



Literature Review

The clinical and histopathological aspect of the liver, lung, and kidney in malaria

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ABSTRACT

Malaria is an infectious disease with worldwide distribution. The symptom ranges from asymptomatic to severe malaria that could cause mortality. Sequestration and rosetting in the capillaries of several organs in combination with the host inflammatory and immune response could cause multi-organ dysfunction including brain, liver, lung, kidney, etc. This review is to summarize the clinical and histopathological aspect of the disease, especially in lung, liver, and kidney. The clinical importance of severe malaria in the lung are acute lung injury or acute respiratory distress syndrome, jaundice in the liver, and acute kidney injury in the kidney. The histopathological change, in general, is the sequestration of infected erythrocytes in the capillaries of the organ. In the lung, the main changes are seen especially the septa. While in the liver, there are various changes including Kupffer cells hyperplasia, the proliferation of portal tract and bile duct, etc. In the kidney, the changes are in the glomerulus, tubules, and interstitial.



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ABSTRAK

Malaria merupakan suatu penyakit infeksi yang tersebar di seluruh dunia. Gejala yang timbul bervariasi mulai dari asimtomatik atau tidak menunjukkan gejala sampai ke malaria berat yang berakibat kematian. Sekuestrasi dan rosetting pada kapiler organ disertai respon inflamasi dan respon imun tubuh hospes dapat menyebabkan kegagalan multi organ yaitu di otak, paru, hati, ginjal, dan lain-lain. Tinjauan ini bertujuan untuk meringkas aspek klinis dan histopatologis malaria pada paru, hati, dan ginjal. Aspek klinis malaria berat pada paru meliputi acute lung injury atau acute respiratory distress syndrome, jaundice pada hati, dan acute kidney injury pada ginjal. Perubahan histopatologi secara umum adalah didapatkan sekuestrasi eritrosit terinfeksi pada kapiler organ. Perubahan yang terjadi pada paru terutama terjadi pada septa. Sedangkan pada hati, terdapat beberapa perubahan termasuk hiperplasia sel Kupffer, proliferasi traktus porta dan duktus biliaris, dan lain-lain. Perubahan pada ginjal dapat terjadi di glomerulus, tubulus, dan interstisial.

Kata Kunci : Malaria, disfungsi organ, paru, hati, ginjal, histopatologi

INTRODUCTION

Malaria, the cause of more than 200.000 death per year globally, is one of the infectious diseases that still affects more than 80 countries in the world. Although there is a decline of the Annual Parasite Index (API), there are still 219 million cases worldwide with Africa and India as the greatest contributor countries (WHO, 2017). This disease is transmitted by the bite of female Anopheles mosquito and caused by five known Plasmodium species namely Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale and Plasmodium knowlesi with P. falciparum as the most important cause due to its high mortality rate (CDC, 2018; White, 2009; and Zaman & Mah-Lee, 2008). In Indonesia, the case prevalence is still more than 300.000 with about 10,000 deaths each year. There are 39 districts in Indonesia with endemic status mostly located in the east part on Indonesia. Five province with high API namely Papua, West Papua, NTT, Maluku, and North Maluku with API of 31.93, 31.29, 7.04, 5.08, and 2,77 respectively (Kemenkes RI, 2016 and 2018; CDC, 2018).

The clinical manifestation of malaria varies from asymptomatic to severe malaria that

could lead to death. The outcome usually depends on the species of Plasmodium, the organs affected, or the proper treatment received. The rupture of schizonts releasing merozoites from the erythrocyte with the release of toxin and parasite products cause the activation of host innate immunity and correspond with the incidents of fever, shivering, and chills in the patient. When the parasite attacks the massive amount of erythrocyte, the erythrocytes were destroyed and causes anemia. In severe malaria, organ dysfunctions tend to happen because of pathologic sequestration caused by the parasite. Sequestration is a phenomenon where the infected erythrocyte adhere to the endothelial cell of the host vital organ's microvascular such as brain, lung, liver, and kidney (Autino et al, 2012; White, 2009). The inflammatory response also underlines the pathology of severe malaria (de Souza et al, 2016).

The diagnosis of malaria is based on symptoms presented (clinical), parasite detection using light microscopy with Giemsa staining, a rapid diagnostic test to detect parasite-specific antigen, and in epidemiological setting sometimes the researchers use immunodiagnostic and nucleic acid amplification test methods such as PCR (WHO, 2015). There are several clinical



symptoms in severe malaria patient depending on the organ affected by the sequestration. The liver, lung, and kidney are the organs involved in malaria besides the brain, and that is the focus of this literature review. This review is to summarize the clinical and histopathologic aspect in lung, liver, and kidney of malaria.

