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Postoperative Pernicious Malarial Crisis in Patient Coming Back from an Endemic Area

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

The case of a young Moroccan doctor who spent Four months in Congo as part of an international humanitarian military mission; he underwent surgery under spinal anesthesia for an anal fissure a week after being returned to Morocco, In the seventh-day postoperative period, acute renal failure with anuria set in, justifying the patient's transfer to an intensive care unit. Upon admission, on the eighth postoperative day, one day after readmission to the emergency room and was put on triple antibiotic therapy ,and liquid resuscitation was carried out immediately by infusion of saline isotonic solution and due to the non-improvement of the hemodynamic state after volume repletion, a vasoactive support was rapidly introduced at the initial dose of 0.2 ug / kg / min, the intravenous quinine was not immediately introduced in the emergency room because the initial thick, thin film and malaria blood smear carried out on admission were negative and the postoperative clinical context argued in favor of bacterial septic shock. A sepsis context not ruled out (blood cultures performed); a surgical revision the morning of his admission to the intensive care by under umbilical laparotomy, didn't showed an intra-abdominal collection. Parallelly a thick film (30% of parasitized red blood cells) revealing *P. falciparum*, and blood smear were performed again and came back positive after a positive malaria antigen detection of specific IgMs in the indirect

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immunofluorescence, confirming the diagnosis. The mode of infection; is associated with the end of chemoprophylaxis rigorously followed up till Finally, the possibility of pernicious malaria aggravating the initial acute renal failure and hipocalcemia is also discussed.

Keywords: Imported malaria; pernicious malarial crisis; postoperative period; prevention.

1. INTRODUCTION

Malaria is a protozoan disease caused by Plasmodium species (*Plasmodium* (P) *falciparum*, *P. Vivax*, *P. ovale, P. malaria, P. knowlesi*) which is transmitted by the bite of infected female Anopheles mosquitoes occurring in tropical areas and subtropics at an altitude of less than of fewer than 1500 meters [1]. In 2019, there were an estimated 229 million cases of malaria worldwide. The estimated number of malaria deaths stood at 409 000 in 2019. Children aged under 5 years are the most vulnerable group affected by malaria; in 2019, they accounted for 67% (274 000) of all malaria deaths worldwide. The World Health Organization (WHO) African Region carries a disproportionately high share of the global malaria burden. In 2019, the region was home to 94% of malaria cases and deaths [2]. The Democratic Republic of Congo (DRC) has the second highest number of malaria cases and deaths globally (12% of cases and 11% of deaths) and 54.6% of cases in Central Africa in 2018 [3]. Malaria is among the principal causes of morbidity and mortality in the DRC, accounting for 44 percent of all outpatient visits and for 22 percent of deaths in 2018 [2]. Approximately 97 percent of the population lives in zones with stable malaria transmission lasting 8–12 months per year. The highest levels of transmission occur in zones situated in the north and center of the country [4]. Between 2016 and 2019, the malaria case burden increased by 7% from 305 to 326 per 1000 of the population at risk. Death rates remained stagnant, at around 0.51 per 1000 of the population at risk [3]. In the past decades, efforts have been made to produce an effective malaria vaccine. These are under development [5]. Even with all these efforts, malaria affects almost every organ in the body. But red blood cells are the main components involved by the parasites. The deadliest form of the parasite is a species called Plasmodium falciparum. The most effective weapon for eliminating malaria from an area is to wipe out the mosquitoes in that area, breaking the cycle of transmission. That approach is difficult bordering on the impossible in some parts of the world. The next most effective is the use of treated bed nets. The nets usually contain insect repellent and insecticide, so they both kill and repel. Killing the mosquitoes is more effective than just repelling them.

Vaccines have been promoted as the most cost-effective method to combat malaria, and efforts have been underway to develop a malaria vaccine for more than 50 years. The Plasmodium parasite has many adaptations to avoid the human immune system, several of which also increase the difficulty of designing an effective vaccine. Although the host is able to develop clinical immunity after multiple exposures and avoid severe disease, sterilizing immunity never develops naturally. There are three main kinds of vaccines in development, each attacking a different stage of the parasites' life cycle, based on the life cycle of the antigen targeted: pre-erythrocytic, blood stage, or transmission blocking. Several vaccines in each category are in the development phase [6,7].

