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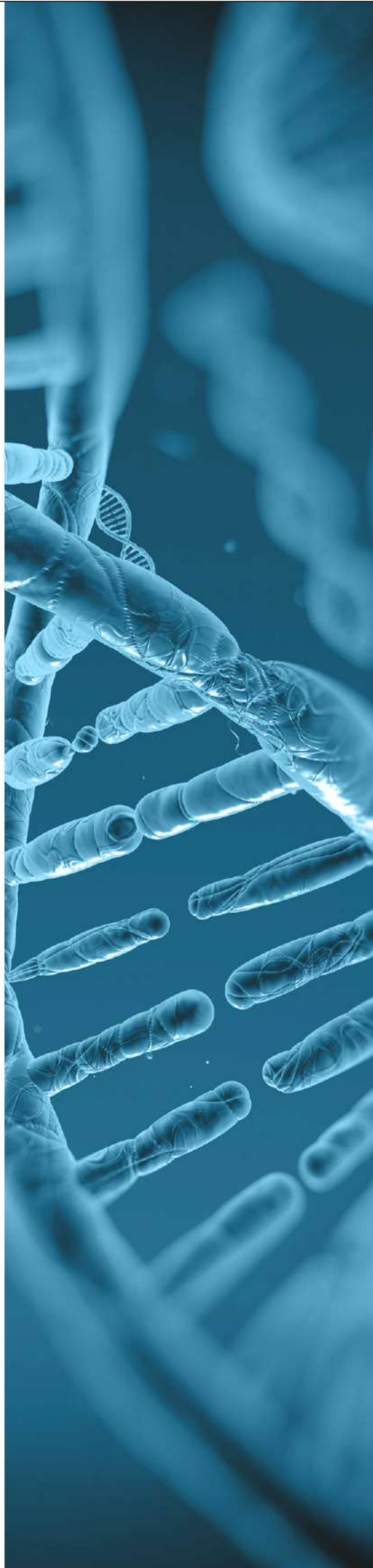

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CASE REPORT

# Cholestatic Jaundice Due To Biliary Atresia With Cytomegalovirus And Malaria Infection: Blood Transfusion-Transmitted Infection?

## Suspek Atresia Bilier Dengan Infeksi Cytomegalovirus dan Malaria : Infeksi Menular Lewat Transfusi Darah?

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**ABSTRACT**

**Introduction:** Blood transfusion can cause infectious complications through transfusion of microbes present in asymptomatic donor blood and/or contamination of stored blood products such as Hepatitis B, Hepatitis C, HIV, syphilis, malaria, Cytomegalovirus (CMV) infection. The risk of infection increases with the amount of blood products transfused.
**Case presentation:** A 5-month-old boy who had never been to malaria endemic area with jaundice and abdominal enlargement since two months ago, fever since one month ago, and icteric sclera. Data from laboratory results shows anemia, leukocytosis, hyperbilirubinemia, elevated liver enzyme, positive IgM and IgG anti-CMV. Blood smear evaluation: Trophozoite and ring forms of malaria parasites. Abdominal USG: Type-I Biliary atresia, Choledochal cyst, splenomegaly, ascites, and right pleural effusion.
**Discussion:** An acute Transfusion-transmitted CMV infection in high-risk patients can have severe complications such as billiary atresia, myocarditis, retinitis, encephalitis, or encephalopathy. Leucodepleted blood products for transfusion can reduce the risk of infection. Thick and thin blood smears which is the gold standard for diagnosing malaria, cannot be used for donor screening. Asymptomatic malaria infections may remain undetected.
**Conclusion:** Blood transfusion screening for infectious diseases is still very limited for Hepatitis B, Hepatitis C, Syphilis, and HIV. It is necessary to think about blood transfusion screening for other infectious diseases, such as CMV and malaria, especially in endemic areas, to prevent the occurrence of transfusion-transmitted infection.

**Keywords**: blood transfusion; CMV; Malaria

**ABSTRAK**

**Pendahuluan:** Transfusi darah dapat menyebabkan komplikasi infeksi melalui: transfusi mikroba dari darah pendonor asimtomatik dan/atau kontaminasi produk darah yang disimpan seperti infeksi Hepatitis B, Hepatitis C, HIV, sifilis, malaria, Cytomegalovirus (CMV). Resiko infeksi meningkat seiring dengan jumlah produk darah yang ditransfusikan.
**Kasus:** Anak laki-laki, lima bulan tanpa ada riwayat ke daerah endemis malaria dengan *jaundice* disertai pembesaran abdomen sejak dua bulan terakhir, demam selama satu bulan, sklera ikterik. Pemeriksaan laboratorium didapatkan anemia, leukositosis, hiperbilirubinemia, peningkatan enzim hepar, IgM dan IgG anti-CMV positif . Hapusan darah tepi ditemukan parasit malaria bentuk tropozoit dan *ring*. USG Abdomen : suspek atresia bilier tipe I, splenomegali, ascites, efusi pleura kanan.
**Diskusi:** Infeksi CMV akut akibat transfusi darah pada pasien dengan resiko tinggi dapat memberikan komplikasi berat seperti atresia bilier, miokarditis, retinitis, ensefalitis, dan ensefalopati. Pemberian transfusi darah jenis *leucodepleted* dapat menurunkan resiko tersebut. Pemeriksaan tetes darah tebal dan tipis masih digunakan sebagai baku emas untuk mendiagnosis malaria namun tidak dapat digunakan untuk skrining darah donor. Infeksi malaria asimtomatik dapat tetap tidak terdeteksi.
**Kesimpulan:** Skrining darah transfusi terhadap penyakit infeksi masih sangat terbatas untuk Hepatitis B, Hepatitis C, Sifilis, dan HIV. Sangatlah penting untuk dipikirkan mengenai pemeriksaan skrining darah transfusi terhadap penyakit infeksi lain seperti CMV dan malaria terutama di daerah endemis untuk mencegah munculnya kejadian IMLTD.

