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Acute Respiratory Distress Syndrome Due to Malaria in a Covid-19 Migrant Worker from Peru, Review of the Literature of a Forgotten Tropical Disease.

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Abstract

Acute respiratory distress syndrome has been reported with Malaria. It has been associated with respiratory decompensation, metabolic acidosis, non-cardiogenic edema and ARDS. We present a case of Malaria in a migrant worker that presented with hypoxic respiratory failure in the middle of the pandemic. The patient was from the Amazonian region of Peru. Further management revealed cyclical fever with anemia and the fact he came to America with a negative PCR for COVID 19 was a clue for further workup. Revealing the presence of Plasmodium vivax malaria, for which the patient was treated, and the ARDS resolved. The patient was successfully extubated and discharged home.

Patient: Male, 57-year-old Male

Final Diagnoses: Malaria, Plasmodium vivax, ARDS, Respiratory Failure, Hypoxemia, COVID-19.

MeSH: Keywords: Peru, Malaria, South America, Respiratory Failure ARDS, COVID-19.

Objective: Unusual clinical course

Case

Malaria caused by *Plasmodium vivax* has been reported to be a cause of ARDS. This is a rare complication in North America, as malaria is not endemic. Nevertheless, with the COVID 19 pandemic, there has been an increase in world migration and the incidence of tropical diseases may be more prominent in non-endemic areas. This is a case of a migrant worker from Peru that presented with increased dyspnea and shortness of breath in the middle of a Pandemic. COVID lung infection was suspected due to the presentation of acute hypoxic respiratory failure. However, PCR was negative and subsequent analyses revealed anemia, fever, and increased hypoxemia. The patient was intubated due to his critical evolution and dyspnea. Blood cultures and sputum cultures were negative. A chest radiograph reveals bilateral ground-glass opacities. His overall condition continued to deteriorate. A tomography angiogram of the chest was ordered, showing bilateral ground-glass opacities with no evidence of pulmonary embolism. The WBC was 13 $x10^3$, Beta natriuretic Peptide of 50 pg./ML, ferritin of 1154ng/L and a D dimer <1.0 the rest of the chemistries were within normal limits. Prothrombin and Partial thrombin time were normal and liver functions were normal. Bronchoscopy was done and was negative for fungi, bacterial, or fungal infections.

An echocardiogram revealed normal cardiac function. Legionella and pneumococcal antigen tests were negative. Nursing staff noticed cyclical fevers every 2 days while on the ventilator. We tested for thick and thin smears and PCR, the diagnosis of *Plasmodium vivax* was reached. Not having a clear past medical history, we were uncertain if this was new-onset malaria or a reactivated infection. The patient was treated besides standard antibiotic therapy with a radical fourteen-day primaquine regimen of 3.5 mg base/kg for a total dose of 15mg/day to treat the *P. vivax* malaria infection. Prior to initiating primaquine, it was necessary to determine the patient's glucose-6-phosphate-dehydrogenase (G6PD) status to establish safety and dosage. Deficiency in G6PD is an X-linked genetic disorder that can result in life-threatening hemolysis when treated with any 8-aminoquinolone (8-AQ) class drug. The degree of hemolysis is dose-dependent and should be closely monitored in patients with G6PD deficiencies. The patient improved over 10 days and was weaned from the ventilator and eventually discharged home with clinic follow up to Pulmonary and Infectious Diseases.

Background

Malaria continues to be an important source of morbidity and mortality throughout the Amazon=jungle and Africa. The World Health Organization started an eradication initiative in 1955 with the use of DDT. **[**2**]** However, that initiative was abandoned in 1969 after concerns with the safety of DDT and the Anopheles mosquito developing resistance to DDT. **[**3**]** Malaria continues affecting many communities in the Amazon region of Peru that have limited access to education, transportation and health centers. Over the years, *Plasmodium* species have developed resistance to traditional treatments and many inhabitants have subclinical infections. **[**2,3,4**]** The infected person has minimal or no signs of an active infection and becomes a reservoir for the parasite. Focusing on the Peruvian Amazon region where our patient originated, the city of Iquitos in the northeastern department of Loreto. **[**1,7**]** Iquitos is the capital of the department and is divided into four districts. The Nanay and Itaya Rivers meet to form the Amazon River, the city is only accessible by water or air. From 2017 Census data, the population of Iquitos was calculated over 374,000 along with the surrounding rural communities.**[**1,4**]**

