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Severe Pediatric COVID-19 Presenting With Respiratory Failure and Severe Thrombocytopenia

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Short Title: Pediatric COVID-19 with Severe Thrombocytopenia

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Conflict of Interest: The authors have no conflicts of interest to disclose.

Abbreviations: Coronavirus disease 2019: COVID-19, Novel coronavirus 2019: SARS-CoV-2, Severe acute respiratory syndrome: SARS, Interleukin-6: IL-6, C-reactive protein: CRP, Polymerase chain reaction: PCR, Immune thrombocytopenia: ITP, Food and Drug Administration: FDA

Table of Contents Summary: We present the successful management of a critically-ill previously healthy child with COVID-19 presenting with respiratory failure and severe thrombocytopenia.

Contributors' Statement Page

Dr. Patel conceptualized and designed the study, collected data, drafted the initial manuscript and reviewed and revised the manuscript.

Dr. Chandrakasan, Mickells, Yildirim, Kao and Bennett were involved in analysis and interpretation of data, critically reviewed for important intellectual content and revised the manuscript.

All authors approved of the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

The novel coronavirus (SARS-CoV-2) is a worldwide pandemic. The severe morbidity and mortality associated with coronavirus disease 2019 (COVID-19) has mostly effected the elderly or those with underlying medical conditions. We present a case of a 12-year-old girl with no past medical history who presented with fever, cough and vomiting. Laboratory evaluation revealed severe thrombocytopenia and elevated markers of inflammation. The patient progressed to respiratory failure and testing for the SARS-CoV-2 returned positive. Due to the severity of her thrombocytopenia, she was treated with intravenous immunoglobulin (IVIG) and steroids with prompt improvement in platelets. The patient's severe acute respiratory distress syndrome was managed with mechanical ventilation, inhaled nitric oxide, and then airway pressure release ventilation. After azithromycin and hydroxychloroquine were given without improvement, our patient received tocilizumab, an anti-IL-6 receptor antibody, and remdesivir, a broad antiviral agent, with significant clinical benefit soon afterwards. Given that severe pediatric COVID-19 is rare, we hope to inform pediatric providers on the clinical course and management considerations as this pandemic continues to spread.

Introduction

As of April 22 2020, the 2019 novel coronavirus (SARS-CoV-2) has been responsible for more than 2.4 million infections and over 150,000 deaths worldwide with the United States now having the largest number of reported cases¹. Available data suggest most children have mild disease and that children with severe disease appear to be younger (usually less than 1 years of age)² or have preexisting medical conditions³. Mild thrombocytopenia has been seen in severe adult COVID-19 patients⁴ and there is one report of immune thrombocytopenia (ITP) associated with COVID-19 in an adult patient with underlying autoimmune hypothyroidism⁵. We report a case of severe COVID-19 in a 12-year-old previously healthy child presenting with respiratory failure and severe thrombocytopenia.

Clinical Presentation

A 12-year-old previously healthy girl presented with 5 days of fever, non-productive cough, 2 days of nonbloody emesis, worsening shortness of breath and hematuria. Her temperature was 39.6°C, pulse 129 beats per minute, respiratory rate 26 breaths per minute, and

oxygen saturation 89% on room air. Her weight was 60 kg and body mass index was 25 kg/m². On physical exam, she had dyspnea, diminished breath sounds diffusely and petechiae. The rest of her exam was unremarkable. Chest x-ray (CXR) demonstrated bilateral diffuse airspace opacities and small pleural effusion.

Laboratory findings on admission were remarkable for severe thrombocytopenia, lymphopenia, and elevated inflammatory markers (CRP, procalcitonin, and ferritin) (Table). The only abnormality on peripheral blood smear was severe macrothrombocytopenia. Nasopharyngeal swab respiratory viral panel by multiplex PCR for 16 common pathogens such as rhinovirus and influenza was negative.