**Kata Kunci**: transfusi darah, CMV, Malaria

## INTRODUCTION

Blood transfusion can cause infectious complications through the following mechanisms: microbial transfusion from asymptomatic donor blood and contamination of stored blood products. The risk of infection increases with the amount of blood products transfused.[1] Transfusion-transmitted infections (TBI) are most often caused by viral infections. Cytomegalovirus (CMV) infection due to blood transfusion often causes morbidity and mortality in newborns, and also causes congenital infection in developing countries, mental retardation, and developmental disorders. The prevalence of anti-CMV in the population ranges from 40%-90%.[2] Although about 50% of transfused blood is CMV seropositive, it is estimated that less than 1% of seropositive blood cell components can transmit infection.[3]

Although rare, malaria is the most common parasitic infection due to blood transfusion. Malaria parasites will survive for at least one week in blood components stored at room temperature or 40 C.[4] Asymptomatic carrier donors are a source of malaria transmission through transfusion. Malaria parasite screening is done by examining peripheral blood smears. Thick and thin blood smears can detect parasitemia between 300-500 /µL, but parasitemia with a minimum level of 10 /µL can cause malaria infection through transfusion.[5] The smear method shows poor results in malaria screening due to low parasite concentrations in infected people, where these samples can be positive in examinations with detection methods using monoclonal antibodies.[6]

This case is about a 5-month-old boy who suffered from cholestasis due to biliary atresia with CMV infection and malaria with a history of transfusion at the age of 3 months and had never traveled to an area endemic for malaria. This patient had increased AST and ALT enzymes, high total

and direct bilirubin levels, accompanied by a positive Immunochromatography Test (ICT) for malaria and positive results for IgM anti-CMV, IgG anti-CMV.

## CASE REPORT

A 5-month-old boy came from the hospital outpatient clinic with a diagnosis of suspected biliary atresia. The patient had symptoms of yellowing of the skin and eyes accompanied by abdominal enlargement since two months ago. The patient also had sub-febrile fever 1 month before admission. The history of defecation and urination was normal. The patient was born normally, according to gestational age with a weight of 3100 grams. The patient is the second child of two siblings. The history of basic immunization (polio, BCG, and Hepatitis B) is complete. History of growth and development according to the patient's age. History of blood transfusion at the age of 3 months due to anemia. History of the same complaint in the family was denied by the patient's parents.

Physical examination found a general condition that appeared weak, GCS score 15 (E4M5V6), pulse 128 x / minute, regular, and strong, respiration 24 x / minute, axillary temperature 37.5 $^{o}$C, body length 64 cm, and weight 5.7 kg. On examination of the head and neck, anemic conjunctiva, and icteric sclera, no signs of cyanosis or shortness of breath were found. Thoracic examination showed a symmetrical chest shape, without chest wall retraction. Single S1 S2 heart sounds without gallops or heart murmurs. Vesicular breath sounds, without rhonchi and wheezing. On examination of the abdomen, normal bowel sounds were found, as supple, abdominal enlargement with a liver size of 4x4x3 cm. There was no enlarged spleen. The acral extremities felt warm, and dry, without edema, and there were no enlarged lymph nodes in the axillary and inguinal regions.

