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International Journal of Gastroenterology Hepatology and Endoscopy



Impact of *Plasmodium falciparum* Malaria on Liver and Red Blood Cell

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ARTICLE INFO

Article history:

Received 20 July 2022

Revised 30 July 2022

Accepted 02 August 2022

Published 10 August 2022

KEYWORDS:

Tropical Diseases

Parasitology

Malaria

P. falciparum

Red Blood Cells

Liver and Pathophysiology

ABSTRACT

Malaria remains one of the greatest public health challenges worldwide, particularly in tropical and sub-tropical countries. Estimates about 212 million and 429,000 death per year worldwide. The liver and red blood cell (RBC) are the organ that has clearly changed in the early stages of infection. The aim of this study was to elucidate the inflamed sinusoidal area showing the change of liver morphology in severe *Plasmodium falciparum* (*P. falciparum*) malaria infection and red blood cell anatomical changes. *P. falciparum* malaria invasion associated with endothelial activation and expression of adhesion molecules. Some infected RBCs can be eliminated by the host immune system. However, some carry on infection which leading to severe malaria. Decrease deformability of erythrocyte infected by malaria parasites may play a role of enrichment in the liver. The different sizes and shapes of infected RBC in the liver were resulted diversity morphological of RBCs and their function in the infected organs

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INTRODUCTION

Malaria transmitted by an infected female *Anopheles* mosquito, to vertebrata host. Five plasmodium malaria species are consisting of *P. ovale*, *P. malariae*, *P. knowlesi*, *P. vivax* and *P. falciparum* [1]. However, *P. vivax* and *P. falciparum* have mostly caused malaria diseases worldwide, nowadays. Most of the cases in 2016 were in the African region (90%), followed by South-East Asia region (7%) and Eastern Mediterranean region (2%) [2]. In Thailand, the incidence rate continues decrease from the average number of cases per 1,000 population was 0.55, 0.48, and 0.24 in 2013, 2014 and 2015, respectively [3].

P. falciparum malaria infection may consequence acute illness such as hepatorenal syndrome, fulminant hepatic failure, acute hepatitis, i.e. jaundice, encephalopathy, pulmonary oedema, anemia, septicemia, hypoglycemia, acidosis, abdominal pain with diarrhea, hepatosplenomegaly, renal failure spontaneous bleeding coagulopathy, hyper-pyrexia, and unarousable coma [4].

During *P. falciparum* infection, infected RBC (iRBC) adheres to

the endothelial microvasculature of several organs, due to expression of a protein named *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) binds to extracellular adhesion molecule 1 (ICAM-1) and mediated cytoadherence [5]. Parasite sequestration correlated with parasitemia level and disease severity. In the lung tissue, the exudative phase is the starting point of the syndrome, where damage to the endothelial barrier occurs, due to necrosis, resulting in edema that spills out into alveoli, causing the formation of a hyaline membrane in the alveolar wall [6].

From any infected organ's tissues the motile sporozoite may enter the blood vessels. Accordingly, in the hepatic sinusoid, they penetrate through Kupffer cells into space of Disse and invade hepatocyte [7]. This process may produce program cell death (PCD) which mediated by various stimuli, including hormones, cytokines, growth factors, bacterial or viral infection as well as immune response. It can occur in the liver and other human organs if left treated [8].

This review provides an overview of the most important scientific literature on malaria infection, which leading to pathophysiology and clinical features in the liver and red blood cells (RBC). Some reviews have been published related with liver involvement in *P. falciparum* malaria and histo-pathological analysis, liver hepatopathy and evaluation of liver function in *P. falciparum* malaria. The aim of this study is to show the process and mechanism of malaria infection which caused severe malaria in the liver stage and RBCs anatomical changes. The highlight as a knowledge gap of improper function of the infected liver and RBCs as well.

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Plasmodium falciparum Malaria Infection

An infected female *Anopheles* mosquito bites human and transfer motile sporozoite stages into the skin. The sporozoites invade liver then form the schizont. Sporozoites produce more merozoites in the liver stage which called exo-erythrocyte [9]. After passing through kuffer cells, sporozoites inhibit hepatocyte cell death until merozoite mature. The parasites than induce cell death and merozoites are released into blood stream to invade erythrocyte and initiate the asexual blood stage of the life cycle of the plasmodium as indicate in the (Figure 1) *P. falciparum* malaria life cycle.

