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PULMONARY COMPLICATION IN SEVERE MALARIA

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ABSTRACT

Malaria is a potentially fatal disease caused by *Plasmodium* spp. Transmission occurs via the bite of female mosquito, *Anopheles* spp. Epidemiologically, global number of malaria patient are located in Southeast Asia and Africa. Until nowadays, millions of people still living in endemic area, with children and pregnant women are among the most vulnerable group in the population. Although there have been many advances in treatment and management, but the potential for harm remains; one of the example is lung involvement in patients with severe malaria. The paper aim to discuss briefly lung derangement in the severe malaria and the inflammatory response related to the lung dysfunction.

KEYWORDS: blood protozoan, obligate intracellular, complication, ARDS, pulmonary vascular occlusion, inflammation

INTRODUCTION

The long known four species of blood protozoan parasites are *Plasmodium vivax, Plasmodium falciparum, Plasmodium malariae,* and *Plasmodium ovale,* with the addition of the newer confirmed species, that can also infect humans, a zoonosis caused by *Plasmodium knowlesi*.[1] Other species of malaria also reported transmitted from animal to human (zoonosis), but the number reported is not much.

Global malaria epidemiology study conducted by Qiao *et al* revealed its recent trend.[2] Though globally, the malaria age-standardized incidence rate (ASR) already decreased by an average 0.80% (95% confidence interval 0.58–1.02%) per year from 1990 to 2019; however, actually it slightly increased in 5 year period, from 3195.32 per 100 000 in 2015 to 3247.02 per 100 000 in 2019. The incidence rate of children under 5 was still higher than other age groups in the population. A total number of 40 countries had higher ASRs in the year 2019 compared to the data in the year 2015. The fastest augmentation in Cabo Verde (from only 2.02 per 100 000 and soaring very high to a number 597.00 per 100 000 population). After the year 2015, the ASRs in three regions: high-middle, middle and low-middle Socio-demographic Index regions began to arise and the trends remained in the up-rising pattern in the year 2019. Central, Western and Eastern Sub-Saharan Africa had the highest ASRs since 1990, and traveller number in Eastern and Western Sub-Saharan Africa increased by 31.24 and 7.58%, respectively, from 2017 to 2018. Especially, most countries with ASR over 10 000 per 100 000 had increase in traveller number from 2017 to 2018, with the highest change by 89.56% in MozambiqueIn 2019, there were an estimated 229 million cases of malaria worldwide. The estimated number of malaria deaths stood at 409 000 in 2019. Children aged under 5 years are the most vulnerable group affected by malaria; in 2019, they accounted for 67% (274 000) of all malaria deaths worldwide.[2] Children and pregnant woman remain the most susceptible group in the population.[3]

The classic triad of malaria is characterized by sign and symptom of high fever, anemia and splenomegaly. Without proper traetment, susceptible and or vulnerable people can immediately enter the danger phase, the severe malaria.[5] Severe malaria is a systemic and potentially lethal condition of illness which characterized by clearly marked dysfunction of one or more peripheral organs, such as the brain, the kidney and the lung. In the brain, it caused condition called cerebral malaria (CM), while in the kidney it caused acute kidney injury (AKI), and the last but not least, in the lung it caused acute respiratory distress syndrome (ARDS). This paper aims to review lung derangement in the context of the severe malaria and features of the inflammatory response are related to the lung dysfunction observed in severe malaria.

EARLY PHASE OF MALARIA

This blood protozoa primarily transmitted via the proboscis of a female Anopheles mosquito that contain malarial sporozoit and then inserted them into susceptible humans.[6,7] Mosquitoes with a higher numbers of sporozoites in their salivary glands following blood-

feeding activity, aided by its proboscis, are more possible to have created new infection in susceptible individuals; and in terms of transmission, of course it have done so faster compared to other mosquitoes with fewer number of parasites.[3] The mosquitoes with heavy parasite burdens are consequentially more likely to result in the host's definite clinical blood stage infection.

After entering the bloodstream, at the beginning in the very early phase of infection, this blood protozoan then brought up to the liver and infect hepatocytes; this phase is called "human liver stage".[8] Here, the parasite inside the liver cell change their forms several time; from sporozoites, it develop into schizonts which then burst, and release merozoites into the blood. This transition into a new form believe by many expert is a preparation of the parasite to infect its definite predilection, the erythrocyte and begin the massive reproduction, asexually. Sato *et al* mentioned that the essential role of early host interactions in the liver that may dampen the subsequent pro-inflammatory immune responses and influence the occurrence of vital organ failure such as the brain, and highlighting a novel checkpoint in the fatality of this pathology.[9] Even in this active development, how the parasites evade the host's immune system while moving from the liver to the blood has still in the process of revealing. This obligate intracelular parasite actually dictate its will to a series of host cells as if rendered helpless and does not recognize the dangerous activities carried out by this *Plasmodium* spp.[10,11]

