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Original Research Article

The profile of erythrocyte enlargement due to imported cases of *Plasmodium vivax* infection: its impact to the patient and the community

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ABSTRACT

Background: Imported cases of malarial *vivax* also induce erythrocyte enlargement. The size of enlargement depend on the size of the parasite inside the cells. The aim of the study was to examine 20 slides of positive malaria *vivax* and seek for erythrocyte infected malaria and measure the size of enlarged cells and its shape. As a comparison, a number of normal erythrocyte also evaluated for its size and shape.
Methods: This simple cross sectional design of microscope based study was conducted in Parasitology lab, Faculty of Medicine, Universitas Kristen Indonesia, Jakarta-Indonesia, from January to June of 2019. All data collected and further processed using SPSS™.
Results: A total number of 982 erythrocyte infected with *P. vivax* were examined individually. Those number consist of 243 immature trophozoite, 231 mature trophozoite, 251 micro-gametocyte, and 257 macrogametocyte. As a comparison also being examined 70 normal erythrocyte. Each erythrocyte infected with malaria *vivax* parasite enlarge to some extent, had irregular shape and the size varied based on the stage of the parasite inside the cells.
Discussion: This enlarged erythrocyte is prone to cell sequestration and lysis, a condition that leads to anemia. Anemia affect not just the host but also the community. Proper management of malaria will reduce the burden to the community.
Conclusions: Enlarged infected erythrocyte due to malaria *vivax* can cause anemia with effect to the host and also to the community.

Keywords: Anemia, Community, Microscopy, Blood, Parasite, Red blood cells, Size

INTRODUCTION

Malaria is an obligate intracellular parasitic disease. Globally, its morbidity, even mortality, make this disease popular and its persistency remain constant in endemic area.[1] The causative agent is the blood protozoan, *Plasmodium spp*, which can infect both human and animal, depend on the parasite's host preference. Malaria

is a vector borne disease with Anopheles spp as the main agent of transmission. In human, there are 5 species of Plasmodium, named *P. vivax, P. falciparum, P. malariae, P. ovale, P Knowlesi*.[2] Data showed us that among the five species of Plasmodium that have the ability to infect human, *P. vivax* infections alone threatens approximately 2.8 billion people globally. Most of them are living in endemic area with poor hygine and poverty. Its unique biological characteristics/properties make many expert predicted that *P. vivax* will be more complicated to eradicate than *P. falciparum.*[3] Both *P. vivax* and *P. falciparum* are the most common malaria agent in Indonesia.[4]

Malaria diagnosis made correctly by combination of the result of anamnesis (subjective complaint e.g paroxysm fever, symptom of anemia, history of travel to endemic areas and or previous malaria infection), clinical examination and Parasitology laboratory examination (thick and thin blood smear).

Even many areas in Indonesia can be considered as malarial-prone, but Jakarta, the capitol of Indonesia, actually is not an endemic area of malaria.[5] But still, cases of malaria sometimes detected, and this is called imported malaria.[6] Those cases are usually due to military, forestry, mining, and or tourist activities; mostly facilitated by the availability of transportation facilities, e.g airplane. Faculty of Medicine, Universitas Kristen Indonesia Jakarta Indonesia located in Jakarta have a Parasitology lab, which often diagnosed imported malaria. These patients mostly came from faraway places, usually from endemic region in Indonesia. Actually, infection occured in their area of origin, but for some reason when they travel to Jakarta they then became ill with clinical manifestations leads to the diagnosis of malaria.

Erythrocyte infected *vivax* malaria become enlarge, losing their cellular flexibility and deformability causing the red cells to become more rigid and easily ruptured.[7] Its enlargement increases along with the maturation of malarial parasite stage, to some extent, until it exceed the ability of the cells to enlarge and causing lysis of the erythrocyte.[1,3,7] This study aimed to characterize the profile of erythrocyte enlargement due to imported cases of *P. vivax* infection and furthermore is to review its impact to the patient and the community.

