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The Phenomenon of the 'Starry Sky' on Blood: Lesson Learned From Severe Malaria Falciparum

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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Mini-review Article

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ABSTRACT

Severe malaria occurs when previously uncomplicated malaria infections are then turn to be full blown and tangled by serious, single or multi-organ failures or abnormalities in the patient's blood or metabolism. Clinical deterioration can happen abruptly and unnoticed, due to the masking of other prominent clinical condition like hyperthermia. Making the correct diagnosis as soon as possible is pivotal before administering antimalarial therapy. Diagnosis is made by examining the thick and thin blood films in an attempt to find malaria parasites in the blood sample.The "Starry Sky" appearance is a microscopic feature of severe malaria infection and its exclusively found only in thick blood film. The aim of this minireview is to discuss about the clinical background of "Starry Sky" appearance found in thick blood smear of severe malaria and its brief review combined with our experience in the Deptartment of Parasitology, Faculty of Medicine Universitas Kristen Indonesia, Jakarta-Indonesia, in handled blood test from a vulnerable patient with severe malaria and how we pass on the lessons from that story to our students as part of health communication in community based Parasitology. By inserting this story to our lesson materials, we hope can build awareness among our students as future health practitioners and also to the public they serve as well as all stake holders; this snow ball action are currently and continously required to be done.

Keywords: Thick blood smear; protozoan; Plasmodium; vector; mosquito; deformability; lysis; sequestration.

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1. INTRODUCTION

Malaria in humans is a disease caused by blood protozoan named *Plasmodium falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi*. Until nowadays, malaria as a disease entity, still represents a global medical disaster because it can quickly progress to severe complications and resulting in the death of the unfortunate patient [1]. Without early diagnosis, made on the basis of a brief anamnesis, sufficient physical examination as well as supporting examinations (*e.g.*, Parasitology Laboratory examination and other relevant examination), followed by prompt and appropriate treatment, it is unlikely that the patient will survive [1-4].

Severe malaria arises when the course of the disease are complicated by serious organ failures which can occur simultaneously or fatal abberations in the patient's blood component or in his/her metabolism followed with the loss of consciousness and coma leading to death [1-3]. The various manifestations of severe malaria include the following: pulmonary derangement marked by severe respiratory distress [5], acute renal failure [6], cerebral malaria with abnormal behavior [7], impairment of consciousness [8], seizures [9], coma [10], or other neurologic abnormalities [4,5]. The disturbed diversity of internal organs shows how vulnerable and interrelated these organs are and their main blood supply is supported by a network of capillaries and how microcirculatory obstruction in malaria directly affect the function of these organs [11]. Most of severe malaria cases are caused almost exclusively by *P. falciparum* [1,2,4].

During the blood stage of infection, *P. falciparum* parasites extensively modify the host erythrocyte cytoskeleton and its membrane [12], resulting in conversion of infected red blood cell (IRBC) deformability and new adhesive properties [13]. In particular, IRBCs display knob-like surface protrusions that rigidify the erythrocyte membrane [14] and present the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) family, encoded by var genes [15]. PfEMP1 ligands that conciliate the process of cytoadhesion to the inner wall of microvascular endothelium [16]. By these two mechanisms, both combination of knobs and PfEMP1, are believed to devote to subsequent IRBC lysis and sequestration [11], giving rise to enhanced disease severity through small vessel occlusion, tissue ischemia, and eventual organ failure [1,4].

This minireview focuses on the starry sky appearance in thick blood smear of severe malaria and its brief review combined with our experience in the Department of Parasitology, Faculty of Medicine Universitas Kristen Indonesia, Jakarta-Indonesia handled blood test from a patient with severe malaria and how we pass on the lessons from that story to our students as part of health communication in community based parasitology.

2. EPIDEMIOLOGY OF SEVERE MALARIA

Epidemiologically, the estimated number of malaria deaths was 619 000 in the year of 2021 [3]; WHO report stated that global severe malaria incidence is approximately two million cases with nearly 430,000 deaths annually. The African continent bears a disproportionately lofty portion of the global malaria burden. In 2021, the region was home to 95% of malaria cases and 96% of malaria deaths. Children under 5 accounted for about 80% of all malaria deaths in the region. Four African countries accounted for just over half of all malaria deaths worldwide: Nigeria (31.3%), the Democratic Republic of the Congo (12.6%), United Republic of Tanzania (4.1%) and Niger (3.9%) [3].

