

Original Article

Hematological Changes in Malaria: Relation to *Plasmodium* Species

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ABSTRACT

Objective: To evaluate different hematological changes in patients with malaria and to establish a possible role of *Plasmodium* species in the pathogenesis of these changes.

Design: Hematological changes were prospectively studied in randomly selected patients, immediately on admission and on a daily basis after starting anti-malarial treatment.

Setting: Infectious Diseases Hospital, Kuwait, during the year 2004.

Subjects: The study enrolled 103 patients with malaria, (37 infected with *Plasmodium falciparum*, 34 infected with *Plasmodium vivax*, and 32 infected with both species i.e., mixed infections).

Intervention: Antimalarial drugs

Main Outcome Measures: Beside history taking, clinical examination, and routine laboratory work, thick and thin blood films were prepared and examined from all patients for defining the species involved. In addition,

blood picture (red and white blood cells, platelets, and reticulocytes) was studied in all patients.

Results: Anemia and thrombocytopenia were the two most important hematological abnormalities seen in cases of acute malaria infection. The degree of anemia was related more to *P. falciparum* infection, while, thrombocytopenia was associated with *P. vivax* infection and mixed infections. Hematological changes were mild in the first 24 hours, but continued to deteriorate for few days after anti-malarial therapy. One *P. falciparum* infection was associated with severe hematologic abnormalities, disseminated intravascular coagulopathy (DIC), and acute respiratory distress syndrome (ARDS).

Conclusion: We recommend that subsequent checkup of blood cells and platelets are of utmost importance particularly in cases infected with *P. falciparum* or mixed infections.

KEY WORDS: fibrinogen degradation products, hemoglobin, malaria parasite, platelets, red blood cells, white blood cells

INTRODUCTION

Malaria continues to be a great health problem in some of the most populated areas of the world. The infection rate for the world population is 250 million per year and the mortality rate is 1-2 million per year^[1]. Kuwait is considered as a non-endemic area for malaria. Imported malaria in Kuwait originated from several endemic countries, from where large number of workers migrated to Kuwait. These workers came to Kuwait seeking jobs following the great development of the local economy which requires a large number of skilled workers in different fields. However, it was reported by the Ministry of Health in Kuwait that the number of imported malaria cases is decreasing because the immigrant workers are now screened for the disease in their home countries before coming to Kuwait^[2].

Today, the most important problem in the management of malaria is drug resistance of *Plasmodium falciparum* to the various antimalarial

drugs and occurrence of systemic complications^[3]. Most of the systemic complications from malaria results from hyperparasitemia. Mortality is very high (10-30%) in complicated *P. falciparum* infection. Hematologic changes are the most common complications encountered in malaria and play a major role in the fatality^[3]. Prediction of the hematological changes enables the clinician to establish an effective and early therapeutic intervention in order to prevent the occurrence of major complications. The aim of our study was to investigate the different hematological changes in patients with malaria and to define the possible role of *Plasmodium* species in the pathogenesis of these changes.

SUBJECTS AND METHODS

One hundred and three patients infected with malaria and admitted to the Infectious Diseases Hospital (IDH), Kuwait, during the year 2004 were randomly selected and prospectively studied. It

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included 37 patients infected with *P. falciparum*, 34 patients with *P. vivax* and 32 patients infected with both species, i.e., mixed infections. Infection with *Plasmodium* species was diagnosed after repeated examinations of blood films in the parasitology laboratory of IDH. Patients who were not diagnosed in the IDH laboratory, and those who were not followed up according to the study protocol were excluded from the study.

All patients were subjected to:

- Thorough history taking with a special attention to history of previous malaria infection and travel to an endemic area.

- Complete physical examination.

- Examination of blood film for *Plasmodium* species: venous blood, collected in EDTA tube, was sent to the parasitology laboratory of IDH, Kuwait. This laboratory provides 24 hours service for the diagnosis of malaria. The species of *Plasmodium* was diagnosed by microscopy of 10% Giemsa-stained thick and thin blood films⁽⁴⁾. Slides were examined at least twice to record the species of the *plasmodium* parasite.

- Hematologic investigations: complete blood picture (white and red blood cell count, hematocrit, hemoglobin and red blood cell indices) and coagulation profile were done immediately on admission. Blood cells, hematocrit, hemoglobin, platelet count and blood film were checked on a daily basis after anti-malarial therapy until no evidence of active infection was found as indicated by the absence of schizont or ring stages from the blood films. Cases with active infection by fifth day were followed at day seven and 14.

- Complete biochemical check up including renal and hepatic functions tests and serum electrolytes.