Hospitalization Course

The patient was admitted to the intensive care unit on high flow nasal cannula but subsequently required intubation and mechanical ventilation on 100% oxygen on hospital day (HD) 1. She had continued desaturations so was started on inhaled nitric oxide (iNO) with improvement in PaO₂ and oxygen saturations (oxygen index was 30 before and 9.7 after iNO). Empiric antibiotics for presumed sepsis were initiated. Due to risk for bleeding with concern for immune thrombocytopenia (ITP), intravenous immunoglobulin (IVIG) was given on HD 1 and 2 (1g/kg per dose) along with methylprednisolone (1.5mg/kg) on HD 2 with good recovery of platelets (143 x 10⁹/L on HD 4). Azithromycin was started on HD 2 for 3 days as an anti-inflammatory agent in the setting of ARDS.

A summary of the hospital course and treatments is shown in Figure 1. A nasopharyngeal SARS-CoV-2 real-time reverse transcription polymerase chain reaction (RT-PCR) test was sent upon admission and returned positive on HD 4. The patient did not have any known exposure to

COVID-19 cases or recent travel. Hydroxychloroquine was started (400mg BID on HD 4 followed by 200mg BID daily until HD 7) for off-label treatment of severe COVID-19 infection^{6,7}. A hyperinflammation work-up was performed after the SARS-CoV-2 testing resulted positive to guide additional immunomodulatory therapy (Table). Attempts were made to wean ventilator support and iNO but were unsuccessful. On HD 7, due to continued fever, ARDS and elevated inflammatory markers including IL-6, 2 doses of tocilizumab (8mg/kg 12 hours apart), a humanized monoclonal IL-6 receptor antibody, were given and she was changed to airway pressure release ventilation (APRV) for enhanced ARDS management. We obtained permission for compassionate use of remdesivir which also started on HD 7 (200mg on HD 7 followed by 100mg daily). On HD 8, the patient had significant clinical (oxygen index improved from 7.9 to 5.5) and radiographic (Figure 2) improvement and was weaned off iNO. We discontinued remdesivir on HD 12 due to mildly elevated transaminases per compassionate use guidelines and after a cautious wean of ventilatory support to avoid risk of reintubation per available guidance at the time⁸, the patient was extubated on HD 14. On HD 24, the patient was discharged from the hospital after undergoing a short inpatient rehabilitation stay.

Discussion

We report the successful management of a critically ill child with COVID-19 in the United States. In contrast to children with severe COVID-19 from People's Republic of China³, our patient was older and had no prior medical history. Her presentation with severe thrombocytopenia raised the concern for acute ITP given the degree of thrombocytopenia, peripheral blood smear, and lack of other physical exam findings such as organomegaly. Other causes for thrombocytopenia were considered in the differential including thrombosis, microangiopathic hemolytic anemia, hemophagocytic lymphohistiocytosis, hypersplenism,

ARDS, the coronavirus infection itself and medications. ITP is a diagnosis of exclusion and while the other causes of thrombocytopenia could not be ruled out with complete certainty, the clinical and laboratory findings were not supportive of these alternative diagnoses. Therefore, her thrombocytopenia was treated as ITP with standard first-line treatments, IVIG and corticosteroids⁹, with good recovery of her platelets. While mild thrombocytopenia has been reported in older patients with COVID-19⁴, our patient's presentation with profound thrombocytopenia was atypical. Similar to adult patients, our patient's thrombocytopenia was associated with a more severe disease course¹⁰.

After our patient's SARS-CoV-2 RT-PCR test returned positive, hydroxychloroquine was initiated based on preliminary reports available at the time suggesting enhanced viral clearance in vitro⁶ and in a small case series of adult patients with COVID-19⁷. However, recent evidence suggests hydroxychloroquine provides no benefit¹¹ and our patient showed no improvement with its use.

