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Case Report

Co-infection with *plasmodium falciparum* and COVID-19 with lethal outcome. First clinical case from Bulgaria

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Abstract

The symptoms of COVID-19 include febrility and mainly catarrhal symptoms. In severe cases, patients present with progression to lower respiratory tract and acute respiratory distress (ARDS) and multi-organ dysfunction. Malaria caused by *P. falciparum* is a severe, endemic parasitosis, mainly in Africa. In some cases, it can be complicated with ARDS. We present a case of a patient who returned from Nigeria with respiratory symptoms, in which both COVID-19 infection and tropical malaria were proven; with a fatal outcome.

Keywords: COVID-19, Malaria, ARDS, Co-infection

INTRODUCTION

The ongoing pandemic of COVID-19, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has created a serious global public health. The most common symptoms of COVID-19 include febrility, malaise, dry cough, headache, myalgia, gastrointestinal symptoms [1, 2]. In severe cases, patients present with signs of breathing difficulty, chest tightness, and a feeling of shortness of breath; in some cases of COVID-19, progression to lower respiratory tract disease (e.g. pneumonia) can occur, which can lead to severe respiratory failure. Such patients, especially particularly older patients with multiple medical conditions and multimorbid, may suffer from acute respiratory distress and multi-organ dysfunction [2, 3].

Malaria caused by *P. falciparum* (tropical malaria) is a severe, endemic parasitosis, mainly in Africa and parts of Asia. Untreated tropical malaria usually leads to death [4]. The most severe manifestations include cerebral malaria. A severe complication is acute respiratory distress syndrome (ARDS). The condition is characterized by inhibition of ARDS precipitates a substantial decline in oxygen diffusion to the bloodstream, culminating in hypoxemia characterized by subnormal oxygen levels in the circulatory system.

The pulmonary inflammation, can persist even when parasitaemia is reduced [4, 5]. There are many common symptoms between COVID-19 and malaria that literally overlap and clinicians need to be vigilant, especially in malaria-endemic areas [6].

Case Report.

A 28-year-old man presents with of high fever with chills, muscle pain, sore throat, headache and shortness of breath for 7 days. The reason for the visit to the emergency center was yellowing of the conjunctival icterus and skin. A rapid antigen test was performed for SARS-CoV-2, which was positive. The patient had no chronic illnesses, but 3 days before the onset of complaints he returned from Nigeria. The patient's examination shows, marked conjunctival icterus and skin, as well as hepatosplenomegaly; low arterial pressure—80/45 mmHg, O2 saturation is 90%. There is no evidence of encephalopathy or other neurological symptomatology. qRT-PCR material was positive for virus nucleic acid at Threshold cycle (Ct) 30. In blood drop and smear for malaria Trophozoites of *P. falciparum* are observed under the microscope, parasitemia was estimated at 35%. Dynamics of blood indicators are given in Table 1.

An infusion of glucose-saline solutions was started, the patient received 4 tablets of Artemether (20 mg) + Lumefantrine (120 mg) for lack of another artemisinin preparation. Disorientation set in, headache and vomiting occur; stops urine output. Furosemide and perfuser with Dopamine Hydrochloride in beta doses are without effect. On the second day blood samples showed deterioration (Table. 1). A lung scan showed inflammatory lung changes characteristic of COVID-19 [3]. By the second blood microscopy, parasitemia was around 30%. On attempting to give a third dose of antiparasitic medication per os the patient vomited. The patient developed malarial coma, kidney and liver failure and the onset of severe respiratory failure. Was placed on ventilator and the therapy was supplemented with bioproducts and hemodialysis. Fibrin degradation products (FDPs) were also examined in the intensive care unit. Along with the other indicators, the disseminated intravascular coagulation (DIC) score was 4 [7]. We started

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Table 1. Dynamics in the main laboratory indicators by days

