Case Report
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Efficacy of Amphotericin B on COVID-19: A Case Report Study

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Abstract
The role of amphotericin B (AmB) as an antiviral drug against some enveloped viruses has been studied in previous researches. Coronavirus is an envelope, non-segmented and positive-sense RNA virus which may be targeted by AmB. Our case was a 34-day-old female child with a 4-days history of low consciousness and dry cough, which gradually became productive. The infant was cyanotic at the admission time that transferred to the Neonatal Intensive Care Unit (NICU). After discharge, we were informed that result of PCR (polymerase chain reaction) test was positive which has been first reported as a false negative result. So the results drove our attention to that amphotericin B may cause a dramatic response to the coronavirus. Because of the crucial role of the immune system in viral clearance, the AmB as an immune response and pro-inflammatory stimulator may pave the way for preventing invasion in viral infections such as COVID-19.
Keywords: COVID-19, Amphotericin B (AmB), antiviral drug, severe dyspnea, intensive care units, neonatal

Introduction

The novel coronavirus (2019-nCoV) also named SARS-CoV-2 or Coronavirus Disease-2019 (COVID-19), is an acute infectious disease first manifested in Wuhan, China on December 26, 2019.[1,2] Patients with COVID-19 often experience severe respiratory syndrome with the clinical signs of fever, fatigue, dizziness, dry cough, and gradually develop severe dyspnea.[2] The diagnostic approaches for COVID-19 have mainly relied on reverse transcription-polymerase chain reaction (RT-PCR) or gene sequencing of sputum, throat swabs or lower respiratory tract excretions.[1-3] The best preventive approach is to limit human-to-human transmission by early detection, isolation and caring for patients.[2] Patients with influenza who developed severe acute respiratory distress syndrome (ARDS) may also present invasive pulmonary aspergillosis (IPA), as the main leading cause of prolonged hospitalization and mortality rate.[4,5] Co-infections with bacteria and fungi have more occurred in 40% of hospitalized patients with COVID-19 who developed ARDS, which is often associated with the development of IPA in patients taking corticosteroid drugs.[6,7] It is not currently known whether COVID-19-associated IPA antifungal therapy becomes a survival profit, however, diagnosis in most cases must result in early antifungal therapy.[4] Liposomal amphotericin B has been used as the ancient agent and treatment choice in the first-line therapy for various fungal infections specially IPA treatment in ICU.[8] Amphotericin B (AmB) belongs to the polyene group with broad-spectrum in vitro and in vivo antifungal activities and a valuable pharmaceutical profile which has low fungal resistance.[9,10] Since AmB has a high affinity to ergosterol than cholesterol, it is effective against fungi and single-cell protozoa.[11] Several studies have been focused on the different mechanisms of action and the potential therapeutic effect of AmB derivatives against some enveloped viruses, including human immunodeficiency virus (HIV),[12] herpes simplex virus (HSV),[13] Japanese encephalitis virus and Rubella virus.[14,15] It has been expected that AmB would change viral membrane integrity and envelope structure as well as host immunomodulatory effects.[9,15] Since coronaviruses belong to the enveloped viruses with positive-sense RNA nucleic acid and club-like spikes, AmB, may pave the way for designing a novel therapeutic option in COVID-19 treatment. To the best of our knowledge, there is limited literature on the efficacy of AmB against viral infection and no research is available on the role of AmB in pediatrics with COVID-19, so, we decided to share our experiences on a case report of the Iranian 34-day-old child with signs of suspected COVID-19 which may be of interest to health care workers who involved in health systems all over the world.

Case Report

The patient was a 34-day-old female infant who was admitted to the emergency department (ED) due to decreased level of consciousness. She had a dry cough from 4 days before the admission, which gradually became productive. She had no fever, shortness of breath, seizures, poor feeding and had the excretion of urine and feces. At the time of admission, the infant was cyanotic. Her weight was less than 2,500 g (1900 g and the birth weight of 3000 g) and she was less than two months old, therefore, she was admitted to NICU. She had an opium-addicted mother who gave him opium in a lentil size since birth. The infant had a bilateral cleft lip and palate. Her parents were non-appointed and both had a positive history of cough. No ecchymosis or purpura was found on physical exam, and she had no bulging or sunken fontanelles and her ears were normal. On physical exam of her eyes, the conjunctiva was swollen and the pupils had bilateral meiosis. The abdomen was soft and had no organomegaly. The genitals were girlish and normal. The infant was completely hypotensive with no response to stimulation. In the clinical record, she was reported a term neonate. Totally, at the time of admission, she was cyanotic, unconscious, motionless, and intubated that was given cardiac massage and underwent salvage. In NICU, naloxone was administered and treatment with meropenem and vancomycin was continued, she was then intubated and underwent ventilation.

