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ORIGINAL ARTICLE

The Incredible Presentation of Malaria: A Case Series

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ABSTRACT

Background & Objective: Man and malaria seem to have evolved together. Malaria has always been the subject of research for medical practitioners from time immemorial. Malaria is known for its fever paroxysm, starting with chills, rigors, high grade fever, followed by sweating as the fever declines. However, this classical pattern may not be seen in many patients and frequently manifest as a non-specific illness. Quite often patients do not experience the classic intermittent fever with chills and rigors, while some may do not experience fever at all. Rather they may have a wide spectrum of non-specific symptoms that may mimic other systemic illnesses. So, the consulting physicians must judiciously consider malaria as a diagnostic possibility in an array of probable diagnoses. As the morbidity and mortality of severe malaria are very high, one must not wait for the characteristic paroxysmal fever to ask for a malaria test, with a potential risk of developing fatal malaria. The present study describes a case series of malaria with a myriad of atypical presentations which may sensitize the physicians about abnormal presentations of malaria in our population and aid in early diagnosis and management of the potentially fatal cases of malaria.

Key words: Malaria, atypical presentation, paroxysmal fever, intermittent or on-and-of fever etc.

INTRODUCTION:

Malaria is a disease as old as humanity itself. It is caused by infection with protozoan parasites belonging to the genus Plasmodium transmitted by female Anopheles mosquitoes. It is often called the 'King of Diseases', for it continues to haunt and taunt mankind since the time immemorial. Malaria is the fifth cause of death from infectious diseases worldwide (after respiratory infections, HIV/AIDS, diarrhoeal diseases, and tuberculosis) and the second in Africa, after HIV/AIDS. More than a century after identification of the causative parasites, and more than half a century after finding effective drugs and insecticides, it continues to wreak havoc on millions, particularly in the poorest parts of the our world. An estimated 300–500 million people contract malaria each year, resulting in 1.5–2.7 million deaths annually.[1,2] The intraerythrocytic protozoa of the genus Plasmodium, is responsible for malaria with humans being infected by one or more of the following species: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi*.[2]

The classic presentation of malaria consists of paroxysms of fever alternating with periods of fatigue but otherwise relative wellness. Symptoms associated with febrile paroxysms include high fever, rigors, sweats, and headache, as well as myalgia, back pain, abdominal pain, nausea, vomiting, diarrhea, pallor, and jaundice.[3,4] However, the classic presentation of malaria with paroxysms of fever is seen only in 50–70% of patients with rest having atypical presentation. In endemic regions, malaria can present with unusual features due to development of immunity, increasing resistance to antimalarial drugs and the indiscriminate use of antimalarial drugs.[5] Nystagmus is observed following

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involvement of the cerebellum especially during the postrecovery phase of malaria. While psychotic features such as severe agitation, hallucination, paranoia may be the early symptoms of falciparum malaria among pediatric patients. Urticaria with or without fever can also be the initial manifestation of the disease.[6] Some patients with malaria present with diarrhea and other gastrointestinal (GI) symptoms. Immune individuals may be completely asymptomatic or may present with mild anemia.[6] The predominant atypical manifestations include absence of malarial paroxysm, followed by myalgia, migrainous headache, episodic urticarial rash, relative bradycardia and postural hypotension. Besides this, severe forms like jaundice, cerebral involvement, severe anaemia, thrombocytopenia and pancytopenia had been detected.[7]

As the morbidity and mortality of severe malaria are very high, these atypical presentations of malaria should be considered while diagnosing a disease. As majority of physicians is unaware of atypical manifestations, it is not uncommon for malaria to get diagnosed late or even remain unrecognized, resulting in severe illness or death. The present study describes a case series of malaria with incredibly atypical presentation in the context of Bangladesh.

CASE REPORT:

Case-1:

Iliasur Rahman, aged 55 years, was referred from Prof. B. Chowdhury's clinic to Zainul Haque Sikder Medical College (ZHSMC), Gulshan Branch for admission in ICU. Previously he was treated for the complaints of pain in the extremities & intermittent fever for 6 months (including 3 months stay in the clinic). When his condition deteriorated, he was referred to ZHSMC Various laboratory investigations were done-CBC, ESR, X-ray, bone marrow study, biochemical analysis, CT scan of the brain, etc. ESR was raised but no diagnosis could be made. While in ZHSMC he was running high fever with convulsion and was unconscious. Several broad-spectrum antibiotics were prescribed but without any effect. On the 8th day of unconsciousness, a repeat CBC was done which showed high total count of WBC (50,000/ cu-ml of blood) with polymorphonuclear leukocytosis (95%), platelet count 1,30000/cu-ml of blood. Malarial parasite (MP) test revealed plenty of ring stages of *Plasmodium falciparum* in peripheral blood. Paluther inj. 10 ampoules (1 ampoule twice daily for 5 days) did the miracle. The patient came round, but by this time total cost of treatment incurred more than Tk. 3 Lacs.

