Combined treatment of tocilizumab and chloroquine on severe COVID-19: a case report

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Learning points for clinicians

COVID-19 has become a pandemic since 11 March 2020. There is currently no specific vaccine or specific effective antiviral therapies. we report a case of a 63-year-old male patient with severe COVID-19, who felt chest tightness worsened, and dyspnea occurred suddenly, meanwhile blood gas analysis showed that oxygen saturation dropped to 89%, and oxygen partial pressure dropped to 57.6mmHg on day 4. The combination treatment of CQ and tocilizumab was prescribed and achieved favorable outcome, which appears to us a promising therapy protocol in patients with severe COVID-19 and should be studied urgently in future.

Since December 2019, the corona virus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread rapidly and became a world-wide severe public health challenge, and some of the patients finally developed to acute respiratory distress syndrome (ARDS) and/or multiple organs failure (MOF)[1,2]. The pathophysiological mechanisms of covid-19 remain unclear. There is currently no specific vaccine or specific effective antiviral therapies. The COVID-19 is highly associated with a cytokine storm triggered by over-activated

immune system, involving a considerable release of proinflammatory cytokine including interleukins (IL)-6, tumor necrosis factor α (TNF-α), and IL-12, resulting in severe lung injury and adverse outcomes of SARS and MERS[3,4]. The pro-inflammatory cytokine IL-6 plays a key role in the cytokine storm and has a prominent role in the inflammatory cascade[5].

The antiviral properties of chloroquine (CQ) and hydroxychloroquine (HCQ) have been researched in recent years. HCQ, compared with CQ, is more soluble and has less toxic metabolite and fewer side effects. Previous study has proved that the SARS-CoV-2 binds to cell surface receptor, angiotensin converting enzyme 2 (ACE2), CQ/HCQ could interfere with terminal glycosylation of ACE2[6] . Moreover, CQ/HCQ may also block the production of interleukin-6 and other pro-inflammatory cytokines, which are key mediators of ARDS[7].

In this study, we report the combination treatment of CQ and tocilizumab on a severe COVID-19 patient and achieved favorable outcome.

Case description

A 63-year-old male patient who was diagnosed with infection by SARS-CoV-2 real time polymerase chain reaction test screening (Feb 17, 2020) before hospitalization and had a history of hypertension. Three days later, he presented with fever of 39.0°C, mild cough, then he developed chest tightness, and chest computerized tomography (CT) scan revealed bilateral patchy of ground-glass opacities on Feb 24, 2020 (Figure 1a). The patient was admitted to the COVID-19 ward of our hospital and was closely monitored on Feb 25, 2020. The vital signs were as following: heart rate of 97 beats/min, respiratory rate of 25 breaths/min, axillary temperature at 39°C, SaO2 at 93% (oxygen flow 3L/min), and blood pressure of 119/78mmHg. CQ was used (500mg bid orally) to antiviral therapy after admission and maintained for 7 days. Methylprednisolone was intravenous injected (80-40mg) to inhibit inflammation and reduce pulmonary exudation, which was maintained for 5 days. On day 4, the patients felt chest tightness worsened, and dyspnea occurred suddenly, meanwhile blood gas analysis showed that oxygen saturation dropped to 89%, and oxygen partial pressure dropped to 57.6mmHg. High flow oxygen therapy (flow rate 40L/min, FiO_2 50%) was used to relieve hypoxemia (Figure 2). IL-6 and hypersensitive C-reactive protein in blood, which were surrogate markers of cytokine storm, increased significantly (95.4 pg/ml). The patient was received single doses of tocilizumab, at 8 mg/kg intravenously immediately. On day 5, oxygenation index increased from 144mmHg to 284mmHg. On day 6, IL-6 began to decline gradually after reaching the peak, and hypersensitive C-reactive protein decreased significantly after injection (133.5 to 53.5mg/L). Compared with before injection of tocilizumab, lymphocytes count also was increased significantly after injection (0.31 to 0.82 $\times 10^9$). Finally, the patient was got clinical improvement with gradually decreased oxygen consumption. On day 13, Chest CT confirmed significant improvement by showing that ground-glass opacities were reduced in size and density (Figure 1c). However, there was a mild impairment of liver function on day10 and a transient decrease in

white blood cells on day16. Leukopenia was relieved by himself and liver injury was reduced by polyunsaturated phosphatidylcholine (PPC). Ultimately, the patient was clinically recovered and was sent to the isolation point to observe for 14 days.

