofetil (MMF) is one of the more commonly used drugs for the treatment of AIH. MMF is the prodrug of the mycophenolic acid and is used with a dose of 20 mg/kg, twice daily with predniso(lo)ne. In case of MMF intolerance, calcineurin inhibitors should be considered. Tacrolimus and cyclosporin A are some of the proposed drugs for induction of remission. Previous study showed that tacrolimus monotherapy is not enough for complete remission of AIH. However, it allows smaller dose administration of prednisolone and azathioprine and thus, reducing the adverse reaction.

The use of cyclosporin in a study in Croatia provided new insight into the use of the drug for AIH. Remission was successfully achieved in treatment-naïve children who used cyclosporine A monotherapy for 6 months, and continued with conventional prednisone and azathioprine. The cyclosporine was discontinued after one month. Unfortunately, there was no clear explanation if this protocol has any advantage compared to the conventional treatment.[1,2]

Budesonide is an ideal "topical" liver treatment as the drug has hepatic first-pass clearance of more than 90% upon oral ingestion with fewer side effects than the traditional predniso(lo)ne. However, budesonide cannot be used in children with cirrhosis, which accounts for a large percentage of AIH patients. Rituximab and Infliximab have been reported to be effective in treating refractory AIH. However, their use should be evaluated carefully due to serious potential side effects of immunosuppression.[1,2]

Stopping Treatment

Current guidelines recommend that AIH treatment commences for at least 2 to 3 years before attempting to withdraw the treatment. In addition, ending the therapy should only be considered only if the transaminase and IgG levels have returned to normal limit and auto-antibody becomes very low or even negative for at least one year. If possible, liver biopsy should be repeated to ensure microscopic resolution of the inflammation, which might herald relapse.[1,2]

Table 3. Alternative regimen for autoimmune hepatitis.[1,2,6-10]

Drug	Recommended dose	Side effects
Mycophenolate mofetil (MMF)	20-40 mg/kg, twice daily with predniso(lo)ne	• Teratogenic • Gastrointestinal disturbance
Tacrolimus	0.1 mg/kg/day up to 1-8 mg/day	• Systemic (headache, tremor, paresthesia, insomnia, renal impairment) • Serum electrolyte disorders (hyperkalemia) • Hypercholesterolemia, hypertriglyceridemia, hyperlipidemia • Psychiatric disorders (mood changes, anxiety) • GI disorders (nausea, vomiting, GI bleeding) • CNS disorders (CNS hemorrhage, coma, paralysis, amnesia, speech abnormalities, dizziness, confusion) • Others (ECG abnormalities, uterine bleeding, pancytopenia, etc)
Cyclosporine	4-10 mg/kg/day in 3 divided doses	• Significant (infections, gingival hyperplasia, nephrotoxicity, hypertension) • Blood and lymphatic system disorders (anemia, leukopenia, thrombocytopenia) • Eye disorders (eye pain, burning/foreign body sensation, visual disturbance) • GI disorders (nausea, vomiting, diarrhea, abdominal pain, dyspepsia) • Immune system disorders (angioedema) • CNS disorders (seizures, encephalopathy, tremor, headache, paresthesia) • Others (hematuria, hirsutism, rash, dermatitis, flushing, etc)
Budesonide	6-9 mg/day in 3 divided doses	• Significant (adrenal suppression, immunosuppression, growth retardation, hyperglycemia, fluid retention) • GI disorders (nausea, abdominal pain, abdominal distension, dyspepsia, dry mouth) • CNS disorders (headache, dizziness, tremor) • Others (palpitation, fatigue, malaise, hypokalemia, myalgia, menstrual disorders)

Table 3. Alternative regimen for autoimmune hepatitis (continued).[1,2,6-10]

Drug	Recommended dose	Side effects
Rituximab	375 mg/m²/week for 4 weeks, repeat according to patient's response	• Cardiovascular disorders (arrhythmia, cardiogenic shock) • Blood and lymphatic system disorders (pancytopenia, agranulocytosis) • CNS disorders (paresthesia, hypoesthesia, dizziness, migraine, sciatica) • GI disorders (nausea, vomiting, diarrhea, abdominal pain, stomatitis, constipation, GERD) • Metabolic disorders (hyperglycemia, hypocalcemia, hypercholesterolemia, anorexia) • Psychiatric disorders (depression, anxiety, insomnia, agitation) • Others (hypertension, flushing, respiratory tract infections)
Infliximab	5 mg/kg; 4 infusions in 4 weeks interval	• Opportunistic infections • GI disorders (nausea, vomiting, diarrhea, abdominal pain) • Hepatic manifestations (acute liver failure, jaundice, cholestasis) • Blood and lymphatic system disorders (leucopenia, thrombocytopenia, pancytopenia) • Others (hypotension, chill, fever, dyspnea, exacerbation of demyelinating disorders)