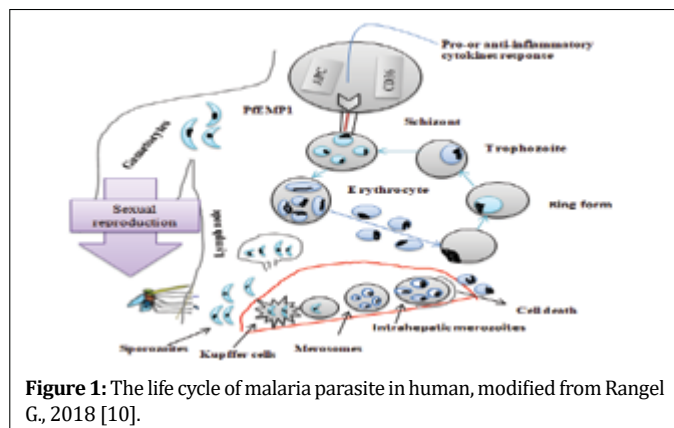


Figure 1: The life cycle of malaria parasite in human, modified from Rangel G., 2018 [10].

In the life cycle, plasmodium parasites are transmitted to human host through bite from an infected *Anopheles* mosquito. Sporozoites enter lymph node while sporozoites remain in the dermis. Sporozoites in lymph vessel stop at the proximal lymph node especially superficial vessel and some partially differentiate into exo-erythrocytic stages. After passing kupffer cells and sporozoites inhibit cell death until merozoites mature, finally. Schizonts rupture and released merozoites into bloodstream to invade erythrocytes than start the asexual blood stage of the life cycle of the plasmodium. *Merozoites* released and invade red blood cells (RBC). On one hand, parasites continue develop itself from one stage to another stages such as immature trophozoites stage, mature trophozoites stage, schizont stage, and *gametocytes* stage. On the other hand, PfEMP-1 expression recognized by host receptor such as cluster differential 36 (CD36). Thus, PfEMP1 mediated adhere of iRBCs to human endothelial receptors are associated with the most severe form of the disease such as cerebral and pregnancy associated malaria.

Anatomical Changes of Liver in Severe Malaria Infection

The liver is organized from many lobules, which constitute its functional units. Each lobule is composed of a central vein (CV), from which hepatocyte cords radiate towards portal triads. The portal triad consists of a portal vein, hepatic artery and biliary duct. Hepatocyte cords are single-cell sheets of hepatocytes separated by sinusoids that carry blood from the portal triads to the central vein (Figure 2A) and within each lobule are number of sinusoids, which are discontinuous vessels built from specialized fenestrated endothelial cells of the liver. Stellate cells are located in the space of Disse between the hepatocyte cords and sinusoids. Kupffer cells, which are the specialized macrophages of the liver, also reside in sinusoids. Hepatocytes secrete bile salt into the bile canaliculi that lead to the bile duct. Cholangiocytes are the epithelial cells lining the bile duct (Figure 2B) [11].

When someone gets malaria, liver involvement in malaria is common in patients of severe malaria and may manifest as jaundice, hepatomegaly, and elevated liver enzymes like aspartate and alanine transaminases [12]. Malaria mechanisms involve female *Anopheles* mosquito and human host. Mosquito transfer sporozoites to liver via blood. Nevertheless, the mechanism of liver damage remain controversial. Parasite damage is not completely known [13]. Hyperbilirubinemia, mainly unconjugated, is a common feature of *P. falciparum* malaria and is attributed to hemolysis of both parasitized and non-parasitized erythrocytes and partly due to liver damage [14]. Therefore, well-informed changes in blood parameters in malaria infection and hepatic function enable the clinician to establish reliable diagnosis and therapeutic interventions.

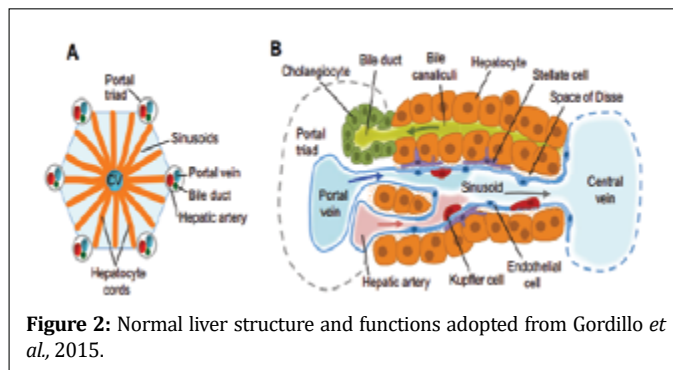


Figure 2: Normal liver structure and functions adopted from Gordillo et al., 2015.