Discussion

There are numerous ongoing clinical trials to explore the effective drugs for COVID-19, however, none of them has achieved satisfactory results in large-scale randomized double-blind clinical trials[8,9]. Inflammatory storm is the leading cause of exacerbation in severe and critical COVID-19 patients, and therefore anti-inflammatory therapy might be a promising treatment strategy. Tocilizumab is a recombinant humanized anti-human IL-6 receptor monoclonal antibody, which can specifically binds to IL-6 receptor (mIL6R) and soluble IL-6 receptor (sIL-6R), thereafter to inhibit signal transduction and reduce inflammatory cascade [10].

In vitro experiments demonstrated CQ and HCQ can reduce the activity of SARS-CoV-2[11]. Gao and colleagues have demonstrated CQ was superior to placebo in reducing pneumonia exacerbation, duration of illness and duration of clearance of virus[12]. An open-label non-randomized clinical trial has showed that HCQ treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin[13]. The anti-viral and anti-inflammatory activities of CQ/HCQ may account for its potent efficacy in treating patients with COVID-19.

Here we first report the successful treatment of a patient with severe Covid-19, who was treated with tocilizumab and CQ. However, there are several limitations in this report. First, the side effects of CQ and tocilizumab can cause leukopenia and liver damage. The combination of two drugs may further aggravate the occurrence of adverse reactions. In this patient, there was a transient decrease in white blood cells and liver damage, which was improved after treatment. Second, the patient was received concomitant therapies, it is hard to clarify which drug played the main role. However, it seems like that anti-cytokine storm may be an effective treatment, because tocilizumab binds to the IL-6 receptor, blocking the signaling pathway of the inflammatory response and CQ reduces the production of pro-inflammatory cytokines theoretically, especially IL-6. But the level of IL-6 in the patient was elevated after injection of tocilizumab. Of course, CQ reduces the levels of ACE2 glycosylation may be another explanation.

Conclusion

Cytokine storm and chemokine dysregulation may play an important role in the worsening of severe COVID-19 disease. The anti-viral and anti-inflammatory activities of CQ/HCQ may account for its potent efficacy in treating patients with COVID-19. We report our observation of a patient with severe Covid-19, who was successfully treated with tocilizumab and CQ. The combination therapy appears to us a promising therapy protocol in patients with severe COVID-19, which should be studied urgently in future.

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Conflict of interest: The authors have no potential conflicts of interest to disclose

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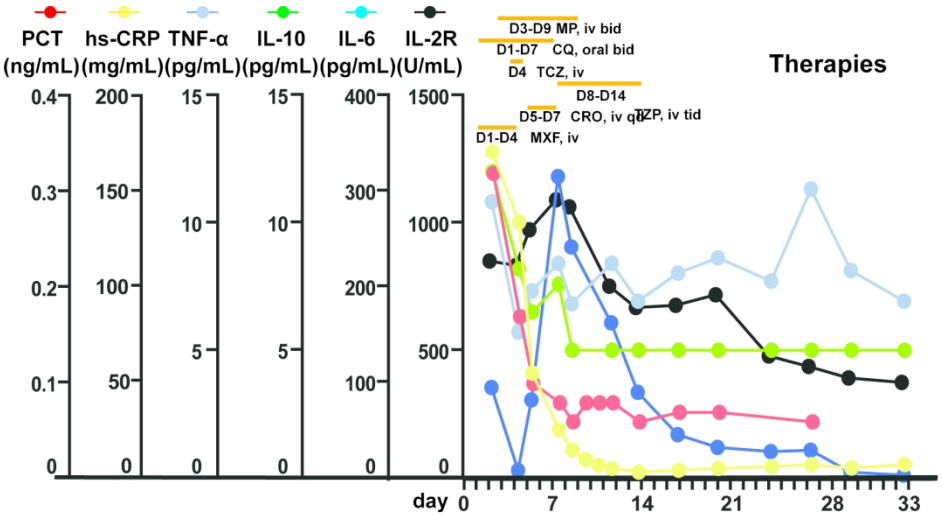
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D1-D7 CQ, oral bid
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D8-D14
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TZP, iv tid
D1-D4 MXF, iv
Therapies