LITERATURE REVIEW

Severe Malaria

Severe malaria without adequate treatment could increase the risk of mortality. Patient with severe malaria showing evidence of organ dysfunction should be given the highest form of care from the health care provider. Thus, the health care provider must understand the clinical signs of severe malaria. The most known species causing severe malaria is predominantly *P. falciparum*, and in some cases are the *P. vivax* and *P. knowlesi*. The criteria for severe malaria can be seen in the WHO Guideline for Treatment. In summary, severe *falciparum* malaria is defined as presence of parasitemia in the form of *P. falciparum* asexual stage with one or more of the clinical symptoms and signs such as impaired consciousness, prostration, convulsion, acidosis, hypoglycemia, renal impairment, severe anemia, jaundice, pulmonary edema, bleeding, shock, and

hyperparasitemia $> 10\%$. While in severe *vivax* malaria, the criteria is similar with severe *falciparum* malaria criteria except without density threshold; while in severe *knowlesi* malaria there are two different criteria with the *falciparum* namely the hyperparasitemia above $100.000/\mu\text{L}$ and jaundice and parasite density more than $20.000/\mu\text{L}$ (WHO, 2015).

This literature review focuses on the liver, lung, and kidney involvement in malaria. Table 1 summarized the clinical symptoms used to identify the organ dysfunction in severe malaria

The Lung in Malaria

The lung is the most affected organ besides the brain during severe malaria. The species responsible for most lung complication are *P. falciparum* and *P. vivax*, and rare in *P. ovale*, *P. malariae*, and *P. knowlesi*. The incidence of pulmonary symptoms usually occur in about 4-18% patient with *P. falciparum* infection (Mazhar and Haider, 2016). The severe clinical changes in the lung of malaria patient usually in the form of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) with case incidence of 5-25% in *P.falciparum* and 1-10% in *P.vivax*. Another fatal complication in malaria is acute pulmonary edema where the endothelial cells look swollen and the lumen of the capillary are narrow. The interstitial is

Table 1. The lung, liver, and kidney in severe malaria

Organ	Clinical signs or symptoms
Lung	Pulmonary edema: Confirmed with radiology examination or oxygen saturation $<92\%$ on room air with respiratory rate $>30\text{x}/\text{min}$, often with chest indrawing and on auscultation shows crepitation
Liver	Jaundice: plasma or serum bilirubin $> 3\text{mg}/\text{dL}$ with parasite count $>100.000 \mu\text{L}$
Kidney	Renal impairment: plasma or serum creatinine $> 3\text{mg}/\text{dL}$ or blood urea $>20 \text{mmol}/\text{L}$

Source: WHO, 2015

also edema and consist of malaria pigment and macrophage (Mazhar and Haider, 2016; Kirchgatter et al, 2015; Seilmaier et al, 2014; Strydom, Ismail, and Frean, 2014; Autino et al, 2012; Martínez-Girón, 2008; Taylor et al, 2006).

The pathogenesis of lung problems in malaria are hypothesized as the effect of the sequestration, the host immunology reaction to the sequestration, the pulmonary infection acquired (such as community-acquired and nosocomial infection), sepsis co-infection, etc. The effect of the adherent infected erythrocyte to the vascular epithelium is capillary damage, which in turn increases the permeability then the plasma liquid fills the alveolar spaces causing pulmonary edema. The symptoms of lung involvement include dry cough or expectoration, shortness of breath or dyspnea, tachypnea, or other respiratory distress. In auscultation of the lung, there could be bilateral fine crepitation. The lung function test also shows obstruction in the small airway and increase in diffusion capacity. In the radiological examination, there could be infiltrates on both lungs, which is small and diffuse, lobar consolidation, an increase of the vascular net, and pleural discharge. (Strydom et al, 2014; Autino et al, 2012; Martínez-Girón, 2008).

The complication of the lung in malaria mimics other acute respiratory illnesses. Early recognition and adequate support will reduce the mortality of severe malaria that affects the lung. The onset of lung complication in malaria usually develops after 5 to 7 days of the malarial fever. The degree of parasitemia has no association with the lung complication that occurs (Safdar et al, 1999). The proper treatment of ARDS and ALI in malaria is the same as the guideline of other causes; however, managing malaria itself is very important for better prognosis of the disease.