Pre-erythrocytic vaccines, or PEVs, reduce the chances of getting infected, target the sporozoite or the liver stage of the life cycle. Proof of principle for immunity against this stage of the parasite was provided more than 50 years ago when the bite of multiple mosquitoes infected with irradiated sporozoites proved to be protective against subsequent challenge.75 Phase I trials are underway in both homologous and heterologous challenge models. These vaccinations still require IV administration, which may limit the scalability to resource challenged settings. An alternate approach to irradiation is the genetic manipulation of the sporozoite, which also can limit the development of the sporozoite and may elicit different immune responses [7].

RTS, S, the malaria vaccine currently furthest along in the developmental pipeline, is a pre-erythrocytic vaccine. It is based on the circumsporozoite (CSP) protein, one of the most abundant proteins on the surface of the sporozoite. The vaccine fuses the central repeat region of CSP with known T-cell epitope regions of the protein and a hepatitis B surface antigen carrier matrix. The vaccine has been in development since the 1980s and was licensed

in Europe in 2015. A large phase III trial in Africa showed efficacy in children of 45% at 20 months but waning efficacy over the subsequent 4 years to 28% [8]. However, a vaccine against malaria has shown promise in early clinical trials, raising hopes that it might one day prove to be an effective weapon against one of the world's biggest killers of children. In a trial in 450 children aged 5–17 months, the vaccine, called R21, was up to 77% effective at preventing malaria over the course of one year — which, if confirmed, would clear a 75% effectiveness target set by the World Health Organization. The results are presented in a preprint posted on the server SSRN on 20 April1 [9]. R21 is a modified form of a vaccine that has already been deployed in an ongoing study in hundreds of thousands of children in Malawi, Kenya and Ghana. That vaccine, called RTS,S or Mosquirix, is about 56% effective over one year, and 36% effective over four years. R21 and Mosquirix, are designed to be both more potent, both target the malaria parasite in the sporozoite phase of its life cycle — the phase in which it enters the human body from its mosquito hosts. The vaccines include a protein secreted by the parasite at that stage, in the hope of stimulating an antibody response against it. R21 includes a higher concentration of these proteins and cheaper to produce than Mosquirix. But it remains to be seen if the promising results from this trial, which was done in Nanoro, Burkina Faso, will hold up when the vaccine is tested in a larger study [10]. Each of the vaccines is administered with a chemical called an adjuvant, which boosts immune responses to the inoculation. But the adjuvant used with R21 is easier to make than that used with Mosquirix, raising hopes that it could be cheaper, as well. Researchers at the Health Sciences Research Institute in Nanoro plan to test R21 in a larger trial of 4,800 children. The team has also been working with the Serum Institute of India, a vaccine-manufacturing powerhouse in Pune that has pledged to produce at least 200 million doses of the vaccine each year if it is eventually authorized for use. Malaria cases were defined as the presence of Plasmodium parasites by microscopy in blood smears. QPCR allows species identification in Ethylenediaminetetraacetic acid (EDTA) anticoagulated blood tubes [11]. Parasite density is identified according to WHO standards for parasite microscopy [12]. Severe signs of malaria are based on World Health Organization (WHO) criteria [13]. Hyperparasitaemia is defined as the density of the parasite in the blood stage above 200,000 asexual parasites / L. Blood-stage vaccines, or BSVs, modulate the infection to lessen the blow of the disease and spare lives in the process, aim to reduce the clinical severity of malaria disease by targeting the stage of the parasite responsible for symptoms. These vaccines would not prevent the initial liver-stage infection, but if completely effective could abort the infection by effecting the clearance of the erythrocytic phase. This would effectively block transmission, as gametocytes would not have the chance to develop. The two targets pursued to date are AMA-1 and MSP-1. Neither of these vaccine candidates resulted in significant reduction of disease in trials in African children. A third candidate, PfRH3 (an antigen involved in red cell invasion), will be evaluated soon [14,15]. The third form, transmission-blocking vaccines, or TBVs do nothing for the infected patient but prevent the mosquitoes from spreading the disease to someone else after biting an infected person. Although BSV or PEV are more attractive because they protect hosts from becoming ill, the model found that using bed nets and BSV or PEV vaccines could actually increase the number of cases morbidity and mortality, especially among older people. The reason has to do with the kind of immunity people get from malarial infections. For instance, an infection from a virus such as measles can provide life-long immunity, assuming the patient survives the disease. Vaccines can provide life-long immunity without the patient having to risk infection, although, in some diseases such as measles, it requires more than one shot. Any malaria vaccine would require a lifetime of shots, roughly every other year. People can get malaria multiple times during their life. The immunity you get from one infection may not last more than a year or two. here is what is called a "herd immunity" with malaria as there is with other infectious diseases—the percentage of people in a population who have to be immune from a disease for it to disappear, but no one knows what that is with malaria. People who don't immunize their children for diseases like measles are relying on herd immunity to protect them. However, the more people who go unimmunized, the less likely herd immunity will provide protection. The researchers, including Mercedes Pascual of Michigan and Andrew Dobson of Princeton University, found that treated bed nets and TBV vaccines would be most effective. But, both BSV and PEV malaria vaccines combined with bed nets made things worse, increasing malaria cases and reducing the levels of natural immunity in the population. Immunity is transient, complex, and not complete. Thus far the