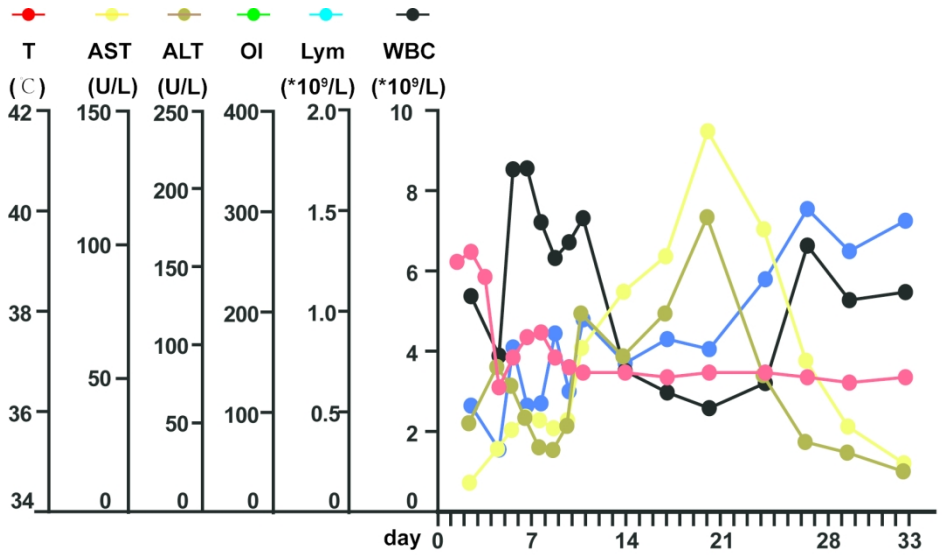
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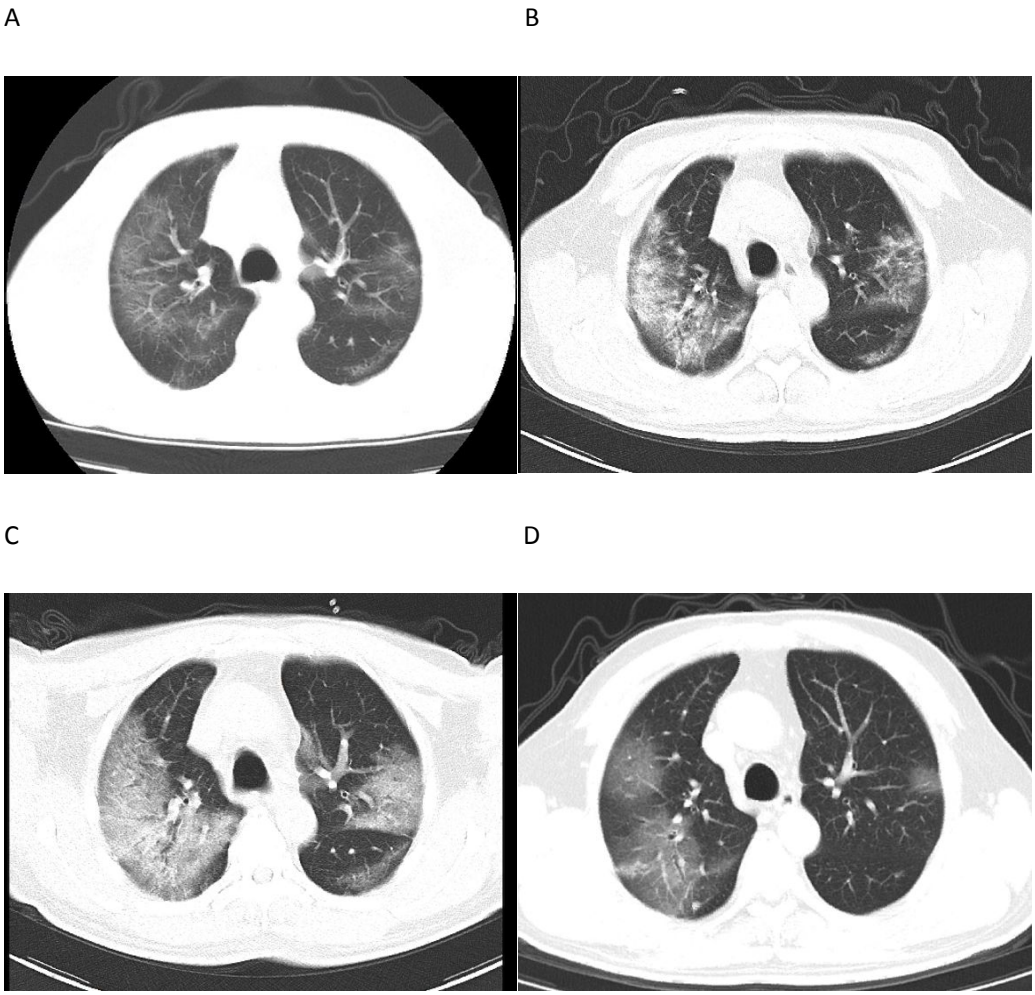
Figure 1