The histopathological changes in the lung may include capillary congestion, pleural edema, hyaline membrane and septa thickening. In general, the alveolar septum is the main site of lung changes, especially in falciparum and vivax malaria. The histological changes in ALI or ARDS are found in capillaries, septa, alveolar space. In capillaries, the parasitized erythrocyte adhere to the endothelium. There is also leucocyte and swollen or thickened endothelium basement membrane. The septa become thicker compared to the septa and showed a high infiltration of leucocyte (macrophage and neutrophil). The alveolar space was edema and showed a lot of cells and cellular debris, and the alveolar macrophage contains hemozoin (Aitken et al, 2014; Martínez-Girón, 2008).

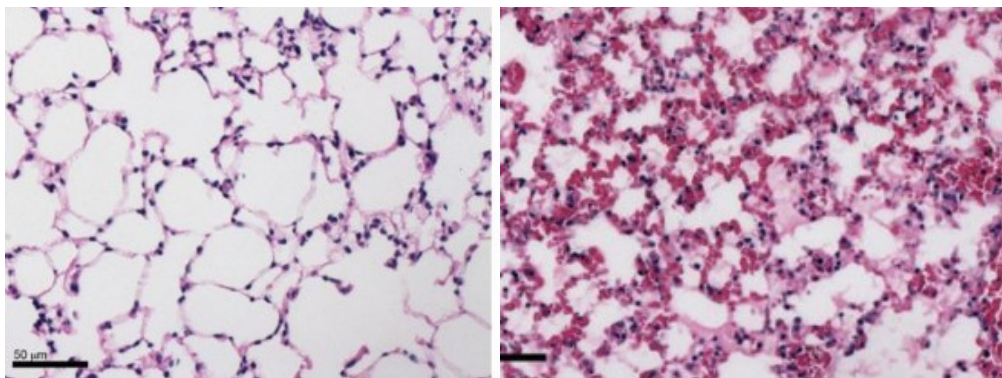


Figure 1. The normal lung (left) compared to ALI/ARDS in severe malaria (right). In the ALI/ARDS lung, there are edema, hemorrhage, and thickening of septa with congested capillaries, infected erythrocytes, and leucocytes (Source: Aitken et al, 2014).

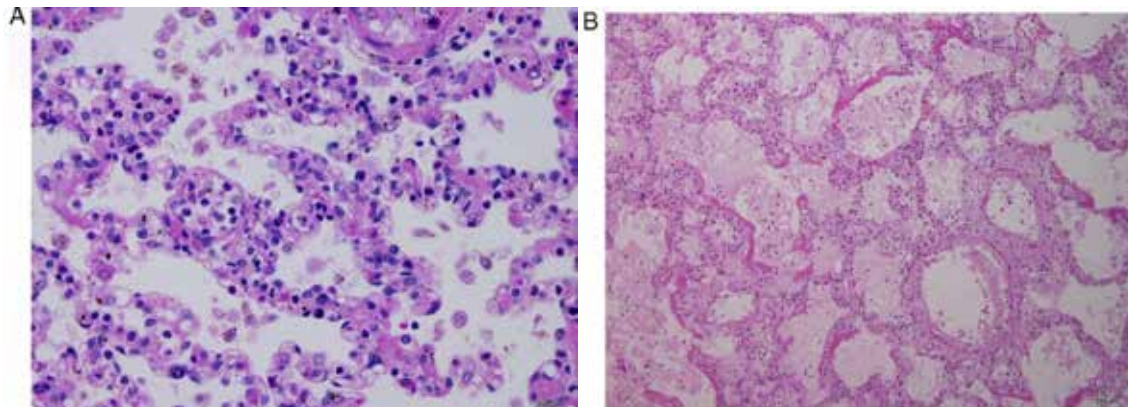


Figure 2. The lung in falciparum malaria. A: The alveolar capillaries expand due to the sequestered erythrocytes and leukocyte. There are also phagocytosed hemozoin pigment. B: Expansion of alveolar septa, hemorrhage on the intraalveolar, pulmonary edema, and formation of hyaline membrane, which is the characteristic of diffuse alveolar damage. (Hematoxylin & eosin staining, 200x, scale bar 200 μ m). (Source: Taylor et al, 2012)

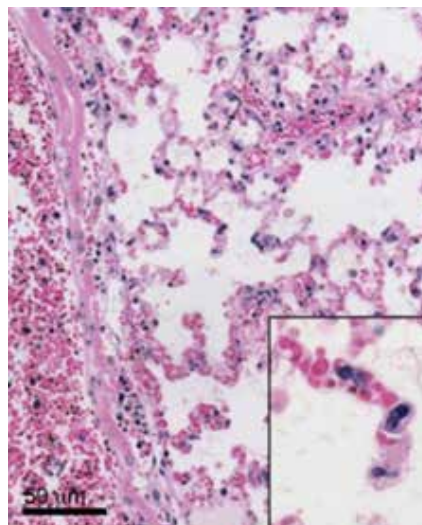


Figure 3. Showing swollen endothelium and congestion on the capillaries (Source: Aitken et al, 2014).