Prevalence of malaria according to Karim Pardo Ruiz, the director of Prevention and Control of Zoonosis and Metaxenic Diseases (under the health strategies and solutions for the Peruvian Ministry of health), there has been a fifty percent decline in malaria cases in Peru.1 The number of cases in 2013 was 40,747 (35,275 due to *P. vivax* and 5,472 due to *P. falciparum*). Peru reduced the number of cases between 2014 and 2017 (from 65,252 to 55,367) by more than fifteen percent. **[**1,2**]** A "Malaria Zero Plan" with the objective of eradicating malaria in the Peruvian Amazon was adopted by the Ministry of Health in 2017. The main focus was the department of Loreto which had 96 percent of the malaria cases in Peru for the same year the initiative was undertaken. **[**3**]** In 2018, there were only 13,349 cases of malaria (10,420 due to *P. vivax* and 2,929 due to *P. falciparum*). The Peruvian Ministry of Health, Regional Health Direction for Loreto, Iquitos indicates the largest number of cases are seen from January to July and start to decline by fifty percent from August to December, the rainy season is from November to May. **[**3,6,10**]** Iquitos have been found to be the main source of parasitic spread to the surrounding areas with *Anopheles darlingi* being the main vector. **[**6,9,10**]**

Table 1 Confirmed cases 2015-2017

Year	*Total Pop at Risk*	*Blood Slides Examined*	*Confirmed Cases*	*P. falciparum/mixed*	*Slide Pos Rate*	*Annual Parasite Index*
2015	4,453,082	865,980	66,609	13,682	7.69	14.96
2016	3,273,897	566,230	56,623	15,319	10.00	17.30

2017	3,843,337	388,699	55,367	13,321	13.75	14.41

Report on the Situation of Malaria in the Americas 2017

Table 2 Malaria cases by age group 2017

AGE GROUP	NUMBER OF CONFIRMED CASES
LESS THAN 5	20%
5-14	35%
15-49	37%
50 AND ABOVE	7%

Infection

When the infected female mosquito bites the human host, it injects the immature sporozoite into the person's bloodstream. **[**2,3**]** This sporozoite travels throughout the body until it reaches the liver where it will mature into a schizont. The mature schizonts multiply over the coming weeks into merozoites. These merozoites can now break free from the liver and enter the bloodstream, invading red blood cells. Merozoites destroy the blood cells as they continue to grow and divide in two- or three-day intervals depending on the *Plasmodium*. **[**3**]** As the reproductive cycle continues, the person can have daily rupture of red blood cells leading to anemia. Merozoites reproduce asexually, it is believed several can continue to a sexual reproductive gametocyte. **[**3,4**]** The new gametocyte circulates in the bloodstream and can only reproduce when a new mosquito bites the host. Upon reproduction, the gametocyte will produce ookinetes which attach to the mosquito's intestine. They will mature and hatch in 9-14 days releasing thousands of new sporozoites which can be released in the mosquito's saliva when it bites a new host, starting a new infective lifecycle. After the initial infective bite, the person has no initial symptoms. Rural areas typically course with monoclonal infections and urban areas have polyclonal infections due to increased exposure. **[**5,6**]** Through genetic analysis, they have been able to identify and group 87 unique haplotypes grouped as a sub-structured parasitic population with 2 or 3 genetic clusters. **[**5**]** The *P.vivax* species circulating in the Iquitos Amazon region was determined to be diverse in five areas with different migration patterns. The city of Iquitos has also been found to be the main source of parasite spread due to it being the largest city in the region colloquially called the capital of the Peruvian Amazon due to its trade activity, commerce and port traffic. **[**3,5**]** Considering Iquitos is surrounded by water, it is also wise to consider the spread of malaria by people traveling in and out of the city by boat on the Nanay River. These people go to the city and tend to their affairs prior to returning to their villages

in the jungle. This creates a flux of infection in both directions that can be determined through genetic mapping. This same population genetics could help determine the impact of treatment, spread, control and eradication. **[**5,8,9**]**.

Symptoms

The symptoms can start anywhere from ten to fifteen days after the bite from a malaria-infected female Anopheles mosquito. **[**3**]** The host has a combination of clinical symptoms such as fever, chills, headache, nausea, vomiting, diarrhea, abdominal cramps and muscle aches. **[**2,4**]** One of the diagnostic aids in determining malaria is the fever and chill presentation in waves or periods lasting four to ten hours and repeating every two to three days. **[**3**]** After the fever, the person starts to perspire profusely as their temperature normalizes. The interval of days depends on the species of *Plasmodium*, tertian malaria (48 hrs. - *P. vivax, P. ovale, P. falciparum)* or quartan malaria (72 hrs. - *P. malariae*). The interval coincides with every release of merozoites into the bloodstream. The infected person can have multiple generations of the same species being released out of synchrony or may be infected by a second parasite.2,4 This unsynchronized release can eliminate the 2-3 day cycle, the person will have more frequent episodes of chills, fever and perspiration. The replication will continue until the person receives treatment for malaria. If there is no treatment, there will be marked anemia with the red blood cell (RBC) destruction, an enlarged spleen trying to rid the body of the broken red blood cells (RBC) and weakness due to the continued and increased anemia.

