CLINICAL VIGNETTE

Importance of Malaria Chemoprophylaxis in High Risk Individuals

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A 79-year-old male presented with high fevers and generalized weakness. His past medical history significant for combined heart and kidney transplant seven years before, type II diabetes, CKD, hyperlipidemia, and hyperparathyroidism. He recently traveled to Ghana and he had no other localizing signs/ symptoms of infection on presentation. While in Ghana, he had not taken any of his malaria prophylaxis medications. He presented to the ER after he noted onset of chills, and increasing heart rate, after returning to the United States. Because of his prior combined heart and kidney transplant he was on immunosuppressive medications including Tacrolimus and Mycophenolate. He was fully vaccinated for COVID-19 and had no other recent illness prior to onset of symptoms.

On presentation, patient was febrile to 39.4 with tachycardia to 136. Blood pressure and oxygen were stable. The patient was very well appearing on physical exam including no evidence of acute decompensated heart failure, abdominal pain or distension, nor any skin rashes. Admission labs were rather unremarkable including WBC, troponin, electrolytes, kidney and liver function. COVID-19 and Influenza were negative. CXR was negative. He was admitted to medicine and started empirically on vancomycin and cefepime. Infectious testing included thin and thick blood smear, typhoid fever, dengue fever, chikungunya, as well as viral hemorrhagic fever. Initial parasite smear revealed plasmodium falciparum species with 0.1% parasitemia. The patient's current symptoms included significant abdominal pain with nausea and vomiting. The rest of his evaluation was negative for concomitant bacterial and viral infection.

Per infectious diseases, patient was started on hydroxychloroquine and then transitioned to artemether lumefantrine when it was available. He was also transferred to a tertiary care hospital for higher level of care. After transfer, he received 3 doses of artesunate. Parasitemia was trended until it was undetectable by the date of discharge. Hospital course was complicated by severe metabolic acidosis with HCO3 < 10 due to malarial hemolysis, which improved with fluids with bicarbonate and treatment of the underlying malaria infection. Transplant cardiology and transplant infectious diseases were consulted. Tacrolimus was continued given no interaction with artesunate, while mycophenolate was held. The patient's symptoms and labs improved. Artesunate was transitioned to coartem to complete course upon discharge. On discharge, mycophenolate was resumed with continued follow-up with his specialty providers. The patient completely recovered from his severe malarial infection, which was documented at outpatient follow-up.

Discussion

Plasmodium Falciparum infections usually present clinically about one month after an exposure to the parasite.[1,2] The cycle begins when the patient is bitten by a female Anopheles mosquito carrying the parasite, inoculating the patient with sporozoites, which then migrate through the bloodstream to the liver and invade the patient's hepatocytes and form schizonts (pre-erythrocytic stage). At this stage, the patient is asymptomatic, but these schizonts will rupture into the circulation with release of merozoites from involved red blood cells. About one month after exposure to the parasite the disease becomes clinically significant with symptoms during the erythrocytic stage.[1,2] Symptoms include irregular fevers, as high as 40°C and other nonspecific symptoms including generalized malaise/ fatigue, nausea/vomiting, abdominal pain, tachycardia, and myalgias.[3,4] Most of these symptoms were present in our patient intermittently throughout his hospitalization. Cyclic fevers may occur due to the life cycle of the parasite, occurring every third day when the schizont ruptures with subsequent release of merozoites from the affected red blood cells.[3]

Diagnosis of uncomplicated symptomatic plasmodium falciparum infection can be established with a positive parasitological test. Testing should be considered in any patient with recent travel to endemic area presenting with fever, about one month after exposure to the parasite. If the initial tests are negative, given propensity for development of severe disease, patients should have follow-up testing for at least two more days.[5] Presumptive diagnosis can also be made with high enough suspicion and in these cases, it may be reasonable to treat empirically. The caveat is potentially missing other disease processes that present similarly to malaria and overlap even in malaria endemic regions.

Malaria causes severe disease by parasite-infected red blood cells sticking to the lining of small blood vessels throughout the body, inhibiting blood flow, potentially causing infarcts that lead to organ dysfunction. These end-organ defects can lead to metabolic acidosis, as in our patient, shock, hepatic/renal failure, severe anemia from massive hemolysis, and seizures.[6,7] If any of these are present in a confirmed malaria patient, prompt treatment is absolutely necessary to prevent possible death, which may occur within hours of presentation. Rapid

initiation of empiric antimalarial therapy via parenteral route for at least 24 hours and supportive management to address severe complications. These include cardiac or renal failure, oxygenation, with potential ventilation, and acidosis. Other concomitant bacterial and viral infections also need to be ruled out. IV or IM artesunate is first line treatment for patients with severe anemia and if it cannot be obtained, the preferred oral agent is artemether-lumefantrine, while awaiting artesunate.[8,9] Malarial infections should be high on the differential diagnosis in patients with no immunity to malaria, including travelers not from endemic regions.[4,5]

There are many considerations when planning travel to malaria-endemic areas. It is Important to discuss itinerary travelers, risk factors, infection prevention strategies, and chemoprophylaxis. Counseling should include discussion of possible infections, signs/symptoms of infection, prevention measures to avoid mosquito bites, and strict adherence to the chemoprophylaxis regimen.[1] Depending on the regimen, the medication may need to be initiated prior to travel to endemic area and continued for a period of time after departure. Most areas of endemic malaria have chloroquine-resistant Plasmodium Falciparum and the mainstays of prophylaxis are atovaquone-proguanil, mefloquine, doxycycline, and tafenoquine.[10]

Conclusion

Given concerns of developing severe malarial infection, it is very important to perform a risk assessment for infection, determine best practices to prevent infection, and the best chemoprophylaxis regimen based upon travel itinerary. If infection occurs or there is high suspicion of malaria parasitic infection prompt initiation of intravenous anti-malarial therapy and supportive management must be performed to prevent significant morbidity and mortality.

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