METHODS

This simple, descriptive cross sectional study were held in parasitology lab and the Centre of Biomedic Research, Faculty of Medicine, Universitas Kristen Indonesia, Jakarta Indonesia from January to June of 2019. This was a very basic microscopic observational study on malaria *vivax* positive thin blood smear. Measurement of the size of erythrocyte using ocular micrometer inside Olympus CX21 light microscope. All samples used are coming from positive blood smear slides of malaria *vivax*, confirmed previously by Parasitologists. All slides used in this study are collection of the dept. of Parasitology. This study were conducted under closed monitoring of trained and experienced lab tech and MD which specialized on Parasitology (all of them are staff of dept. Of Parasitology).

Visual analysis conducted in thin blood smear under the light microscope Using smaller magnification (400 X) until area suspected were found, then moved to higher magnification (1000 X) to get a better visualization. For each malaria infected erythrocyte, the stage were identified individually, then being re-check by an experienced lab tech and further was confirmed by a Parasitologist. Notes were made on the stage of malaria, diameter size (in µm) and shape (regular/irregular). The size of infected erythrocyte measured using ocular gauge; for each infected cells, measurement conducted several times, with the result recorded was the result of the furthest between 2 opposite point, and then stated as diameter size of the infected erythrocytes. Photographs were also made based on shape considered unusual (pronounced irregularity).

Inclusion criteria

All erythrocyte infected malaria found on the slide.

Exclusion criteria

All erythrocyte that become lysis or broken after infection occur.

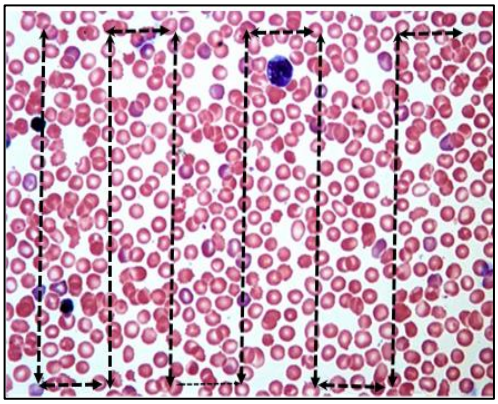

Figure 1: Pattern of examination for each slide, under light microscope using magnification 400 X and 1000 X.

All slides are the collection of department of parasitology, faculty of medicine, Universitas Kristen Indonesia, Jakarta Indonesia.

All data were collected and inputed on Microsoft Excel™, then exported to SPPS™ for further statistical analysis. The data collected analysed using descriptive statistic using SPSS™ ver 21 to characterize erythrocytes enlargement during infected with *P. vivax* at each stage of infection.

RESULTS

The result of observation on 20 positive slides of malaria *vivax* collection of department of parasitology are presented as follow. All the 20 slide had been re-confirmed its positivity in 2 ways: microscopically, and also by re-examined the patient examination book record and matched it with the slide ID.

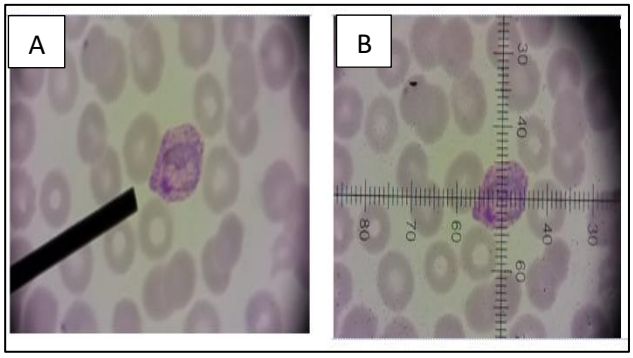

Figure 2: (A) Infected erythrocyte by mature trophozoite of *P. vivax* (ring form) with normal erythrocyte on its surrounding, (B) the size of infected erythrocyte measured using ocular gauge; for each infected cells, measurement conducted several times, with the result being recorded was the result of the furthest between 2 opposite point.