Among the protozoan species that cause malaria, P. *falciparum* is considered the most dangerous of the parasites because it has higher virulence by infecting a greater number of RBC. **[**2,3**]** The person is said to have malignant tertian malaria and can deteriorate rapidly into coma and death if not treated rapidly. **[**4**]** On diagnosis, they are typically found to have ten times more parasites than other infective species. The RBC acquires affinity to agglutinate in capillaries causing circulatory impedance. This obstruction in blood flow is most severe in the kidneys and brain which can lead to kidney failure and cerebral malaria resulting in demise for the human host. Several P. *falciparum* strains have become resistant to both preventative and curative medications for malaria. **[**3,7**]** For infections with *P. ovale* or *P. vivax* it is important to keep in mind that dormant sporozoites can remain in the liver as hypnozoites for months or years and can reactivate. There is no diagnostic test to detect the presence of dormant liver parasites and they are not detected in blood smear tests. **[**3**]** The person is asymptomatic and becomes a reservoir for future infections with possible relapse weeks, months or years after initial infection. The human host presents a moderate disease with high number of parasites in the blood, infecting reticulocytes. Infections by *P. vivax* in comparison are more severe and have frequent relapses, vague symptoms appear within the first seven to ten days. The symptoms are headache, anorexia, photophobia and muscle aches lasting three to four days. After the initial symptoms, the person develops low-grade fever that can be cyclic appearing every forty-eight hours. **[**2,3,4**]** They can also present splenomegaly and

leukopenia in the first few weeks of infection. Infections caused by *P. vivax* may have renal failure, pulmonary failure or neurological signs when the person develops cerebral malaria. **[**4**]**

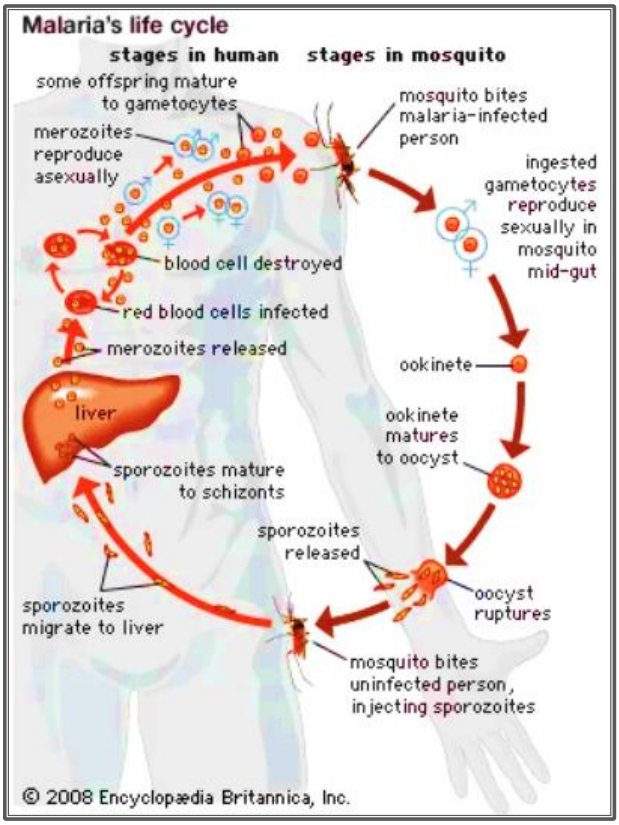

Figure 1

Diagnosis

To properly diagnose malaria, laboratory confirmation is mandatory. The combination of clinical symptoms can be misleading and lead to an erroneous diagnosis and ineffective treatment. **[**3,9**]** A peripheral blood sample is taken to produce a smear on a glass slide and is viewed under a microscope, this will help identify the parasitic species and give an idea of the number of circulating parasites. This traditional test has limitations, it can be difficult to identify parasites when few are circulating in the bloodstream, it is time-consuming and requires a skilled microscopist. **[**4**]** There are also rapid tests (RDT) that can be conducted when there is no microscope or skilled technician to identify *Plasmodium* in a blood sample. The RDT can detect four species of *Plasmodium* (*P. ovale*, *P. falciparum, P. malariae* and *P. vivax).* These rapid tests target *P. falciparum* antigens which are rich in histidine protein 2 (HRP2) and also target Plasmodium lactate dehydrogenase (pLDH) found in *P. malariae, P. vivax, P. ovale* and *P. falciparum.* There are genome assemblies for approximately 16 mosquito vectors and gene mapping of five species of Anopheles. **[**5**]** The mapping of mosquito genes allows for the determination of proper treatment in areas where mosquitos may have developed resistance to