Following an infective mosquito bite, which is when the mosquito proboscis pierces the surface of the skin in search of food, sporozoites move with its gliding motility in the direction from the mosquito's salivary gland cavities and then are discharged within the small vessels of the host's skin.[12] After entering the blood stream, sporozoites carried away via the blood stream inside the blood vessels and enter the liver cells. Here they evolve into schizonts, which then burst and release a huge number merozoites into the blood, leading to the clinical symptoms of malaria.[13,14]

Each invading sporozoite develop into a schizont that become very matures to yield up to 40 000 merozoites over a period of one to several weeks (long-term latent forms of 2 species of malaria belongs to *P. vivax* and also *P. ovale;* it called hypnozoites stage that may endure quiescent that clinically, it has been reported that it can last for months or years).[13,15] In some species of parasite, particularly *P. vivax*, some sporozoites become hypnozoites. This form lies dormant in the liver and can reactivate leading to schizont formation and the ensuing symptoms of malaria in the absence of an infectious mosquito bite.[16] According to Adekunle, based on their modeling of *P. vivax* primary infection and hypnozoite reactivation, that 90–96% of intra-erythrocyte infections emerge from the reactivation of *dormant* hypnozoite.[16]

For most people, symptoms may occur in 10 days to 4 weeks after infection, although for a susceptible and immunological naive individual, he/she may feel ill as early as 1 week after the bite of mosquito or perhaps up to years later.[5,17,18] Infected individual with clear clinical symptoms may suffer from cycles of malaria "attacks." An attack usually starts with shivering and chills, followed by a high fever, followed by sweating and a return to normal temperature. Malaria signs and symptoms typically begin within a few weeks after being

bitten by an infected mosquito. The species *P. falciparum* requires shorter duration to advance its erythrocytic stage compared to the other four species of human plasmodium while the longer ones are observed in *P. malariae*.[20,21]

Study conducted by Brasil *et al* showed us that on the hundreds of reported cases of imported *P. vivax* malaria patients hospitalized in the city of Rio de Janeiro, where there is no vector-borne transmission at all, the patient's clinical data has made feasible for them to analyse the time-length of the incubation period between patients. The result made them realize that the time-period may be extended in certain cases. The heterogeneity in essential biological characteristics is traditionally appraised as one possible description to the origination of relapse in malaria and also to the differences in the time duration of the malaria incubation period among patients, a condition which can also be elucidated by the application of antimalaria chemoprophylaxis.[22]

One of the most common condition found in malaria survivors is the repetitive occurence of malaria attack.[23] The term relapse is now used specifically to describe recurrences of malaria derived from persistent liver stages of the parasite (hypnozoites).[19] The number of sporozoites inserted and inoculated by the anopheline mosquito into the susceptible and vulnerable host is a crucial determinant of both the number and also the timing of relapses.[24] The time intervals between each relapses reveal an exceptional periodicity with evidence is presented that the proportion of patients who unfortunately have repetitive relapses is relatively persistent. The internal factor which initiates *dormant* hypnozoites to 'wake up' and become active and then escort to regular interval relapse in malaria is the condition of systemic febrile illness itself.[25] It is suggested that in an endemic areas of malaria where transmission of infection occurs heavily, then a large portion of the population bears *dormant* but latent hypnozoites which can be stimulated by an acute systemic infection, *e.g* falciparum or vivax malaria. That is why, for returned travelers from malaria endemic area, they should consult to the doctor or healthcare providers of any travel in areas where definite malaria occurs during the past 12 months.

UNCOMPLICATED AND COMPLICATED MALARIA

Infection with malaria parasites may result in a wide variety of symptoms, ranging from absent or very mild symptoms to severe disease and even death, and the term "uncomplicated" and "complicated" is intended to make the division of symptoms a little easier, even though in daily practice, what was previously classified as uncomplicated malaria can very quickly t urn into complicated malaria.[18,26] Delay in receiving treatment for uncomplicated malaria (UM) is often reported to increase the risk of developing severe malaria (SM).[27]

In patients with uncomplicated malaria, the classical subjective complain that infrequently observed during malaria episode may lasts 6–10 hours; the episodes consists of a cold phase (sensation of cold, shivering), and immediately followed by hot phase (fever, headaches, vomiting, and seizures in young children), and then ends in a sweating phase (sweats, return to normal tem- perature, tiredness).[17,28]