During the course of hospitalization, the patient developed convulsive movements that started phenobarbital and then underwent echocardiography, which she showed small Patent Ductus Arteriosus (PDA), mild to moderate Myocardial Infarction (MI), and mild Tricuspid Regurgitation (TR). In electroencephalogram (EEG) monitoring, the epileptic waves were reported. Extensive multicystic encephalomalacia was reported in Brain Computed Tomography (CT). The test result was negative for COVID-19, while bilateral lung opacity was seen on chest X-ray (CXR). Because of non-response to 3-week-treatment with meropenem and vancomycin, the drugs were switched to cefepime and clindamycin, and amphotericin B was then started about 6 days later. The result of fungal test was negative but due to the organic response to amphotericin B, the drug continued and the ventilator set-up was rapidly reduced. The infant was disconnected from the ventilation device. The milk started and she was finally discharged with an improved general condition. After discharge, we were informed that result of PCR (polymerase chain reaction) test was positive which has been first reported as a false negative result. So the results drove our attention to that amphotericin B may cause a dramatic response to the coronavirus.

Discussion

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) occurred in Wuhan, Hubei Province, China, in early December 2019 in patients who had a history of entrancing to the Huanan Seafood Wholesale Market.[16] The novel COVID-19 caused by an un-segmented (+RNA) coronaviruses presents the continuous spreading with arising mortality rate in the world.[17] Therefore, designing more effective therapeutic strategies and targeted therapies seem highly necessary to avert the spread of the upsetting pandemic worldwide. So far, there is no specific drug to directly target this novel virus and support organ failure in seriously ill patients which is considered as the main phase in clinical management.[18] However, there are some marketed drugs available to avert ARDS as a main outcome of COVID-19 in combination with nutrient supplements.[18] In addition, applying drugs such as Chloroquine and hydroxychloroquine in some COVID-19 patients may be associated with many side effects.[19] Our case received treatment with naloxone followed by meropenem and vancomycin, both of them are antimicrobial agents which improve outcomes and shorten the duration of hospitalization in some cases with respiratory infections including pneumonia.[20] Recently, the clinical significance of therapeutic combination regimens in the management and monitoring of patients who suffer from COVID-19 pneumonia has been considered.[20] The use of the different combination regimens has been indicated to improve outcomes of COVID-19 patients; the regimens include meropenem, levofloxacin, vancomycin as the antibacterial agents, and hydroxychloroquine, and oseltamivir as the antiviral agents.[20] In addition to current therapeutic strategies, AmB has become the center of attention recently as a possible antiviral agent for COVID-19 treatment.[15] Therefore, its optimal therapeutic application is required to be more clarified by clinical trials. It seemed that AmB has a more toxic effect on the virion of enveloped viruses than on the host cell, which is probably due to the differences and changes in the viral proteins derived from the host cell composition.[15] Therefore, these morphological and biological aspects of the viral envelope make it a suitable target for designing a novel antiviral therapy. In our case report, the patient did not show any improvement in the clinical outcome after long-term use of meropenem and vancomycin resulted in switching to cefepime and clindamycin, and finally AmB. We observed the considerably improved outcomes immediately after starting the AmB which may be due to the proper efficacy of this drug. Moreover, AmB has many indicative characteristics including accessibility, rare resistance, as well as broad-spectrum activity against many fungal and microbial infections, and viral RNA nucleic acid and envelopes; therefore, designing further research studies and clinical trials seems necessary to fully recognize the role of AmB in patients with COVID-19. To the best of our knowledge, most enveloped viruses targeted by AmB may have similar complexity and viral-specific proteins; moreover, considering the crucial role of the immune system in viral clearance, the AmB as an immune response and pro-inflammatory stimulator may pave the way to prevent invasion in viral infections such as COVID-19.

The major aspects in the recovery of patients with COVID-19 are establishing proper supportive maintenance and antibiotics-antiviral combination therapies which may take a long time to evaluate, and choosing specific antiviral agents as suitable therapeutic regimes for novel COVID-19. Relying on the results of previous studies about the unique characteristics and efficiency of AmB against various enveloped viruses, the application of AmB alone or in combination regimens may be effective in the reduction of drug side effects and improved prognosis of patients with COVID-19 pneumonia.

Abbreviations

AmB: Amphotericin B
NICU: Neonatal Intensive Care Unit
2019-nCoV: 2019-novel coronavirus
RT-PCR: Reverse transcription-polymerase chain reaction
ARDS: Acute respiratory distress syndrome
HIV: Human immunodeficiency virus
HSV: Herpes simplex virus
ED: Emergency department
PDA: Patent Ductus Arteriosus
MI: Myocardial Infarction
TR: Tricuspid Regurgitation
EEG: Electroencephalogram
CT: Brain Computed Tomography
CR: Chain Reaction
SARS-CoV-2: Severe acute respiratory syndrome coronavirus

Ethics Approval

Institutional review board approval for case report was not required at our institution at the time of the study. Written informed consent was obtained from the patient for publication of this case report. To keeping ethical principles, the name of the patient was not pointed in the paper and the rights of the subject were protected. The patient received treatment consistent with the current standard of care.

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Conflict of Interest

The author reports no conflicts of interest in this work.

Consent for Publication

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images.

Informed Consent

Written informed consent was obtained from the patient's legal guardian for participation of the infant in the study.

Data Availability Statements

The data that support the findings of this study are available from corresponding author on reasonable request.

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