The Liver in Malaria

The liver is involved during the pre-erythrocyte and the erythrocyte cycle of malaria infection. However, liver dysfunction during malaria is uncommon. The liver damage is minimal and mostly reversible. On the contrary, jaundice is common in severe malaria due to intravascular hemolysis of erythrocyte, which in turn causes the increase of unconjugated bilirubinemia (Autino et al, 2012). The jaundice is seen in 20% of the patient with more than 53% case

showed the increase of bilirubin to more than 1 mg%. When there is an increase of conjugated bilirubin, there is a hepatocyte dysfunction. Centro lobular liver damage is also one of the factors resulting in hyperbilirubinemia. The serum bilirubin concentration increases in the host due to damage to liver drainage capacity (Patel et al, 2015; Seilmaier et al, 2014).

Hepatocytes that were injured caused the release of aminotransferase enzymes, namely serum glutamate pyruvate transaminase (SGPT) or



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alanine aminotransferase (ALT) and serum glutamate oxaloacetate transaminase (SGOT) or aspartate aminotransferase (AST). The SGOT are normally located intracellularly in liver, heart, kidney, brain, and muscle and SGPT is mostly located in the liver. There is a significant increase of those enzymes in the malaria patients' serum especially the SGPT (Kalia et al, 2015; and Patel et al, 2015). The mechanism of liver damage is obstruction of the portal vein (due to sequestration of parasitized erythrocyte) which causes a reduction in the blood flow, cholestasis in the liver due to blockage of reticuloendothelial and microvilli dysfunction, suppression of bilirubin excretion, apoptosis and oxidative stress.

Malaria also causes some histopathological changes in the liver of the patient. The changes include hyperplastic of Kupffer cells, inflammation of portal tract, fatty change, cholestasis, sequestration of erythrocyte infected with the parasite, and deposition of hemozoin pigment. The summary of histopathological change is in Table 2. The changes happened because of inflammation

and direct effect of the parasites to the hepatocytes in the liver. The grading range from 0 (zero) which means no change in the liver tissue up to 18 which means the liver damage is severe. In falciparum malaria, the most common changes are inflammation of the portal and deposition of hemozoin in Kupffer cells (Viriyavejakul et al, 2014).

The example of a microscopic examination of the liver between normal liver tissue and malaria liver tissue is described in Figure 4. In the normal liver, the portal tract is normal with a hepatic vein, hepatic artery, bile duct, hepatocyte, and some inflammatory cells. In the malaria liver with no hyperbilirubinemia, the sinusoid seemed enlarged, there are hyperplastic Kupffer cells containing hemozoin pigment and an abundant number of inflammatory cells within the portal tract. In malaria with hyperbilirubinemia, there is also infiltration in the inflammatory cells at the portal tract, and with bigger magnification, the Kupffer cells with hemozoin pigment are more visible, and the sinusoids are congested. The central vein also shows a lot of infected erythrocytes

Table 2. Histopathological changes and grading schemes in evaluating liver changes.

Histopathologic changes	Histopathologic grading			
	0	1	2	3
Fatty change	No fatty change	< 10%	10-50%	> 50%
Kupffer cells/ HPF	< 20/HPF	20-35/HPF	36-50/HPF	> 50/HPF
Portal tract inflammation	< 5% of portal tract area	5-15% of portal tract area	16-30% of portal tract area	> 30% of portal tract area
Bile duct proliferation	No proliferation	Mild proliferation	Moderate proliferation	Severe proliferation
Sinusoid congestion	No congestion	Mild congestion	Moderate congestion	Severe congestion
Haemozoin deposition	No deposition	Mild deposition	Moderate deposition	Severe deposition