Statistical analysis:

Data were collected and coded then entered into an IBM compatible computer using the SPSS version 12 for Windows. Qualitative variables were expressed as number and percentage while quantitative variables were expressed as mean (X)

and standard deviation (S). The arithmetic mean (X) was used as a measure of central tendency, while the standard deviation (S) was used as a measure of dispersion.

The following statistical tests were used:

- Independent samples t-test was used as a parametric test of significance for comparison between two sample means, after performing the Levene's test for equality of variances.

- The Fisher's exact test was used as a non-parametric test of significance for comparison between the distribution of two qualitative variables whenever the 2 -test was not appropriate. This gives a p-value directly.

A 5% level was chosen as the level of significance in all statistical tests.

RESULTS

This study included 103 patients infected with malaria. Seventy-seven were male (74.8%) and 26 were female (25.2%). Their ages ranged from 18 to 55 years with a mean of 33.2 ± 8.3 (Table 1).

Table 1: Some demographic data

	Falciparum malaria n = 37	Vivax malaria n = 34	Mixed malaria n = 32	Total n = 103	p-value
Age (years) Mean \pm SD	30.9 \pm 7.6	33.97 \pm 7.9	34.9 \pm 9.1	33.2 \pm 8.3	0.099
Sex: n (%)					
Male	30 (81)	20 (58.8)	27 (84.4)	77 (74.8)	0.019*
Female	7 (19)	14 (41.2)	5 (15.6)	26 (25.2)	
+ve travel	16 (43.2)	21 (61.8)	14 (43.7)	51 (49.5)	0.169
Previous infection	7 (18.9)	3 (8.8)	4 (12.5)	14 (13.6)	0.413

*: significant at level of $p < 0.05$

Nationality-wise, there were 71 (68.9%) Indians, 20 (19.4%) Pakistanis, six Africans (5.8%), three Kuwaitis (2.9%), two Afghanistan and one patient from Bangladesh (Fig. 1). Past history of travel to endemic areas was encountered in 51 patients (49.5%, Table 1). Fourteen patients (13.6%) had past history of malaria infection (Table 1). Most patients

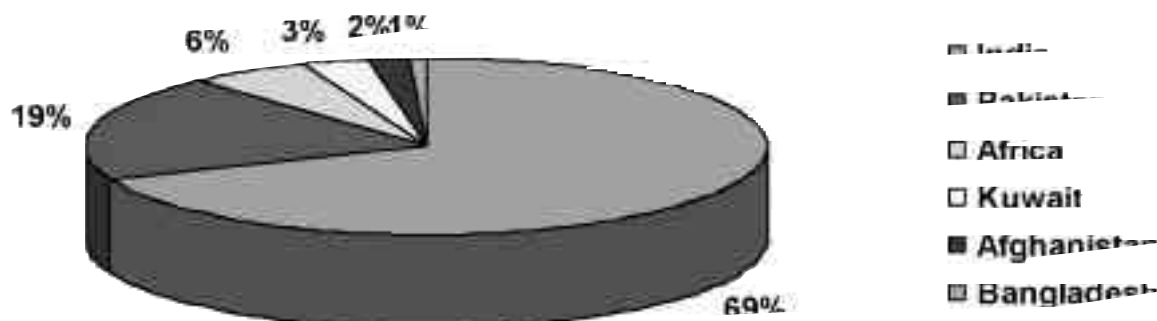


Fig 1: Nationality of patients

Table 2: Some clinical data

	Falciparum malaria n = 37 n (%)	Vivax malaria n = 34 n (%)	Mixed malaria n = 32 n (%)	Total n = 103 n (%)	p-value
Symptoms:					
Classic	27 (73)	33 (97.1)	27 (84.4)	87 (84.5)	0.016*
Other	10 (27)*	1 (2.9)	5 (15.6)*	16 (15.5)	
Splenomegaly	23 (62.2)	22 (64.7)	16 (50)	61 (59.2)	0.313
Hepatomegaly	11 (29.7)	9 (26.5)	11 (34.4)	31 (30.1)	0.806
Complications	1 (2.7)	0.00	0.00	1 (0.97)	—

*: significant at level of $p < 0.05$

presented with classic malarial symptoms in the form of fever, rigors and sweating (84.5%), while 15.5% patients presented with other symptoms such as jaundice, diarrhea, vomiting, and even shock (Table 2).