Specific attention must be aimed at vulnerable group among the population. The first is young children (especially aged under 5 years old) who immunologically have not yet developed partial immunity against malaria. The second group is pregnant women, whose immunity is partially reduced by pregnancy, especially during the first and second pregnancies. The third group is travelers or migrants or soldier/police coming from areas with little or no malaria transmission and then stay temporarily in an endemic areas; this third group can be considered as immune-naive.

The risk of getting malaria infection is partially explained by social background of vulnerable populations. Since vulnerability to malaria is both influenced by social and environmental factors, its complexity cannot be measured by a single value. There is also a strong contribution of geographical position to the risk of transmission from the vector side, which includes: perrenial temperature, vegetation thickness, composition of clay in soil, total frequency and bulk of rain fall and distance from nearest source of body of water.

As severe malaria clinically is always the progression of uncomplicated malaria [1,4], its diagnosis is actually similar to that of uncomplicated malaria with an addition to close observations of danger signs [14].

According to the WHO/UNICEF iCCM guidelines cited by Okitawutshu et al. [17], there are four general danger signs: convulsions, unusually sleepy or unconscious, not able to drink or feed anything and vomits everything. Timely identification of these non pathognomonic clinical signs actually can lead to a minimalization in malaria patients underwent fatal complications and deaths [14,17].

As noted in WHO's Management of Severe Malaria, the most important element in the clinical diagnosis of malaria is a high index of suspicion [3,18]. Malaria is conventionally diagnosed by microscopic examination of stained blood films using Giemsa, Wright's, or Field's stains [19]. Microscopically, for parasitologists or trained laboratory technicians, making correct diagnosis of malaria is easy and actually is not complicated. Early detection is the key to success in preventing full blown malaria exacerbation and can change the individual patterns of health seeking in Vietnam [20].

Administering antimalarial chemotherapy as soon as possible can prevent the progression and severity of malaria and epidemiologically prevents further transmission from human to vector mosquito [21].

2.1 Clinical Spectrum of Severe Malaria

Severe malaria is almost exclusively caused by *Plasmodium falciparum*. In the southeast Asia region, young adults are the most affected population [2], while in the Africa region, it mainly affect children [22]. With the rising incidence of imported malaria [23] the number of case fatality rate remains sky-scraping, especially among children under five [24] despite many progress and achievement in intensive care and antimalarial treatment. Clinical deterioration usually appears 3–7 days after onset of fever [1,4,25]. Complications involve the nervous, respiratory, renal, and/or hematopoietic systems like malignant anemia [5-10,16-17,25], Metabolic acidosis [26] and hypoglycemia [27] are also common systemic complications.

Nowadays, iv artesunate is the first-line drug for treatment of severe malaria in many countries [28,29]. As soon as the patient's condition is clinically stable, and he/she able to swallow, oral treatment should be administered [30]. The intravascular volume should be carefully monitored [31] at the lowest level sufficient for adequate systemic perfusion to prevent development of acute respiratory distress syndrome [5]. Optimising the fluid resuscitation of patients with severe malaria is a simple and potentially cost-effective intervention [32]. Immediately after appropriate clinical judgement, renal replacement therapy should be initiated [10]. Exchange blood transfusion can be considered and has been recommended in the advanced stage of clinical management of patients with severe malaria accompanied with malignant parasitemia [33]. For early diagnosis, it is always cardinal to think malaria in every febrile patient who came to the primary health center, especially when in anamnesis, there was a history of travel to an endemic area [34] or with history of previous attack of malaria [35].