Remdesivir is an adenosine analog that inhibits viral replication with broad antiviral activity including against SARS-CoV-2 in vitro¹². While there are currently no approved therapies for SARS-CoV-2, preliminary evidence from a case series of adult patients seems to suggest some clinical improvement with the use of remdesivir,¹³ but results from placebo controlled randomized trials are still pending. Our patient received remdesivir under compassionate use and tolerated it well aside from mildly elevated transaminases which were also reported in adults. The patient had clear signs of clinical improvement after remdesivir however its role as a single agent is unclear since it was given in combination with tocilizumab.

Due to severity of the patient's SARS in an otherwise healthy child, a hyperinflammation work-up was initiated to guide additional immunomodulatory therapy. Adult data suggest that

cytokine storm syndrome may play a role in the morbidity and mortality in a subset of COVID-19 patients¹⁴. IL-6 is a pro-inflammatory cytokine implicated in cytokine release syndrome (CRS) which is sometimes seen after chimeric antigen T cell therapies for malignancies¹⁵. In a retrospective review of 150 hospitalized adult patients with COVID-19, CRP, another marker of acute inflammation, and IL-6 were significantly higher in those patients who died than in those who were discharged from the hospital¹⁶. Elevated IL-6 levels were also reported in 2 of the 3 critically ill children with COVID-19 from Wuhan, China¹⁷.

Tocilizumab is a humanized IL-6 receptor monoclonal antibody FDA approved to treat rheumatologic disease¹⁸ as well as CRS¹⁹. Reports in adults have shown a potential benefit of tocilizumab in COVID-19^{20,21} and clinical trials in adult patients with COVID-19 pneumonia are ongoing^{22,23}. Our patient's inflammatory labs before administration of tocilizumab were elevated (Table) but not to the extent in other literature¹⁷. Since our patient received other immunomodulatory medications (IVIg and corticosteroids) early in her disease course for treatment of presumed ITP, this may have reduced the inflammation to some degree as evidenced by declining markers of inflammation from HD 3 to 5 (Figure 1). While our patient was treated with multiple SARS-CoV-2 directed (hydroxychloroquine and remdesivir) as well as ARDS directed therapies (iNO and APRV), her sustained improvement after the administration of tocilizumab with normalization of inflammatory markers and extubation within 7 days is consistent with results of its use in CRS¹⁹. Our patient tolerated it well without any significant toxicities aside from mildly elevated transaminases which may have been precipitated or exacerbated by concomitant administration of remdesivir.

In addition to tocilizumab, other cytokine directed therapies such as sarilumab another IL-6 receptor antibody, anakinra an IL-1 receptor antagonist, and emapalumab an interferon-

gamma antibody, are all under investigation in clinical trials for the management of COVID-19 associated hyperinflammation and acute lung injury^{24,25}. We acknowledge the limitations of drawing treatment conclusions from our single case but given that severe COVID-19 is uncommon in children and current clinical trials for immunomodulatory drugs are being conducted only in adults, our report serves to inform the pediatric community about the potential use of antiviral agents such as remdesivir and immunomodulatory agents such as tocilizumab in severe pediatric cases.

Conclusion

We report a case of severe pediatric COVID-19 in the United States in an otherwise healthy child presenting with severe thrombocytopenia and ARDS. Consistent with adult literature on COVID-19, our patient's severe disease course was associated with thrombocytopenia and elevated inflammatory markers. The patient's severe respiratory disease did not improve on IVIG, steroids, azithromycin, and hydroxychloroquine. We did observe a temporal clinical improvement following administration of tocilizumab and remdesivir. To the best of our knowledge, there have been no reports to date involving the use of either remdesivir or tocilizumab in pediatric patients with severe COVID-19. Our report contributes to the evolving literature on COVID-19 showing that, while rare, severe COVID-19 does occur in the pediatric age group even in previously healthy children. In addition, our case illustrates that hyperinflammation may be important in the pathophysiology of COVID-19 SARS and that treatment with cytokine-directed agents such as tocilizumab could be considered in critically ill patients. Finally, we advocate for randomized placebo-controlled clinical trials studying drugs like tocilizumab and remdesivir to include children in addition to adults with COVID-19 given our patient's presentation and response.