Statistical analysis showed that the classic malarial symptoms of fever, rigor and sweating were significantly found in all groups of malaria. Meanwhile, the other symptoms were significantly detected in patients with *P. falciparum* and mixed *Plasmodium* infection (Table 2, $p = 0.016^*$). Clinical examination of the study cases showed that splenic enlargement was encountered in 61 (59.2%) patients and hepatomegaly was seen in 31 (30.1%) patients. There was no significant difference in the occurrence of hepatomegaly or splenomegaly between patients with different malaria species (Table 2). Moreover, one patient infected with *P. falciparum* had developed acute respiratory distress syndrome (ARDS) and shock and was immediately transferred to the Intensive Care Unit (ICU) (Table 2).

Results of blood film examination for malaria species are shown in Table 1. Thirty seven patients (36%) had *P. falciparum*, 34 (33%) had *P. vivax* and 32 (31%) had mixed infection with *P. vivax* and *P. falciparum*. No cases with *P. ovale* or *P. malariae* were detected. All patients had active malaria as evidenced by presence of schizont and ring stages. Cases started to be inactive by the third day and most of them (96 patients, 93%) were rendered inactive by the fifth day after starting anti-malarial therapy. Other patients became inactive by day seven after treatment.

Changes in the red blood cells (RBCs):

On admission, the total RBC count ranged between $1.9 - 5.6 \times 10^{12}/l$ (normal = 4 - 5.4) with a mean of $4.22 \pm 0.84 \times 10^{12}/l$. Hemoglobin level had a mean value of 120.57 ± 22.09 g/l (normal = 120 - 160) with no significant difference between the groups of different malarial parasites. Packed cell volume (hematocrit value) was within normal range with a mean of 0.36 ± 0.07 and there was no

Table 3: Blood cells on admission and after 3-5 days treatment

	On admission Mean \pm SD	After treatment Mean \pm SD	p-value
RBCs $\times 10^{12}/l$	4.22 ± 0.84	3.98 ± 1.02	0.316
Hb (g/l)	120.57 ± 22.09	112.04 ± 20.17	0.425
Hematocrit	0.36 ± 0.07	0.31 ± 0.05	0.05*
TWBC $\times 10^9/l$	6.41 ± 2.67	7.21 ± 2.14	0.816
Platelet $\times 10^9/l$	123.23 ± 91.29	129.54 ± 82.41	0.523

*: significant at level of $p < 0.05$

significant difference between the studied groups of plasmodia. Blood indices including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), showed normocytic normochromic RBCs. Reticulocyte percentage was within normal range with a mean of $1.94 \pm 1.01\%$ (normal = 0.2 - 2.02%), and there was no significant difference between the groups.

However, on repeating the blood picture 3-5 days after starting the anti-malarial treatment, mild drop in the mean hematocrit values, RBC counts and hemoglobin levels was detected. Yet, these changes were not statistically significant except for the hematocrit value which showed a significant difference ($p = 0.05^*$, Table 3).

Changes in the white blood cells (WBCs):

At the time of diagnosis, total WBCs had a mean count of $6.41 \pm 2.67 \times 10^9/l$ with no significant difference between the different malaria species (Table 4). The neutrophil percentage was significantly higher in patients infected with *P. falciparum* and mixed *Plasmodium* species ($p = 0.01^*$). The mean lymphocyte percentage was within normal ($25.6\% \pm 13.33$) with a significant lower value in mixed infection. However, a significant relative monocytosis was detected in patients infected with *P. vivax* as compared to the other groups ($p = 0.001^*$). Similarly, the mean eosinophil percentage was normal in all groups. However, statistical comparison between the groups demonstrated significantly low eosinophil percentages in patients infected with *falciparum* and mixed malaria ($p = 0.037^*$, Table 4).

On repeating the blood picture 3-5 days after starting the anti-malarial treatment, there was a non-significant rise of the mean total WBC count, ($p = 0.816$, Table 3).

Changes in the blood platelets:

The mean platelet count in patients with *falciparum* malaria was normal ($168.8 \pm 100.4 \times 10^9/l$), while the mean count in patients with malaria *vivax* showed mild thrombocytopenia ($107.06 \pm 92.12 \times 10^9/l$), and it was lowest in cases

Table 4: Changes in the white blood cells

	Falciparum malaria n = 37 Mean ± SD	Vivax malaria n = 34 Mean ± SD	Mixed malaria n = 32 Mean ± SD	Total n = 103 Mean ± SD	p-value
TWBCs x 10 ⁹ /l	6.51 ± 3.26	6.08 ± 2.26	6.64 ± 2.32	6.41 ± 2.67	0.664
Neutrophil %	60.00 ± 15.4	56.1 ± 14.8	67.61 ± 15.4	61.07 ± 15.8	0.010*
Lymphocyte %	28.2 ± 12.5	26.4 ± 13.8	21.6 ± 13.2	25.6 ± 13.3	0.001*
Monocyte%	8.3 ± 4.84	13.9 ± 5.39	9.75 ± 4.4	10.6 ± 5.41	0.001*
Eosinophil %	0.65 ± 0.62	3.24 ± 7.8	0.75 ± 1.12	1.615 ± 4.85	0.037*
Basophil %	0.28 ± 0.27	0.39 ± 0.23	0.23 ± 0.25	0.30 ± 0.26	0.023*

