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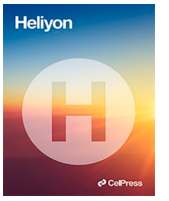

Case Report of COVID-19 and Pneumocystis coinfection in a pediatric patient with a history of receiving high dose steroid therapy

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ABSTRACT

We report the first case of a critically ill pediatric patient coinfected with coronavirus disease 2019 (COVID-19) and Pneumocystis jirovecii pneumonia (PCP). Instances of coinfection of COVID-19 and PCP are being increasingly reported as the COVID-19 pandemic continues. Because the combination can be life-threatening, timely diagnosis and treatment for PCP is necessary in cases where an immunocompromised patient contracts COVID-19.

1. Introduction

Reports of coinfections of coronavirus disease 2019 (COVID-19) and fungal infections have been increasingly common [1]. Although Aspergillus spp. appears to be the primary fungal pathogen in such cases, Pneumocystis jirovecii pneumonia (PCP) is emerging and is now frequently reported in adults [1,2].

To our knowledge, coinfection of COVID-19 and PCP has not yet been reported in pediatric patients. We first report a case of life-threatening coinfection of COVID-19 and PCP in a pediatric patient who received high-dose steroid therapy prior to his COVID-19 diagnosis.

2. Case description

A four year old male, taking anti-seizure medication and oral prednisolone at high dose (4mg/kg/day for 30 days and being tapered – 3mg/kg/day for 21 days) after being diagnosed with Doose syndrome at 19 months old and with drug resistant epilepsy, presented to a local hospital on April 20, 2023, with fever, cough, and poor oral intake for the past 4 days. He and his parents had been diagnosed with COVID-19 four days before visiting this local hospital, and he was admitted to the local hospital to treat COVID-19 pneumonia. COVID-19 vaccine or PCP prophylaxis treatment had not been given previously. The next day he developed hypoxemic respiratory failure, whereupon the patient was transferred to Jeonbuk National University Hospital. At the time of his arrival at our emergency department, his percutaneous oxygen saturation (SpO_2) was 84 %, with 10 L/min of oxygen delivered via facial mask. He was admitted

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to a negative-pressured isolation room in the pediatric intensive care unit (PICU). On PICU admission, his vital signs were as follows: blood pressure of 96/64 mmHg, pulse rate of 164 beats/minute, and body temperature of 37.2 °C. His respiratory rate was 55 breaths/minute, and his SpO2 was 90 % with high-flow nasal cannula at 35L/min, FiO2 60 %. His height was 97 cm (<3rd percentile), and his weight was 20 kg (50-75th percentile) (BMI 21.26). The patient appeared drowsy, and his physical examination showed mild chest retractions in both subcostal areas, coarse inspiratory crackle on the left lung field, and markedly decreased aeration throughout both lungs.

The initial laboratory findings were as follows: white blood cell count: 13,100/μL (lymphocyte: 5 %, segmented neutrophil: 87 %), absolute lymphocyte count: 700/μL, absolute neutrophil count: 11,500/μL; hemoglobin: 11.6 g/dL, platelet count: 107,000/μL, C-reactive protein (CRP): 298 mg/L, and procalcitonin: 0.52 ng/mL, serum lactate dehydrogenase: 517 U/L and β-*d*-glucan level: >1000 pg/mL. Blood electrolytes, renal function, liver function, cardiac enzymes, and lactic acid level were each within the normal reference range. An arterial blood gas analysis revealed pH 7.46, pCO_2 40.6 mmHg, pO_2 59.7 mmHg, and HCO_3 29.2 mmol/L with 10 L/min of oxygen administered via facial mask. An initial chest x-ray showed diffuse bilateral ground-glass opacity on both lung fields (Fig. 1). Blood cultures were all negative. Sputum culture for bacteria was also negative. A nasopharyngeal swab for polymerase chain reaction (PCR) exam to check for other respiratory viruses, including influenza and respiratory syncytial virus, was negative.