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Case Report

Clinical Manifestation of Peutz-Jeghers Syndrome in Children with Gastrointestinal Bleeding: A Case Report

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Abstract: The Peutz-Jeghers Syndrome (PJS) is a rare familial disorder with manifestation that varies from asymptomatic to a life-threatening emergency. The PJS is caused by mutations of the tumor suppressor gene STK11 in embryonic cells, which is traditionally characterized by the development of melanotic macules and intestinal polyps. This case is about a boy, five years old, admitted to the emergency unit with a chief complaint of dark-red blood stool, pale appearance, abdominal pain, and nausea. Upon physical examination, there were multiple black spots on the lips and buccal mucosa (melanotic macules). Laboratory findings showed hemoglobin levels of 5.9 g/dL and a hematocrit of 18.7%. Multiple polyps at the fundus, corpus, antral, ileocecal, terminal ileal, transverse colon, sigmoid colon, and rectum were identified from the endoscopy examination. There were signs of upper and lower gastrointestinal bleeding in the pylorus of the stomach and the middle part of the descendent colon from the scintigraphy, respectively.

Keywords: children, Peutz-Jeghers Syndrome, gastrointestinal bleeding, choledochal cysts

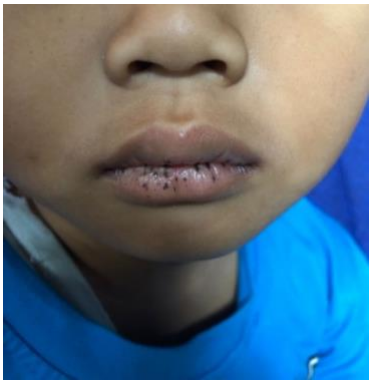
Introduction

Gastrointestinal polyps commonly cause lower gastrointestinal bleeding in children over one-year-old. The Peutz-Jeghers syndrome (PJS) is a polypotic hamartoma syndrome with typical mucocutaneous pigmentation. It is a rare autosomal dominant inherited disorder. PJS occurs in one in 50,000–200,000 live births and is associated with an increased risk of gastrointestinal and extraintestinal cancer. Patients usually complained of painless rectal bleeding. The PJS is characterized by hamartomatous intestinal polyps in association with a distinct pattern of skin and mucosal macular melanin deposition.[1,2] This report aims to describe the gastrointestinal bleeding manifestation found in the pediatric PJS patients.

Case

A 5-year-old boy complained of dark and bloody stool, pallor, abdominal pain, and nausea. Anemic conjunctiva and multiple black spots on the lips and buccal mucosa (melanotic macules) were found upon the physical examination. Abdominal tenderness was present, especially in the epigastric area. The patient had a similar complaint prior to the current admission. He was hospitalized at a district hospital and received a red blood cell transfusion, then discharged after improvement of condition. Three days after being discharged, he complained of bloody stool. Therefore, he was referred to our hospital. His father had the same complaints but had not received further examination.

(a)



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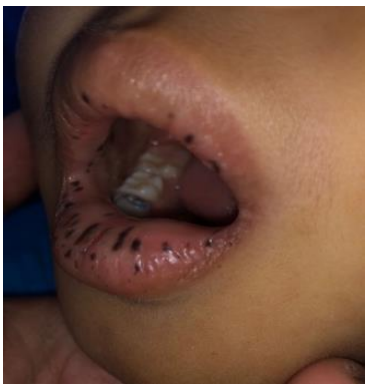

(c)

Figure 1. Physical examination (a) Dark Stool. (b) Melanotic macules on Lips. (c) Melanotic macules on buccal of a child with Peutz-Jeghers syndrome.

Upon laboratory findings during emergency admission, the hemoglobin level was 5.9 g/dL, the hematocrit 18.7%, leukocyte 9,540/mm^3, and the platelet count 756,000/mm^3. He was diagnosed with anemia due to gastrointestinal bleeding. He received transfusion therapy, but his hemoglobin level further declined during hospitalization due to the recurrence of bloody stool. The laboratory findings of the subjects are described in **Table 1**.

Table 1. Laboratory finding of the subject.