Source: Viriyavejakul et al, 2014

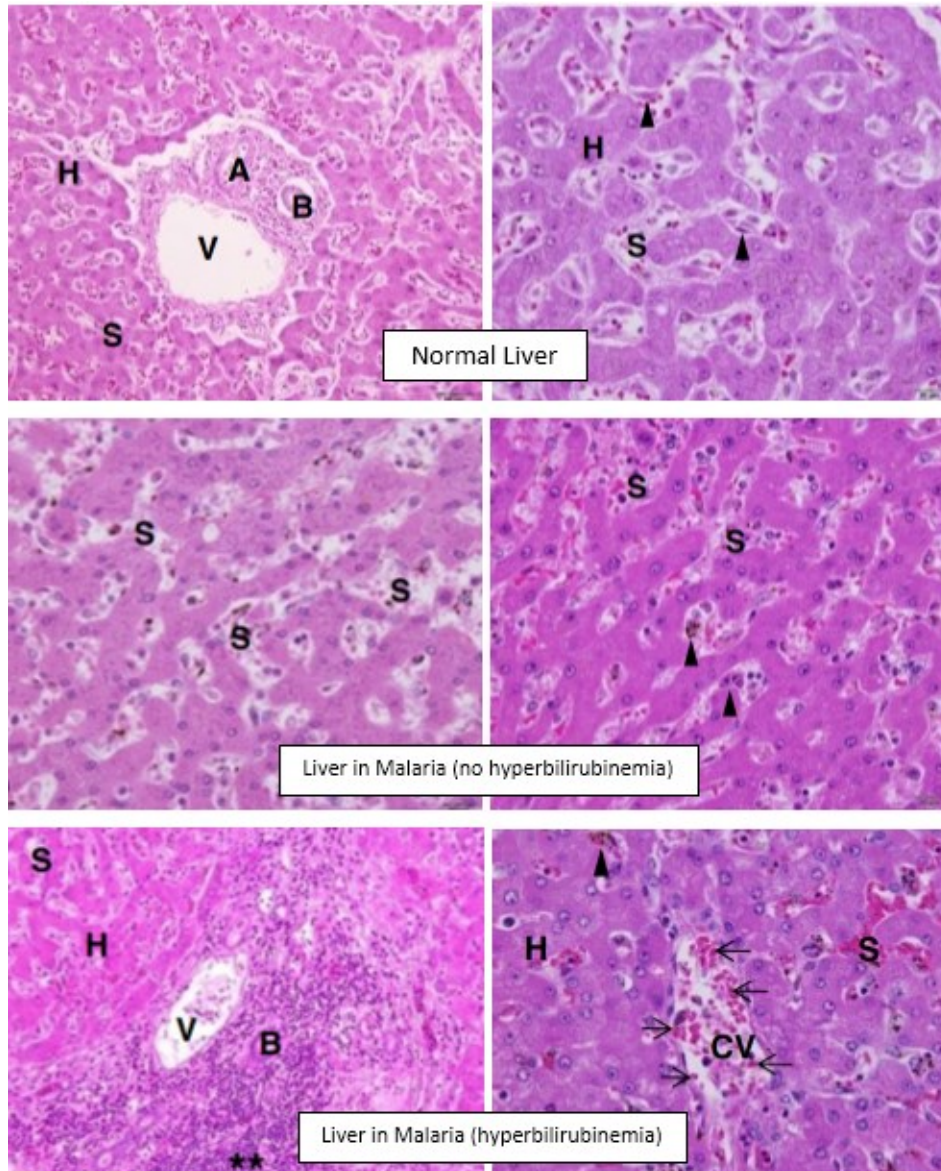


Figure 4. The comparison of normal liver tissue and malaria-infected liver tissue (with and without hyperbilirubinemia) (Source: *Viriyavejakul et al, 2014*).

The Kidney in Malaria

The kidney is the organ maintaining the chemical composition of the body fluid through urine acidification and elimination of metabolic waste (such as urea, uric acid, creatinine, and other ions). When there are abnormalities of the kidney, those metabolite concentrations will increase in the serum. The evaluation of blood urea nitrogen and creatinine serum above normal could predict the kidney dysfunction

(Kalia et al, 2015). In WHO criteria of severe malaria, the plasma or serum creatinine >3 mg/dL or blood urea >20 mmol/L indicates renal impairment (WHO, 2015).