With a diagnosis of COVID-19 infection and superimposed bacterial pneumonia, the patient received intravenous Remdesivir 5 mg/kg/dose per day on the first day and 2.5 mg/kg/dose per day for the following 4 days as well as antibiotics vancomycin for 6 days and piperacillin-tazobactam for 10 days.

In light of the patient's history of high-dose steroid treatment, as well as the rapid respiratory deterioration and bilateral diffuse opacity on the initial chest X-ray, the possibility of PCP from immunosuppression was considered. The patient's induced sputum specimen was collected for qualitative PCP PCR exam on the first day of PICU admission. The exam took 5days, and the result was positive for PCP PCR exam. The patient was diagnosed with PCP and COVID-19 coinfection. He was treated with 15mg/kg/day oral trimethoprim/sulfamethoxazole (TMP/SMX) for the TMP component, administered every 8 hours for 21 days. The steroid he had been taking prior to this infection was tapered at 2.3 mg/kg/day on the 5th day of admission and 1.5 mg/kg/day until he was discharged. On the 11th day of hospitalization, the patient showed a CD4 count of 885/μL.

The patient was weaned off of the high-flow nasal cannula over a total of 10 days. On the 15th day of admission, the patient was discharged in a relatively stable condition without any adverse event from PCP and COVID-19 pneumonia treatment and without the need for oxygen.

3. Ethics statement

The Jeonbuk National University Hospital Institutional Review Board (IRB) approved this study (IRB No. 2023-05-019). Written informed consent was obtained from the parents/guardian for the publication of all images, clinical data and other data included in the main manuscript.

4. Discussion

This case highlights how COVID-19 and PCP can present as co-occurring diseases that progress to life-threatening conditions in

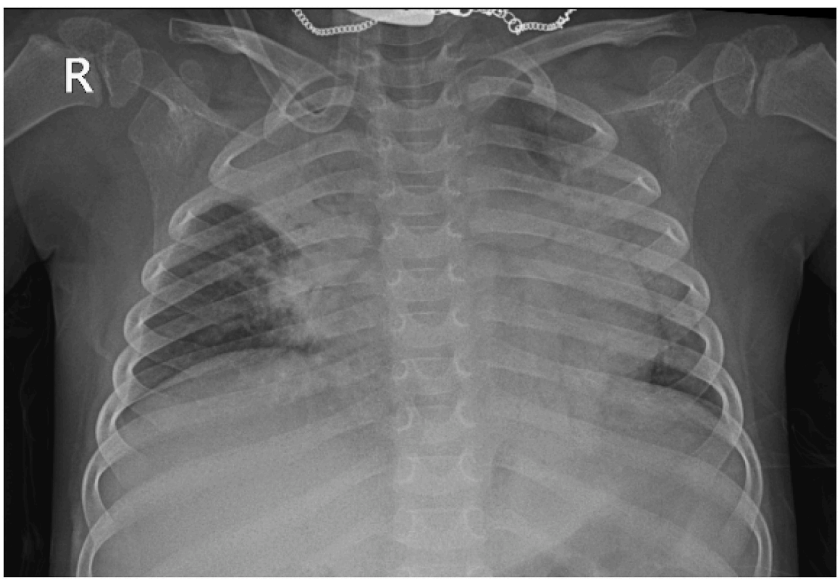

Fig. 1. Chest X-ray on transfer to our hospital, showing diffuse and hazy opacities on both lung fields.

immunocompromised pediatric patients.

Although the majority of children that contract COVID-19 appear to have milder disease courses and a better prognosis than adults, a small number of patients may experience a severe and life-threatening disease progression [3,4]. Chronic lung disease, neurologic disease, cardiovascular disease, prematurity, airway abnormality, feeding tube dependence, diabetes, and obesity have been associated with severe COVID-19 in hospitalized children [4]. PCP, an opportunistic infection caused by Pneumocystis jirovecii, can also cause life-threatening conditions in immunocompromised children [5]. PCP is prevalent in children with lymphoid malignancies, HIV infection, and primary immunodeficiency conditions, as well as those that have received corticosteroid therapy or transplants [5]. Our patient initially presented with all risk factors for COVID-19 and PCP, including a neurologic disorder and a history of corticosteroid treatment.

