Lung damages of malaria: a differential diagnosis and treatment in emergency room of a rare case

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ABSTRACT

Pulmonary involvement occurs in 3 to 10% of the cases of *Plasmodium* falciparum malaria and represents the most severe complication of this infection, with a lethality of about 70%. The antigens released by the parasite play an important role in the induction and worsening of lung damage. Capillary endothelial cells, which control the flux of fluids to the interstitial space, appear to be the most complicated structures. The clinical manifestations of pulmonary involvement may start suddenly at any time during the course of malaria, even after the disappearance of the circulating parasite. Hyperparasitemia predisposes to these factors. Treatment with corticosteroids is optional, and that is not often a benefit.

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Background

According to the Malaria Report 2021, in 29 countries of the European Union and the European Economic Area, 8641 cases of malaria have been recorded (1.3 cases per 100,000 inhabitants). France reported the most significant number of cases, followed by the UK and Germany. 99.8% of patients were associated with travel to endemic areas. Nine cases were reported as locally acquired: 2 in Germany, 2 in Greece, 2 in Spain, 2 in France, and 1 in the Netherlands. The seasonal trend is confirmed with a peak in cases corresponding to the summer vacation period (July-September), which was higher in 2019 than in previous years. The number of cases remains higher among men than among women (ratio 1.8: 1). The age group most involved remains between 24-44 years.[1]

Malaria was eliminated from the European region around 1970. Since then, malaria control programs were replaced by surveillance systems to carefully monitor disease importation and prevent its possible re-emergence.[2,3] Malaria still represents the central imported infectious disease in non-endemic countries, strongly related to the increase in travelers and migratory flows to and from endemic areas.[2] We would like to highlight another infection that can cause diffuse lung disease and is common in extensive not only in tropical and subtropical regions, to migrants events: malaria, caused by the protozoan *Plasmodium* sp.

Clinically we have some criteria for the severity of

malaria, such as coma status, shock, acidosis, severe anaemia, acute respiratory distress syndrome, renal failure, hypoglycemia, disseminated intravascular coagulation, and hemoglobinuria.[4]

Case history

In November 2022, we observed a case of Pnemonia severa to Malaria Falciparum in the emergency room of Cotugno Hospital; a young woman of 25 years who had toured 3 hospitals before coming to our hospital for fever and severe dyspnea.

The patient was transferred to our emergency room for persistent fever and dyspnea. Immediately come to our observation, we performed a rapid test of Binax Now for Malaria that was positive for Malaria Falciparum, and a peripheral smear was performed from the blood count where P. falciparum was highlighted.

We observed a clinical picture of severe malaria with sensory alteration, pleural effusion, thrombocytopenia, hypoalbuminemia, alterated procalcitonin (PCT) and polymerase chain reaction, with blood to *Plasmodium* spp: positive; Sequential organ failure assessment score: 2, CURB65:2 and Pneumonia severity index score (PSI): 90 points.

After a computed tomography (CT) and biochemical routine, the patient began therapy with IV Artesunate according to the WHO protocol, with clinical improvement after 3 days and decreased parasitemia values (Table 1).

CT radiogram presented bilateral pleural effusion in gravitational disposition with thickening and dysventilation of the neighboring parenchyma. Thickening of the interlobular septa borne by lysergic acid diethylamide. No evidence of ilomediastinal lymphadenopathy.

After the resolution of this clinical picture, the patient was also addressed to follow up after 15 days and one month. Physical examination was normal both times, fever and/or dyspnea were not reported, lymphadenopathies were not detected. Haemocrome did not reveal any alteration as far as procalcitonin levels (Table 1).

Discussion

Malaria is a parasitic infection, caused by parasites of the genus *Plasmodium* and transmitted by Anopheles mosquitoes, that leads to an acute and potentially life-threatening disease. The clinical features of Malaria range from mild to severe clinical manifestation and depend on the host's immune status, infection history, parasite virulence, and genetic variations in both the host and parasite.[5] Patients with uncomplicated malaria present nonspecific symptoms like fever while severe and complicated malaria is characterized by multiorgan involvement including acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).[4] Respiratory involvement has been described in malaria, respiratory symptoms in uncomplicated malaria are common in African children and may overlap with clinical features of pneumonia.[2] In adults, respiratory symptoms and signs also occur in uncomplicated falciparum malaria, with a reported frequency of 4-18%. Main pulmonary alterations consist of airflow obstruction, impaired ventilation, reduced gas transfer, and increased pulmonary phagocytic activity.[6] ALI and ARDS are important complications in severe, complicated falciparum malaria. It has been described in p. *vivax* and p. *ovale* malaria also. ARDS in malaria is a condition with high mortality; for this reason, patients with malarial ARDS should be managed in intensive care units.[7]

P. falciparum or P. knowlesi associated ARDS often starts after the onset of other complications and is commonly associated with a history of high parasitemia.[8] In Malarial ALI and ARDS is reported pulmonary edema rich in protein due to rupture of the alveolar-capillary membrane;[9] *post-mortem* observations highlighted the presence of abundant inflammatory infiltrates in the lungs characterized by monocytes and macrophages. The malarial pigment is seen inside these cells, reflecting phagocytosis's role.[10] In P. falciparum malaria ARDS microvascular disease and high cytokine levels are considered important factors in the pathogenesis.[11] Thus, Cytokines such as TNF-α may promote cytoadherence by increasing the expression of endothelial receptors needed in the binding of the parasitized cells to endothelium.[12] Important pathogenetic findings in com-

Table 1. Prognostic values used for the reported case.