Malaria can cause acute or chronic disease in the kidney. Severe malaria could cause a disturbance in the glomeruli, tubules, and interstitial region of the kidney. The kidney involvement occur to about 40% patient diagnosed with severe malaria (da Silva



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et al., 2017). The adherence of infected erythrocyte to the capillary endothelium, also cause adherence of the healthy erythrocytes and platelets and leads to the formation of rosettes. Those series of events finally result in microcirculation abnormalities and causes kidney injury. The most challenging complication that malaria cause to the kidney is acute kidney injury (AKI). The RIFLE criteria were used to diagnose it, which stands for risk, injury, failure, loss, and end-stage renal failure. The severe infection of *P. falciparum* and *P. vivax* are the causes of severe malaria-derived AKI (smAKI); however, AKI has also been reported in the infection of *P. ovale*, *P. malariae*, or *P. knowlesi*. Almost half of the severe malaria cases reported has AKI as the complication and the mortality is very high. The clinical symptoms are oliguria or anuria, severe metabolic acidosis, and hypercatabolic state. The mortality increased when the patient is in an advanced age, have hyperkalemia, jaundice, leukocytosis, oligo-anuria, and the consciousness level is altered. Early diagnosis and treatment can reduce mortality and have a better prognosis with peritoneal dialysis (da Silva et al, 2017; de Souza et al, 2016; Seilmaier et al, 2014; Kirchgatter et al, 2005). One study showed that almost 50% of cases didn't meet the renal impairment WHO criteria of severe malaria which is the creatinine level didn't go above 3 mg/dL. However, those patients died. And this is something to be evaluated because of the difficulty of assessing clinical symptoms of renal impairment (such as oliguria) on a patient at early admission with malaria diagnosis (Nguansangiam et al, 2007).

The pathophysiology and pathogenesis of smAKI are still not well understood. It was hypothesized that smAKI develop secondary due to a systemic inflammatory response of the host to the parasite which causes functional and structural damage to the kidney. Some other studies suggest that the smAKI is induced locally based on the finding of intense inflammatory cell accumulation in the renal tissue (de Souza et al, 2016). The pathogenesis of smAKI where cytokines released after endothelial activation is in conjunction through either Th1 or Th2 response. When the Th2 response prevails, it causes activation of complement with immune complex deposit leading to glomerulonephritis which usually seen in *P. malariae* infection. While in *P. falciparum* infection, the hyperparasitemia causes instability in the host hemodynamic, which in turn leads to acute tubular necrosis. On the contrary, when the Th1 response prevails, there could be acute interstitial nephritis and acute glomerulonephritis (da Silva et al, 2017).

The factors that can cause kidney complication are vasoconstriction, hypovolemia, hemolysis leading to hemoglobinuria, deposition of immune complex in the glomerulus, dysfunction of microcirculation, hyperbilirubinemia leading to nephropathy and AKI, or rhabdomyolysis. Although rare, AKI can also be associated with rhabdomyolysis due to the sequestration of infected erythrocyte in the skeletal muscle capillaries, which then cause occlusion. The myoglobin nephrotoxic effect is the main pathogenesis, and the condition such as hypotension, hypovolemia, acidosis, and the