vaccines have not been shown to prevent infection. There are, however, good drugs for malaria if a person becomes infected -- where they are available [16].

2. CASE REPORT

A young man of 30 years, Moroccan, following for more than four months rigorous chemoprophylaxis Chloroquine (Nivaquine®) during his stay in the Republic Democratic of Congo (RDC) and on his return to Morocco, he was operated on one week later, for an anal fissure that he presented the last month of his stay in RDC, and on the seventh day of the postoperative he was readmitted to the emergency room, he occurred fever at 38.5°C, nausea, vomiting, generalized asthenia, rare and dark urine knowing that he was discharged from the hospital on the 2nd postoperative day under analgesic treatment based on paracetamol and antibiotic oral amoxicillin and clavulanic acid. The intervention was performed seven days ago under spinal anesthesia carried out at the L3 L4. The intervention was performed seven days ago under spinal anesthesia at the L3 L4 level by an injection of 10 mg of bupivacaine and 50 gammas of fentanyl, 50 µg of fentanyl. A drop in blood pressure was managed quickly by an injection of 6mg of ephedrine. Examination in the emergency room revealed a tense, painful abdomen, no splenomegaly, transitory diarrhea. The patient was febrile at 38.5°C and the patient was put on triple antibiotic therapy based on ceftriaxone 3 g / day, gentamicin 260 mg / day, and metronidazole 500 mg three times a day, vascular infusion with isotonic saline NACl. Biologically, the picture is Biological evaluation showed severe renal failure: blood urea 35 mmol. L, serum creatinine 1200 µmol / L, serum calcium 1.8 mmol / L, serum potassium 2.67 mmol / L, L, albuminemia 300 µmol / L, amylasemia was normal, hemoglobin 4.9 g, platelets 120,000 / mm 3, normal cephalin-kaolin time, thick, thin film and malaria blood smear were initially negative.. The renal ultrasound did not show any obstruction on the urinary tract, the abdominal ultrasound had returned without abnormality.

Patient was admitted to intensive care on the eighth postoperative day, one day after readmission to the emergency room and was put on on triple antibiotic therapy based on ceftriaxone 3g / day, gentamicin 260 mg / day, and metronidazole three times a day, Intravenous treatment with quinine (Quinimax ®), and liquid resuscitation was carried out immediately by infusion of saline isotonic solution NACL 0.5% 20 cc / kg followed by a second infusion of 30 cc / kg of the same solution and due to the non-improvement of the hemodynamic state after volume repletion, especially the persistence of a deep Prolonged hypotension more than 15 min, Oligo-anuria and the signs of peripheral hypoperfusion has type of coldness of the extremities and skin mottling, a vasoactive support was rapidly introduced at the initial dose of 0.2 ug / kg / min, the intravenous quinine was not immediately introduced in the emergency room because the initial thick, thin film and malaria blood smear carried out on admission were negative and the postoperative clinical context argued in favor of bacterial septic shock knowing that our patient was not febrile preoperatively. The sepsis was not ruled out (blood cultures performed); a surgical revision the morning of his admission to the intensive care under umbilical laparotomy, didn't showed an intra-abdominal collection. Parallelly a thick film (30% of parasitized red blood cells) revealing *P. falciparum*, and blood smear were performed again and came back positive after a positive malaria antigen detection of specific IgMs in the indirect immunofluorescence, confirming the diagnosis.