Case-2

A 5-year-old child with fever and arthritis involving both ankles and knee joints (patient hailing from Vulta, Gausia, Narayanganj) was brought to us. He was seen by a registered physician of the locality and was advised to have CBC and ASO tests. ASO was within normal range. CBC was also normal but plenty of ring-stages of *Plasmodium falciparum* appeared in peripheral blood. He was going to be referred to Dhaka Shishu Hospital but the concerned laboratory consultant preferred to treat the child by himself. He prescribed Malacide 1½ tablet (Single dose of Sulfadoxine & Pyrimethamin). And the response was dramatic.

Case-3

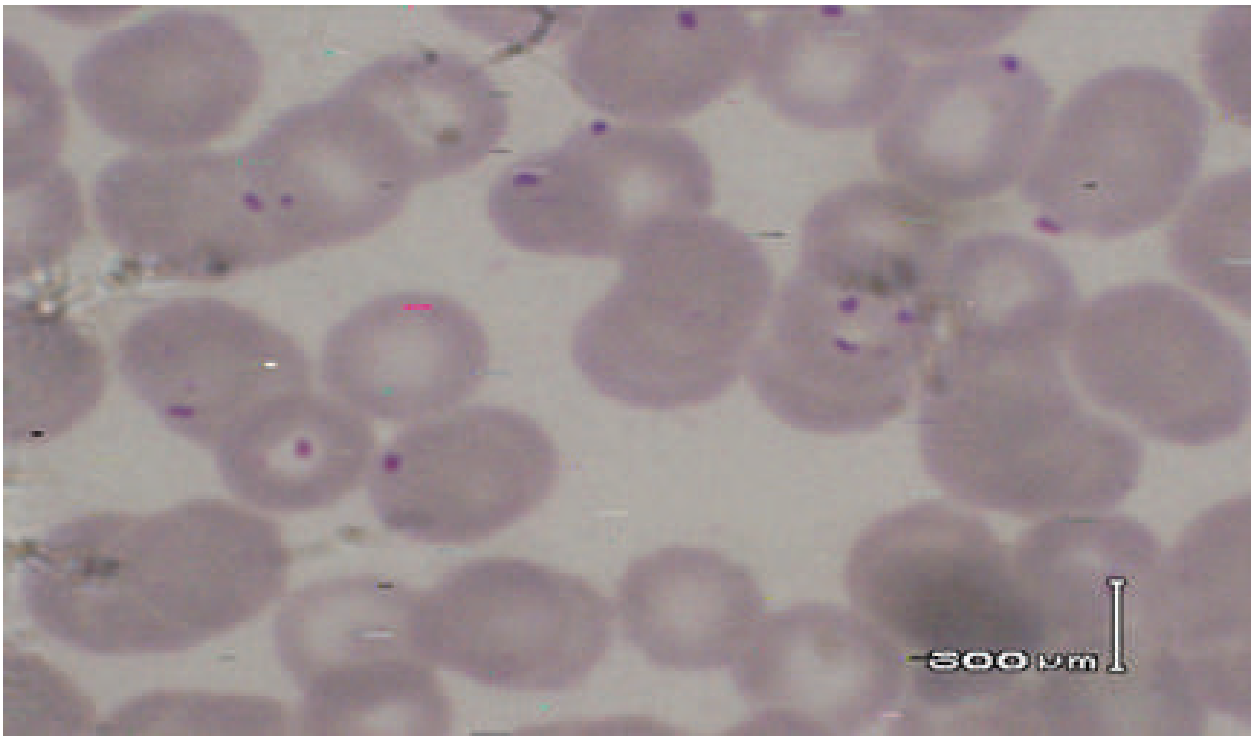
Murad, aged 30 years, working at Ananda Transport, Jashore complained of extreme weakness and fatigue for 1½ years. He was consulted by a number of physicians and lot of medications were prescribed, but of no benefit. He came to Dhaka for treatment. Casually the WBC DC (differential count) slide was examined by us. Numerous pinkish red cells were seen (like blooming rose). Three tablets of Malacide in a single dose followed by 100 mg of Doxycycline capsule twice daily were prescribed for seven days. The patient was miraculously cured.