Liver Tissues of malaria patient without hyperbilirubinaemia show enlarged sinusoidal area, haemozoin pigment within the hyperplastic Kupffer cells, and inflammatory cells within the portal tract (Figure 3, D-F). In hyperbilirubinaemia group (Figure 3, G-I), liver tissues show dense inflammatory cell infiltration in the portal tract. At higher magnification, hyperplastic Kupffer cells are visible and contain haemozoin pigment. Sinusoid areas are often congested. CV contains numerous PRBCs [15].

Anatomical Changes of Red Blood Cell in Severe Malaria Infection

Blood consist of red blood cells (RBC), white blood cells (WBC), plasma, and platelets. They have three main functions: transportation, regulation and protection. RBCs are the most abundant cell type in the human body. It has more hemoglobin to be stored in human RBC. Hemoglobin is a respiratory pigment, which binds to either oxygen or carbon dioxide. This allows oxygen to be transported around our body to our tissues and organs. On one hand, WBC has an important role to against external invaders such as parasites, bacteria and other infectious diseases. They made up in the bone marrow from multiple-potent cells called hematopoietic stem cells. They also exist in all parts of the body, including connective tissue, lymph system and the blood stream. On the other hand, platelets have an essential role as clotting [16]. Normal blood cells can be seen in the (Figure 4A). Normal matures RBCs are biconcave, disc-shaped, and anuclear. It is approximately 7-8 microns in diameter. Once normal RBCs infected by *P. falciparum* malaria, the RBC shape and size normally changed from normal shape to abnormal shaped based on the duration of infection [17]. The changing of infected RBCs as indicated in the (Figure 4B).

P. falciparum development on infected RBCs based on the malaria parasite stages and as well as time consuming. The infection may cause RBC unable do the function properly. *P. falciparum* stages are consisting of early ring (ER) stage, late ring (LR) stage, early trophozoite

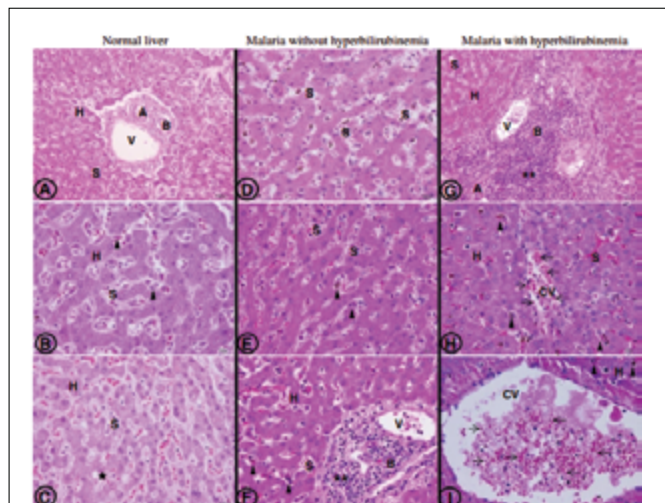


Figure 3: Histopathological changes of liver tissue from normal controls (A-C), from severe *P. falciparum* malaria patients without hyperbilirubinaemia (D-F) and from severe *P. falciparum* malaria with hyperbilirubinaemia (G-I). Images A and G are shown at 200x magnification, adopted from Viriyavejakul et al., 2014.