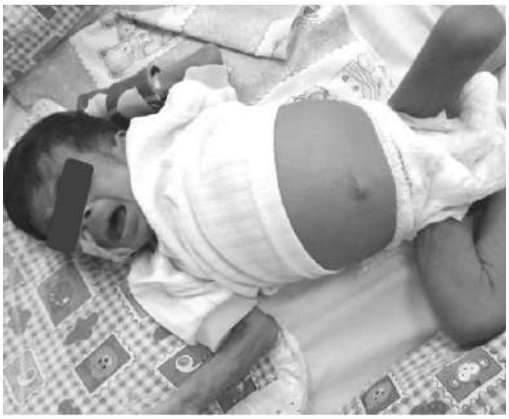

**Figure 1.** Patient's condition

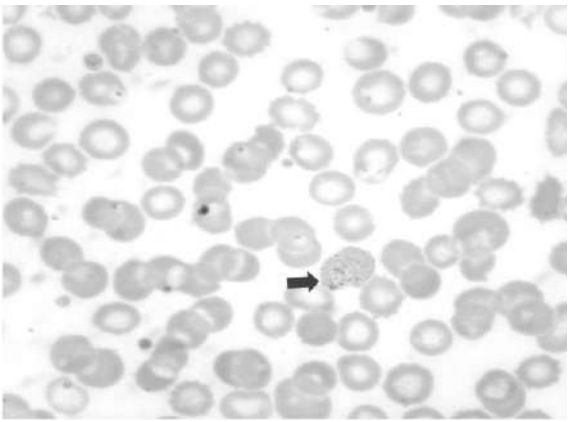

**Figure 2.** Trophozoite Forms

Routine blood tests showed anemia and leukocytosis. Peripheral blood smear examination (SADT) found malaria parasites in the form of trophozoites and rings. Clinical chemistry examination found hypoalbuminemia, hyperbilirubinemia, increased levels of aspartate transferase (AST), and alanine transferase (ALT) accompanied by hyponatremia. Immunology examination found increased levels of ANA, and C3, positive results for IgM anti-CMV, IgG anti-CMV, increased ferritin levels, and decreased levels of Total Iron Binding Capacity (TIBC). In the infection examination, positive results for the Pan and Pv malaria Rapid tests were obtained.

**Table 1.** Hematology Laboratory Examination

| Parameter | Day 1 | Day 7 | Normal Value |
|---|---|---|---|
| Hb (g/dL) | 7.44 | 11.8 | 12.9-15.9 |
| RBC (m/µL) | 2.90 | 4.51 | 4.06-5.58 |
| Hct (%) | 24.2 | 38.0 | 37.7-53.7 |
| MCV (fl) | 83.5 | 84.3 | 81.1-96 |
| MCH (pg) | 25.7 | 26.2 | 27.0-31.2 |
| MCHC | 30.7 | 31.0 | 31.8-35.4 |
| RDW (%) | 21.0 | 17.3 | 11.5-14.5 |
| Plt($10^3$/µl) | 233 | 259 | 155-366 |
| WBC($10^3$/µl) | 18.4 | 24.51 | 3.7-10.1 |
| Blood type count | 2/0/59/29/10 | 1/0/79/14/6 | - |
| SADT/Blood smear | Malaria parasites (+) : Tropozoites and rings | | |

**Table 2.** Clinical Chemistry Laboratory Examination

| Parameter | Day 1 | Day 7 | Day 11 | Normal Value |
|---|---|---|---|---|
| AST (U/L) | 112 | - | 136 | 15-37 |
| ALT (U/L) | 152 | - | 210 | 12-78 |
| GDP (mg/dL) | 75 | - | - | < 100 |
| BUN(mg/dL) | 5 | 9 | 13 | 7-18 |
| Cr (mg/dL) | 0.4 | 0.55 | 0.56 | 0,6-1,3 |
| Alb (g/dL) | 2.4 | 3.2 | 2.9 | 3,4-5,0 |
| Bil. Total (mg/dL) | 7.48 | - | 10.06 | 0.2-1.00 |
| Bil. Direct (mg/dL) | 5.66 | - | 7.80 | 0.00-0.20 |
| Na (mmol/L) | 123 | 128 | 137 | 136-145 |
| K (mmol/L) | 4.1 | 3.5 | 4.1 | 3.5-5.1 |
| Cl (mmol/L) | 91 | 98 | 108 | 98-107 |
| Ca (mg/dL) | 8.3 | 7.9 | 7.8 | 8.0-10.1 |
| TIBC (µg/dL) | - | - | 102 | 250-450 |
| Feritin (ng/mL) | - | - | 742.3 | 30-434 |
| SI (µg/dL) | - | - | 83 | 35-150 |

Cr : *Creatinine;* Alb : Albumin; SI : *Serum Iron*

**Table 3.** Immunology & Infection Laboratory Examination

| Parameter | | Day 11 | Normal Value |
|---|---|---|---|
| ANA | | 40.35 | 0.35-5.5 |
| C3 (mg/dL) | | <16.4 | 0.89-1.76 |
| HBsAg | | Non-reactive | 4.30-22.4 |
| IgG anti-CMV | | + 108 | 1.5-9.3 |
| IgM anti-CMV | | + 1.62 | 1.4-18.1 |
| IgG anti-Toxoplasma | | - | 15-60 |
| IgG anti-Toxoplasma | | - | 0.1-1 |
| ICT | Pan | Positive | Negative |
| Malaria | Pv | Positive | Negative |
| | Pf | Negative | Negative |

Radiology Examination: Abdominal USG (Day 8); Impression: suspected biliary atresia type I, suspected choledochal cyst, hepatomegaly, minimal ascites, right pleural effusion. Bladder, pancreas, spleen, and right and left kidneys within normal limits. Pathological anatomy examination: liver biopsy (day 11); impression: extrahepatic cholestasis.