Further analysis of as many as 982 erythrocyte infected with *P. vivax* and those consist of 243 erythrocyte infected with immature trophozoite, 231 erythrocyte infected with mature trophozoite, 251 erythrocyte infected with micro-gametocyte, and 257 erythrocyte infected with macrogametocyte was examined; as a comparison another 70 normal erythrocyte were examined to measure its size and shape.

Table 1 shown the scope of the red blood cells enlargement. In normal erythrocyte, the diameter ranging from 7-9 µm, with its shape uniform and regular/typical. But in contrary, for each infected erythrocyte show atypical appearance. Immature trophozoite infected erythrocyte causing enlargement of the cells, ranging from 9-15 µm with mean 10.80 mm (SD±0.968), mature trophozoite infected erythrocyte causing enlargement of the cells, ranging from 10-15 µm with mean 11.69 mm (SD±0.993), micro-gametocyite infected erythrocyte causing enlargement of the cells, ranging from 10-18 µm with mean 11.73 mm (SD±1.185), and macro-gametocyite infected erythrocyte causing enlargement of the cells, ranging from 9-15 µm with mean 11.80 mm (SD±1.162). In normal erythrocyte, the diameter ranging from 7-9 µm with mean 8.0 µm (SD±0.659).

In all stage of infection, infected erythrocyte also changed their shape. Most of them become irregular in shape while all normal erythrocyte have a nice regular oval-rounded shape. The more mature the stadium that infected the erythrocyte, the more irregular the shape of the erythrocyte.

To seek whether there is a correlation between the enlargement of malaria *vivax* infected erythrocyte and the normal erythrocyte, statistical test was conducted. In order to do that, first of all we test all data of diameter (both normal and infected) for normality distribution, using Kolmogorov-Smirnov test. The result of the first step showed us that all data distributed normally, for both un-infected/normal and infected erythrocyte (immature trophozoite, mature trophozoite, micro-gametosit, and macrogametosit). Statistical test conducted using Pearson's chi-square tests.

Table 1: Distribution of normal erythrocyte and stage-based malaria *vivax* infected erythrocyte.

Erythrocyte	Dia (µm)	N	(%)	Shape
Normal (n=70)	7	15	21.4	Uniform, regular
	8	40	57.1	Uniform, regular
	9	15	21.4	Uniform, regular
Stage-based malaria *vivax* infected eyrthrocyte				
Stage of infection	**Dia (µm)**	**N**	**(%)**	**Shape**
Immature trophozoite (n=243)	9	7	2.9	Mostly irregular
	10	88	36.2	Mostly irregular
	11	103	42.4	Mostly irregular
	12	34	14.0	Mostly irregular
	13	6	2.5	Mostly irregular
	14	3	1.2	Mostly irregular
	15	2	0.8	Mostly irregular
Mature trophozoite (n=251)	10	12	5.2	Mostly irregular
	11	99	42.9	Mostly irregular
	12	87	37.7	Mostly irregular
	13	17	7.4	Mostly irregular
	14	12	5.2	Mostly irregular
	15	4	1.7	Mostly irregular
Micro-gametocyte (n=251)	10	23	8.9	Mostly irregular
	11	102	39.7	Mostly irregular
	12	75	29.2	Mostly irregular
	13	32	12.5	Mostly irregular
	14	11	4.3	Mostly irregular
	15	7	2.7	Mostly irregular
	18	1	0.4	Mostly irregular
Macro-gametocyte (n=257)	10	19	7.4	Mostly irregular
	11	105	40.9	Mostly irregular
	12	71	27.6	Mostly irregular
	13	37	14.4	Mostly irregular
	14	19	7.4	Mostly irregular
	15	5	1.9	Mostly irregular
	16	1	0.4	Mostly irregular

Statistic test conducted to find out whether there was a correlation between enlargement of infected erythrocyte

and normal erythrocyte. After performing the test, all the result showed us that it reject the null hypothesis. In short, the null hypothesis stated that there is no meaningful relationship between two measured phenomena.