*:significant at level of p < 0.05
TWBCs: total white blood cells

Table 5: Changes in blood platelets

	Falciparum malaria n = 37 Mean ± SD	Vivax malaria n = 34 Mean ± SD	Mixed malaria n = 32 Mean ± SD	Total n = 103 Mean ± SD	p-value
Platelet x 10 ⁹ /l	168.8 ± 100.4	107.1 ± 92.1	87.7 ± 51.1	123.2 ± 91.3	0.001*
Platelet volume	8.04 ± 1.23	8.2 ± 1.04	8.81 ± 1.12	8.33 ± 1.17	0.016*

*: significant at level of p < 0.05

with mixed infections (87.72 ± 51.14 x 10⁹/l) (Table 5). Statistical analysis demonstrated a significant lower mean platelet count in cases infected with malaria *vivax* and mixed infections (p = 0.001*).

The mean platelet volume was normal in all groups. However, patients with mixed infections showed a significantly bigger platelet volume (p = 0.016*, Table 5).

Despite the presence of mild to moderate degrees of thrombocytopenia, no cases had hemorrhagic manifestations. On repeating platelet examination 3-5 days after anti-malarial treatment, the mean platelet count started to rise and continued to increase slowly thereafter (Table 3).

Patients showed continuous improvement in all blood elements with no evidence of active infection in their blood films when investigated on day 7 and 14 post-treatment.

Changes in blood coagulation:

The mean prothrombin time of all the studied groups was within normal range but it was significantly less in patients with *P. falciparum* infection when compared to the other groups (p = 0.005*) (Table 6). Similarly, international normalized ratio (INR) ranged between 1.07 - 1.65 with a total mean of 1.31 ± 0.11. Statistical analysis revealed a significant reduction of INR in patients with *falciparum* malaria than those with mixed malaria (p = 0.007*). The activated partial thromboplastin time

Table 6: Changes in blood coagulation

	Falciparum malaria n = 37 Mean ± SD	Vivax malaria n = 34 Mean ± SD	Mixed malaria n = 32 Mean ± SD	Total n = 103 Mean ± SD	p-value
PT (Sec)	12.83 ± 1.03	13.19 ± 0.87	13.65 ± 1.12	13.2 ± 1.06	0.005*
INR	1.27 ± 0.10	1.31 ± 0.09	1.35 ± 0.13	1.31 ± 0.11	0.007*
APTT (Sec)	35.44 ± 1.41	35.53 ± 1.44	36.47 ± 2.29	35.79 ± 1.78	0.032*
FDPs : n (%)					
<500 (IU/L)	21 (58.3)	19 (55.9)	13 (39.4)	53 (51.5)	NS
500-1000 (IU/L)	11 (30.6)	10 (29.4)	13 (39.4)	34 (33.0)	NS
>1000 (IU/L)	4 (11.1)	5 (14.7)	7 (21.2)	16 (15.5)	NS

* : significant at level of p < 0.05
NS : not significant.

(APTT) was significantly prolonged in patients with mixed malaria infections than those with single species infection (p = 0.032*).

Moreover, fibrinogen degradation products (FDPs) were estimated to predict the development of disseminated intravascular coagulopathy (DIC, Table 6). Fifty three patients out of 103 had normal FDPs levels (less than 500 IU/l), 34 patients had FDPs between 500 - 1000 and 16 patients exceeded FDPs level of 1000 IU/l. There was no significant difference between the three groups of patients.

DISCUSSION

The development of Kuwait economy, due to oil revenues, has attracted a large labor force from many malaria endemic countries such as India, Pakistan, Srilanka, Bangladesh, Afghanistan, Philippines, and some African countries like Sudan, Nigeria, and Borkina Faso^[2].