Test	Results				Reference range
	Illness Day 7, Hospital Day 1	Illness Day 8, Hospital Day 2	Illness Day 9, Hospital Day 3		
Haematology					
WBC count	14.9	16.2		16.31	4.00–10.00 × 103/μL
RBC count	3.8	3.6	2.0		4.50–5.50 × 106/μL
Haemoglobin	12.1	11.8		6.21	13.8–17.2 g/dl
Platelet count	27.2	28.0		33.2	150.00–410.00 x103/μL
Neutrophils	87.2	76.5		71.9	40.00%–80.00%
Lymphocyte	1.6	16.8		24.2	20.00%–40.00%
Monocyte	0.2	6.8	7.8		2.00%–10.00%
CRP	3.7	3.8	2.3		0.3–1.0 mg/dL
aPTT	37.1	34.6	36.2		25.3–34.5 sec
INR	9.4	4.9	5.7		0.8–1.1
D-dimer	1.8	2.1	1.9		0–0.5 mg/L
Biochemistry					
Urea	89.63	97.42		126.0	12.00–42.00 mg/dL
Creatinine	9.8	10.6		6.86	0.90–1.30 mg/dL
AST	184.0	174.0		376.0	0.00–40 U/l
ALT	72.0	64.0		124.0	5.00–40.00 U/l
DBIL	14.78	20.0		20.89	0.00–0.30 mg/dL
TBIL	28.2	30.6		31.42	0.20–1.20 mg/dL
Albumin	3.2	3.4	-		3.4–5.4 g/dL
Total protein	5.55	5.1	-		6.0–8.3 g/dL
LDH	904	982		787	140–280 U/l
Chloride	92.1	91.0	-		95.00–110.00 mmol/L
Potassium	4.8	5.0	-		3.50–5.50 mmol/L
Sodium	126	132	-		136.00–145.00

Dexamethasone on schedule, but did not include an interleukin-6 inhibitors. Despite some contraindications, it was applied etiologic treatment for COVID-19 "off label" with Remdesivir [3, 7].

Antiparasitic therapy continued through a nasogastric tube. Parasitaemia dropped to 3%. Of the third day, blood tests showed an unsatisfactory response (Table 1). The developed acute poly-organ failure with hemolytic uremic syndrome, encephalopathy, melena and the patient was pronounced dead after hemodynamic collapse.

DISCUSSION

This is the first report in Bulgaria of a patient with imported malaria in the course of SARS-CoV-2 infection.

This death in a relatively short time indicates some less common complication of parasitic-viral co-infection can act as a double burden on the immune system [6–8]. A storm of pro-inflammatory cytokines like IL-1 and IL-6 and IFN-γ are produced in early malaria infection due to the direct destruction of parasitized RBCs by antigen-presenting cells such as NK and ect. This induces inflammation to restrict parasite growth [8]. But, the level of the proinflammatory cytokine IL-6 was decreased in the plasma of patients with acute COVID-19. The decreased IL-6 level overturns IFN-γ production in NK cells in vitro and possibly affects the normal function of NK cells in patients with severe illness [6, 8]. IL-17 is a pro-inflammatory cytokine that has been shown to protect against some viruses [6, 9]. In *P. falciparum* infection, the secretion level of IL-17 was positively related to the severity and multiple-organ dysfunction including kidney and liver failure [6–9]. An in vitro study is described that in some cases NK cells display an anti-SARS-CoV-2 activity and also limit tissue fibrosis [6, 10]. However, NK cells from patients with COVID-19 were found to display a dysfunctional status, which might compromise their anti-SARS-CoV-2 activity and potential antifibrotic activity, especially in individuals with severe disease [10]. Production of cytokines and chemokines, which induce the immune cells in the lungs was increased, hence resulting in ARDS, which is fatal for patients [3, 6, 9]. Anti-inflammatory cytokines due to malaria did not protect the patient because he was living in an endemic area for the first time. Multiple-organ failure can occur in both diseases [6, 8, 9]. The platelet drop is probably in the course of Disseminated Intravascular Coagulation Syndrome [3, 5]. The encephalopathy was most likely due to hypoxia, but also due to diffuse obstruction of the microcirculation in the central nervous system as a consequence of the malaria [4, 5]. Judging from the threshold cycle (Ct), COVID-19 may have occurred some time ago and may not strictly as a co-infection. However, it is quite possible that COVID-19 contributed to the severity of malaria.

Further studies at the molecular level on the interaction of proinflammatory cytokines in co-infection with non-immune malaria patients are needed. In cases of return from malaria endemic areas and febrility, patients must be tested for both diseases. The early diagnosis of such co-infections, will improve the prognosis for patients.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing.

FUNDING

The study did not receive any funding.

ETHICAL APPROVAL

This study is exempt from ethical approval at our hospital.

CONSENT

The direct heirs of the patient gave written consent for publication of this case.

GUARANTOR

Dr. Valeri Velev.

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