The result was that to all variable of infected erythrocyte (immature trophozoite, mature trophozoite, micro-gametosit, and macrogametosit) the diameter of enlargement was correlated statistically with the diameter of normal erythrocyte ($p<0.05$). In more explicitly, it means there is a definite, consequential relationship between the size of infected erythrocyte and the normal ones.

Table 2: Hypothesis test summary.

Null hypothesis	Test	Sig.	Decision
The distribution of im-mature trophozoithe is normal with mean 10.840 and standard deviation 0.97	One-sample Kolmogorov-Smirnov test	0.000	Reject the null hypothesis
The distribution of mature trophozoithe is normal with mean 11.697 and standard deviation 0.99	One-sample Kolmogorov-Smirnov test	0.000	Reject the null hypothesis
The distribution of micro-gametocyte is normal with mean 11.733 and standard deviation 1.19	One-sample Kolmogorov-Smirnov test	0.000	Reject the null hypothesis
The distribution of macro-gametocyte is normal with mean 11.809 and standard deviation 1.16	One-sample Kolmogorov-Smirnov test	0.000	Reject the null hypothesis
The distribution of normal erythrocyteis normal with mean 8.000 and standard deviation 0.66	One-sample Kolmogorov-Smirnov test	0.000	Reject the null hypothesis

DISCUSSION

Enlargement of erythrocyte infected with malaria *vivax* is commonly found, this feature distinguishes it from other type of malaria (e.g. *Malaria falciparum*).[8] To our knowledge, study about measurement of erythrocyte enlargement due to malaria *vivax* infection is rarely reported. The result of this study showed us how erythrocyte enlargement due to *Malaria vivax* infection varied. During infection occured, parasite shaped their host to some extent.[9]

The size of infected erythrocyte depends on the stage of *P. vivax* inside the cells, as this genus known as an obligat intracellular parasite.[1] The young stage caused a slight increased in size and the more mature the parasite inside the cell, the bigger the size of the cell.[8,16]

If the mean size of infected erythrocyte divided with the size of normal erythrocyte, the results are as follows. The immature trophozoite, as the youngest form/stage to infect blood caused only a slight enlargement, about 1,355 times greater than the normal cell. The mature trophozoite, as the more mature form, enlarge about 1,462 times bigger than the normal erythrocyte. The microgametocyte mean size enlarge about 1.466 times bigger than the normal erythrocyte. And the last but not least, for the macrogametocyte mean size enlarge about 1.47 times bigger than the normal erythrocyte.

Previous study conducted by Handayani et al, showed us that the size of *P. vivax*–infected erythrocytes in solution condition was quiet resemble to the size of normal, uninfected erythrocytes (~8 µm) but which contrasts with the feature enlargement of *P. vivax*–infected erythrocytes observed in thin blood smear specimens.[8] In this kind of condition, erythrocytes infected with *P. vivax* tend to be more dispersed, because they are actually being compressed during the process of smeared on the surface of the glass. This resulting in the possible artificially larger surface area observed in *P. vivax* thin films.[8] Even though that to our knowledge, that explanation is quiet confusing because that never happen to other type of malaria infection. All blood samples suspected for malaria will be smeared by the procedure for malaria (Giemsa staining), and to all treated by the same treatment.[1] Further study needed to justify what factor responsible for this enlargement seen in thin blood smear.

Normal erythrocyte shaped appeared as biconcave discs with very shallow centers. Its size is compact with diameter 7-8 µm with a central pallor area (about one third the diameter of erythrocyte).[10] The size of normal erythrocyte is just right fit the diameter of blood capillaries.[11] Even though the shape of blood capillaries is not like a straight pipe, but rather meander and often in some point it become narrower than the size of red blood cells in their normal regular disc shape.[12] In order to manage and maintain constan flow inside capillaries, red blood cells have the ability to change their shape, to fit

through them, pass easily and prevent attachment to the capillaries wall. This feature known as deformability.[10-12] Deformability of erythrocytes is a very important properties that enables individual cells to pass and travel all the way through the host's vessels, especially the smallest one, named capillaries of the human body.[13] This deformability function is a combination of contribution from each structural elements of cytoskeletal proteins, tight restrained controlling for each and every intracellular ion and also water handling, and membrane surface-to-volume ratio.