Table 1. Danger signs in severe malaria

No	Changes inside the body of the patient
1	Neurological/cerebral change: cognitive, seizure, coma [7-9]
2	Pulmonary change: abnormal breathing pattern, respiratory distress syndrome [5]
3	GI Tract change: persistent vomiting and diarrhea [36]
4	Metabolic change: Jaundice [36,17]
5	Hematology change: bleeding [13]
6	Renal change: dark urine, acute renal failure [2,6,10]
7	Vascular change: delayed capillary refill [11]
8	Skin change: intense pallor [17]
9	Basal metabolic change: hyperpyrexia [36,17]
10	Parasite virulence factor: hyperparasitemia and schizontemia [17,18]

Note: It should be remembered that numbers do not always indicate the sequence of events

2.2 The “Starry Sky” Story

Department of Parasitology, Faculty of Medicine, Universitas Kristen Indonesia is located in Jakarta, Indonesia. As the nation's capital which is rapidly developing into a big metropolitan city, it is actually not a malaria endemic area. Only occasional cases of imported malaria were found in our laboratory. Usually it is an imported cases of malaria, as the result of people travel to or come from endemic area of malaria. To our experience, usually people who travel to endemic areas are for business assignments such as the army or police or tourists/tourists while those who come from endemic areas are more often students for academic matters. but sometimes, there are also patients who come from endemic areas for business or work even though the number is even less.

The ”Starry Sky” story was my personal experience receiving a blood sample of suspected severe malaria at the beginning of my career as a doctor serving in the Department of Parasitology in late 2002.

That blood sample was sent along with a laboratory examination request for blood malaria examination with very minimal medical information. It was from a male patient aged around mid 40 with hyperthermia, who have just been admitted to the emergency unit and were referral from a small hospital outside Jakarta, Indonesia. At that time, as one of the reference laboratories for Parasitology, we often only received clinical samples without knowing for sure the patient's condition, especially the information included in the examination sheet was also minimal. So that our examinations are really only carried out on request; unless the patient also comes to the laboratory so that our clinical staff can have a more focused discussion with the patient regarding his/her complaints that need to be examined.

As soon as we received the sample, we made several thin and thick blood film, stained 3 slide for each (thin and thick) with Giemsa stain [37] and directly examined it under light microscope. We started with lower magnification (400× magnification) and when we reach the suspected object, the magnification was switched to 1000×. Just as the protocol for examining blood films stained with Giemsa, when 1000× magnification was used, we always apply immersion oil to the slide. The area examined in the thick blood film looks like the image below.

The paradox of beauty regarding the microscopic appearance of thick blood smears of severe falciparum malaria is indicated by the appearance of a starry sky, which can be seen under 1000× magnification using immersion oil to improve visibility, and make the object looks brighter and sharper. The observer can see: against a combination of dark and pale purplish-red background (because the lysed part of the erythrocytes is still remained and also stained), and some parts appear pink but are fainter and slightly lighter (the non-cell parts that is also stained) there is an apparition in the form of multiple dots that appear like open rings, or commas, or exclamation points and even if using a bit of imagination like the wings of a bird in flight.

Immediately after finding these images scattered throughout the slide and combined with the result of examination of thin blood preparations, we immediately answered the request for examination by writing the results as severe falciparum malaria infection. The results were immediately delivered by a special courier to the emergency department, so that there was no delay and the patient can be treated adequately, immediately. But unfortunately, the antimalarial therapy could not be administered to the patient at the emergency unit as he was not able to survive.

Then we had the story about this poor vulnerable patient just a couple days after he died. This patient was a pastor who serves congregations in the hinterlands of Sumatra. The location he served included forest areas which at that time were still being watched out for as malaria endemic areas. He left for Jakarta for the purpose of participating in the national church congress, and actually, the priest already had an intermittent fever. He was finally able to get to Jakarta and to save money he did not stay in a hotel but stayed at his relative's house in one of the small satellite towns outside the city of Jakarta, namely the city of Bekasi. When he arrived in Bekasi, his condition did not improve at all, his relatives immediately took him to a small private hospital, where he was treated for 3 days there but with no improvement, instead his condition got worse. His relatives, which was worried about his deteriorating condition, then took the initiative to move him to a bigger hospital which is still in the Bekasi area, was treated there for 3 days but his condition worsened without clarity regarding the diagnosis. He began to show signs of decreased

consciousness and impaired internal organ function. In a panic, the family forced to transfer the patient to our hospital and what happened was as stated before.

3. LESSON LEARNED

Because Severe malaria requires rapid and prompt diagnosis and then followed by adequate anti-malarial treatment to avoid significant risk of further morbidity or mortality, we strongly recommend that a suspected case of severe malaria must always be treated as an emergency case [38,39]. Many cases of severe malaria, including our story of “Starry Sky”, teach how time is the pivotal determinant of whether doctors can identify and clearly assess the magnitude of the problem at hand, determine the steps that need to be taken and implementing them as soon as possible while continuing to evaluate the patient's progress [39,40].