it should be noted that the Malaria serology antibody detection and antigen malaria detection were not performed at its readmission when the smear came back negative for first day after the readmission, on the seventh postoperative day. The evolution was marked on the fourth day after readmission, on the tenth postoperative day by the installation of a clinical picture of refractory septic shock with encephalitic impairment (clouding, then coma) and biological stigmata of disseminated intravascular coagulation (platelets: 60,000 elements/mm^3 and drop in the rate. 48% prothrombin), and was reported rapidly to a pernicious attack of severe malaria (30% of parasitized red blood cells). and the course was rapidly fatal in a picture of multi-organ failure.

3. DISCUSSION

Malaria is most commonly transmitted during the bite of an infected female Anopheles mosquito or, more rarely, can be transmitted through the direct inoculation of infected red blood cells (i.e., congenital malaria, transfusion malaria, and malaria from contaminated needles). Vector abundance and longevity are major contributors to transmission rates, and these are strongly

influenced by temperature, rainfall, and humidity. The most direct measure of transmission intensity is the entomologic inoculation rate (EIR)—the number of infectious female anopheline bites per person per year. For clinicians working in settings where data on EIRs are not readily available, surrogate measures include the spleen rate and parasite prevalence rates in children. Parasite prevalence rates in children. Malaria transmission is also influenced by climate. The optimal conditions occur when the temperature is between 20°C and 30°C and the mean relative humidity is at least 60%. Water temperatures regulate the duration of the aquatic cycle of the mosquito vector. A high relative humidity increases mosquito longevity and therefore increases the probability that an infected mosquito will survive long enough to become infective. The proximity of human habitation to breeding sites directly influences vector–human contact and therefore transmission. The stability of breeding sites is influenced by water supply, soil, and vegetation. Irrigation schemes, dams, and other man-made changes affecting land use can radically alter stable patterns of malaria transmission. Additionally, new breeding sites can be introduced into communities when water reservoirs are introduced by humans; open household containers left with standing water are sufficient to serve as a breeding site [17]. Any of the five species of human malaria can be transmitted directly from an infected blood donor, accidental infection by a contaminated needle, or infected intravenous (IV) drug users sharing needles. The incubation period after infection is as short as a few days for *P. falciparum* but can be up to 40 days or longer for *P. malariae* [18]. *P. falciparum* and *P. knowlesi* are capable of invading erythrocytes of any age. *P. vivax* and *P. ovale* preferentially invade younger erythrocytes, whereas *P. malariae* prefer senescent erythrocytes. Serial cycles of asexual replication take place in erythrocytes; the duration varies with the species. The youngest stages found in the bloodstream are small, rounded trophozoites, known as ring forms. As they grow, they become more irregular and ameboid. During development, the parasites consume hemoglobin, leaving behind an iron-containing compound known as hematin or hemozoin as the product of digestion; it is visible in the cytoplasm of the parasite as dark granules. The schizont stage begins when the parasite undergoes nuclear division and culminates in segmentation, when merozoites are formed. Some parasites in the erythrocytic stage undergo gametocytogenesis, producing the sexual forms of the disease: the male microgamete and the female macrogamete. Male and female gametes are ingested by a female anopheline when taking a blood meal from a human host; the sexual replication phase of the malaria parasite ensues in the mosquito mid-gut and ends in the salivary glands. Infection begins when sporozoites in mosquito saliva enter the skin and bloodstream and, within 30 minutes, invade hepatocytes. The duration of the asexual replication phase inside the hepatocytes varies from 11 to 12 days in *P. falciparum*, *P. vivax*, and *P. ovale*, to 35 days in *P. malariae*. The nucleus of the parasite undergoes repeated division, resulting in the formation of thousands of uninucleate merozoites. There is no inflammatory reaction in the surrounding liver tissue, and at this stage, the host is asymptomatic. In *P. falciparum* and *P. malariae* infections, the liver tissue merozoites rupture the hepatocyte at about the same time, with none remaining in the liver. This can result in as many as 10,000 merozoites released into the bloodstream. In contrast, *P. vivax* and *P. ovale* have two types of exoerythrocytic forms: a primary type develops and ruptures within 6 to 9 days; the secondary type—the hypnozoite—may remain dormant in the liver for weeks, months, or up to 5 years before developing, later causing relapses of erythrocytic infection. The pre-patent period for *P. knowlesi* in humans is 9 to 12 days [19].