Case-4

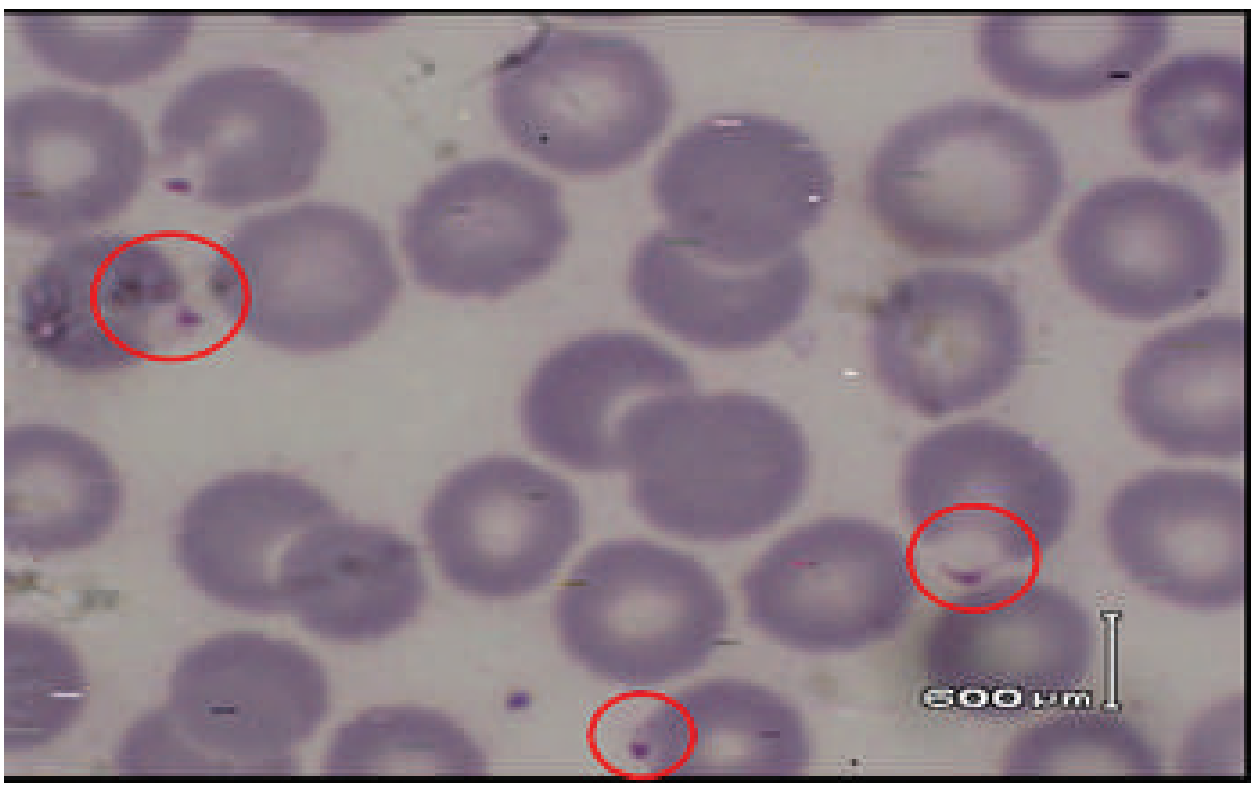
Ratna, a 35-year-old female, was having an intense pain in the back (dorsolumbar region) for 5 days. She consulted an orthopaedic surgeon who prescribed analgesics. Since there was no improvement, she consulted nephrologists and medicine specialists who advised a lot of investigations relating to the kidney ailment. The results of the investigations were normal. A peripheral blood film was examined. Ring stages of

Slide 1 showing schizont and ring forms P. falciparum (International Medical College)