Normal erythrocyte actually experiencing many external pressure in various forms from different sources but it can stand all of that challenge without become rupture, even be able to return to its original normal shape. The life span of human red blood cells (RBC), if calculated since right after differentiating from erythroblasts in the bone marrow, then released into the blood stream and usually be able to survive in the circulation for approximately 115-120 days.[10,11]

Deformability is a very important feature of the cells, because it determine the life span of the erythrocyte, in vivo.[11,14] Derangement in this feature cause its life span to shorten.[15-17] Enlarge erythrocytes will experience a loss of their self-adjustment ability to their vessel, especially very small vessel like capillaries, which normally has an exact diameter of erythrocyte size.[15] Rigid and enlarge erythrocyte will surely loss their deformability, and this definitely will make them prone and vulnerable.[16] Affected erythrocyte usually break off easily, and the life span will reduce significantly.[15,17]

If the number of infected erythrocyte is limited, the overall performance of the red blood cells in the circulation remain the same and within time, the host's body is able to maintain homeostasis, in order to overcome the problem by producing new erythrocyte, as this might happen when transient or mild infection occurred. But if moderate to even severe infection occurred, and a lot of erythrocyte infected at the same time, this can cause lysis of the erythrocyte and the formation of new cells cannot catch up the destruction. This condition surely will affect the performance and function of the erythrocyte.[17,18]

Intracellular invasion by this blood protozoan brings gradual but prominent changes in the host's erythrocytes. These lists of changes are as follows: diminished of the normal discoid shape due to the movement of the parasite inside the cells, increased rigidity of the cell's surface membrane due to the derangement of the structural protein, increased the erythrocyte cell wall's permeability to a wide variety of soluble ionic and other free species, and last but not least increased their cell wall adhesiveness, most notably to the inner wall of vasculature which consists of endothelial surfaces.[16,18] Infected erythrocytes also suffer from the potency of easily become attach to each other/clumping. And it is not easy for enlarged erythrocyte to enter the capillaries vasculature. Rigidity become a problem for the enlarge erythrocyte in order to maintain its function. Cell lysis also become a huge problem, if it happens to so many cells at the same time.

Loss of the deformability of the erythrocyte intrinsically also affect the blood flow, especially in micro-circulation with the aid of a the host's immune system, a series of sequestration, clotting and or clumping took place inside small vasculature, and this prevent sufficient blood supply to certain areas of the organ.[19,20] Organs which rich in microvasculature, e.g. brain and kidney, are commonly affected.[20] Clotting and clumping in certain areas of this vital organ are always found in severe infection.[20,21] This can lead to the disruption of its function and even ends in a failure of the organ which can make the host's condition getting worse.[20]

It is crystal clear that the majority of malarial infections are always causing certain stage of anemia (mild, moderate to severe) the severity of which depends upon both parasite-related properties (e.g. species, adhesiveness, and drug-resistance phenotype) as well as, host-specific characteristics (e.g. gender, age, innate and acquired resistance, existing comorbid condition).[1,16,20] Malarial anemia is capable of causing severe morbidity and mortality especially in vulnerable group in the population, e.g. children and pregnant women.[7]

Direct effect to the host

Lysis of the infected red blood cells cause anemia. The spectrum of anemia varied from just transient or mild to severe anemia. Lysis of the cells in cases of Malaria actually is not just due to one condition, but instead of the combination of several condition leads to the lysis.[7,22]

Besides due to the enlargement of the cells, sequestration and lysis of the RBCs also happened because of host's inflammatory response against circulating antigen.[20] This factor must also be considered, because without proper immune response, it is impossible for the host to combat the disease; but too active immune armamanterium also potentially may give harm to the host.[23]

Malarial parasite itself have a profound effect on derangement in physiological iron distribution and utilization.[24] Through a series and simultan mechanisms, disturbance first of all started from sequestration of the cells, hemolysis, release of heme, dyserythropoiesis, anemia, deposition of iron in macrophages, and even inhibition of dietary iron absorption.[18] These effects also have prominent impact to the hemodynamic properties of the host. Without early diagnosis and prompt treatment, this could endanger the life of the patient.