## DISCUSSION

In particular, cases of biliary atresia with positive IgM Anti-CMV results have been quite widely reported. To prove the relationship between CMV infection and biliary atresia, CMV DNA was successfully detected in 60% of liver biopsies in patients with biliary atresia with positive IgG anti-CMV, which was associated with histological changes typical of biliary atresia. This led to CMV being considered as the causative agent of biliary atresia.[7] Biliary atresia caused by positive IgM Anti-CMV is different from other types of biliary atresia, clinical manifestations usually appear later. Patients usually appear healthy, but after a few weeks, obstructive cholestasis may occur.[8] Xu et al. in 2014 stated that CMV infection decreases the expression of interferon-gamma (IFN-γ) cytokines and transcription factor T-bet, and significantly increases the expression of IL-4 cytokines and transcription factor GATA-3. This indicates that CMV infection can cause an imbalance in Th1/Th2 cell differentiation and the expression of their respective cytokines, leading to a decrease in the function of cellular immunity of infected individuals. This is also one of the reasons why CMV can escape the host's specific cellular immunity, causing persistent or latent infection, and leading to biliary atresia.[9,10] Several studies have also shown that progressive fibrosis inflammation in the liver causes the loss of bile ducts, leading to the theory that biliary atresia is caused by an immune response whose trigger is unknown. Xu et al.'s study also added that CMV infection has the potential to be an initiating factor for this immune process.[9]

Supporting examinations needed to confirm the diagnosis of biliary atresia include increased liver enzymes and hyperbilirubinemia due to increased direct bilirubin levels; serological examinations that provide positive results for IgM anti-CMV; radiological examinations such as abdominal ultrasound that confirm biliary atresia, and liver biopsy where increased fibrosis and histological changes are found consistent with biliary atresia.[7,10] Acute CMV infection due to transfusion in high-risk patients can cause severe complications, so appropriate action is needed to reduce this risk. The only strategy that has been confirmed in clinical trials is the administration of leucodepletion blood and ensuring that the blood products come from seronegative donors.[11]

Recent estimates suggest that the incidence of transfusion-associated malaria infection is <0.2 cases per 1,000,000 in non-endemic countries and >50 cases per 1,000,000 in endemic countries.[12] The risk of transfusion-associated malaria infection in non-malaria-endemic areas is due to donor blood previously living in or traveling to malaria-endemic areas.[13] An important difference between natural malaria infection and transfusion-associated malaria infection is that natural malaria infection passes through an asymptomatic (pre-erythrocytic) phase, which causes activation of innate immune cells against the malaria parasite, allowing the host time to develop more specific protective immunity. In transfusion-associated malaria infection, infected donor blood directly releases malaria parasites into the recipient's bloodstream, preventing innate immunity from being activated and increasing the risk of complications.[14]

The main problem of malaria infection due to blood transfusion is related to donor blood from asymptomatic donors who have very low parasite counts. This makes the thick and thin blood drop test, which is still used as the gold standard for diagnosing malaria, unsuitable for screening donor blood.[5] This asymptomatic infection can remain undetected and a study by Dover et al. reported that as few as 10 infected red blood cells are sufficient to transmit malaria to the recipient.[15,16] All Plasmodium species can survive in stored donor blood, even in frozen conditions for approximately

ten days, depending on storage conditions.[15,17] However, administration of donor blood that has been stored for too long can also produce a pro-inflammatory response associated with increased iron levels in the liver, spleen, and kidneys, and increased levels of nontransferrin bound iron (NTBI) have dangerous side effects such as increased risk of bacterial infection.[18]

In this case, the patient presented with the main complaint of yellow skin and eyes accompanied by abdominal enlargement and fever. This is a sign of cholestasis and infection. Physical examination of this patient showed anemic conjunctiva, icteric sclera, and hepatomegaly. All of these symptoms are by the results of the initial laboratory examination, namely anemia, increased liver enzyme levels, and hyperbilirubinemia, which indicate that there is extrahepatic cholestasis and liver disorders. The second laboratory examination was performed after the patient received a transfusion to treat anemia in the patient and found an increase in hemoglobin levels but an increase in leukocyte levels due to the patient's worsening condition. Immunological examinations showed positive CMV IgG and IgM results indicating that this patient had CMV infection. Malaria examination on thick and thin blood smears found malaria parasites in the form of trophozoites and rings and continued with ICT malaria examination with positive results for malaria vivax which supported the diagnosis of malaria infection in this patient. Abdominal USG examination showing type I biliary atresia and hepatomegaly supported the results of laboratory examinations.

Research conducted by Mangano et al. stated that all donor blood from malaria-endemic areas should be tested for anti-malarial antibodies, even if the donor has long left the endemic area. To reduce cases of malaria due to blood transfusion, surveillance strategies such as conducting questionnaires before donating blood and/or laboratory screening tests can be carried out.[19] Serological examinations have limitations in terms of sensitivity. A 2018 study of five types of Enzyme-linked immunosorbent assay (ELISA) examination products produced high specificity (100%) but sensitivity between 53-64%. Serological examination is also an indirect examination so it does not directly indicate parasitemia and can cause uninfected donors to be excluded.[20] The World Health Organization (WHO) recommends nucleic acid amplification examinations for epidemiological studies and surveys of sub-microscopic infections. Polymerase chain reaction (PCR) examination is the most sensitive examination method, detecting parasitemia from 2-5 parasites/µL, unlike microscopic examination with a sensitivity of 50-500 parasites/µL and Rapid Diagnostic Test (RDT) which has a sensitivity of ~100 parasites/µL. However, PCR examination requires expensive costs and complicated examination methods.[21]