Parameters	Unit	Day 1	Day 2	Day 7	Day 8	Day 15	Day 18
Hemoglobin	(g/dL)	5.9	9.5	8.8	11.9	8.1	9.2
Hematocrit	(%)	18.7	30.1	27.2	35.8	24.3	28.3
Leukocyte	(/mm^3)	9,540	8,980	5,850	8,290	7,240	6,910
Platelet	(/mm^3)	756,000	572,000	582,000	538,000	696,000	648,000
PT	second	-	-	-	11.60	-	-
aPTT	second	-	-	-	21.50	-	-
INR	-	-	-	-	1.60	-	-
AST	(U/L)	-	-	-	28	19	-
ALT	(U/L)	-	-	-	25	20	-

Notes: PT = prothrombin time; aPTT = activated partial thromboplastin time; INR = international normalized ratio; AST = aspartate aminotransaminase; ALT = alanine aminotransferase.

Endoscopy and colonoscopy were performed. **Figure 2** showed the description and results of the endoscopy and colonoscopy examinations. The black bloody stool was identified from the terminal ileum upon endoscopy examination.

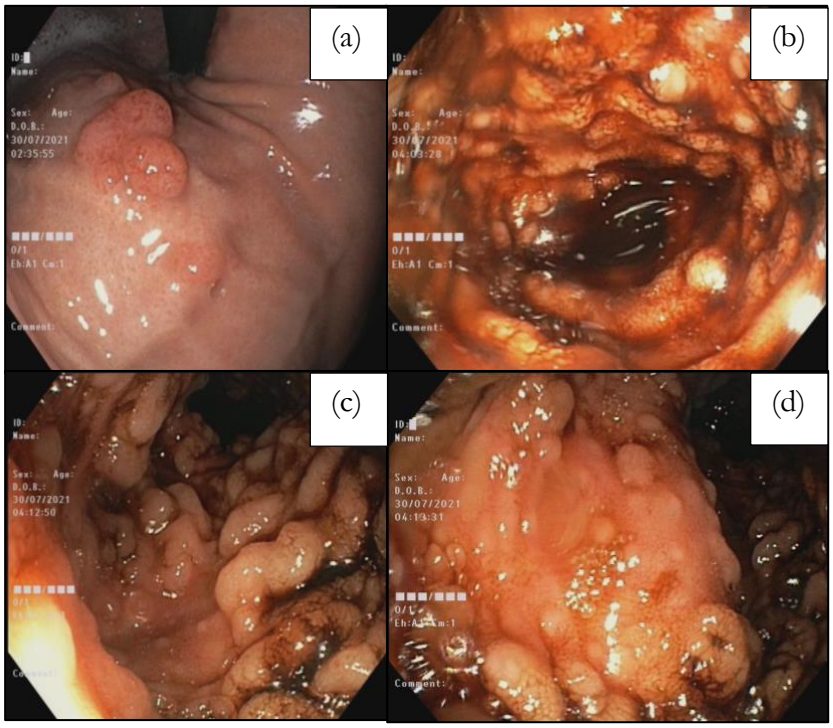

Figure 2. Endoscopy and colonoscopy of upper gastrointestinal tract. (a) Multiple polyps dominated by gastric fundus and corpus. (b) Multiple rectal polyps. (c) Multiple transverse colon polyps. (d) Multiple terminal ileal polyps.

(c) (d)

Upper gastrointestinal tract endoscopy showed esophagitis, erosive gastro-duodenitis, multiple polyposis, multiple scar ulcers in the region of the duodenal bulb, bile reflux, and antral hypoperistalsis. Lower gastrointestinal tract colonoscopy showed colitis, ileitis, cryptitis, and multiple polyposis. A biopsy was performed on all sections. Hyperplastic polyps were found in the fundus, corpus, antral, ileocecal, terminal ileal, transverse colon, sigmoid colon, and rectum.

A gastrointestinal scintigraphy examination was subsequently performed to identify any potential bleeding sites that could not visualized by endoscopy. Technetium injection was used for scintigraphy (**Figure 3**). The scintigraphy showed signs of upper gastrointestinal bleeding in the gastric pylorus and lower gastrointestinal bleeding in the mid descending colon. The gastric pylorus showed pathologically increased radioactivity from the planar imaging and single-photon emission computed tomography (SPECT) during the fifth minute that became more apparent over time. During the 120th minute, pathologically increased radioactivity appeared in the mid descending colon at the third lumbar vertebra level which became clearer and began to progress toward distal projection over time. No radioactivity was seen in other parts of the body.

The patient was also consulted to the pediatric surgeon and planned for surgical bleeding control with combined colonoscopy and laparotomy exploration. However, the patient's family refused to undergo the operation. Although the patient still had a bloody stool, he was discharged from the hospital when the abdominal pain had reduced. The patient's family was educated about the medicine and was recommended to be followed up in the pediatric gastro-hepatology polyclinic. The patient received omeprazole and ciprofloxacin when discharged.

