

THE “STARRY SKY” STORY

by Forman Erwin Siagian

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THE “STARRY SKY” STORY: LESSON LEARNED FROM SEVERE MALARIA FALCIPARUM

Forman Erwin Siagian

Dept. of Parasitology, faculty of Medicine, universitas Kristen Indonesia

Email: forman.siagian@uki.ac.id

Abstract

Introduction

Malaria in humans is caused by blood protozoan named *Plasmodium falciparum*, *P. vivax*, *P. malarie*, *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 (1) complicated by serious organ failures which can occur simultaneously or (2) fatal aberrations in the patient's blood component or in his/her metabolism followed with (3) 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 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*.

During the blood stage of infection, *P. falciparum* parasites extensively modify the host erythrocyte cytoskeleton and its membrane [12], resulting in conversion of red blood cell (RBC) 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 focus on the starry sky appearance in thick blood smear of severe malaria and its brief review combined with our experience in the dept. of Parasitology, faculty of Medicine Universitas kristen Indonesia, Jakarta-Indonesia handled blod 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.

Epidemiology of Severe Malaria

Epidemiologically, The estimated number of malaria deaths estimated at 619 000 in the year of 2021 [3]; while Plewes [10] that cited 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].

As severe malaria is always the progression of uncomplicated malaria [1,4], its diagnosis is similar to that of uncomplicated malaria plus observations of danger signs [14]. Danger signs include (1) neurological change, (2) abnormal breathing pattern, (3) persistent vomiting and diarrhea, (4) jaundice, (4) bleeding, (5) dark urine, (6) delayed capillary refill, (6) intense pallor, (7) hyperpyrexia, (8) hyperparasitemia and (9) schizontemia [14]. It should be remembered that numbers do not indicate the sequence of events. According to the WHO/UNICEF ICCM guidelines cited by Okitawutshu *et al* [19], there are four general danger signs: (1) convulsions, (2) unusually sleepy or unconscious, (3) not able to drink or feed anything and (4) vomits everything. Timely identification of these non pathognomonic clinical signs actually can lead to a minimalization in malaria patients underwent fatal complications and deaths [14,19].

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 [3,20]. Malaria is conventionally diagnosed by microscopic examination of stained blood films using Giemsa, Wright's, or Field's stains [21]. 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 [22].

Administering antimalarial chemotherapy as soon as possible can prevent the progression and severity of malaria and epidemiologically prevents further transmission from human to mosquito [23].

Clinical Spectrum of Severe Malaria

Severe malaria is almost exclusively caused by *Plasmodium falciparum*. In the southeast Asia region, young adult are the most affected population [2], while in the Africa region, it mainly affect children [24]. With the incidence of imported malaria is rising [25] and the number of case fatality rate remains sky-scraping, especially among children under five [26] despite many progress and achievement in intensive care and antimalarial treatment. Clinical deterioration usually appears 3–7 days after onset of fever.^{1,4,27} Complications involve the nervous, respiratory, renal, and/or hematopoietic systems.^{5-10,16-19,27} Metabolic acidosis [28] and hypoglycemia[29] are also common systemic complications.

Nowadays, IV artemunate is the first-line drug for treatment of severe malaria in many countries [30,31]. As soon as the patient is the condition of stable, clinically and he/she able to swallow, oral treatment should be administered [32]. The intravascular volume should be carefully monitored [33] 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 [34]. Immediate renal replacement therapy should be initiated as soon as possible after appropriate clinical judgement [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. For early diagnosis, it is always cardinal to think malaria in every febrile patient who came to the primary health center (something that will be the next subject of discussion in sharing our experiences regarding cases like this), especially when in anamnesis, there was a history of travel to an endemic area [35] or with history of previous attack of malaria [36].

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 lab.

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 those 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 dept. of Parasitology in late 2002 or early 2003. I just joined the departement for a couple of months soon after finished my MD education in the same institution.

That blood sample was sent along with a laboratory examination request for blood malaria examination with very minimal medical information. It came from a male patient, in his mid 40, with hyperthermia, who have just been admitted to the emergency room unit and were referral from a small hospital outside Jakarta, Indonesia. At that time, as one of the reference labs for Parsitology, we often only received clinical samples without knowing for sure the patient's condition, especially if 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 lab 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 receive 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 start with lower magnification (400× magnification) and when we reach the

suspected object, the magnification is switched to 1000×. The area examined in the thick blood film looks like the image below.

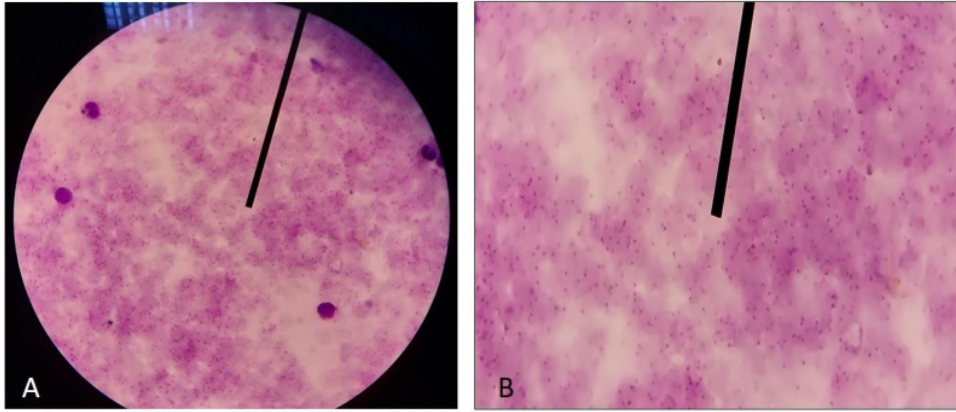


Fig. 1. The starry sky appearance of malignant malaria in thick blood film smeared with Giemsa stain. Blood sample of a patient with suspected of severe malaria and the diagnosis was made by our findings. A. Magnification 400×, B. Magnification 1000× (slides courtesy of Department of Parasitology, Faculty of Medicine, Universitas Kristen Indonesia is located in Jakarta, Indonesia)

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 1000X 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 is no delay and the patient can be treated adequately, immediately. But unfortunately, what we hear is that the patient did not able to survive; he died before antimalarial therapy was started, while he still in the emergency unit.

Then we get a fuller story about this poor 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.

But because when he arrived in Bekasi his condition did not improve at all, his relatives immediately took him to a small private hospital, and was treated for 3 days but there was 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 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 the transfer of the patient to our hospital and what happened was as stated before.

Lesson Learned

Because Severe malaria requires rapid and prompt diagnosis and then followed by adequate anti-malarial treatment to avoid significant morbidity or mortality, we strongly recommend that it is always 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 by mouth and forced doctors to instal parenteral treatment required by the patient. Clearly, the step by step patient management will need to be tailored, *e.g.*, depending 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 accesible [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 (1) the integration of inter and transdisciplinary perspectives and also to (2) 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 safety and outcome [43].

This complexity is transferred to the training of the general practitioner since from their very early medical education, because it requires to appropriate during his/her 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.

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 used 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 brings 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 stakeholders 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.

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