This patient has a history of blood transfusion at the age of 3 months without a history of exposure to CMV and no history of traveling to malaria-endemic areas, so the possibility of IMLTD needs to be considered. Currently, blood transfusion screening for infectious diseases is still very limited. Screening for blood transfusions is based on donor evaluation, laboratory screening examinations, and pathogen inactivation procedures, but this still does not eliminate all risks.[22] Blood transfusion screening for infectious diseases caused by viruses currently uses the Nucleic Acid Testing (NAT) method. NAT itself still has several limitations such as low levels of viremia that cannot be detected by NAT. The combination of serological and NAT examinations has been quite helpful in reducing the risk of viral infections due to blood transfusions.[23,24]

## CONCLUSION

The patient was diagnosed with biliary atresia cholestasis type I with CMV infection and malaria which is suspected to be an IMLTD. Blood transfusion screening for infectious diseases is still very limited for Hepatitis B, Hepatitis C, Syphilis, and HIV, so it is necessary to consider screening blood transfusions for other infectious diseases such as CMV and malaria, especially in endemic areas to prevent the occurrence of IMLTD. It is also necessary to consider giving leucodepletation blood products to patients with immune system disorders.

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None

## AUTHORS CONTRIBUTION

All authors contributed to this article.

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## CONFLICT OF INTEREST

The authors declared no conflict of interest related to this article.

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# Cholestatic Jaundice Due To Biliary Atresia

*by* yasmine mashabi

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CASE REPORT

# Cholestatic Jaundice Due To Biliary Atresia With Cytomegalovirus And Malaria Infection: Blood Transfusion-Transmitted Infection?

## Suspek Atresia Bilier Dengan Infeksi Cytomegalovirus dan Malaria : Infeksi Menular Lewat Transfusi Darah?

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## ABSTRACT

**Introduction:** Blood transfusion can cause infectious complications through transfusion of microbes present in asymptomatic donor blood and/or contamination of stored blood products such as Hepatitis B, Hepatitis C, HIV, syphilis, malaria, Cytomegalovirus (CMV) infection. The risk of infection increases with the amount of blood products transfused.

**Case presentation:** A 5-month-old boy who had never been to malaria endemic area with jaundice and abdominal enlargement since two months ago, fever since one month ago, and icteric sclera. Data from laboratory results shows anemia, leukocytosis, hyperbilirubinemia, elevated liver enzyme, positive IgM and IgG anti-CMV. Blood smear evaluation: Trophozoite and ring forms of malaria parasites. Abdominal USG: Type-I Biliary atresia, Choledochal cyst, splenomegaly, ascites, and right pleural effusion.

**Discussion:** An acute Transfusion-transmitted CMV infection in high-risk patients can have severe complications such as billiary atresia, myocarditis, retinitis, encephalitis, or encephalopathy. Leucodepleted blood products for transfusion can reduce the risk of infection. Thick and thin blood smears which is the gold standard for diagnosing malaria, cannot be used for donor screening. Asymptomatic malaria infections may remain undetected.

**Conclusion:** Blood transfusion screening for infectious diseases is still very limited for Hepatitis B, Hepatitis C, Syphilis, and HIV. It is necessary to think about blood transfusion screening for other infectious diseases, such as CMV and malaria, especially in endemic areas, to prevent the occurrence of transfusion-transmitted infection.

**Keywords:** blood transfusion; CMV; Malaria

## ABSTRAK

**Pendahuluan:** Transfusi darah dapat menyebabkan komplikasi infeksi melalui: transfusi mikroba dari darah pendonor asimtomatik dan/atau kontaminasi produk darah yang disimpan seperti infeksi Hepatitis B, Hepatitis C, HIV, sifilis, malaria, Cytomegalovirus (CMV). Resiko infeksi meningkat seiring dengan jumlah produk darah yang ditransfusikan.
**Kasus:** Anak laki-laki, lima bulan tanpa ada riwayat ke daerah endemis malaria dengan *jaundice* disertai pembesaran abdomen sejak dua bulan terakhir, demam selama satu bulan, sklera ikterik. Pemeriksaan laboratorium didapatkan anemia, leukositosis, hiperbilirubinemia, peningkatan enzim hepar, IgM dan IgG anti-CMV positif . Hapusan darah tepi ditemukan parasit malaria bentuk tropozoit dan *ring*. USG Abdomen : suspek atresia bilier tipe I, splenomegali, ascites, efusi pleura kanan.
**Diskusi:** Infeksi CMV akut akibat transfusi darah pada pasien dengan resiko tinggi dapat memberikan komplikasi berat seperti atresia bilier, miokarditis, retinitis, ensefalitis, dan ensefalopati. Pemberian transfusi darah jenis *leucodepleted* dapat menurunkan resiko tersebut. Pemeriksaan tetes darah tebal dan tipis masih digunakan sebagai baku emas untuk mendiagnosis malaria namun tidak dapat digunakan untuk skrining darah donor. Infeksi malaria asimtomatik dapat tetap tidak terdeteksi.
**Kesimpulan:** Skrining darah transfusi terhadap penyakit infeksi masih sangat terbatas untuk Hepatitis B, Hepatitis C, Sifilis, dan HIV. Sangatlah penting untuk dipikirkan mengenai pemeriksaan skrining darah transfusi terhadap penyakit infeksi lain seperti CMV dan malaria terutama di daerah endemis untuk mencegah munculnya kejadian IMLTD.