A. Initial transverse CT image obtained on February 24 shows bilateral multiple patchy ground-glass opacities with subtle consolidations.

B. Transverse CT image obtained on March 1 shows progressive ground-glass opacities with larger superimposed consolidations.

C. Transverse CT image obtained on March 8 shows ground-glass opacities reduced in size.

D. Transverse CT image obtained on March 22 shows ground-glass opacities significantly reduced in density.

Figure 2

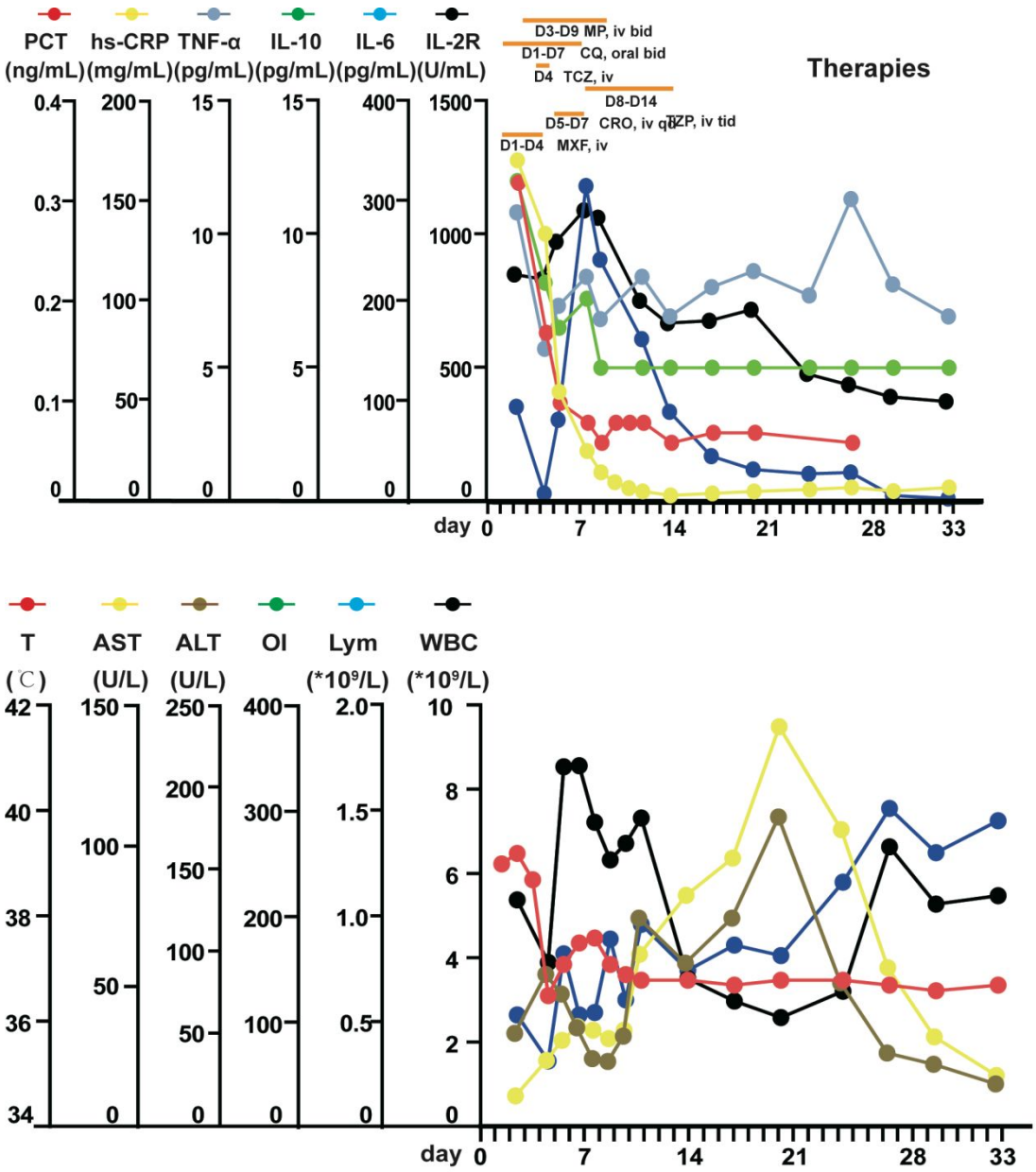
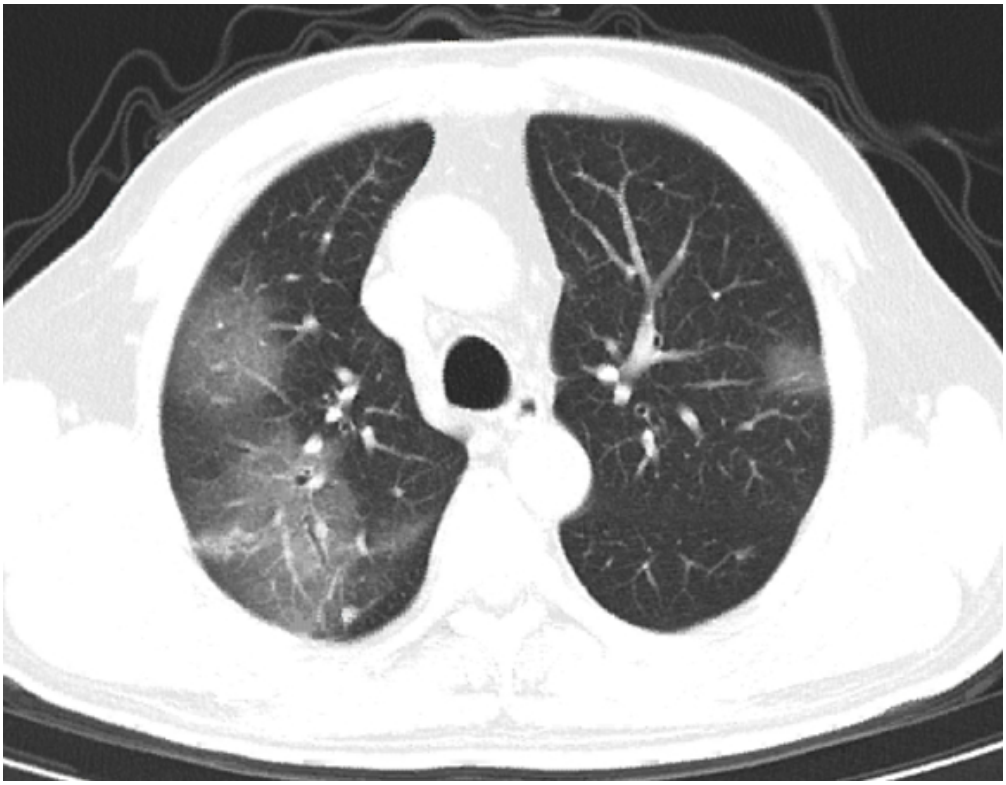


Figure 2. Outcome of patient with Covid-19 before and after tocilizumab and CQ. The concentration of inflammatory index, liver function and oxygenation function were evaluated in blood. All therapies given for covid-19 were summarized at the top of the figure 1.PCT: Procalcitonin; TNF-α: Tumor necrosis factor - α; IL-10:Interleukin 10; IL-6:Interleukin 6; IL-2R:Interleukin 2 receptor; MP： Methylprednisolone; CQ： Chloroquine; TCZ： Tocilizumab; TZP： Piperacillin tazobactam; CRO： Ceftriaxone MXF： Moxifloxacin; T: Temperature ; AST: Aspartate aminotransferase; ALT : Alanine transaminase; OI : Oxygenation index; Lym: Lymphocyte; WBC： White blood cells.