Discussions

Gastrointestinal bleeding is frequently found in children. The condition is further divided into upper and lower gastrointestinal bleeding based on the injury site. In children, upper gastrointestinal bleeding is seen to occur more than lower gastrointestinal bleeding, with total incidents of 6.4% and 0.3%, respectively.[3,4] The etiology and manifestation of gastrointestinal bleeding may vary depending on the age and location of the bleeding. Among children aged 2-5 years old, the differential diagnosis of upper gastrointestinal bleeding includes erosive esophagitis, esophageal varices, gastritis, gastric ulcer, and vomit-induced bleeding. The commonly found manifestation of upper GI bleeding includes melena (dark, tarry, stool).[3] However, melena may also be found in the small intestine and ascending colon bleeding.

In contrasts, lower gastrointestinal bleeding is frequently caused by polyps, intussusception, Merkel's diverticulum, infectious enterocolitis, and anal fissure. In this type of bleeding, the manifestation is frequently appeared as hematochezia (fresh

blood through the anal).[5,6] In our case, the patient presented with dark, bloody stool, pallor, abdominal pain, and nausea. According to the explanation above, we concluded that the patient might suffer from esophageal until ascending colon bleeding.

Among children aged 2-5 years old, one of the most common etiologies of lower gastrointestinal bleeding is polyp. The condition is further classified into several categories, which are juvenile polyps, inherited hamartomatous polyposis syndromes, inherited adenomatous polyposis syndromes, and non-inherited polyposis. The manifestation of polyps may vary, including abdominal pain and melena. In particular, melena is more prevalent in the cases of polyposis syndrome. The diagnosis of polyps is made through endoscopy and colonoscopy. The diagnosis is further confirmed through biopsy, which is essential to differentiate the type of polyps.[7,8] In our case, the patient is showing recurrent hospitalization due to bloody stool and a family history of similar condition. This might indicate that the condition is an inherted disorder.

During the physical examination, anemic conjunctiva, multiple black spots on the lips and buccal mucosa (melanotic macules), and epigastric tenderness were found in this patient. Evaluation using endoscopy and colonoscopy examination was then conducted to locate the gastrointestinal bleeding. Through the examination, multiple polyposis, scar ulcers in the duodenal region, and erosive inflammation along the GI tract were found. These findings supports the suspicion towards PJS.

PJS patients were at approximately 37-93% increased risk of developing malignancy.[8,9] Peutz-Jeghers Syndrome is caused by the mutation of embryonic cells in the STK11 tumor suppressor gene.[7] Typical pigmentations, small blackish macules measuring 1–5 mm, are commonly seen around the corners of the lips and may extend to the buccal mucosa. These macules can also be found on the hands, feet, and genital area and may fade over time with age.[8,9]

In the case of PJS, polyps were commonly found in the small intestine (64%), followed by colon (53%), stomach (49%), and rectum (32%). This is in accordance with our patient, who displayed the presence of polyps in gaster, small intestine, large intestine, and rectum. The number of PJS polyps is usually low (20 polyps), and their diameter ranges from a few millimeters to more than 5 cm. The polyp is usually a hamartomatous polyp.[9]