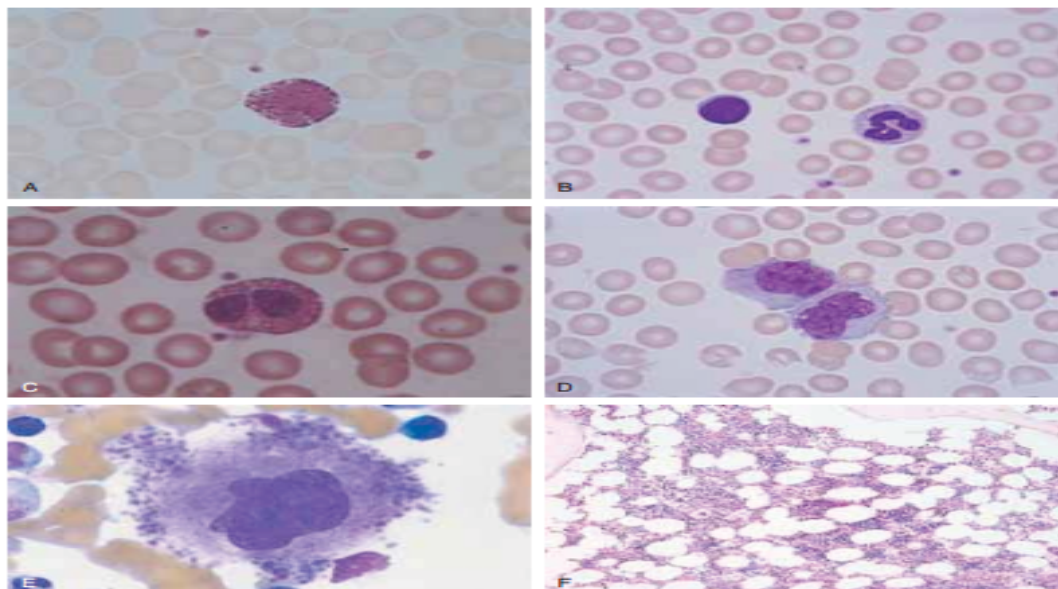


Figure 4a: (A) Red blood cells, platelets, and a basophil. (B) Lymphocyte (left) and neutrophil (right). (C) Eosinophil. (D) Monocytes. (E) Megakaryocyte with platelets. (A-E 600) (F) Normal bone marrow (200). (From Valerie: Essential of anatomy and physiology, ed. 5. F.A. Davis, 2007, p. 256.)

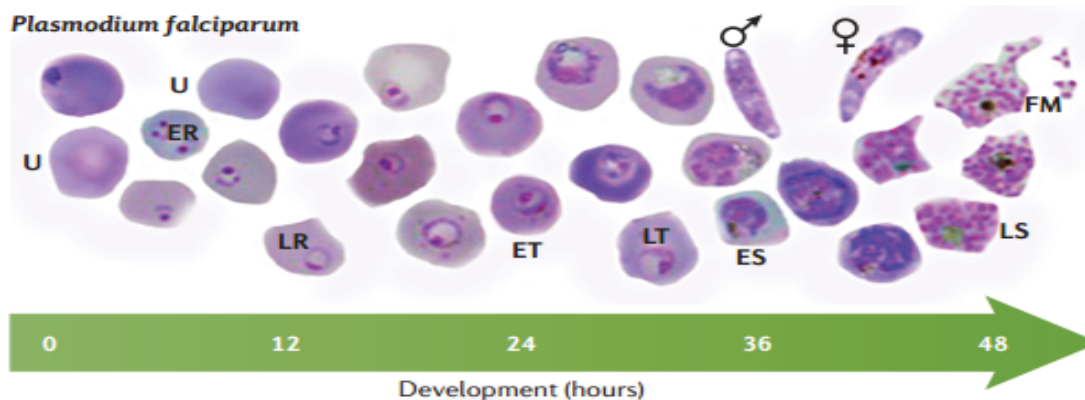


Figure 4b: Uninfected RBC (U), early ring stage (ER), late ring stage (LR), early trophozoite stage (ET), late trophozoite stage (LT), early schizont (ES), late schizont (LS), and a type of form merozoite (FM) that can be seen in the above figure.

(ET) stage, late trophozoite (LT) stage, early schizont (ES), late schizont (LS), female gametocyte, and male gametocyte. The parasite stages develop itself from ER to gametocyte based on the hours.

Mostly, infected RBC (iRBC) forms and sizes totally distinct from normal RBC because of malaria parasites multiply in the RBC. In trophozoites stages, iRBC a little bit enlarge if compared with normal RBC due to parasites progress to be schizonts which contain thousands merozoites. Schizont stages, iRBC absolutely increased to develop merozoites become mature to release. Gametocytes stage development, early-stage gametocytes are sequestered (from stage 1-3; however, in stage 4 start change the shape to be mature), and only mature stage V gametocytes can be formed as banana shape.

Discussion

Cytoadherence is the ability of parasites to adhere to the vascular endothelium. Mature forms of parasites (asexual stage and gametocytes) can adhere to the vascular endothelium of several organs (lung, heart, brain, lung, liver, and kidney), the subcutaneous adipose tissues and the placenta [13]. The development of malaria parasite within certain period may cause severe malaria. Severe infestation of RBC by *P. falciparum* and resultant hemolysis results in rising bilirubin. Sequestration of the parasite-infected RBC in the capillaries causes clogging of the capillaries in the important organs and the resultant

ischemia can lead to organ system dysfunction [8]. Therefore, left treated malaria parasites; it may lead to the pathogenesis of malaria such as severe malaria anemia and cerebral malaria.

Concluding remarks

In summary, this study highlighted the findings of this review showed that *P. falciparum* malaria infection is causing liver damage and RBC destruction. As a result, liver tissue from malaria patients showed that enlarged sinusoidal area and infected RBC indicated inflamed to change the sizes and shapes RBC in various stages such as early infected stages, late infected stages, schizont, and gametocytes stages.

Acknowledgements

Department of Biomedical Laboratory sciences and Ubon Ratchathani University, Thailand.

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