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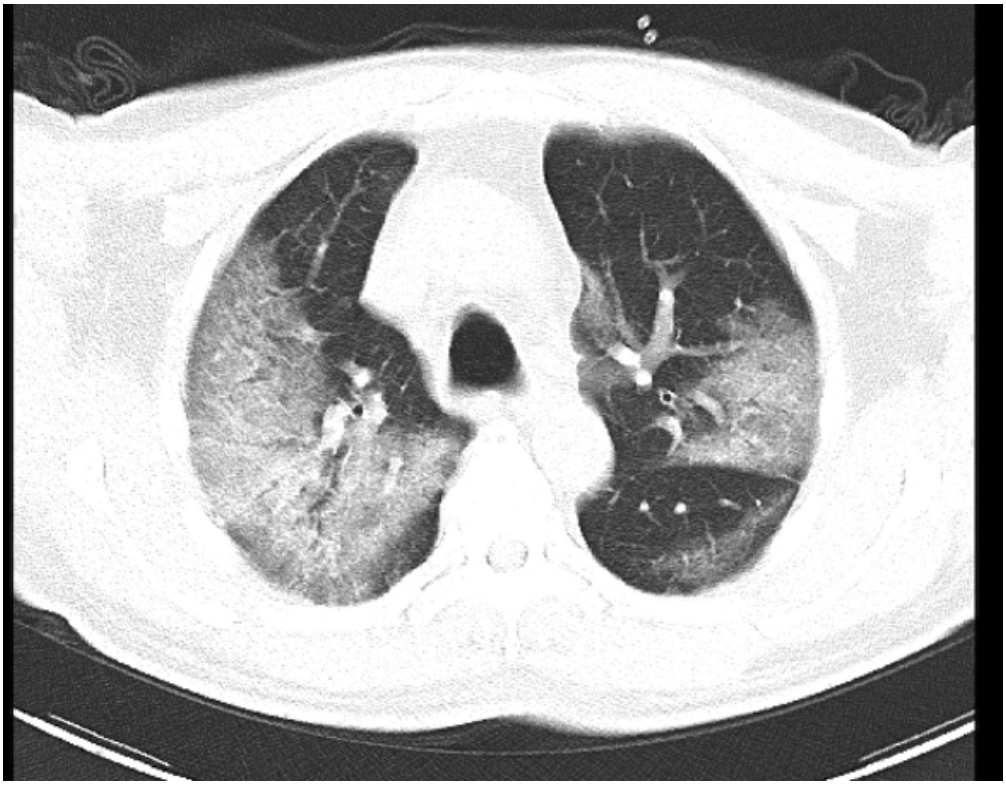