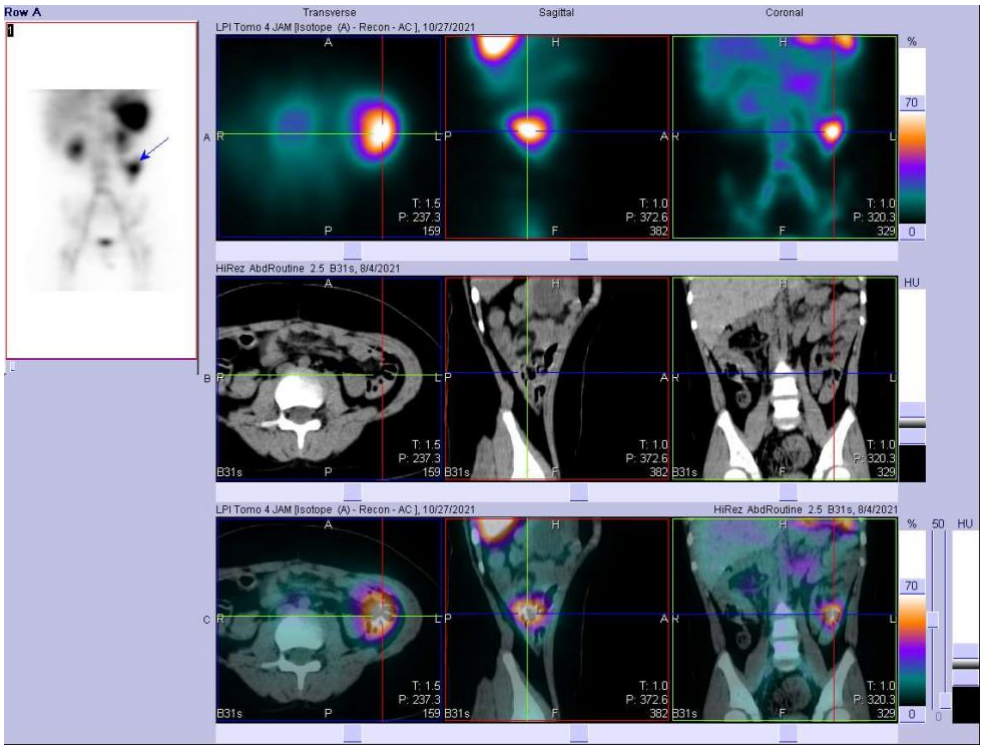

Figure 3. Scintigraphy: signs of upper gastrointestinal bleeding in the pylorus of the stomach and lower gastrointestinal bleeding in the middle part of the descendent colon were found.

PJS is diagnosed if one of the following conditions is found: (a) two or more histologically confirmed PJS hamartomatous polyps; (b) any number of PJS polyps and has a family history of PJS; (c) PJS polyps with the characteristic of mucocutaneous pigmentation; (d) characteristic pigmentation combined with a family history of PJS. Meanwhile, on the physical examination, pigmentation of the lip mucosa is the most prominent feature.[10] Based on this knowledge, the patient had met the diagnostic criteria for PJS. Hence, biopsy and scintigraphy were planned to establish the diagnosis and find other sources of bleeding in the abdomen cavity. Despite not being done in this study, we also recommend further examination using molecular genetic testing to identify the mutation of embryonic cells in the STK11 tumor suppressor gene, as the syndrome is caused by the mutation in this particular suppressor gene.[1,7]

The histopathological features of PJS polyps are unique; their smooth muscle proliferation extends to the lamina propria with a pattern resembling a tree branch and extends to the mucosal surface of the polyp.[9] In our case, hyperplastic polyps in the fundus, corpus, antral, ileocecal, terminal ileal, transverse colon, sigmoid colon, and rectum were found in the patient's biopsy sample.

PJS patients are at approximately 37-93% increased risk of developing malignancy.[8,9] The most commonly reported disease is colorectal carcinoma, followed by the breast, small intestine, gastric, pancreatic, gynecology, lung, and esophagus.[8] Appendix cancer was reported in an adult patient with PJS in Japan.[11] Thus, malignancy screening is essential and should be included in the PJS treatment planning. During hospitalization, the GI bleeding in this patient got worsening. The patient was planned for surgical bleeding control with combined colonoscopy and laparotomy exploration. Unfortunately, after explaining and educating about the condition, the patient's family objected the plan. The patient was discharged after the abdominal pain relieved, and was recommended for routine control in the policlinic

Conclusion

Gastrointestinal bleeding in children over one year of age is commonly caused by polyps with clinical manifestations of hematochezia and melena as found in this patient. There are various types of polyps in the child's age group, one of which is the PJS, characterized by mucocutaneous pigmentation as found in this patient. In particular, this patient also has a family history of similar complaints. Periodic evaluation with upper and lower gastrointestinal endoscopy may be considered in these patients, considering the risk of malignancy in PJS.

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Case Report

A 10-year-old Boy with Giant Choledochal Cyst: A Case Report

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Abstract: Choledochal duct cyst is a rare congenital anomaly in the form of cystic dilatation of both intrahepatic and extrahepatic bile ducts. The clinical symptoms of choledochal cysts are generally due to bile stasis, stone formation, recurrent superinfection, and inflammation. This case depicts a 10-year-old boy presented with a chief complaint of an enlarged abdomen that was rapidly growing, sub-febrile fever and yellowing of the sclera. A choledochal duct cyst was shown in the abdominal ultrasonography. Laboratory examination showed an increase in liver function test, hypoalbuminemia, and prolonged coagulation profile. Magnetic resonance cholangiopancreatography showed a significant cystic dilatation of the common bile duct extending to the common hepatic duct. Surgery was performed twice, first to drain the cyst and second to perform complete excision and anastomoses to the jejunum, as fluid continued to refill the cyst.