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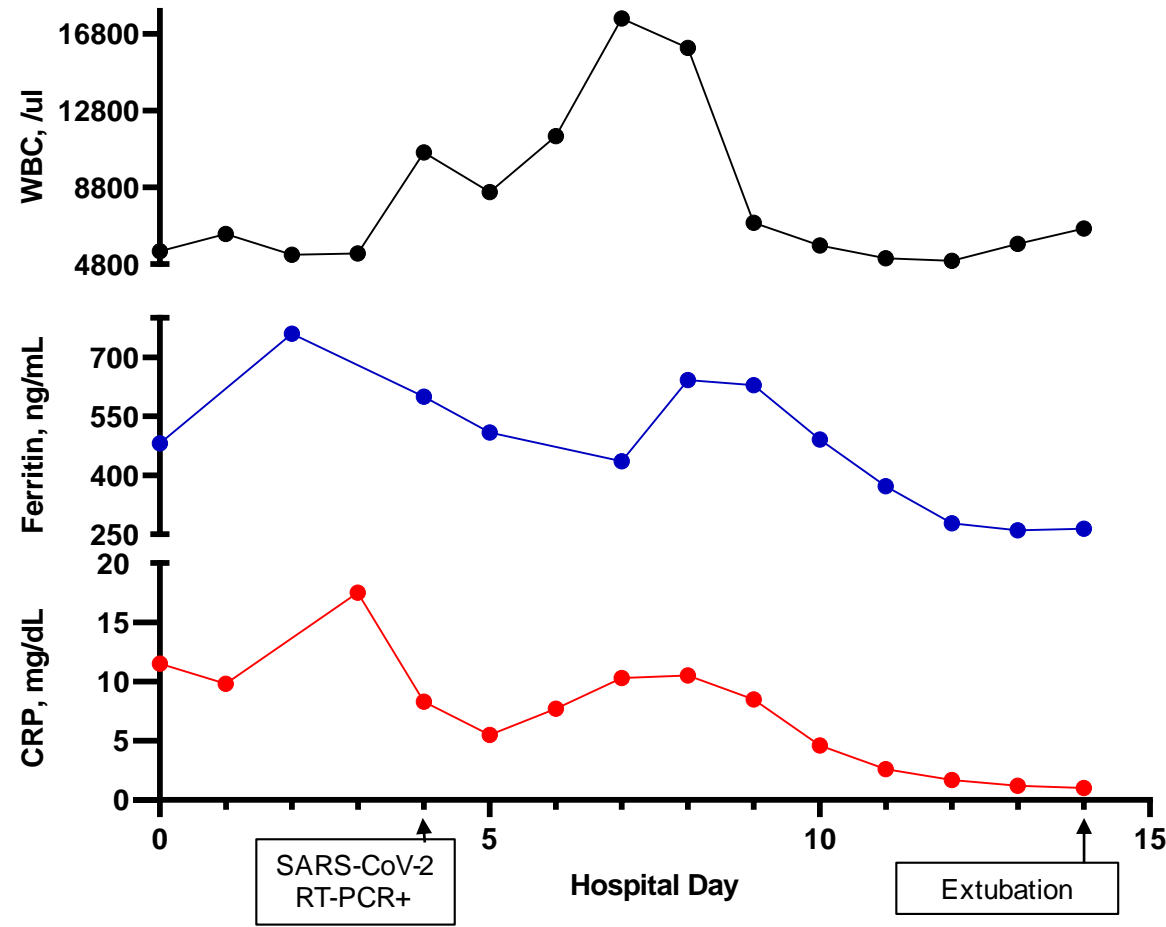
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Table. Admission and Hyperinflammation Laboratory Results