The life cycle of *P. falciparum* differs from the other four human malaria parasites in one important respect: during the latter half of the intra-erythrocytic cycle, mature falciparum-infected red blood cells are not seen in the peripheral blood. This is due to sequestration—the binding of late-stage parasitized erythrocytes to the luminal surface of vascular endothelial cells. This interaction is mediated by parasite-encoded proteins (primarily PfEMP1) present on the erythrocyte surface, appearing as protuberant knobs. Their irregular shape leads to sequestration of the parasitized red cells in the capillaries and post-capillary venules of various organs, often to such an extent that blood flow is compromised [20].

The modes of contamination seem to us to be able to be retained from the analysis of the preceding data. First of all, the stopping of chemotherapy before the operation, without resumption in the postoperative period, and the absence of protective antibodies placed our patient in the situation of subjects at risk (who

are immunologically new, who may be victim pernicious access). In malaria-endemic areas, these are usually young children under the age of four [21]. For those living outside this area, this is the case with our patient, any contact with the parasite (infesting bite) can determine a pernicious attack, in particular if the chemotherapy was stopped knowing that in Morocco, it is always recommended to only continue chemoprophylaxis with chloroquine one week after the return from endemic area as was the case of our patient. The incidence and prevalence of malaria illness is significantly influenced by acquired immunity. The burden of disease and death is borne by those individuals with less exposure and thus minimal immunity, mainly young children. Older children and adults are partially immune due to their repeated infections over time. The age at which this transition from susceptible to resistant to life-threatening malaria occurs is dependent on the EIR of the location; those areas with higher EIRs result in clinical immunity at an earlier age. Travelers from non-malaria-endemic regions, having never been exposed to malaria, would be comparable to the youngest of children from malaria-endemic regions and are thus susceptible to life-threatening disease as is the case with our patient. In regions where transmission is unstable, there is little acquired immunity and individuals from any age group can develop severe disease [19].

Chemoprophylaxis with 4-aminoquinolines does not prevent malaria since the parasite remains immune to the liver [22]. It only suppresses the multiplication of the hematozoa in the red blood cells. The invasion therefore occurs after elimination of the drug used. Taking into account the kinetics of chloroquine, the usual delay is of the order of 10 to 30 days [23], *P. falciparum* fever is not seen more than three months after the last infesting bite [23], our patient reported pernicious access after the seventh day after the cessation of chloroquine. The onset of pernicious access coincided with the discontinuation of chemoprophylaxis and may therefore be the main factor in P. falciparum malaria. Diagnosis at the individual patient level, accurate diagnosis and treatment of uncomplicated malaria enhances the chances of a prompt cure and minimizes the likelihood of disease progression. At the population level, the appropriate management of large numbers of patients with uncomplicated malaria will decrease the incidence of severe and complicated malaria and will diminish the reservoir of infected individuals while slowing the development and spread of drug resistant parasites. To minimize the unnecessary or inappropriate use of antimalarial drugs, parasitological confirmation of clinically suspected cases is recommended by the World Health Organization (WHO) [24]. Malaria parasites can be identified in a sample of peripheral blood via light microscopy or by using rapid diagnostic tests (RDTs), which are based on the detection of parasite enzymes or antigens. When it is performed well, light microscopy is sensitive and specific and allows for the recognition of various malaria parasite species and estimation of parasitemia. The “gold standard” approach uses Giemsa stain and oil-immersion microscopy. In resource-constrained endemic areas, when parasitological diagnoses are not available, algorithms devised on the basis of the prevalence of parasitemia in various age groups help to balance the risk of undertreating those at risk of progressing to severe disease against the risks of unnecessary drug use, excessive costs, and drug pressure, which could accelerate the development of drug-resistant parasites.