Keywords: giant choledochal cyst, bile stasis

Citation:
Kusumawati NRD and Pratiwi J. A 10-year-old Boy with Giant Choledochal Cyst: A Case Report. *Arch Pediatr Gastr Hepatol Nutr*. 2022(1):35-40.

Introduction

Choledochal duct cyst is a rare congenital anomaly in the form of cystic dilatation of both intrahepatic and extrahepatic bile ducts. It often occurs in children under ten years of age and is four times more common in women than men. The pathogenesis of common bile duct cysts is unknown, but some studies conclude that it is caused by the irritation of the reflux pancreatic enzymes to the bile duct wall.[1,2,3] Another well-known cause is the Abnormal Pancreatic-biliary Junction (APBJ), which generates the abnormal connection between the bile duct system and the pancreas. 4 As there is no sphincter to prevent the reflux of pancreatic juice to the biliary duct, any abnormality such as APBJ or other cause that could increase the pressure of pancreatic secretory will cause the reflux.[2,4]

The clinical symptoms of choledochal cysts are generally due to bile stasis, stone formation, recurrent superinfection, and inflammation. Obstruction and infection in all choledochal cysts, especially those involving the intrahepatic tract, will cause secondary hepatic cirrhosis in 40-50% of patients. Signs of portal hypertension will

appear, such as upper gastrointestinal bleeding, splenomegaly, and pancytopenia. Therefore, the accuracy of diagnosis is needed to reduce patient mortality and morbidity.[4]

The diagnosis of choledochal duct cyst is made by combining signs and symptoms that arise from the history, physical examination, laboratory examination, and radiological examination

Case

A 10-year-old boy presented with a chief complaint of an enlarged abdomen. Three months before admission to the hospital, the patient complained of an enlarged abdomen and a palpable lump on the right side of the abdomen that was felt to be growing rapidly. These complaints were accompanied by: sub febrile fever and yellow eyes. There was no abdominal pain, no nausea and vomiting, and no complaint of defecation. Abdominal Ultrasound showed that the patient has a choledochal duct cyst. The patient was then referred to our center for further examination.

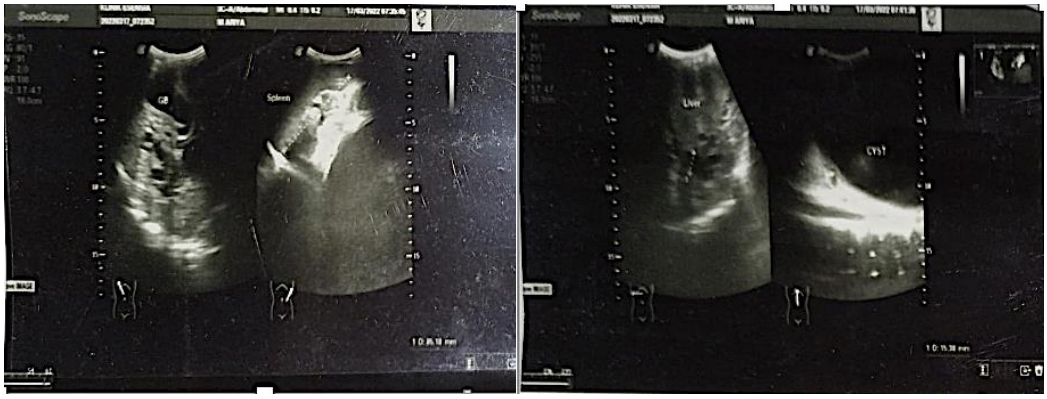

Figure 1. USG Abdomen: Large cystic lesions on the upper to lower abdomen (the size cannot be reached by the probe) with widening of the intrahepatic bile ducts, tending to be choledochal cysts (Todani classification type IVa)

The child looked thin with an enlarged, distended abdomen on the physical examination. A palpable mass was found in the right abdomen extending to the left abdomen. The largest abdominal circumference was 79 cm, and the umbilical circumference was 74 cm (pre-operative). The sclera was also icteric. Vital signs were within normal limits, while the anthropometry examination showed the impression of malnutrition with normal stature.