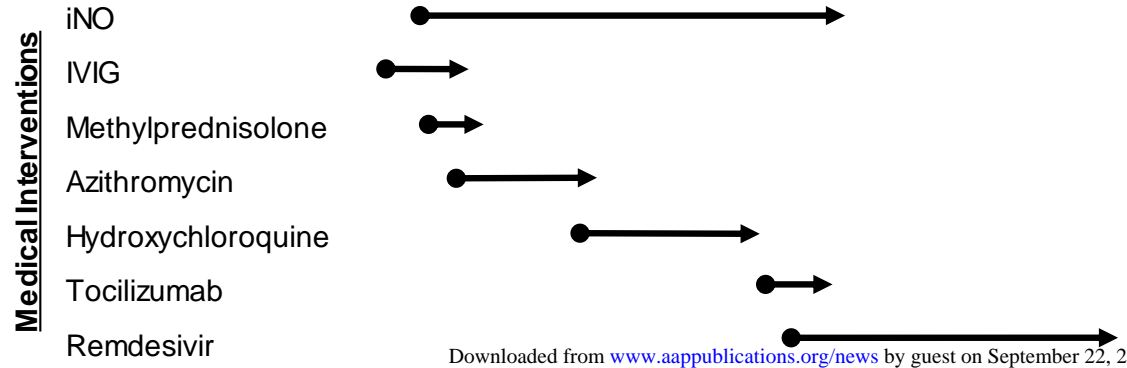
Admission (Hospital Day 0) Laboratory Measures	Value	Reference Range
White blood cell count, / μ l	5470	4500-13500
Absolute lymphocyte count, / μ l	711 (L)	1485-6480
Hemoglobin, g/dL	12.3	12-16
Platelet count, $\times 10^3$ / μ l	<10 (L)	150-450
Prothrombin Time, sec	15.3	12.6-15.9
Activated Partial Thromboplastin Time, sec	53.6 (H)	26-38
Fibrinogen, mg/dL	424 (H)	200-400
Sodium, mmol/L	132 (L)	134-143
Creatinine, mg/dL	0.69	0.30-0.80
Total bilirubin, mg/dL	0.8	0.2-1.0
Aspartate aminotransferase, U/L	37 (H)	17-33
Alanine aminotransferase, U/L	25	11-33
C-reactive protein, mg/dL	11.5 (H)	<1.0
Procalcitonin, ng/mL	0.83 (H)	<0.10
Ferritin, ng/mL	481 (H)	14-79
Hospital Day 4^a		
C-reactive protein, mg/dL	8.3 (H)	<1.0
Ferritin, ng/mL	600 (H)	14-79
IL-2 receptor, pg/mL	910	<1033
IL-6, pg/mL	10 (H)	<5
Interferon-gamma, pg/mL	<5	<5
IL-10, pg/mL	<5	<18
Hospital Day 7^b		
C-reactive protein, mg/dL	10.3 (H)	<1.0
Ferritin, ng/mL	436 (H)	14-79
IL-2 receptor, pg/mL	1486 (H)	<1033
IL-6, pg/mL	34 (H)	<5
Interferon-gamma, pg/mL	10 (H)	<5
IL-10, pg/mL	9	<18
CXCL9, pg/ml	248(H)	<121
IL-18, pg/mL	1184 (H)	89-540

^aDrawn on hospital day 4^bDrawn before administration of tocilizumab on hospital day 7

Figure 1. Timeline of Medical Interventions and Inflammatory Labs: WBC (black), ferritin (blue), and CRP (red).