Co-infection of malaria with other bacteria or parasite also occurred, especially in endemic areas where economy level is also low. Poor personal hygiene and bad

sanitation, in combination with poverty also worsen the condition, where possible transmission of malaria persist. Soil transmitted helminthes infections are a good example. The haematological effects of persistent chronic blood loss caused by intestinal helminthiasis are exacerbated by nutritional iron deficiency which in turn may interact with the haematological effects of *P. vivax* malaria. This kind of co-infection may worsen the host's clinical condition.

In areas where persistent transmission occurred and possible co-infection took place, it is amenable that the whole community member are also become very vulnerable. Malaria is a vector borne disease, so whenever there is a case of infection in the community and with the availability of the proper vector, then the whole community are at risk of become infected.

Effect to the community

An interesting data of global anemia prevalence estimation by a meta-analysis study conducted in 2010, that the cases of anemia attained 32.9% in prevalence. It is also estimated that as much as 8.8% of total years of life lived with disability worldwide.[25] In malaria-endemic countries, malaria is a major contributor to anemia at the population level, that in sub-Saharan African, it is predicted 24.7% of anemia is attributable or as a consequences to malaria.[1] This data confirmed how Anemia due to malaria also have an indirect effect to the community.[26]

Malaria is a major cause of anaemia in areas where transmission of malaria occur. Malaria infestation causes their host suffer from haemolysis; both can happen on infected and uninfected erythrocytes.[22] The possibility of bone marrow dyserythropoiesis, probably as part of the host's effort to produce more new erythrocytes, but in turns compromises rapid recovery from anaemia.[18]

In regions of high malaria transmission and persistent infection, it is not surprisingly that nearly all infants and young children, and even many older children and adults have a diminished haemoglobin concentration level as a direct consequences of the derangement of the host's blood production effort.[26,27] In these high transmission areas, severe and life-threatening malarial anaemia almost always requiring immediate blood transfusion in young children. And this is a major cause of admitting children as patient to the hospital. Seasonality also might have a role, because particularly during the rainy season semesters when malaria transmission is highest, the number of admission to the hospital due to the urgency of blood transfusion for patients suffer from severe malarial anemia is also increasing.[28]

This showed us the possible direct additional costs of malaria care-seeking, from formal and informal health services, especially when this malaria develop into severe condition. In severe malaria with involvement of vital organ, the cost of care and treatment will be the same as treatment for other serious illnesses. Further study need to be conducted to measure the economic/financial burden for the household and even for the health system (BPJS in Indonesia) in the endemic area. Even in imported cases, malaria still also overburden for the hospital that taking care such patient.[6]

In more detailed, malaria lead to a direct economic impact on the household level.[29] When one member of the family infected with malaria, the illness prevents households member from completing their normal, physically demanding, productive duties and activities. This illness condition make the infected person unable to work, or to be productive.

Malaria and its related illness challenges the productivity of this vulnerable population year by year, with the effect in turn likely to be cumulative (in negative aspect). The level of productivity that was calculated to estimate income loss was the level of normal productivity minus the productivity loss predicted to happen from each episode of malaria illness. This level of normal productivity is likely always to be lower than it would be if malaria were not affecting household members year upon year (chronicity).

Prevention of malaria is not an easy task to do. Combination of vector control, deployment of insecticide-treated bed nets, prompt and accurate, early diagnosis of illness and appropriate use of effective anti-malarial drugs substantially reduces the burden of anaemia in tropical countries and minimize the effects to the potential hosts and even the community.

CONCLUSION

Enlargement of erythrocyte infected with *P. vivax* happen even in imported cases. The size of enlargement varied, based on the stage of parasite inside the cells. Infected cells become more rigid, losing its deformability properties that lead to sequestration of the cells and anemia. This malaria anemia affect not only the host but also the community.

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