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Role of pheniramine maleate in cytokine storm of COVID-19: A case report

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Abstract
COVID-19 is transmitted via droplets or direct contact and infects the respiratory tract resulting in pneumonia and acute respiratory distress syndrome due to excessive production of proinflammatory cytokines leading to widespread tissue damage and multi-organ failure. Targeting cytokines during the management of COVID-19 patients could improve survival rates and reduce mortality.
We are presenting a case of a 55 years old female patient with COVID-19 pneumonia with cytokine storm. The patient was treated according to standard treatment guidelines along with Injection Pheniramine maleate. Dramatic improvement in the patient's condition and shorter duration of hospital stay compared to the other cases of severe COVID-19 pneumonia having cytokine storm with longer time of recovery and longer duration of high oxygen demand suggests the role of antihistaminic agents in the treatment of cytokine storm.
Hence, we conclude that the inhibition of the inflammatory pathway by an antihistaminic agent (pheniramine maleate) halted the progression of cytokine storm in this patient thus reducing the days in the high dependency unit and favorable clinical outcome.

Keywords: pheniramine maleate, cytokine storm, COVID-19, antihistaminic, pneumonia, proinflammatory, multi-organ failure

Introduction
COVID-19 is a rapidly spreading global threat that has been declared a pandemic by the WHO (world health organization). COVID-19 is transmitted via droplets or direct contact and infects the respiratory tract resulting in pneumonia in most cases and ARDS (acute respiratory distress syndrome) in about 15 % of the cases. Cytokine storm due to dysregulated immune response to the virus is responsible for most of the mortalities in COVID-19 patients. Widespread tissue damage leading to multiorgan failure including ARDS can be attributed to excessive proinflammatory cytokines production resulting in poor prognosis and death. Cytokine inhibition can be targeted in the management of COVID-19 patients and could improve survival rates and reduce mortality [1]. Antihistaminic agents (Pheniramine maleate) can control cytokine storm of COVID-19 and prevent ARDS aggravation and multi-organ failure. Pheniramine maleate was successfully used in this case to manage the cytokine storm of COVID-19.

Case Presentation
A 55 years old female patient, unvaccinated for COVID-19, without any known co-morbidities, presented to our hospital with a history of productive cough and profound dyspnea for the last 1 week with generalized weakness. On admission, she was afebrile having SpO2- 34 % at room air with tachypnoea and tachycardia, and tested positive for COVID-19 and was admitted to COVID HDU (high dependency unit) with arterial PO2(partial pressure of oxygen)-51.6 mmHg on high flow oxygen (16 L) via NRBM (non-rebreather mask). She was categorized as having severe COVID-19 pneumonia with cytokine storm, based on the chest x-ray (Fig-1) showing bilateral lung fields with ill-defined opacities and fibro-linear strands and high inflammatory markers (IL-6- 420.6 pg/ml, Ferritin-683.8 mcg/L, CRP (C-reactive protein) -90 mg/L, D-dimer >10000 ng/ml). The patient was started with Injection of Methylprednisolone, Inj Enoxaparin, Inj Remdesivir, Tab Baricitinib along with Inj Pheniramine maleate stat dose and repeated after 12 hours. ABG (arterial blood gas analysis) repeated after 1st and 2nd dose of Inj Pheniramine maleate revealed PO2- 84.2 mmHg and PO2-102 mmHg respectively associated with significant improvement in dyspnea and overall clinical condition. After 4 doses (12 hourly) of Inj Pheniramine maleate, oxygen was tapered to 4 L via nasal prongs with adequate oxygen saturation and was shifted out of HDU. Repeated inflammatory markers after 2 days of admission were markedly improved (D-dimer- 2935.63 ng/ml, IL-6-2.76 pg/ml, CRP-31.1 mg/L). She tested negative for COVID-19 after 5 days of admission and was shifted out to a non-COVID ward with adequate saturation (97%) at 2 to 3 L of O2 via nasal prongs. The patient was tapered off from oxygen support in the next 24 hours and was discharged from the

hospital. The patient was asymptomatic on serial follow-up visits in OPD, and the repeat chest radiograph was normal without any residual respiratory difficulty.