COVID-19 and PCP coinfections are frequently reported in adults [2], though to date, there have been no case reports of coinfection in pediatric patients. In our case, the patient presented with lymphopenia and a history of high-dose steroid treatment prior to the COVID-19 diagnosis, both of which are considered significant risk factors associated with coinfection by COVID-19 and PCP [2].

PCP and severe COVID-19 share numerous clinical and radiological characteristics, which can make them difficult to distinguish [6]. Both frequently manifest with fever, dyspnea, and hypoxia, as well as a variety of radiographic findings, such as diffuse ground-glass opacities [6]. Similarities in presentation may be attributable to an underlying pathogenic mechanisms shared by the two infections and their similar interactions with pulmonary surfactant [7]. Further, co-diagnosis can be challenging, as COVID-19 diagnostic testing is rapidly and readily available via nasopharyngeal swabs, while PCP is diagnosed by microscopic examination or PCR from respiratory secretions (bronchial alveolar lavage or sputum) –which is less ordinary as a bronchoscopy cannot be readily performed in severe hypoxic patients with COVID-19 due to the risk of SARS-CoV-2 aerosolization and hazardous procedure [6]. Moreover, as steroids are known to have a beneficial effect in cases of severe PCP, the use of corticosteroids for treatment of severe COVID-19 may further delay the diagnosis of any co-occurring PCP by improving that condition [6]. Due to the absence of β-*d*-glucan polysaccharides in the COVID-19 virus, serum β-*d*-glucan levels may aid in the diagnosis of co-infected PCP in cases of COVID-19 [8,9].

In this patient, a history of high-dose steroid use over the long-term, significant hypoxemia, severe radiologic findings, and lymphopenia were factors that led us to consider the possibility of coinfection of PCP. With this in mind, we performed a PCR for detection of *Pneumocystis* DNA and β-D-glucan tests on the first day of the patient's admission at our hospital. The positive results from these tests confirmed the diagnosis of PCP. As microscopic examination for PCP was not available at our hospital, it could not be performed.

Most patients begin PCP treatment with Trimethoprim/sulfamethoxazole (TMP/SMX) [5]. In this patient, the PCR for PCP and β-*d*-glucan test on the 1st day of admission were confirmed positive on the 5th day of hospitalization, which led to delayed administration of TMP/SMZ. Our patient did show a slight improvement in clinical features and radiologic findings even before the TMP/SMX was administered, which we attribute to temporary improvement in the COVID-19 pneumonia by remdesivir or to the PCP by continuing steroid administration.

This report details the case of a child with concurrent COVID-19 and PCP. A limitation in this report is that both clinical and radiologic findings overlap in COVID-19 pneumonia and PCP, making it difficult to distinguish between them. Therefore, chronological order of COVID-19 and PCP becomes ambiguous. Despite the chronological order of the coinfection, we believe that the patient made a successful recovery despite severe clinical symptoms due to accurate diagnosis and the administration of appropriate treatments for both COVID-19 and PCP at the early stages of the disease. Clinicians treating immunocompromised COVID-19 patients should be alert to the possibility of co-infection with PCP.

5. Conclusion

In summary, PCP is co-occurring with severe COVID-19 with increasing frequency, primarily in immunocompromised patients. PCP diagnostic testing in COVID-19 patients should be considered a standard part of the screening of immunosuppressed patients, particularly those presenting with hypoxic respiratory failure and lymphopenia. A comprehensive diagnosic examination and treatment appropriate for cases of PCP coinfection are essential to reducing rates of morbidity and mortality in these COVID-19 patients.

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Declaration of interest's statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Sun Oh Yum: Writing - original draft. **Hwanhee Park:** Conceptualization. **Esther Park:** Writing - review & editing,

Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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