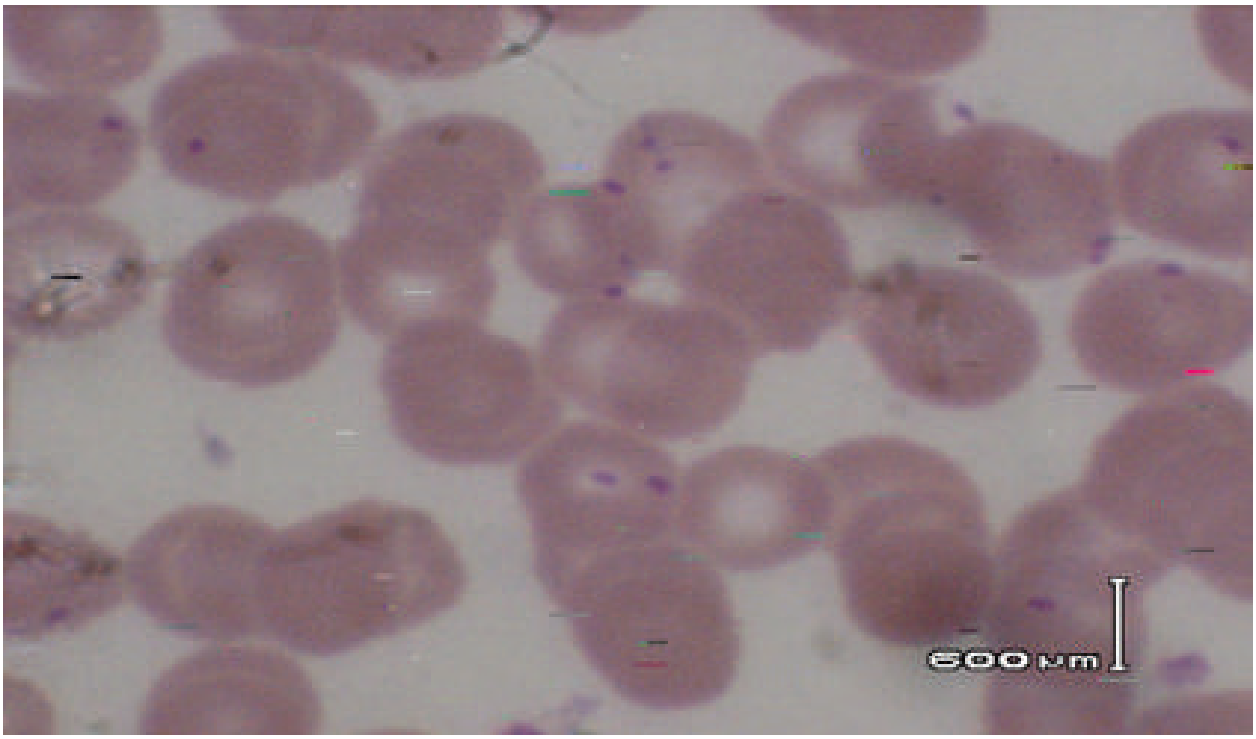
Slide 2 showing schizont forms P. falciparum (International Medical College)



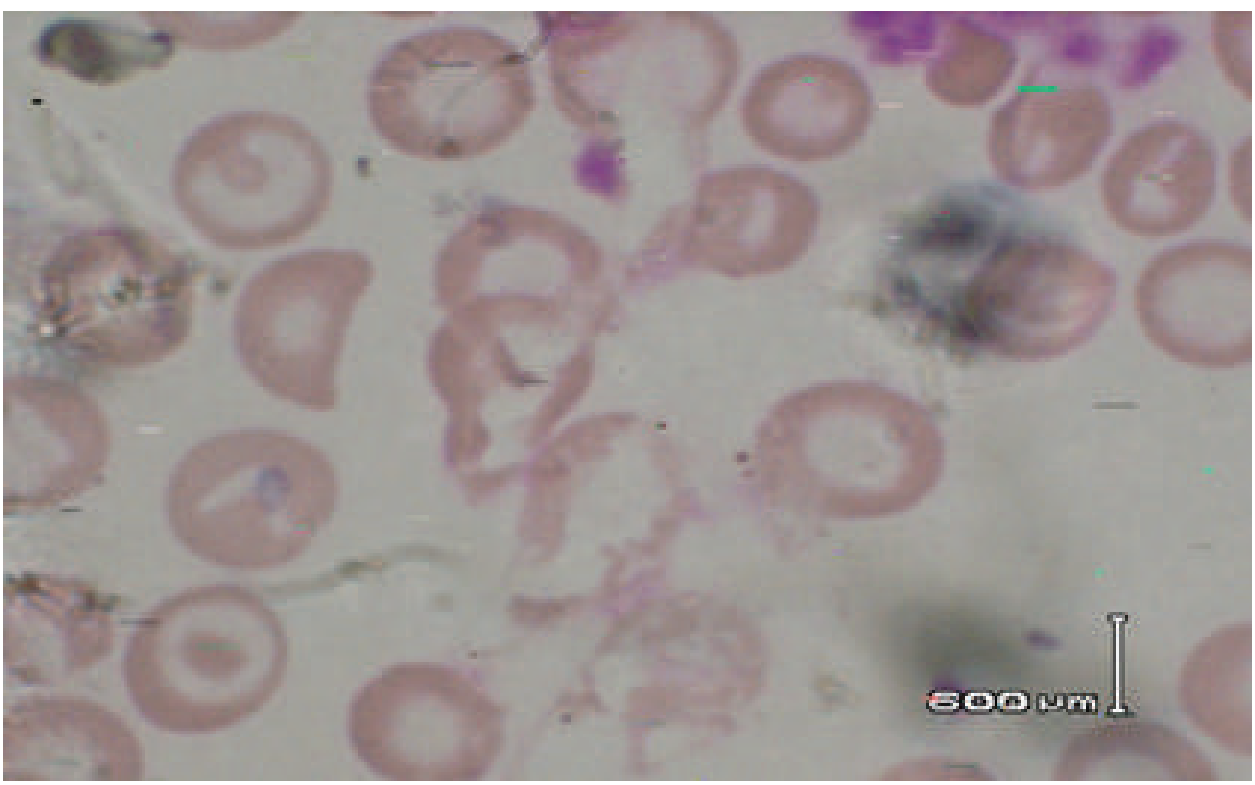
Slide 3 showing ring stages P. falciparum