traditional medications. [10] Special considerations should be taken in the detection of malaria in pregnant women, this is done through traditional blood smear, PCR, testing of cord blood and testing placental tissue. [6] PCR testing provides a real-time qualitative determination of *Plasmodium* species. With knowing the prevalence of the type of mosquito and parasite, it is easier to prevent complications during pregnancy to the mother and when the baby is born. [6] The most significant complications for the mother are coursing with anemia throughout the pregnancy that can negatively impact the child due to placental insufficiency. There can be a spontaneous abortion, stillbirth, premature delivery, low birth weight, fetal anemia. [4,6] The goal is to prevent any of these from happening to both the mother and her child. Ideally to treat with sulfadoxine-pyrimethamine prophylaxis to prevent malaria and any adverse events during pregnancy. [4,6] The WHO has established treatment guidelines for malaria during pregnancy, the recommended cure for infections by *Plasmodium vivax* is chloroquine 25mg/kg/d for 3 days in conjunction with primaquine 0.5mg/kg/d for 7 days. [4,6]

Treatment

Historically, Peru provided the world with its first treatment against malaria. It was produced from the bark of the "Chincona tree" that was used by early Peruvian Indians as tea for fever. [3,7] The same bark was used to derive quinine in the 1820s which was the established treatment for malaria for many years. Treatment with Pamaquine, mepacrine and chloroquine were developed in the 1930s. Of these, chloroquine was found to be the least toxic and most cost effective. [3] Resistance to treatment with chloroquine started in the 1960s and spread around the world, rendering it no longer the primary choice for treatment. The main goal for any treatment is to eliminate, contain and prevent transmission of the infection. [2,7,9] A combination of medications has been found to be more effective than a single antimalarial drug. Uncomplicated malaria is treated differently than complicated malaria. The treatment depends on the type of infection, host status, and if there are any other associated conditions. Prior to initiating treatment with any 8-aminoquinolone (8-AQ) class drug, it was necessary to determine the patient's glucose-6-phosphate-dehydrogenase (G6PD) status to establish safety and dosage. Deficiency in G6PD is an X-linked genetic disorder that can result in life-threatening hemolysis when treated with 8-AQ drugs. For travelers to endemic areas and pregnant women living in endemic areas, prophylactic treatment should be given.

Prevention

The prompt diagnosis and treatment for malaria also helps reduce transmission and is a source of prevention. This can be done with continued surveillance and active case detection with consecutive screenings for malaria. This would identify carriers who are in latent state parasitemia. Education is

also a cornerstone of prevention and transmission. If susceptible populations are aware of signs and symptoms, they will be more likely to visit one of the local health posts within the jungle or travel to the city to receive medical attention. Taking into consideration, education levels, remote locations and decreased sanitation an extra effort have to be placed on general health education and in eliciting the help of health promoters to assist with the supervision and reporting of persons with signs or symptoms of malaria. The health promoter can also aid the person in seeking medical attention. **[**2,9,10**]**

Conclusion

ARDS combined with malaria is a rare presentation in North America. Currently, with the increased migration from Latin America to the North, it is conceivable that we will see additional infections and complications due to tropical diseases in our hospitals. ARDS has an inflammatory mediated capillary leak that leads to non-cardiogenic edema. In a world where SARS-CoV-2 is causing increased migration due to economic damage to society. We need to keep in mind the presence of non-common diseases in areas where prevalence is not common. At the time of this article's elaboration, the US has recorded a lamentable 831,000 deaths. The CDC estimates an average of 100,000 new cases per day as a new surge pommel the US. The current Omicron variant has presented with symptoms like infection by P. *vivax*: headache, anorexia, and muscle aches lasting three to four days differing from other SARS-CoV-2 variants. Making the diagnosis of malaria seem unrealistic in nonendemic areas, led us to widen our considerations for a differential diagnosis. It is important to keep lung protective strategies, pruning, peep, antibiotics, steroids and antivirals as the cornerstone for these patients. Suspicion of a tropical disease such as malaria needs to be considered based on each individual's exposure and origin. Bacterial pneumonia and even coinfections with SARS-CoV-2 needs to be among your differential diagnosis. For this case, antimalarial therapy was a key point to the patient's recovery. Further studies of malaria in the pandemic must be considered in regions such as Africa and the Amazon where malaria is more prominent.

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