**Kata Kunci**: transfusi darah, CMV, Malaria

## INTRODUCTION

Blood transfusion can cause infectious complications through the following mechanisms: microbial transfusion from asymptomatic donor blood and contamination of stored blood products. The risk of infection increases with the amount of blood products transfused.[1] Transfusion-transmitted infections (TBI) are most often caused by viral infections. Cytomegalovirus (CMV) infection due to blood transfusion often causes morbidity and mortality in newborns, and also causes congenital infection in developing countries, mental retardation, and developmental disorders. The prevalence of anti-CMV in the population ranges from 40%-90%.[2] Although about 50% of transfused blood is CMV seropositive, it is estimated that less than 1% of seropositive blood cell components can transmit infection.[3]

Although rare, malaria is the most common parasitic infection due to blood transfusion. Malaria parasites will survive for at least one week in blood components stored at room temperature or 40 C.[4] Asymptomatic carrier donors are a source of malaria transmission through transfusion. Malaria parasite screening is done by examining peripheral blood smears. Thick and thin blood smears can detect parasitemia between 300-500 /µL, but parasitemia with a minimum level of 10 /µL can cause malaria infection through transfusion.[5] The smear method shows poor results in malaria screening due to low parasite concentrations in infected people, where these samples can be positive in examinations with detection methods using monoclonal antibodies.[6]

This case is about a 5-month-old boy who suffered from cholestasis due to biliary atresia with CMV infection and malaria with a history of transfusion at the age of 3 months and had never traveled to an area endemic for malaria. This patient had increased AST and ALT enzymes, high total

and direct bilirubin levels, accompanied by a positive Immunochromatography Test (ICT) for malaria and positive results for IgM anti-CMV, IgG anti-CMV.

## CASE REPORT

A 5-month-old boy came from the hospital outpatient clinic with a diagnosis of suspected biliary atresia. The patient had symptoms of yellowing of the skin and eyes accompanied by abdominal enlargement since two months ago. The patient also had sub-febrile fever 1 month before admission. The history of defecation and urination was normal. The patient was born normally, according to gestational age with a weight of 3100 grams. The patient is the second child of two siblings. The history of basic immunization (polio, BCG, and Hepatitis B) is complete. History of growth and development according to the patient's age. History of blood transfusion at the age of 3 months due to anemia. History of the same complaint in the family was denied by the patient's parents.

Physical examination found a general condition that appeared weak, GCS score 15 (E4M5V6), pulse 128 x / minute, regular, and strong, respiration 24 x / minute, axillary temperature 37.5 °C, body length 64 cm, and weight 5.7 kg. On examination of the head and neck anemic conjunctiva, and icteric sclera, no signs of cyanosis or shortness of breath were found. Thoracic examination showed a symmetrical chest shape, without chest wall retraction. Single S1 S2 heart sounds without gallops or heart murmurs. Vesicular breath sounds, without rhonchi and wheezing. On examination of the abdomen, normal bowel sounds were found, as supple, abdominal enlargement with a liver size of 4x4x3 cm. There was no enlarged spleen. The acral extremities felt warm, and dry, without edema, and there were no enlarged lymph nodes in the axillary and inguinal regions.

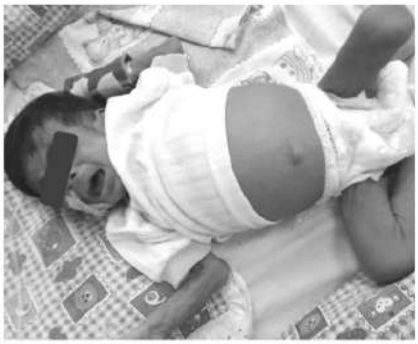

**Figure 1.** Patient's condition

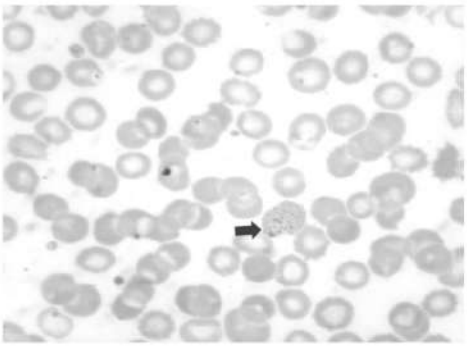

**Figure 2.** Trophozoite Forms

Routine blood tests showed anemia and leukocytosis. Peripheral blood smear examination (SADT) found malaria parasites in the form of trophozoites and rings. Clinical chemistry examination found hypoalbuminemia, hyperbilirubinemia, increased levels of aspartate transferase (AST), and alanine transferase (ALT) accompanied by hyponatremia. Immunology examination found increased levels of ANA, and C3, positive results for IgM anti-CMV, IgG anti-CMV, increased ferritin levels, and decreased levels of Total Iron Binding Capacity (TIBC). In the infection examination, positive results for the Pan and Pv malaria Rapid tests were obtained.