Traditionally based on the duration of asymptomatic period, classic malaria has a fever pattern that appears over a period of time, which is the attacks occur on every second day with the type of "tertian" malaria parasites (*P. falciparum, P. vivax,* and *P. ovale*) and on every third day with the type of "quartan" parasite (*P. malariae*).[17,24,26] More commonly, the patients present with a combination of the following symptoms: high fever, systemic malaise, chills, headaches, myalgia, nausea, and vomiting. During physical examination, doctor may found: the patient's body temperatures rises, increased respiratory rate, massive perspiration, weakness of the muscle, light jaundice, enlargement of the liver and splenomegali (enlargement of the spleen). Splenomegali usually only occurs in people who live in endemic areas and a marker of chronicity, although it is possible that the patient actually does not show significant clinical symptoms.[29]

In patients with severe malaria, the clinical manifestations include cerebral malaria (abnormal behavior, impairment of consciousness, seizures, coma, or other neurological abnormalities), severe anemia due to hemolysis, hemoglobinuria due to hemolysis, abnormal blood coagulation, low blood pressure, acute renal failure, hyperparasitemia (more than of the malaria parasite-infected erythrocytes, hypoglycemia, metabolic acidosis, and acute respiratory distress syndrome) [7]. Recurrent infections with Plasmod- ium falciparum may result in severe anemia [7]. Nephrotic syndrome can result from repeated infections with Plasmodium malariae [7]. Hyperreactive malarial splenomegaly (or called "tropical splenomegaly syndrome") is marked by the much enlarged spleen and liver, anemia, abnormal immunological findings, and a susceptibility to other infections and is attributed to an abnormal immune response to repeated malarial infections [7].

ORIGIN OF SEVERITY OF THE LUNG DERANGEMENT

In malaria, the main finding of patients with falciparum malaria, the deadliest type of malaria infection, is the sequences of sequestration of infected erythrocytes within the microvasculature of the vital organs, *e.g.*, the brain or the lung. Infected erythrocytes that contain falciparum malaria become mored rigid due to the loss of deformability and flexibility properties.[30-33] Infected red blood cells actualy underwent certain modifications right in its outer facet, a condition named knobs, and it seem to facilitate its adherence to the inner vascular endothelium and also perhaps to other erythrocytes, infected or non-infected ones.[34-36]The study conducted by Raj and Anderson revealed the role of erythrocyte (RBC) deformability and perfusate viscosity on lung segmental vascular resistance that in the end affect pulmonary hemodynamics.[33] These findings suggest that decreases in erythrocyte deformability make it probably becomes stiffer intravascularly, so that it is easier to adhere to the vessel wall and then ends up with erythrocyte sequestration.[34] Infected erythrocytes will never be the same as before.

Adhesion actually supply better chance for the parasite's ontogenesis in the condition that resembles microaerophilic venous atmosphere, cytoadherence contribute significantly in Plasmodium's immune-escape/evade mechanism, but at the same time also responsible to the pathogenesis of complication named severe malaria.[37] Mature trophozoites and schizonts are sequestered and released from the peripheral circulation due to adhesion of infected

erythrocytes to the host's endothelial cells. This chain of events directs the parasite to escape clearance by the spleen which actually recognizes the erythrocytes already loss its deformability.[38]

Pathogenesis and worsening of the disease actually rely on adhesion to the inner part of microvasculature's endothelium, a conditon termed cytoadherence, because adhesion contributed to occlusion of microvasculature, prevent sufficient bood supply to vital organs and leading to organ failure.[39] Cytoadherence can also describe adhesion of infected erythrocytes to uninfected erythrocytes, a phenomenon widely known as rosetting.[37,40] rosettes were easily deranged by high shear forces inside the artery, but when it comes to the capillaries and post-capillary venules where where the blood flow slows down dramatically, rosetting parasitized erythrocytes is easily bound to the inner microvasculature's endothelial cells and at the same time allows uninfected erythrocytes simultaneously to occlude vessels and reduce blood flow significantly.[41] This condition is very danger to vital organs because permanent impedement of microvasculature's blood flow leading to the condition of reduced supply of oxygen and causing cell's hypoxia, that lead to ischemia, and even metabolic disturbances. These serial of events surely caused permanent tissue damage, multi-organ failure and death in susceptible patient that suffer from severe malaria.