complicated malaria illnesses. In clinical trials, mortality rates in adults with severe malaria ranged from 15% to 22%, and those in children ranged from 8.5% to 10.9% [25,26]. Acute Kidney Injury Mild proteinuria, azotemia, and oliguria occur frequently in otherwise uncomplicated *P. falciparum* infections. Acute renal failure is far more common among adults than among children; it is also more common in patients with hemoglobinuria (“blackwater fever”) as it was the case with our patient [27]. Non-specific mildly elevated urea nitrogen and creatinine levels, proteinuria, and abnormal urinary sediment are common in adult malaria. Acute renal failure is a common complication of severe malaria, particularly in adults. Most patients do not require long-term dialysis. Acute kidney injury (AKI) is becoming a more recognized complication of pediatric malaria, with one study finding 50% of children meeting the definition of AKI. Histologically, about 50% of autopsy cases show glomerular thrombi [28]. It can result from acute tubular necrosis, a sequela of reduced renal perfusion, or from the downstream effects of intravascular hemolysis, which results in increased concentrations of cell-free hemoglobin [29]. Anuria is a poor prognostic sign, and hemoperfusion or renal or peritoneal dialysis is often necessary. Many renal abnormalities are reversible, and patients appropriately supported through the critical

period often enjoy a full recovery [30], the occurrence of a pernicious malarial crisis bout on the seventh postoperative day predominated by acute postoperative renal failure allows to support the initial responsibility of *P. falciparum*, and its role as a factor in the maintenance of renal disorders and in the constitution of cortical necrosis with intraglomerular coagulopathy seems likely [31].

The entry serum calcium at 1.8 mmol / L is probably related to a low serum albumin level and to the initial acute renal failure. On the other hand, the measured and corrected hypocalcemia, observed during the pernicious attack of malaria without modification of the renal function, can be related to the malaria attack. This is a biological stigma now well known in the course of this disease [32]. No decisive argument allows us to go further in this discussion. Various possibilities of occurrence of malaria should be considered in the light of anamnestic, clinical, parasitological and immunological data. Anemia, leukopenia, and thrombocytopenia are usual. The reticulocyte count is normal or depressed, despite the hemolysis, and becomes elevated usually 5 to 7 days after the parasitemia has cleared. Urinalysis reveals albuminuria and urobilinogen; increased conjugated bilirubin is present in many patients. Some patients are jaundiced, and concomitant abnormalities in liver function tests may cause diagnostic confusion with viral hepatitis. Serum alanine aminotransferase (ALT) and aspartate transaminase (AST) are usually elevated. Both the direct and the indirect bilirubin can be elevated. Prothrombin times can be prolonged. Increases in serum creatinine and blood urea nitrogen may be transient, or they may presage acute renal failure. Hypoglycemia frequently complicates falciparum malaria and can occur both before treatment and as a result of quinine therapy.

A septicemic picture with a state of shock associated with encephalic signs appeared on the tenth postoperative days and quickly associated with a pernicious attack of malaria, the evolution of which was fatal in the context of multi-organ failure with a very high parasite load of trophozoites despite all the measures, resuscitation and treatment with intravenous quinine. Important elements of the physical examination include inspection for prostration (the inability to sit unaided or, in infants who cannot yet sit, to feed) and deep breathing, assessing Glasgow Coma Score, inspecting nail beds and conjunctivae for pallor, cardiac and pulmonary auscultation for signs of high-output cardiac failure, measuring blood pressure and checking capillary refill, and palpating the abdomen to identify hepatomegaly and splenomegaly or urinary retention. Decreased urinary output suggests acute renal failure and can be confirmed by measures of serum creatinine. Long considered to be unique to falciparum malaria, several of the features of complicated malaria have now been described in patients with *P. vivax* and *P. knowlesi* infections. In addition to the complications described, splenic rupture is a rare complication of *P. vivax* infections, and nephrotic syndrome is occasionally seen in patients after P. malariae illness. In a parasitemic patient, the presence of any of the clinical or laboratory features of complicated (life-threatening) malaria represents a medical emergency; these patients should be provided with the best available medical care. The clinical presentation of complicated malaria is different in adults than it is in children. Cerebral malaria alone is more characteristic of pediatric severe malaria, whereas multi-organ system involvement is seen frequently in adults with neurologic Changes and Coma Explanations of cerebral pathology in cerebral malaria (CM) have included mechanical obstruction or inflammation. Brain imaging studies point to the presence of severely increased brain volume as the main risk factor for death in children. Possible causes of increased brain volume include vascular congestion from sequestration, cytotoxic or vasogenic edema, or hyperemia. Cerebral malaria is a highly variable clinical syndrome consisting of *P. falciparum* parasitemia of any density and coma (Blantyre Coma Score ≤2 in children/Glasgow Coma Score ≤9 in adults, unrelated to hypoglycemia, meningitis, a postictal state, or any other cause of encephalopathy). Children with CM frequently demonstrate symptoms suggesting widespread involvement of the CNS, including generalized tonic-clonic convulsions, focal seizures. Parasitemic individuals with any of the clinical or laboratory features are likely to have complicated malaria, but the possibility of a “false-positive” assessment should be considered, particularly (but not exclusively) in the semi-immune population. The mortality rate of untreated severe malaria is probably over 75%; with good management, the mortality rate of CM is roughly 15% to 20%. Concomitant meningitis can be excluded via lumbar puncture in this setting [33], if a lumbar puncture is contraindicated on clinical grounds, the patient should be provided with the