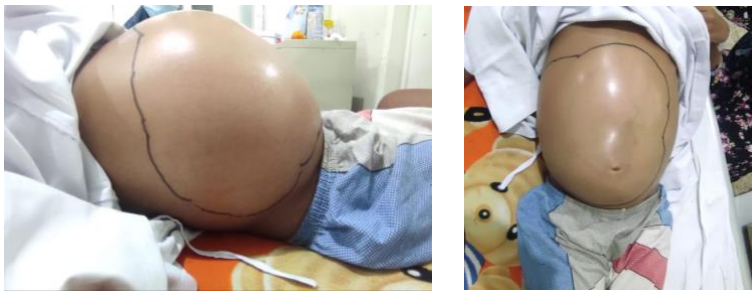

Figure 2. Patient clinical photo pre-operative

Laboratory examination showed an increase in liver function test (LFT), hypoalbuminemia, and prolongation of the coagulation study. Magnetic resonance cholangiopancreatography (MRCP) showed a significant cystic dilatation of the common bile duct extending to the common hepatic duct (size ± AP 16.7 x CC 26.4 x LL 18.3 cm), pressing the pancreas, stomach, and the surrounding bowel structures to the left lateral and accompanied by minimal sludge. Dilated right hepatic duct (± 1.5 cm in diameter) and left hepatic duct (± 1.7 cm in diameter) showed the impression of a choledochal cyst (Todani Classification type IVA), cystic duct dilation (± 1.3 cm diameter), and minimal ascites. The drainage of the choledochal duct cyst was performed by extracting around 3 liters of greenish-yellow fluid.

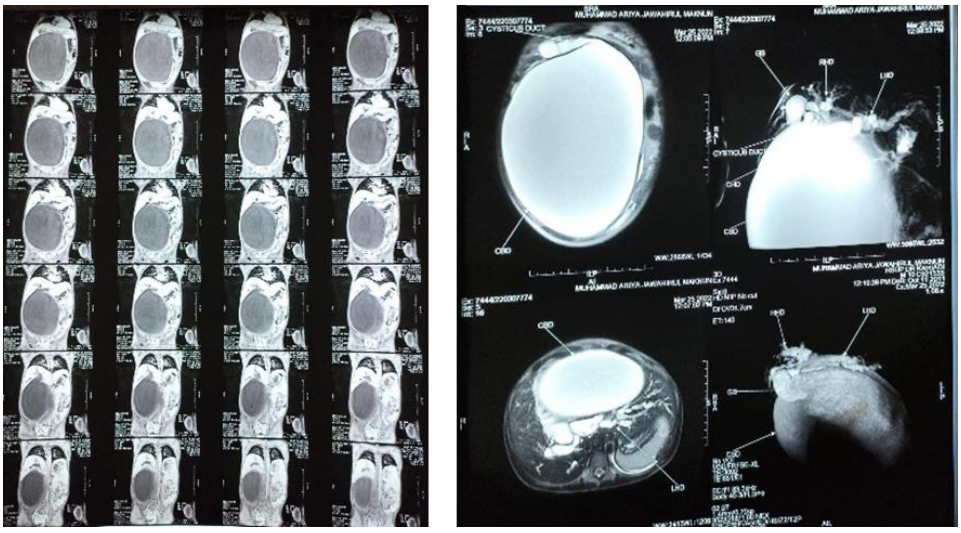

Figure 3. Magnetic resonance cholangiopancreatography (MRCP).

On the fifth day after the drainage procedure, the stomach enlarged, accompanied by fever, nausea and vomiting. An abdominal x-ray was performed and the results showed broad ground glass opacity from the right to the left hemiabdomen accompanied by increased pressure to the left side of bowel loops. The opacity was suspected to be an intra-abdominal mass. There was no picture of ileus or pneumoperitoneum. An exploratory relaparotomy was then further planned.

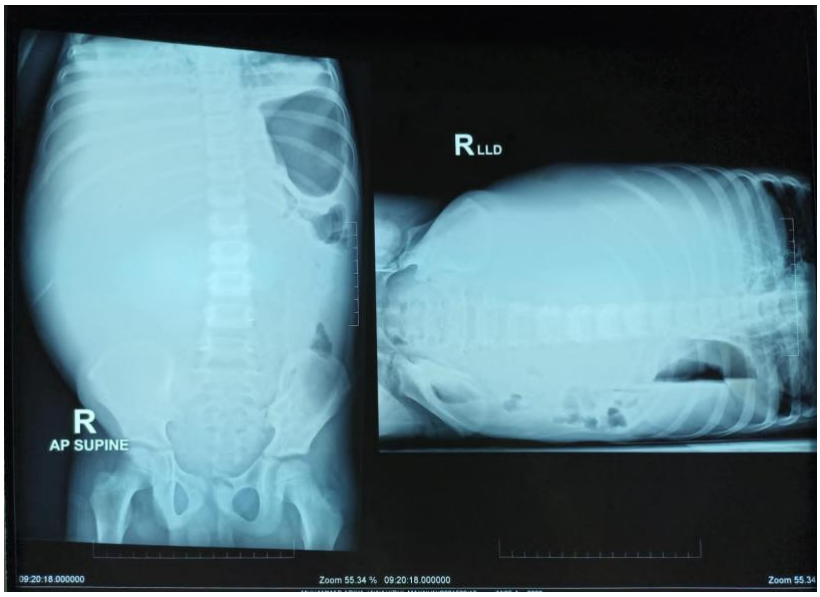

Figure 4. Abdominal x-ray after the first surgery

The results of the relaparotomy showed that the bile duct cyst was again filled with fluid for more than 2 liters; thus, a Roux en Y cystojejunostomy and open drainage were then performed.