LUNG DERANGEMENT IN SEVERE MALARIA

Patients with severe falciparum, vivax, and knowlesi malaria may develop acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).[42,43] Ironically this conditon often developed just only several days after antimalarial medication was started, this condition could be due to the medication failure.[44] In south east Asia, decreased artesunate eficacy was already noted, and just as reported by Landre *et al*, combination of polymorphisms on the Kelch 13 (K13) gene and pharmacology of Artesunate itself was involved in theraupetic failure.[44]

Epidemiologically, the rates ARDS incidence among severe falciparum malaria cases are 5% to 25% in adults and up to 29% in pregnant women the condition of ARDS is scarce in the group of young children.[32] Condition of malignant respiratory distress evolves in up to 25% of adults and 40% of children. The underlying cause is a combination of several interrelated conditions including severe anemia, respiratory compensation of metabolic acidosis, noncardiogenic pulmonary edema and concomitant pneumonia.[23,27,42,45]

Gas exchange is significantly impaired in patients with severe malaria.[46] Pulmonary edema is the most severe form of lung involvement among patient suffer from severe malaria, and this condition worsening the need for oxygen.[47] Increased alveolar capillary permeability leading to intravascular fluid loss into the lungs is the main pathophysiologic mechanism. This defines malaria as another cause of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

In the case of severe falciparum malaria, it was associated with increased oxygen consumption but this was not related to disease severity.[48] Lactic acidosis did not result from inadequate overall macrocirculatory tissue oxygen delivery, but more likely from patchy

microvascular perfusion abnormalities result in focal tissue hypoxia and combined with impaired hepatic clearance.[43,45,46] The haemodynamic status must kept optimized all the time to prevent the possibilities of decompensation in the period after antimalarial treatment.[46]

Malaria related ARDS pathophysiology actually based on microvasculature's inflammatory-mediated responses that increased the capillary's permeability and even to trigger dangerous endothelial damage that can happened diffusely; a condition that can persist even after post medication and after the clearance of the parasite with microvascular dysfunction likely contributing to impaired tissue perfusion.[42,49,50]

The role of parasite sequestration in the human pulmonary microvasculature is indefinite due difficulties in establishing solid prove of sequestration, ethical issues and definitely the limitation of clinical report in human subjects.[51-53] It should not be forgotten also that clinico-epidemiologically, sequestration occurs intensely only in cases of *falciparum* infection, but less reported in the species *P knowlesi*, and has not been shown credibly in *P vivax* infection.[51] In Animal model, a group of scientist from Surabaya, Indonesia discovered all the histopathological parameters of severity took place; including *oedema*, hemosiderin, thickened alveolar septa and inflammatory cell inside the lung from all infected mice with *P. berghei* that Exposed to Repeated Artemisinin.[52] The histological changes were severe. Those changes including diffuse *oedema*, increasing number of cellularity of the alveolar septa and thickening of the *alveolar septa* wall and massive infiltration of inflammatory cell in all affected areas of the lung's functional units with the existence of hemosiderin accumulation in *septum inter-alveolar* and degeneration of the bronchial epithelial. The finding of sequestered parasites and tissue damage in the lung infiltration clearly occurred in the lung.[52]

In severe human malaria clinical case, ALI and ARDS be seen as part of a severe multi-system failure or may be the only main clinical attribute and often happens in condition of reduced *parasitemia*, soon after antimalarial medication given. In severe falciparum malaria, the roentgenographic presentations include diffuse interstitial edema, pulmonary edema, pleural effusion, and lobar consolidation.

Sometimes, doctors who treat patients with severe lung disorders due to malaria must make sure that fluid overload condition is prohibited and follow the old adage to "keep them parched/dry" because the earliest conclusive markers of ARDS are not yet available and do not forget that cases like this often occur in primary health care facilities with very limited equipment and resources.[54,55] Mechanical ventilation can save life in ALI/ARDS. Basic critical care facilities are increasingly available in tropical countries. The use of early lung-protective ventilation has helped to reduce mortality from malaria-induced ALI/ARDS, but unfortunately this action is not recommended for patient underwent permissive hypercapnia in unconscious severe malaria patient. This is due to the risk of elevated intracranial pressure and the potency of cerebral swelling that might occur in cerebral malaria. The best antimalarial treatment of severe malaria is IV artesunate. Even when proper treatment started immediately, and the parasite blood count showed improvement, the doctor must keep the patient closely observed in order to prevent the occurrence of post-treatment complication.

CONCLUSION

The best and optimal management of malaria-induced lung derangement includes early recognition via a close observation to patient's subjective complaint, clinical and laboratory findings and made the proper diagnosis, *cito*. Malaria cases must always be suspected if during *anamnesis*, the subject is complaining about acute febrile illness and just returned from a malaria endemic region, *e.g.,* a returning ttourist or traveler or even just a short- term period visitor. Slide microscopy and/or the use of rapid antigen tests are standard diagnostic tools to make the correct diagnosis of malaria. Malaria must be treated with effective drugs, even current options are limited. Preventing clinical deterioration in malaria sufferers continues to be a challenge for health professionals.

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