appropriate antibiotic coverage (penicillin + gentamicin, or ceftriaxone). Coinfections with bacteria are common and should be sought using blood culture when the capacity exists [34,35], what was done in our patient. Septic shock should be considered in the differential diagnosis and empiric antibiotic therapy administered if there are signs of acidosis or impaired perfusion. An autopsy series demonstrated that the standard clinical case definition of CM was incorrect in approximately 25% of pediatric cases—non-malarial causes of death were identified. In contrast, 75% of cases in this series did have cerebral sequestration of parasitized erythrocytes and no other causes of death were identified at autopsy [36]. The best clinical indicator of "true" CM was the presence of at least one of the three features of malarial retinopathy: vessel color changes, macular or extra-macular whitening, and white-centered hemorrhages [37].

The patient, a doctor, had conscientiously been taking chemoprophylactic treatment with nivaquine for more than four months, which was stopped the day before his surgery in which was continued a week after his return and its stop was on the day before the intervention in Morocco. On the seventh postoperative day, he had oligo-anuria with signs of severe sepsis led in principle to think a pernicious access, smears and thick film revealed malaria were initially negative and became back positive the next day, the day of his admission to the intensive care unit after a positive malaria antigen detection of specific IgM in the indirect immunofluorescence which was not performed on the first day of his hospital readmission. In semi-immune individuals, asymptomatic or "incidental" parasitemia is common, and the presence of peripheral parasitemia can be misleading. In these individuals, it would be prudent to consider other etiologies for the symptoms, particularly in patients with lower-density parasitemias as was the case of our patient.

Antimalarial treatment is warranted if parasites are detected, but additional treatment may also be required. Another dilemma is the febrile individual with a negative malaria test after exposure in an endemic region. Withholding anti-malarial drugs in situations where malarial infection is a real possibility is difficult for clinicians. The dangers of missing a malaria diagnosis and thus delaying treatment are well known. This apprehension, accompanied by skepticism regarding the reliability of the parasitologic diagnosis (especially via microscopy), is used to justify a "better safe than sorry" approach to the use of anti-malarial drugs. In malaria-endemic areas, patients themselves, along with parents and other caregivers, have come to expect malaria chemotherapy for many febrile illnesses. Clinical evidence for other non-malaria diagnoses should be sought to support the decision to withhold anti-malarials in patients who are not infected with Plasmodia. Experience since the widespread introduction of malaria RDTs in 2010 suggests that increased use is associated with significantly lower use of anti-malarial drugs overall. In non-immune patients at risk for malaria infection, several parasitologic assessments carried out at 12-hour intervals during a 36- to 48-hour period are recommended before concluding that the individual is free of infection. What was done with our patient although the introduction of quinine was started the day after his hospitalization. Intra-erythrocytic *P. falciparum* parasites are typically in circulation for the first 24 to 36 hours of the 48-hour life cycle, and the intra-erythrocytic parasites for the other four infecting species are always present in the peripheral blood, so it is not necessary to "time" blood collections to any particular symptoms (e.g., fever, rigor, diaphoresis). The five human malaria parasites have similar clinical presentations for uncomplicated disease and are best distinguished from each other by geography, by parasite density (parasitemias >2% are more commonly seen in *P. falciparum* and *P. knowlesi*), and by parasite morphology—best appreciated on thin blood films. Low-grade infections of *P. malariae* can persist for years, and individuals with *P. vivax* and *P. ovale* may have pre-patent periods of a year or more. Non-immune individuals with *P. falciparum* infections may deteriorate very rapidly; prompt and effective treatment in this high-risk group is important and should be provided on an emergent basis. Patients should be monitored closely to detect early signs of clinical deterioration. Serial examination of the peripheral blood (every 12 hours) may aid in the identification of low-density parasitemia; thrombocytopenia is another helpful clue in oligoparasitemic or initially aparasitemic patients what it was done with our patient. **Blood Films** For detecting parasites, a thick blood film is superior, as it concentrates the red cells by a factor of 20 to 40. Identifying species on thick films may be difficult because the red cells have lysed and the morphologic features of the parasites have been altered. Species identifications are made more easily using thin