Slide 4 showing schizont and ring forms P. falciparum (International Medical College)

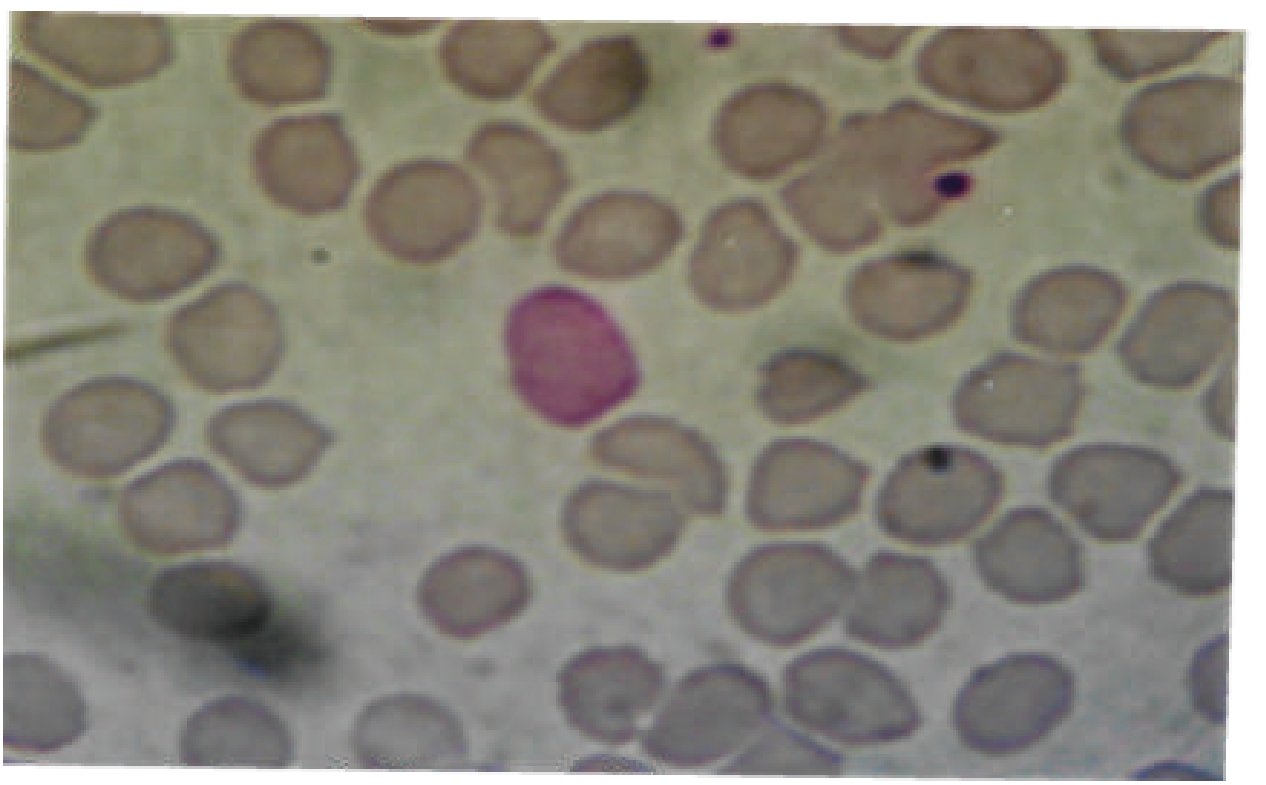


Slide 5 showing ring forms P. falciparum



Slide 6 showing ring forms P. falciparum

Slide 7 showing schizonts of P. falciparum (International Medical College)



Slide 8: Schizont stage of the parasite transforming the red cell into a blooming rose

Plasmodium falciparum were detected. Three (3) tablets of Malacide (single dose) dramatically cured the lady. She was highly satisfied.

Case-5

Alamgir Noori, a 40-year-old gentleman, had been suffering from multiple joint pain and occasional swelling for 5 years. Leading medicine specialists were consulted, and a lot of investigations were done. ESR was raised (80 mm in 1st hour). Since there was no improvement, he went to Calcutta to consult renowned physicians there. A diagnosis of RA (rheumatoid arthritis) was made. Methotrexate was prescribed. He was asked to visit for follow-up every 3 months. Casually a DLC (differential leukocytes count) slide was examined by us. There were numerous pinkish red cells (Schizont stage of *Plasmodium falciparum*). Three tablets of Malacide in a single dose followed by 100 mg of Doxycycline capsule twice daily were prescribed for seven days. He improved but was not completely cured. Later on Jasoquine (Quinine sulphate) 42 tablets (2 tablets three times daily for 7 days) were prescribed. He responded very well and there was an end of his Calcutta visits.