**Table 1.** Hematology Laboratory Examination

| Parameter | Day 1 | Day 7 | Normal Value |
|---|---|---|---|
| Hb (g/dL) | 7.44 | 11.8 | 12.9-15.9 |
| RBC (m/µL) | 2.90 | 4.51 | 4.06-5.58 |
| Hct (%) | 24.2 | 38.0 | 37.7-53.7 |
| MCV (fl) | 83.5 | 84.3 | 81.1-96 |
| MCH (pg) | 25.7 | 26.2 | 27.0-31.2 |
| MCHC | 30.7 | 31.0 | 31.8-35.4 |
| RDW (%) | 21.0 | 17.3 | 11.5-14.5 |
| Plt($10^3$/µl) | 233 | 259 | 155-366 |
| WBC($10^3$/µl) | 18.4 | 24.51 | 3.7-10.1 |
| Blood type count | 2/0/59/29/10 | 1/0/79/14/6 | - |
| SADT/Blood smear | Malaria parasites (+) : Tropozoites and rings | | |

**Table 2.** Clinical Chemistry Laboratory Examination

| Parameter | Day 1 | Day 7 | Day 11 | Normal Value |
|---|---|---|---|---|
| AST (U/L) | 112 | - | 136 | 15-37 |
| ALT (U/L) | 152 | - | 210 | 12-78 |
| GDP (mg/dL) | 75 | - | - | <100 |
| BUN(mg/dL) | 5 | 9 | 13 | 7-18 |
| Cr (mg/dL) | 0.4 | 0.55 | 0.56 | 0,6-1,3 |
| Alb (g/dL) | 2.4 | 3.2 | 2.9 | 3,4-5,0 |
| Bil. Total (mg/dL) | 7.48 | - | 10.06 | 0.2-1.00 |
| Direct (mg/dL) | 5.66 | - | 7.80 | 0.00-0.20 |
| Na (mmol/L) | 123 | 128 | 137 | 136-145 |
| K (mmol/L) | 4.1 | 3.5 | 4.1 | 3.5-5.1 |
| Cl (mmol/L) | 91 | 98 | 108 | 98-107 |
| Ca (mg/dL) | 8.3 | 7.9 | 7.8 | 8.0-10.1 |
| TIBC (µg/dL) | - | - | 102 | 250-450 |
| Feritin (ng/mL) | - | - | 742.3 | 30-434 |
| SI (µg/dL) | - | - | 83 | 35-150 |

Cr : *Creatinine;* Alb : Albumin; SI : *Serum Iron*

**Table 3.** Immunology & Infection Laboratory Examination

| Parameter | | Day 11 | Normal Value |
|---|---|---|---|
| ANA | | 40.35 | 0.35-5.5 |
| C3 (mg/dL) | | <16.4 | 0.89-1.76 |
| HBsAg | | Non-reactive | 4.30-22.4 |
| IgG anti-CMV | | + 108 | 1.5-9.3 |
| IgM anti-CMV | | + 1.62 | 1.4-18.1 |
| IgG anti-Toxoplasma | | - | 15-60 |
| IgG anti-Toxoplasma | | - | 0.1-1 |
| ICT | Pan | Positive | Negative |
| Malaria | Pv | Positive | Negative |
| | Pf | Negative | Negative |

Radiology Examination: Abdominal USG (Day 8); Impression: suspected biliary atresia type I, suspected choledochal cyst, hepatomegaly, minimal ascites, right pleural effusion. Bladder, pancreas, spleen, and right and left kidneys within normal limits. Pathological anatomy examination: liver biopsy (day 11); impression: extrahepatic cholestasis.

## DISCUSSION

In particular, cases of biliary atresia with positive IgM Anti-CMV results have been quite widely reported. To prove the relationship between CMV infection and biliary atresia, CMV DNA was successfully detected in 60% of liver biopsies in patients with biliary atresia with positive IgG anti-CMV, which was associated with histological changes typical of biliary atresia. This led to CMV being considered as the causative agent of biliary atresia.[7] Biliary atresia caused by positive IgM Anti-CMV is different from other types of biliary atresia, clinical manifestations usually appear later. Patients usually appear healthy, but after a few weeks, obstructive cholestasis may occur.[8] Xu et al. in 2014 stated that CMV infection decreases the expression of interferon-gamma (IFN-γ) cytokines and transcription factor T-bet, and significantly increases the expression of IL-4 cytokines and transcription factor GATA-3. This indicates that CMV infection can cause an imbalance in Th1/Th2 cell differentiation and the expression of their respective cytokines, leading to a decrease in the function of cellular immunity of infected individuals. This is also one of the reasons why CMV can escape the host's specific cellular immunity, causing persistent or latent infection, and leading to biliary atresia.[9,10] Several studies have also shown that progressive fibrosis inflammation in the liver causes the loss of bile ducts, leading to the theory that biliary atresia is caused by an immune response whose trigger is unknown. Xu et al.'s study also added that CMV infection has the potential to be an initiating factor for this immune process.[9]

Supporting examinations needed to confirm the diagnosis of biliary atresia include increased liver enzymes and hyperbilirubinemia due to increased direct bilirubin levels; serological examinations that provide positive results for IgM anti-CMV; radiological examinations such as abdominal ultrasound that confirm biliary atresia, and liver biopsy where increased fibrosis and histological changes are found consistent with biliary atresia.[7,10] Acute CMV infection due to transfusion in high-risk patients can cause severe complications, so appropriate action is needed to reduce this risk. The only strategy that has been confirmed in clinical trials is the administration of leucodepletion blood and ensuring that the blood products come from seronegative donors.[11]