blood films. Thick and thin films can be prepared on the same slide, although they are processed differently (thin films must be fixed in methanol before they are stained). Blood can be stained with Giemsa, Leishman, Field, or Wright's stains. The golden-brown malaria pigment (hemozoin) in monocytes or leukocytes suggests a current or recent malaria infection. Parasites can be counted as a percentage of red cells on a thin film or against white blood cells on a thick film, and if the total red cell or white cell counts are known, the parasite densities can be calculated. Quantifying parasitemia is useful for predicting whether the illness is likely to be caused by malaria, for anticipating the need for blood transfusion, and for following response to anti-malarial treatment. Rapid Diagnostic (Tests RDTs) are antigen-based dipstick, cassette, or card tests in which a colored line indicates that plasmodial antigens have been detected. They are relatively simple to perform and interpret, and they do not require electricity, but not all tests can distinguish between species, some cannot distinguish new infections from recently and effectively treated infections, and none indicate parasite density. The choice of a specific RDT depends on its intended use. For example, does it need to distinguish between a recent malaria infection and a current infection? Should it be able to distinguish between falciparum and non-falciparum species? Will treatment decisions be based on the results, or is it being employed for epidemiologic purposes? The choice of which malaria RDT to use in a given situation is complex and depends on availability, cost, quality of the test, and performance characteristics. The WHO sponsors independent RDT product testing performed at the U.S. Centers for Disease Control and Prevention (CDC). Summary results of the most recent round are available online [38].

Patients with severe malaria should receive parenteral anti-malarials for at least 24 hours; after that, a full course of an ACT drug can be administered, beginning as soon as the patient can swallow. The two parenteral drug options are contemporary formulations of traditional, plant-based remedies. Quinine (and its stereoisomer, quinidine) comes from the bark of the cinchona tree, and the artemisinins are derived from Artemesia annua, known as sweet wormwood. The artemisinin-based compounds have recently replaced the cinchona alkaloids as the preferred treatment of severe malaria. Randomized clinical trials comparing IV quinine with IV artesunate have established the superiority of artesunate in adults and children. IV artesunate is the first-line treatment for complicated malaria, with intramuscular (IM) artemether being second line. Parenteral quinine should be administered only in the absence of an artemisinin-based compound. In settings where a complete treatment regimen for severe malaria is not available, patients should receive an IM dose of artesunate, artemether, or quinine before transfer to a higher level of care. If IM injections are not available, children should receive a single dose of rectal artesunate before immediate transfer to a health care setting where the treatment regimen can be completed [39].

4. CONCLUSION

This observation makes it possible to specify the multiple aspects of malaria in the postoperative period, their treatment and their prevention. First of all, chloroquine chemoprophylaxis must be continued in the postoperative period, despite the fact that in Morocco it is only recommended to continue chemoprophylaxis only one week after returning from an endemic area, which was the case with our patient, who is immunologically new exposed to a pernicious postoperative malaria attack, when the day of his intervention coincided with the end of the chemoprophylaxis. Chemo prophylaxis should be continued for six to eight weeks. If the oral route cannot be used, intravenous quinine is then indicated. Secondly, the transfusion of blood or derivatives, in an area endemic to malaria, must give rise to chemoprophylactic treatment of the recipient with chloroquine, and this in the absence of a reliable method of serological detection, the best prevention rests on the Temporary eviction from donating blood for any subject who has recently moved to a malarious area. Finally, cases of accidental contamination should make hospital staff vigilant when handling malarious blood, especially during samples, injections and bloody gestures (shunt, extracorporeal circuit).

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline Patient's consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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