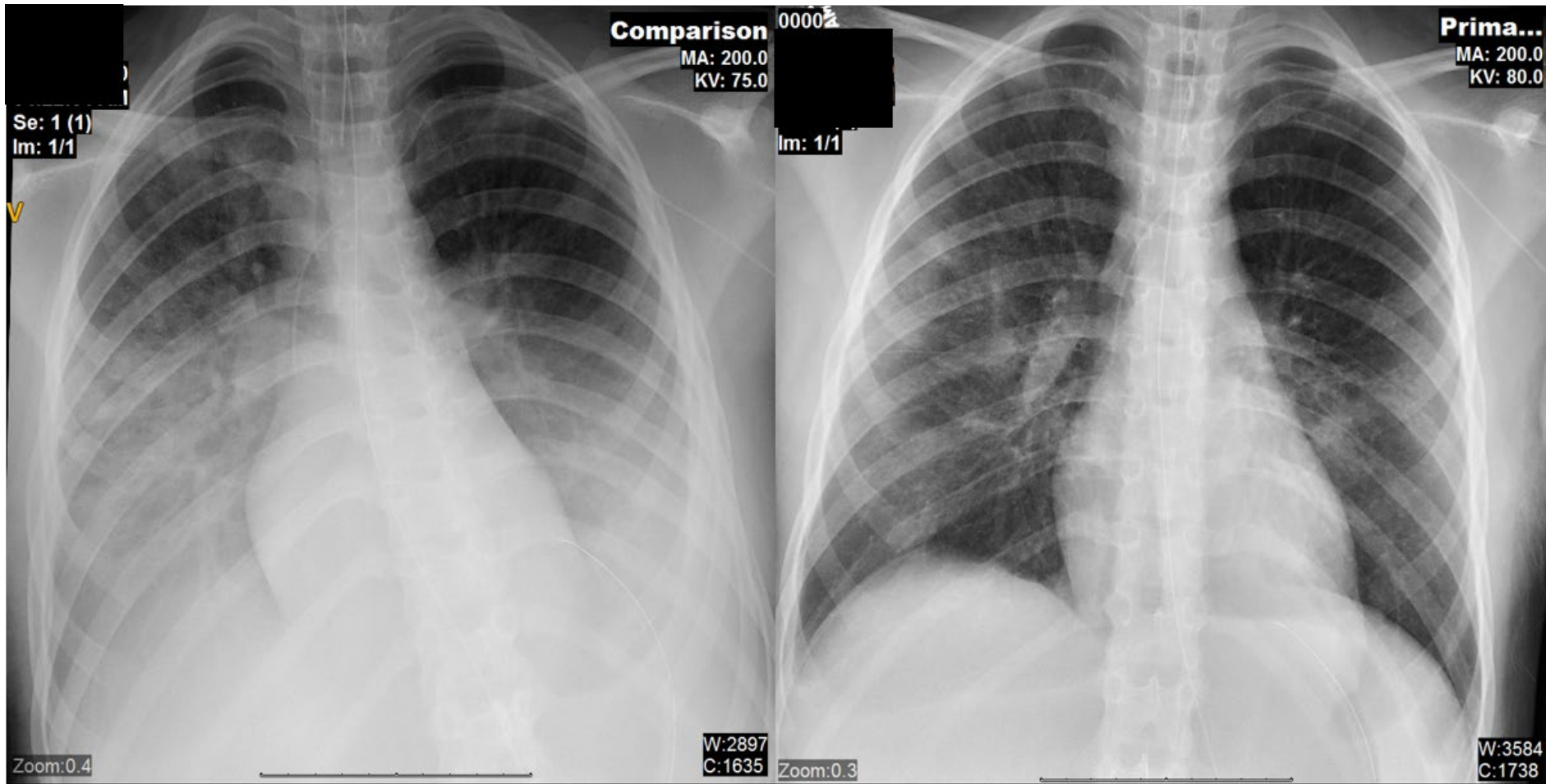
SARS-CoV-2 RT-PCR+ Hospital Day Extubation



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WBC: White blood cell, RT-PCR: reverse-transcriptase polymerase chain reaction, CRP: C-reactive protein, iNO: inhaled nitric oxide, IVIG: intravenous immunoglobulin

Figure 2. Chest X-Ray Findings Hospital Day 7 (left) and Day 8 (right).



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