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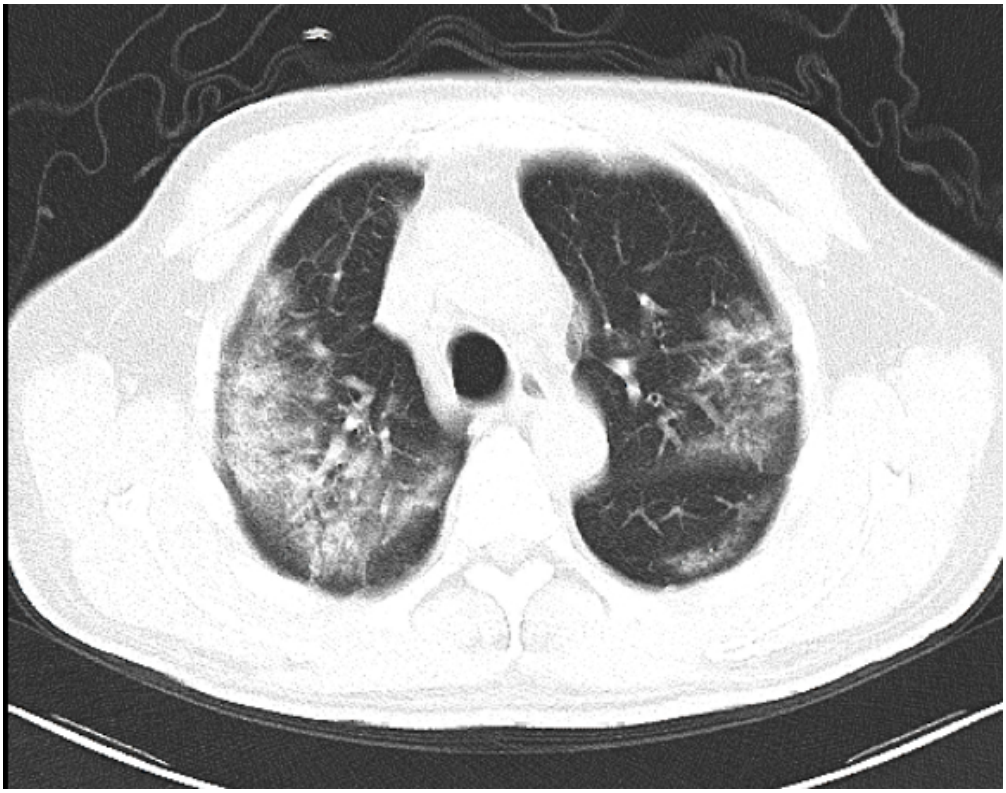

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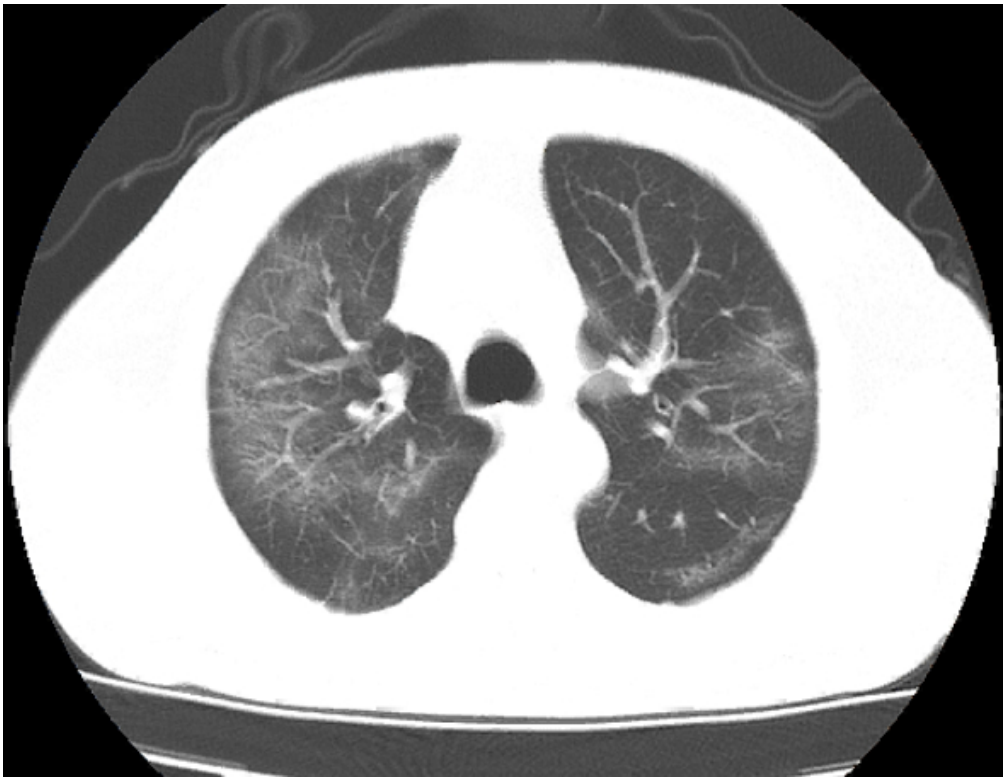

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