Malaria continues to be a great health problem in some of the most populated areas of the world. The global resurgence of malaria has also impacted on Kuwait, a non-endemic country. Imported malaria continues to be a problem since most of the 60% of the resident population come from endemic areas of Asia and Africa^[5]. In contrast to previous reports from Kuwait^[6,7], mixed malaria was relatively high among the studied malaria patients admitted to IDH. Such finding might be explained by the fact that not all malaria cases in Kuwait are referred to the IDH. Asymptomatic cases are usually treated as outpatients and many single-species malaria cases are treated in their local area hospitals. Moreover, many asymptomatic cases of malaria were referred from ports and borders health section and were treated as outpatients without hospital admission.

Red blood cells, hemoglobin, and packed cell volume:

On admission, our patients had mild reduction

in the red blood cells (RBCs), hemoglobin (Hb) level and packed cell volume (PCV) with normochromic normocytic features of the RBCs. The reduction was more evident in *falciparum* infection. Moreover, these parameters fell after start of anti-malarial treatment and continued to fall slowly for some days. This drop was statistically significant for PCV (Table 3). Our results coincides with the previous report which stated that in uncomplicated acute malaria the hemoglobin and hematocrit (PCV) are usually normal during the first 24 hours after the onset of fever. The PCV continues to falls for some days after antimalarial therapy^[8]. A community-based study of malaria prevention in Tanzania^[9] has confirmed that *falciparum* malaria was an important cause of childhood anemia with PCV falls comparable to our results.

White blood cells:

During the first day of admission, the mean WBC and neutrophil counts were within normal range. However, neutrophil percentage was significantly higher in mixed malaria infection while *falciparum* malaria showed a significantly higher lymphocyte percentage. There was no significant difference in WBC and neutrophil counts before and after anti-malarial treatment. Previous studies demonstrated an increase of neutrophil count during the first two days of fever due to *falciparum* malaria and subsequent decrease^[10]. Similarly, mean lymphocyte percentage was normal in our cases. However, other reports showed lymphopenia in some cases of acute malaria^[11] which is probably caused by a redistribution of lymphocytes with sequestration in the spleen^[12]. There was significantly lower eosinophil percentage in our patients with *falciparum* and mixed malaria infections and this is in agreement with previous studies which reported eosinopenia in patients with acute *P. falciparum* infection^[10,13].

During malaria infection, leukocyte activation is associated with release of cytokines like TNF, IL-1, IL-2, IL-6 and IFN which are involved in the pathogenesis of hematological abnormalities such as cyto-adherence, thrombocytopenia, DIC, hypoglycemia and lactic acidosis^[14,15].

Platelet changes:

A mild to moderate thrombocytopenia was demonstrated in our patients who had *P. vivax* and mixed malaria infection. This is in agreement with previous studies which reported frequent incidence of thrombocytopenia in acute malaria and usually unassociated with DIC^[12,16]. This thrombocytopenia

seems to be due mainly to a reduced platelet life span and splenic pooling. The reduced platelet life span may be caused by binding of malaria antigen onto platelets followed by antibody mediated phagocytosis^[17] or to platelet activation in vivo^[18]. Macrophage activation and hyperplasia especially in the spleen may also play a role^[18]. The release of platelet contents can activate the coagulation cascade and contributes to DIC and consequently further thrombocytopenia^[19].

The incidence of DIC is reported to be 4 - 13% and usually occurs in patients with *P. falciparum* infection and hyperparasitemia^[1,3]. DIC was found in one of our patients with *falciparum* malaria which was complicated by ARDS, thrombocytopenia, increased FDPs and prolonged prothrombin time. It was reported that *P. falciparum* infection is associated with increased levels of plasminogen activator inhibitor, factor VIII, reduced levels of protein C, protein S and anti-thrombin III. Moreover, in severe complicated malaria there is activation of coagulation cascade by release of various procoagulants due to lysis of platelets and RBCs, release of tissue factor from monocytes and damaged endothelial cells, cytokines and microcirculatory stasis^[19].

In conclusion, the pathophysiological processes causing the hematological changes in malaria are complex, multiple and incompletely understood. Anemia and thrombocytopenia were the two most important hematological abnormalities seen in our cases of acute malaria infection. The degree of anemia was related more to *P. falciparum* infection, while, thrombocytopenia was associated with *P. vivax* infection and mixed infection due to *vivax* and *falciparum* species. Some *P. falciparum* infection may be associated with severe hematologic abnormalities, DIC, and even ARDS.

As the hematological changes in our patients were usually mild during the first 24 hours and continued to deteriorate for a few days after anti-malarial therapy, we recommend that subsequent blood count check should be performed especially in cases infected with *P. falciparum* or mixed infections. We also recommend that these hematological changes should be further studied in relation to the level of parasitemia. Moreover, similar multi-center studies should be carried out all over Kuwait to define the prevalence pattern of all types of malaria infections.

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