Patient	T0	T1 follow up day 15	T2 follow up day 30
Number parasites/µL	1.5%	0%	0%
SOFA score	2	0	0
Procalcitonin ng/mL	9.71	<0.5	
Hemoglobin mg/dL	9.1	11.2	12.9
PSICURB65	902	-	-

PSI, pneumonia severity index; SOFA, sequential organ failure assessment.

plicated malaria are the sequestration and destruction of parasite and erythrocyte material into the circulation and the host's inflammatory response to these events (chest).[4] To notice that inflammatory infiltrates in malaria consist mostly of monocytes, macrophages, and lymphocytes compared with nonmalarial ARDS where neutrophils are predominant.[13] CD8+ cells are also involved in the pathogenesis of malarial ARDS.[14]

Malaria may appear with different clinical presentations that vary from oligosymptomatic to ARDS. Together with ARDS, one of the most different scenarios may be dangerous in case of severe malaria as ALI, in which admission to ICU is frequent. From a pathophysiological point of view erythrocyte sequestration and disruption induce a cytokine storm starting from the release of IL-1 and IL-6 that may induce a SIRS. Different types of plasmodium are also able to induce different damages in the lung and in several cases, airflow obstruction, impaired ventilation, and reduced gas exchanges are early detected. Microscopically, alveolar capillaries demonstrate the sequestration of erythrocytes causes congestion of pulmonary capillaries with large numbers of monocytes and neutrophils, often containing phagocytosed malaria pigments that facilitate alveolar dysfunction. Overlapping of bacteria may also appear during ALI so inducing a further activation of the inflammatory response, *Staphylococcus* spp, *Streptococcus* spp, and *Klebsiella* spp are mainly frequent. Metabolic acidosis or respiratory alkalosis are the two induced most common patterns of ventilation present during ALI and they are related to the severity and extension of lung damage. PaO2 /FIO2 <300 with Pulmonary capillary wedge pressure <18 mmhg with atrial enlargement are other most common findings of ALI, while ARDS is similar to those occurring in other clinical pictures (*e.g.* COVID-19, and so on). Management of malarial ARDS consists of general supportive therapies, specific antimalarial therapy, and respiratory support (continuous positive airway pressure).[15] The administration of steroids in ARDS has been associated with a reduction in mortality, however, because of negative results with corticosteroids in treatments of cerebral malaria, its use remains controversial, but in selected cases, the use of cortisone could be promising.[12] Pneumonia and malaria are important causes of mortality and illness in children under five years, clinical manifestations of malaria with respiratory symptoms and pneumonia can be similar, for which WHO guidelines suggest a clinical case approach,[3] because of this similarity, there is a risk of under and overdiagnosis of pneumonia and malaria.[16] Diagnosis of both diseases is based on clinical findings, chest radiology, culture, and malaria testing, including microscopy/RDT.[17] According to WHO recommendations, the clinical definition of severe pneumonia is characterized by cough or difficulty in breathing and at least another one clinical criteria (severe respiratory distress, hypoxemia: spo2 <90%, unable to breastfeed or drink adequately, decreased conscious state, seizures), while severe malaria is defined by fever (or history of fever), and positive malaria test and at least another one clinical criteria (severe anemia, decreased conscious state, seizures).[18] Some local hospitals do not offer blood cultures and chest X-rays. Using only a combination of clinical signs might not be able to discriminate between malaria and severe pneumonia, especially in the absence of a chest X-ray.[17] A cohort study in Nigerian Hospitals highlights that diagnostic practice based only on clinical signs with low use of chest radiology links with a high rate of missed diagnosis of pneumonia and consequently delayed therapy administration, undertreatment, or bad clinical outcome. Several studies describe that the clinical presentation of pneumonia and malaria may overlap while the coexistence of both severe diseases is less common.[19-21] Coinfection has a higher mortality rate than clinical malaria alone.[22] Clinical findings of severe malaria and severe pneumonia are fever, respiratory distress, and tachypnoea. In pneumonia, respiratory distress correlates with a degree of lung injury.[16] Respiratory distress in malaria is a consolidated predictor of mortality among children.[23] Existing guidelines suggest that all patients matching clinical WHO criteria for pneumonia should receive treatment for that.[3] The clinical overlap between pneumonia and malaria is an important clinical challenge in regions in which both pneumonia and malaria are prevalent. Patients with severe pneumonia should be investigated for malaria, and *vice versa* in order to minimize the risk of misdiagnosis and undertreatment.