Case-6

Nahin Ferdous, a 22-year-old 4th year MBBS student had acute pain in the right loin. The intensity was so much that she could not even sit down. Gynecologist advised her X-ray KUB, USG of the whole abdomen, and urine for R/M/E. No clues were found. She came to the present investegator. CBC was done; ring stages of *Plasmodium falciparum* were found. Coartem (Artemether and Lumefantrine) 24 tablets (4 tablets twice daily) miraculously cured her ailments.

Case-7

Mr. Mohiuddin (age 40 years), working as a security guard, complained of intense pain in both thighs for few days. Local pharmacist prescribed calcium tablets and analgesics. But there was no improvement. Because of the severity of pain, he asked his children to stand up on his thighs. His serum calcium and uric acid levels were normal. DLC slide showed ring stages of *Plasmodium falciparum*. Three tablets of Malacide in a single dose followed by 100 mg of Doxycycline capsule twice daily were prescribed for seven days which cured his ailment.

Case-8

Dr. Mamun, Lecturer of Pharmacology, came to my office with the complaints of severe pain in the throat and facial flushing. He reported that he had been suffering from the disease for more than a week and consulted several medicine and ENT consultants. Oral Ciprofloxacin, Injection Ceftriaxone & Dexamethasone were given but without any effects. A peripheral blood film showed presence of few ring stages of *Plasmodium falciparum*. 3 tablets of Malacide in a single dose followed by 100 mg of Doxycycline capsule twice daily for seven days were sufficient for his recovery.

Case-9

Mohna's mother had intense pain in the left ankle. She was seen by several physicians in Bogra and orthopedics consultant in BSMMU, Dhaka. As per request of the consulting physicians CBC, ESR, X-ray chest (P/A view) were done. By chance, the DC slide was examined by me wherein TC, DC, ESR were normal. Many pinkish red cells were seen in the slide but not reported. The receptionist of Al Manar Hospital asked me to explain the findings to the patient. The patient was examined and 3 tablets of Malacide in a single dose followed by 100 mg of Doxycycline capsule twice daily were prescribed. The patient recovered completely and was highly pleased.

DISCUSSION:

The malaria parasite has a complex, multistage life cycle taking place in two living beings: mosquito vectors and vertebrate hosts. The survival and development of the parasite within the invertebrate and vertebrate hosts, in intracellular and extracellular environments, is made possible by a toolkit of more than 5,000 genes and their specialized proteins that help the parasite to invade and grow within multiple cell types and to evade host immune responses.[8,9]