Recent estimates suggest that the incidence of transfusion-associated malaria infection is <0.2 cases per 1,000,000 in non-endemic countries and >50 cases per 1,000,000 in endemic countries.[12] The risk of transfusion-associated malaria infection in non-malaria-endemic areas is due to donor blood previously living in or traveling to malaria-endemic areas.[13] An important difference between natural malaria infection and transfusion-associated malaria infection is that natural malaria infection passes through an asymptomatic (pre-erythrocytic) phase, which causes activation of innate immune cells against the malaria parasite, allowing the host time to develop more specific protective immunity. In transfusion-associated malaria infection, infected donor blood directly releases malaria parasites into the recipient's bloodstream, preventing innate immunity from being activated and increasing the risk of complications.[14]

The main problem of malaria infection due to blood transfusion is related to donor blood from asymptomatic donors who have very low parasite counts. This makes the thick and thin blood drop test, which is still used as the gold standard for diagnosing malaria, unsuitable for screening donor blood.[5] This asymptomatic infection can remain undetected and a study by Dover et al. reported that as few as 10 infected red blood cells are sufficient to transmit malaria to the recipient.[15,16] All Plasmodium species can survive in stored donor blood, even in frozen conditions for approximately

ten days, depending on storage conditions.[15,17] However, administration of donor blood that has been stored for too long can also produce a pro-inflammatory response associated with increased iron levels in the liver, spleen, and kidneys, and increased levels of nontransferrin bound iron (NTBI) have dangerous side effects such as increased risk of bacterial infection.[18]

In this case, the patient presented with the main complaint of yellow skin and eyes accompanied by abdominal enlargement and fever. This is a sign of cholestasis and infection. Physical examination of this patient showed anemic conjunctiva, icteric sclera, and hepatomegaly. All of these symptoms are by the results of the initial laboratory examination, namely anemia, increased liver enzyme levels, and hyperbilirubinemia, which indicate that there is extrahepatic cholestasis and liver disorders. The second laboratory examination was performed after the patient received a transfusion to treat anemia in the patient and found an increase in hemoglobin levels but an increase in leukocyte levels due to the patient's worsening condition. Immunological examinations showed positive CMV IgG and IgM results indicating that this patient had CMV infection. Malaria examination on thick and thin blood smears found malaria parasites in the form of trophozoites and rings and continued with ICT malaria examination with positive results for malaria vivax which supported the diagnosis of malaria infection in this patient. Abdominal USG examination showing type I biliary atresia and hepatomegaly supported the results of laboratory examinations.

Research conducted by Mangano et al. stated that all donor blood from malaria-endemic areas should be tested for anti-malarial antibodies, even if the donor has long left the endemic area. To reduce cases of malaria due to blood transfusion, surveillance strategies such as conducting questionnaires before donating blood and/or laboratory screening tests can be carried out.[19] Serological examinations have limitations in terms of sensitivity. A 2018 study of five types of Enzyme-linked immunosorbent assay (ELISA) examination products produced high specificity (100%) but sensitivity between 53-64%. Serological examination is also an indirect examination so it does not directly indicate parasitemia and can cause uninfected donors to be excluded.[20] The World Health Organization (WHO) recommends nucleic acid amplification examinations for epidemiological studies and surveys of sub-microscopic infections. Polymerase chain reaction (PCR) examination is the most sensitive examination method, detecting parasitemia from 2-5 parasites/µL, unlike microscopic examination with a sensitivity of 50-500 parasites/µL and Rapid Diagnostic Test (RDT) which has a sensitivity of ~100 parasites/µL. However, PCR examination requires expensive costs and complicated examination methods.[21]

This patient has a history of blood transfusion at the age of 3 months without a history of exposure to CMV and no history of traveling to malaria-endemic areas, so the possibility of IMLTD needs to be considered. Currently, blood transfusion screening for infectious diseases is still very limited. Screening for blood transfusions is based on donor evaluation, laboratory screening examinations, and pathogen inactivation procedures, but this still does not eliminate all risks.[22] Blood transfusion screening for infectious diseases caused by viruses currently uses the Nucleic Acid Testing (NAT) method. NAT itself still has several limitations such as low levels of viremia that cannot be detected by NAT. The combination of serological and NAT examinations has been quite helpful in reducing the risk of viral infections due to blood transfusions.[23,24]

## CONCLUSION

The patient was diagnosed with biliary atresia cholestasis type I with CMV infection and malaria which is suspected to be an IMLTD. Blood transfusion screening for infectious diseases is still very limited for Hepatitis B, Hepatitis C, Syphilis, and HIV, so it is necessary to consider screening blood transfusions for other infectious diseases such as CMV and malaria, especially in endemic areas to prevent the occurrence of IMLTD. It is also necessary to consider giving leucodepletation blood products to patients with immune system disorders.

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## AUTHORS CONTRIBUTION

All authors contributed to this article.

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## CONFLICT OF INTEREST

The authors declared no conflict of interest related to this article.

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