Disease due to P. falciparum infection is more severe and qualitatively different from disease caused by the other plasmodia that infect humans. *Plasmodium* falciparum is the only human malaria parasite that produces microvascular disease. As P. falciparum parasites mature, knobs appear on the surface of the parasitized red cell that facilitates the cytoadherence of P. falciparum parasitized red cell to endothelial cells in capillaries and post-capillary venules of the brain, kidney, pneumonia and other affected organs. The concentration of cytokines and TNF-α is increased in severe P. falciparum infection and may thus exacerbate the microvascular pathology by enhancing cytoadherence. The elevated TNF-α levels produce the pulmonary edema observed in severe malaria (as it may in gram-negative bacteremia). The damage to the lung is like in multiorgan failure.

Furthermore, hyperparasitemia is a risk factor for severe *P. falciparum* malaria, and recently also, PCT has been related to the severity of malaria.[16] Hyperparasitemia (defined as more than 2% parasitized red blood cells or 100,000 parasites/μL) may be very useful in ruling out patients with severe malaria. Overall, hyperpar-

asitemia correlates with poor outcomes and with an interest in complicated lungs.[3]

Conclusions

Previous reports have highlighted the risk of under and overdiagnosis of pneumonia and malaria, recommending identifying potentially missed cases of severe pneumonia and severe malaria when a patient is admitted to the hospital. Patient with severe pneumonia in malaria has a history of fever and anemia, and are less likely to have a history of cough or difficulty in breathing, severe distress respiratory, diarrhea, and severe dehydration. However, the clinical presentation of pneumonia and malaria can be similar.

The type of respiratory distress is ALI and acute respiratory distress syndrome. Malaria is defined as MA-ARDS a severe complication of malaria.

Pulmonary edema is a major complication of severe malaria, with a high mortality rate. It is often difficult to differentiate between pulmonary edema and ARDS.[23] The development of pulmonary edema in association with malaria characteristically occurs in the absence of cardiac failure or fluid overload.

In patients with acute lung injury/ARDS due to malaria, chest X-rays may reveal bilateral opacities and increased interstitial markings mimicking the pattern observed in patients with ARDS due to other causes (Figure 1).[21] Small pleural effusions may be observed. Pulmonary edema may occur early due to heavy parasitemia or later due to prolonged altered capillary permeability in severe malaria.[24] Malaria is diagnosed parasitologically and is usually confirmed by thick (for parasitemia detection) and thin (for species identification) peripheral blood smear examinations.[21,24]

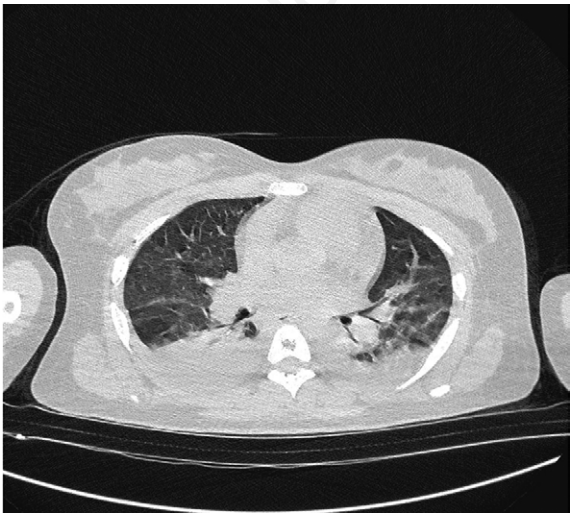

Figure 1. Bilateral pulmonary exudation and infiltration due to acute lung injury during malaria.

The common cause of ARDS includes sepsis, bacterial o viral infectious disease, and aspiration pneumonia. In malaria the problem is the presence of abundant monocytes and macrophages both inside the blood capillaries and in the interstitium and sometimes also in the alveolar spaces. Sequestration of P. falciparum occurs in several organs, including the lungs and brain. Important conclusions about MA-ARDS in clinical studies are the presence of prominent inflammatory infiltrates in the lungs, considerable differences in patient outcomes, and the observation that this complication has a high mortality rate, even with clinical management involving antimalarial drugs and positive pressure ventilation. A particular condition is that in this MA-ARDS the glucocorticoids have no similar effects as ARDS of other infections because malaria is mainly mediated by neutrophils, which are notoriously unresponsive to glucocorticoids.

We conclude that is very important in the emergency room to differentiate the diagnosis of ARDS in infectious diseases; so it's very important for rapid etiological diagnosis for targeted therapy in patients with severe complicated malaria, the early administration of specific antimalarial therapy is life-saving, and the use of corticosteroids in good with a low dosage for complications in severe malaria. It can be too useful a trial with the utilization of corticosteroids in malaria complications.

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