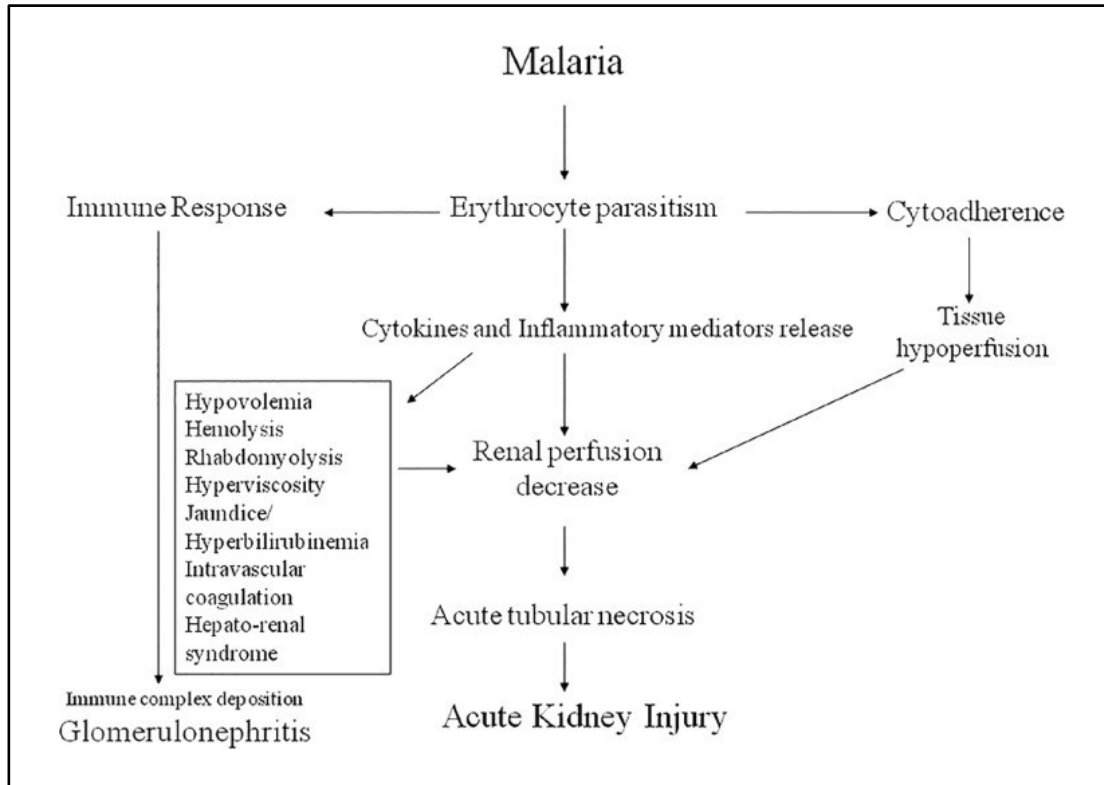


FIGURE 5. The pathophysiology of malaria-induced kidney injury (Source: da Silva et al, 2017)

Another kidney complication is quartan malaria nephropathy (QMN), with clinical sign of edema and hypertension, and urine analysis presents proteinuria and microhematuria. The pathogenesis is due to the deposit of the immune complex (IgG, IgM, C3, and malaria antigen) in the subendothelial as the consequence of TH2 type lymphocytes activation. The more severe form of kidney injury is the cortical necrosis and when this happen, the renal function can no longer recover and finally develop the end-stage kidney disease (da Silva et al, 2017; and de Souza et al, 2016).

The histopathology examination shows the characteristic of glomerulonephritis, acute tubular necrosis, and interstitial nephritis. There are inflammatory infiltration and infected erythrocytes in the lumen vessel of the kidney tissue. In *P. falciparum*-infected kidney, there can be a lesion on the glomerulus characterized by proliferation of mesangial, mesangial matrix

enlargement, thickening of basal membrane, and deposition of granular eosinophilic material in the endothelium, mesangium, and Bowman's capsule. In the tubules, there is hemosiderin granular deposit, presence of urinary cast with infiltration of mononuclear cells and interstitial edema. There are also phagocytosed malarial pigment in the mononuclear cell's cytoplasm. In addition, different from the brain, there was no malarial hemorrhage found. In the histopathological examination of smAKI, there are endothelial cell swelling, hypertrophy, and cytoplasmic vacuolization. There are also mononuclear cells found in the peritubular capillaries, but they do not infiltrate renal tissue interstitial likely because the tight junction in renal tissue is not fully disrupted. There is also deposition of the immune complex such as immunoglobulin (Ig) isotype G and M (da Silva et al, 2017; de Souza et al, 2016; Nguansangiam et al, 2007).

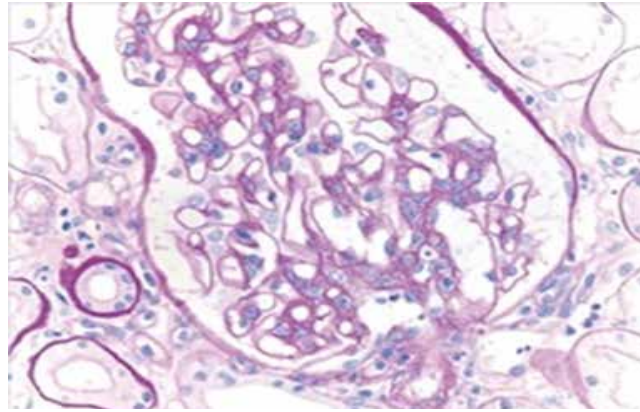


Figure 6. Mild mesangial proliferation and expansion in the kidney biopsy of malaria associated nephropathy: (x400). Source: da Silva et al, 2017 (Reproduced by Yoo et al. 2012, The Korean Academy of Medical Sciences)