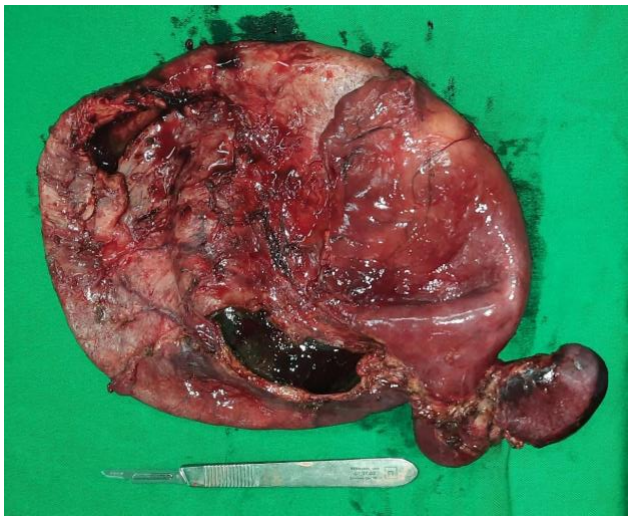

Figure 5. Choledochal duct cyst

The biopsy result revealed that the primary diagnosis of this case is choledochal duct cysts. The test also demonstrated the occurrence of chronic non-specific cholecystitis and hepatic cirrhosis with F4 degree of fibrosis. There was no sign of malignancy.

Discussion

This case described a 10-year-old boy presented with an abdominal lump that progressively enlarged within three months, accompanied by complaints of jaundice, weight loss, and increased liver function test. The lump was caused by obstruction, which damaged the hepatocytes. The hepatocytes injury could be assessed through the histopathological results, in which our patient exhibited grade 4 fibrosis. Portal hypertension often occurs in patients with choledochal cysts; however, in this particular patient, there are no signs of portal hypertension or large cysts that obstruct the biliary tract.

Ultrasonography is the initial modality used to evaluate abnormalities in the biliary tract. The diagnostic technique adequately shows cystic or fusiform structures of the hepatic portal area in choledochal cysts. A biliary CT scan, either ERCP or percutaneous retrograde cholangiography, could be performed to confirm the ultrasound examination results.[5,6] In this patient, the ultrasound results from the previous hospital detected the impression of a choledochal cyst. To verify the ultrasound result and confirm the diagnosis, MRCP was performed. The result demonstrated a type IV-A choledochal duct cyst, and the patient was scheduled for surgery.

Recently, the surgical management of choledochal cysts has been developing. Surgical management of choledochal cysts mainly consists of drainage by cyst enterostomy. However, patients who undergo cyst drainage without cyst excision had an increased risk of carcinoma and incidence of cholangitis or pancreatitis. Thus, cyst excision is currently the prioritized method in the surgical management of choledochal cysts.[7] The surgical management preferred in choledochal cysts cases varies depending on its type in type-IV cysts, particularly type-IVA.[8,9]

Cholangiocarcinoma is an ominous complication of unresected choledochal cysts, occurring around 20-30% in early adulthood. The risk of cholangiocarcinoma remains high in patients who underwent drainage procedures with either partial cyst resection or no cyst resection. The risk of cholangiocarcinoma also increases in the type-I and type-IV choledochal cyst. In our case, surgery was performed twice, first to drain the cyst and second to perform complete excision and anastomoses to the jejunum, as fluid continued to refill the cyst.[10] The anatomical pathology of the patient showed no signs of malignancy. However, the biopsy result suggests a grade 4 fibrosis; hence further monitoring of liver function is needed in this patient

Conclusion

Choledochal duct cyst is a rare congenital anomaly in children. Complaints that arise vary but are often symptoms due to biliary obstruction. The diagnosis is based on history, physical examination, laboratory and radiological examination. Abdominal ultrasound can provide significant input in cases with common bile duct cysts. Surgical management of choledocal cyst is currently developing rapidly. Approximately 20-30% will develop into malignancy in early adulthood. Thus, early diagnosis and the type of cyst determine the patient's prognosis.

Abbreviation

AP : anteroposterior
LL : laterolateral
CC : craniocaudal

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