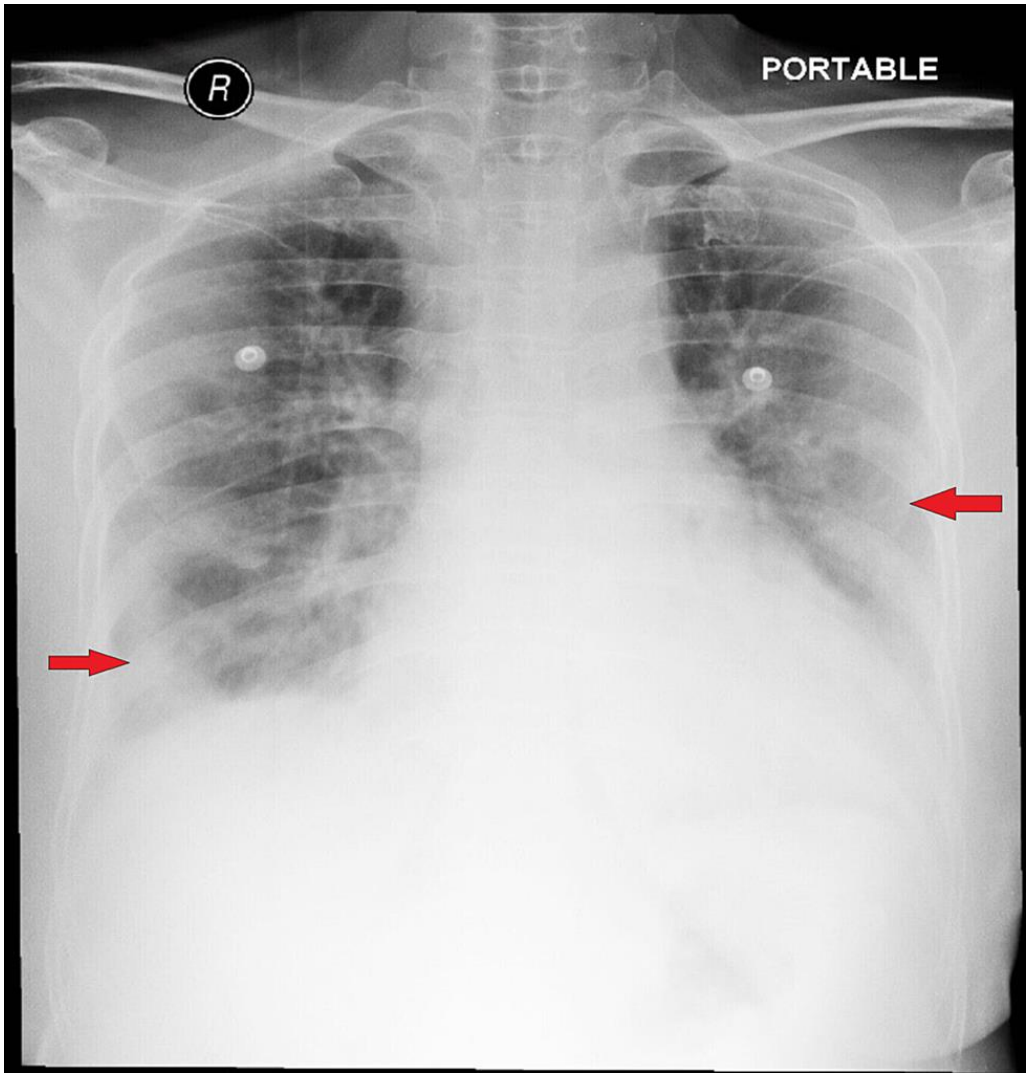

Fig 1: Portable chest x-ray of the patient on the day of hospital admission, showing ill-defined opacities and fibro-linear strands in bilateral lung fields (red arrows).

Discussion

COVID-19 infection is accompanied by the "cytokine storm" (CS), which is an aggressive inflammatory response with the release of an excessive amount of pro-inflammatory cytokines. The hyperactive host immune response to the SARS-CoV-2 virus is, results in an excessive inflammatory reaction. Several studies analyzing cytokine profiles from COVID-19 patients suggested that the cytokine storm correlated directly with lung injury, multiorgan failure, and unfavorable prognosis of severe COVID-19 [1].

Cytokine storm (CS) is a critical life-threatening condition requiring intensive care unit admission and having very high mortality. It is characterized by a clinical presentation of overwhelming systemic inflammation, hyperferritinemia, hemodynamic instability, and multi-organ dysfunction, it leads to death if left untreated [1].

Once, immunologic complications like cytokine storm occur, anti-viral treatment alone is not enough and should be combined with appropriate anti-inflammatory treatment for the management of dysregulated immune response [1].

Therefore, based on prior efficacious dual-histamine receptor blocker studies in humans and animal models in a variety of diseases and the well-known role of histamine, in immune response, we believe it is reasonable to bridge into humans infected by COVID-19 using dual-histamine receptor blockade, to prevent or diminish the cytokine storm [3].

Our patient with markedly raised inflammatory markers, severe clinical condition, and high oxygen demand was a case of cytokine storm in COVID-19 infection. The inhibition of cytokine storm by an antihistaminic agent (pheniramine maleate) used in our patient, improved the arterial PO2, and overall clinical condition and reduced the oxygen requirement as well as the duration of hospital stay. Compared to other cases of severe COVID-19 pneumonia having a cytokine storm with a long time of recovery and a longer duration of high oxygen demand.

Hence, we conclude that the inhibition of the inflammatory pathway by antihistaminic (pheniramine maleate) halted the progression of cytokine storm in this patient, thus reducing the days in the high dependency unit and favorable clinical outcome.

Conclusion

Physicians and researchers should remember that the cytokine storm of COVID-19 is mainly an outcome of hyperactive dysregulated immune response rather than viral activity. Hence the management of cytokine storms should be directed towards immune response to the virus. Our case depicts the successful use of an antihistaminic agent (pheniramine maleate) in suppressing cytokine storm and a better clinical outcome. Given the successful recovery achieved in this case, we suggest that further research, such as randomized controlled trials, needs to be considered in cases of cytokine storm of COVID-19 to utilize the benefits of the medication and the concept behind it depicted in this case report. Given the widespread availability and cost-effectiveness of this drug under discussion, especially for use in resource-limited settings, we suggest further studies on the use of pheniramine maleate for the management of cytokine storms in COVID-19 patients. We also put forward the idea of utilizing the principle of this drug for further ongoing research work in the field of COVID-19 and other causes of the cytokine storm.

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