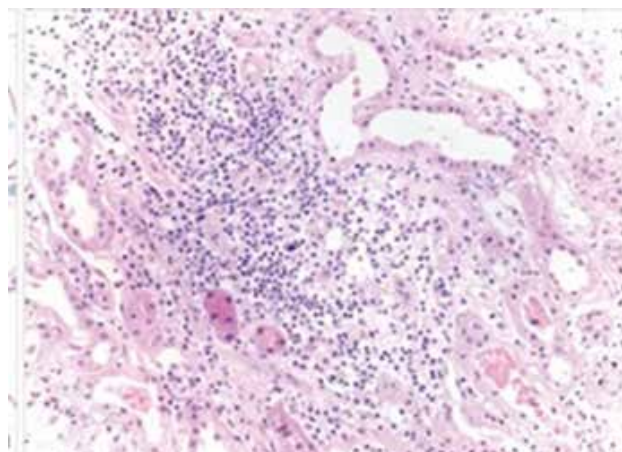


Figure 7. Infiltration of acute and chronic inflammatory cell in tubules and interstitial with hemosiderin cast in the kidney biopsy of malaria associated nephropathy (x200). Source: da Silva et al, 2017 (Reproduced by Yoo et al. 2012, The Korean Academy of Medical Sciences)

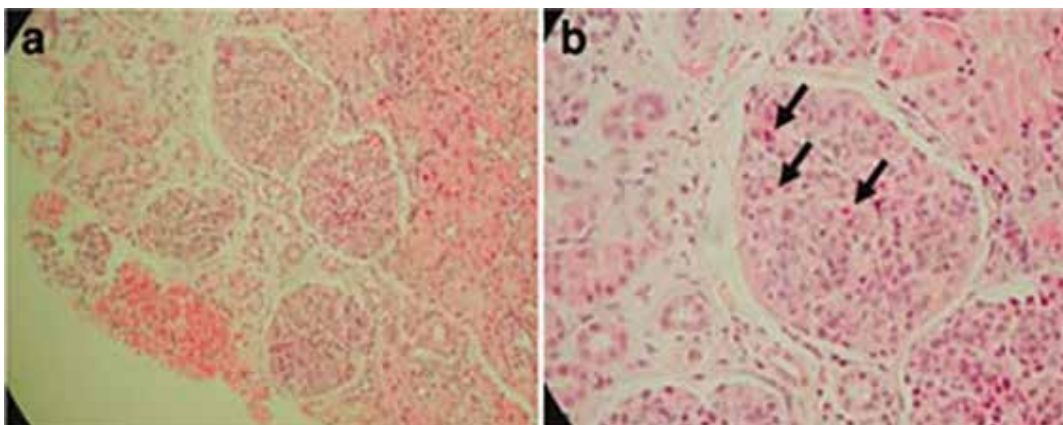


Figure 8. The kidney biopsy of malaria associated glomerulonephritis: A) Eosinophilic diffuse proliferative glomerulonephritis (H&E staining); B) Eosinophils on the glomerulus (black arrows). Source: da Silva et al, 2017 (Reproduced by Walker et al, 2007, Elsevier – The International Society of Nephrology)



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CONCLUSION

Severe malaria pathogenicity is regulated by parasite and host factor and it is very complex. The cytoadherence of the infected erythrocyte to the endothelial and rosetting are important features of Plasmodium which lead to vascular damage in many important body organs and causes the inflammatory or immune response of the host. Acute lung injury or acute respiratory distress syndrome can be seen in severe malaria and have high mortality. In the liver, severe malaria could cause jaundice and minimal liver damage which is shown as the increase of the SGOT, SGPT, and bilirubin. However, liver damage is mostly reversible. In the kidney, the acute kidney injury may happen as the secondary effect of systemic inflammatory response. In addition, there are also some cases of quartan malaria nephropathy and glomerulonephritis. Unfortunately, these abnormalities could persist even after the proper treatment of malaria drugs. And one contradictive fact is many of the patients who develop kidney problems didn't meet the criteria of renal impairment of WHO but still died because of the complication.

The main histopathological changes in lung, liver, and kidney are the remark sequestration in capillaries. The changes in lung mainly occur in the septa, capillaries, and alveolar space including capillary congestion, pleural or pulmonary edema, and thickening of hyaline membrane and septa. Changes in the liver are fatty change, Kupffer cells hyperplasia, portal tract and bile duct proliferation, sinusoid congestion, and hemozoin deposition. In the kidney, the changes can occur in the glomerulus, tubules, and interstitial with the common pathologic characteristic of glomerulonephritis, acute tubular necrosis, and interstitial nephritis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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