It must always be remembered that clinical deterioration among malaria patient can occur rapidly and sometimes suddenly [41]. Moreover, some patients because of nausea or vomiting, induced by either disease or drug(s), are fail to eat independently by mouth and forced doctors to install parenteral treatment required by the patient [17]. Clearly, the step by step patient management will need to be tailor-made and individually adjusted [17], *e.g*., depending on general conditions and medical complaints, for the particular patient in a particular setting especially where appropriate diagnostic laboratories, sufficient drugs and other supporting facilities may not be accessible [39].

Therefore, health education especially in the context of the 5 stages of health fulfillment needs to be continuously strengthened [42]. The complexity of the clinical course of Malaria, from simple uncomplicated one to severe and complicated cases process is actually recognizeable, so that as part of its study in the effort to the integration of interdisciplinary and transdisciplinary perspectives and also to build awareness among health practitioners and the public as well as all stake holders, are currently and continously required. In delivering health care, an effective teamwork can immediately and positively affect patient’s safety and outcome [43,44].

This complexity is transferred to the training of the general practitioner since from their very early medical education, because it requires appropriate training, different conceptual approaches and perspectives to address the patient's care. This is also the reason why we always teach the story of the starry sky to our students in the context of malaria as a parasitic entity, also when studying the internal organs, for example the brain, kidneys, lungs, which may be affected when someone has severe malaria. In addition, the scientific advance and the technological application to the field of medical sciences, increases the level of complexity for the learning of medicine even though that the basic concepts of health communication is always the same.

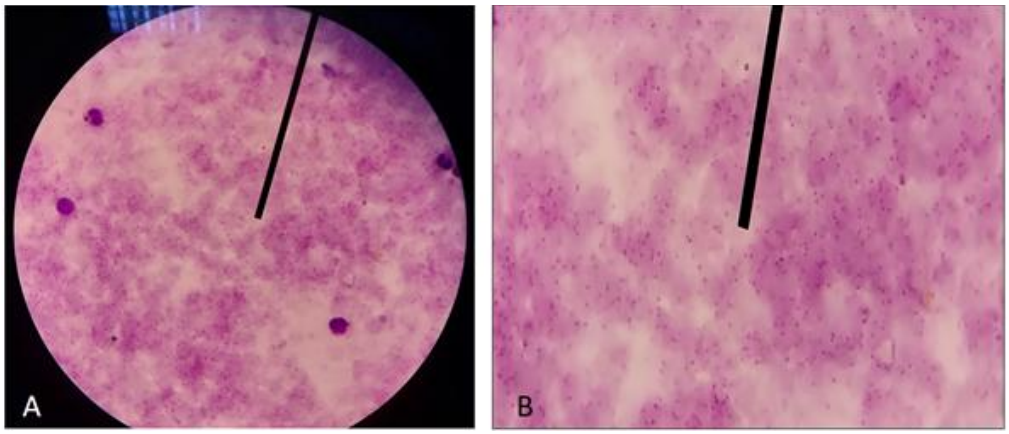

Fig. 1. The starry sky appearance of severe malaria in thick blood film smeared with Giemsa stain. The Starry Sky appearance is exclusively only can be seen in thick blood film. Blood sample came from a patient with working diagnosis of (suspected) severe malaria and the diagnosis was made by our findings in both thick and thin blood film. A. Magnification 400×, B. Magnification 1000× (slides courtesy of Department of Parasitology, Faculty of Medicine, Universitas Kristen Indonesia, Jakarta-Indonesia)

4. CONCLUSION

Malarial management depends on rapid identification of the disease, as well as identification of the malaria species and level of parasitemia. The knowledge about malaria must be use to raise public awareness; because it is a key factor in malaria prevention and control and in improving treatment-seeking behaviour. Health communication encompasses and bringing together all knowledge starting from basic medical science, clinical knowledge and disease management packaged in the form of health education; delivery of important information to all stake holders and use of communication strategies to inform and influence individual and community knowledge. Our past experience was also part of our teaching to our medical students so they can understand the holistic aspect of patient care.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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