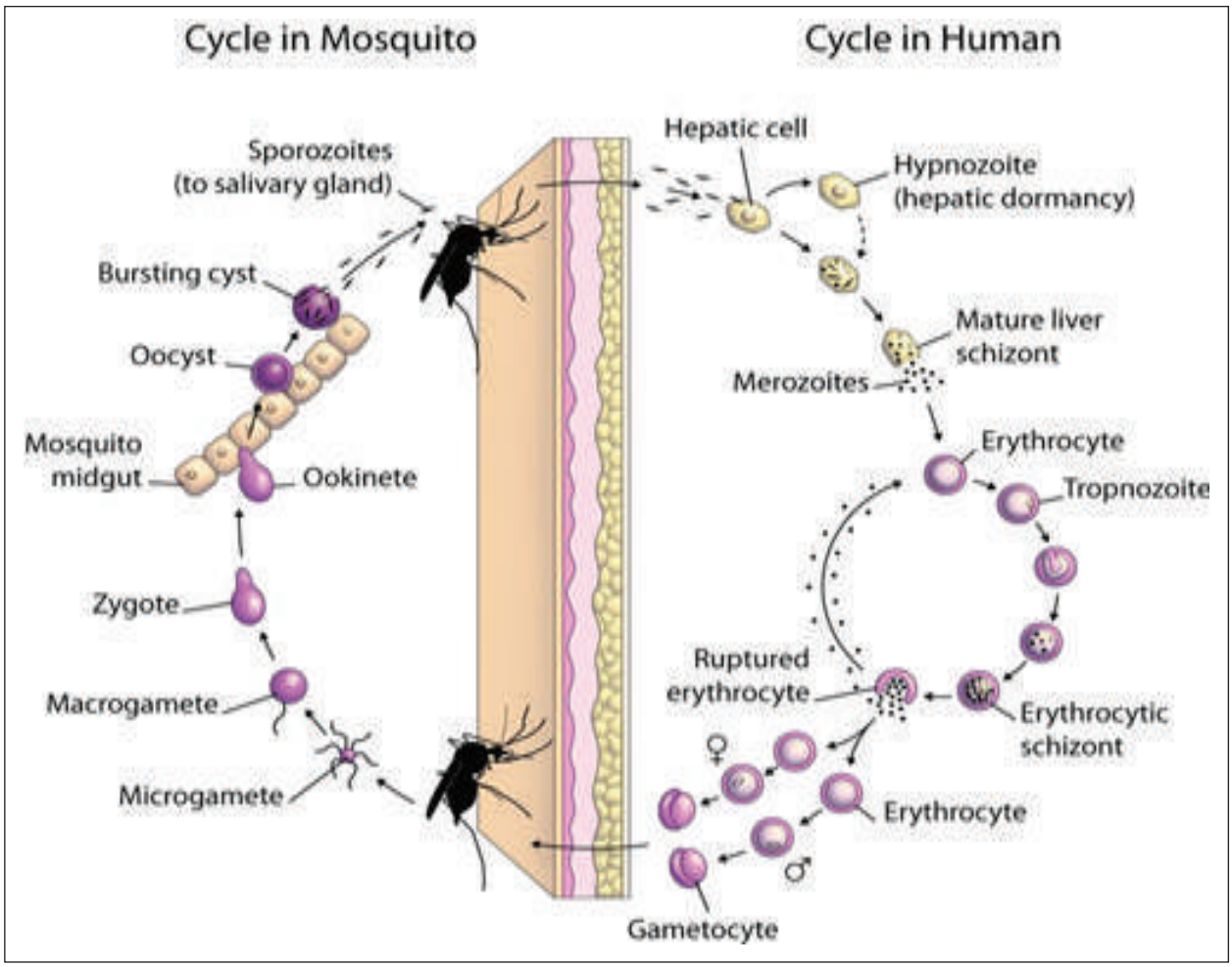


Fig. 1: Life cycle of P. falciparum: Infection of the human host occurs when a female Anopheles mosquito bites and injects P. falciparum sporozoites from their salivary glands into a host capillary during a blood meal. Sporozoites that enter the bloodstream travel to the liver and invade hepatocytes. Over the course of 7 days, a single sporozoite undergoes asexual reproduction within a hepatocyte to produce ~40,000 merozoites that are released into the bloodstream when the hepatocyte ruptures. The released merozoites invade erythrocytes, beginning the 48 hr erythrocytic life cycle as ring stage parasites. During maturation to a trophozoite, the parasites modify the erythrocyte surface by forming knobs containing PfEMP1 proteins that adhere to the microvasculature and prevent parasite clearance by the spleen. The parasite remains sequestered as it undergoes 4–5 rounds of asexual reproduction, producing a schizont containing 16–32 merozoites that are released during schizont rupture along with hemozoin, membranes, and antigenic debris that can stimulate early innate immunity. A subset of intraerythrocytic parasites undergo sexual differentiation and develop for 10–12 days within the bone marrow into either a male or a female gametocyte. Mature stage V gametocytes re-enter the circulation and can be taken up by a female mosquito to continue the infection cycle. Within the mosquito midgut, these male and female gametocytes are stimulated immediately to form microgametes and macrogametes, respectively, which fertilize. Over the next 24 hr, the zygote develops into an ookinete, migrates across the midgut epithelium and becomes an oocyst that in 2–3 weeks can produce thousands of sporozoites. The sporozoites are released upon oocyst rupture and migrate to the mosquito salivary glands, ready to begin the cycle in a new human host.[10]

The parasite goes through several phases of development, including trophozoites, schizont, merozoites, sporozoites and gametocytes (sexual stages), each with its own distinct shape and structure, as well as protein complements. The surface proteins and metabolic pathways keep changing during these distinct stages that help the parasite to avoid immune clearance while also complicating treatment and vaccine development.[9]

In the present study we have presented 9 patients with atypical manifestations of malaria. All of them responded well with antimalarial drugs or a combination of antimalarial and Doxicycline. Summarizing the findings of the cases as described in the case-report we find that there were variable atypical manifestations:

The cases were 5-55 years old. Of the 9 cases only 2(22.2%) presented with fever with one having typical malarial fever. The rest 7(77.8%) did not have fever but their main complaints were arthritis with involvement of multiple joints (knees, ankles and lumber joints) with occasional swelling and pain in the extremities and back. Considering the symptoms, the index physicians (first consulting physicians) suspected arthritis, rheumatic fever, tuberculosis, kidney ailment and so on. Accordingly, they did a lot investigations (CBC, ESR, X-ray chest and KUB region, bone marrow study, biochemical analysis, USG of abdomen, CT scan of the brain, urine for R/M/E etc.) and treated the patients for variable durations with lot of medications including immunosuppressant, toxic drugs like methotrexate without reaching a definitive diagnosis. When condition of the patients deteriorated, they referred the patients to a higher tertiary care center or patients themselves sought advice from other leading physicians of the country. One patient having multiple joint pain even went abroad (Calcutta) and returned with a diagnosis of RA and treatment with methotrexate. But the treatment did not make the patient cure. When these patients consulted with the present investigator, he took peripheral blood from them and made an MP test or examined their DLC slide which in each case revealed numerous pinkish red-cells, the schizont stages of *Plasmodium falciparum*. Usually the ring-stages of *Plasmodium falciparum* are found inside the red-cells surrounded by a vacuole. But in the present study, some cases were found attached to the red-cell membrane which were really difficult to diagnose (see slides of the cases). Besides, schizont stage of parasites transforming red cell into pinkish blooming rose is also not know to physicians.

Malaria nowadays most often presents as a non-specific illness, and many patients do not experience the classic paroxysmal fever. Many patients present with a not-so-typical fever, while some may have no fever at all. Malaria patients might have a wide range of symptoms that can be mistaken for any other systemic illnesses. As a result, one must be cautious enough while considering malaria as a diagnostic option in a variety of diseases. Waiting for the characteristic paroxysmal fever to request a malaria test may result in under-diagnosis or delayed diagnosis, with a potential risk of developing severe malaria; on the other hand, relying solely on fever for clinical diagnosis & treatment may result in over-diagnosis and increase the risk of financial burden.[11-15]

Diagnosis of malaria rests on identification of malaria parasite or its antigens/products in the patient's blood. Although this appears to be straightforward, the diagnostic accuracy is dependent on a number of factors. The different forms of the four malaria species; the distinct stages of erythrocytic schizogony; the endemicity of different species; host immunity, parasitemia, and the symptoms; the problems of recurrent malaria, drug resistance, and sequestration of the parasites in the deeper tissues; & the use of chemoprophylaxis or even presumptive treatment on the basis of clinical diagnosis can all influence the identification and interpretation of malaria parasitemia on a diagnostic test.

The microscopic tests involve staining and direct visualization of the parasite under the microscope. For more than hundred years, the direct microscopic visualization of the parasite on the thick and/or thin blood films has been the accepted norm for the diagnosis of malaria in most settings, from the clinical laboratory to the field surveys. The careful

examination of a well-prepared and well-stained blood film currently remains the "gold standard" for malaria diagnosis. None of the other newer tests have surpassed the 'gold standard' peripheral smear study. So, it is advisable to ask for MP test in all cases of fever and related symptoms and also whenever there is high level of suspicion. MP test can be done at any time and one should not wait for typical symptoms and signs or for chills. A negative test does not rule out malaria and repeated tests should be done in all doubtful cases, for duration of the illness, level of parasitemia, quality of the equipment and reagents, the type and quality of the smear, expertise of the technician and the method of examination may all have a bearing on the result of the MP test. Light microscopy of thick and thin stained blood smears remains the standard method for diagnosing malaria. However, thick smears are 20–40 times more sensitive than thin smears for screening of Plasmodium parasites, with a detection limit of 10–50 trophozoites/µl. Thin smears allow one to identify malaria species (including the diagnosis of mixed infections), quantify parasitemia, and assess for the presence of schizonts, gametocytes, and malarial pigment in neutrophils and monocytes.

Thus, peripheral blood smear provides comprehensive information on the species, the stages, and the density of parasitemia. The test takes about 20 to 60 minutes and its estimated cost is about 12 to 40 US cents per slide in the endemic countries. Therefore, before reporting a negative result, at least 200 oil immersion visual fields at a magnification of 1000× should be examined on both thick and thin smears, which have a sensitivity of 90%. The clinical course of malaria is influenced by several factors. The variable degrees of antimalarial immunity among people living in the endemic areas, low or non-existing immunity among the non-endemic, non-immune population and returning travelers all may influence the clinical manifestations significantly. Atypical presentation is more common in early infection, falciparum malaria, those who have received malaria chemoprophylaxis,[16] extremes of age 17-19 and pregnancy.[20]

CONCLUSIONS:

The disease, malaria can be treated in just 48 hours, yet it can cause fatal complications if the diagnosis and treatment are delayed. Despite centuries of efforts, malaria continues to infect millions and kill thousands. As the morbidity and mortality of severe malaria are no less in Bangladesh, the atypical presentations described in the case-reports should be considered during diagnosis. We believe our report on atypical cases of falciparum malaria will aware doctors and health personnel about rare presentations of malaria in our population and aid in early diagnosis and management to reduce the severity and death toll caused by the disease.

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