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PIV PEDIATRIC INFECTION & VACCINE

Case Report

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Immune Reconstitution Inflammatory Syndrome-Like Reaction During the Treatment of *Pneumocystis jirovecii* Pneumonia in an Infant With Severe Combined Immunodeficiency

Ching-Yu Lin[1], **Sung-Min Lim**[2], **Soo-Yeon Kim**[1], **Seung-Min Hahn**[1], **Jong-Gyun Ahn**[1,3], **Ji-Man Kang**[1,3]

[1]Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, the Republic of Korea
[2]Department of Pediatrics, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, the Republic of Korea
[3]Institute for Immunology and Immunological Disease, Yonsei University College of Medicine, Seoul, the Republic of Korea

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Correspondence to
Ji-Man Kang
Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, the Republic of Korea.
Email: umi87c@yuhs.ac

ORCID iDs
Ching-Yu Lin
https://orcid.org/0009-0008-5530-637X
Sung-Min Lim
https://orcid.org/0000-0001-5208-5892
Soo-Yeon Kim
https://orcid.org/0000-0003-2244-9776
Seung-Min Hahn
https://orcid.org/0000-0001-9832-6380
Jong-Gyun Ahn
https://orcid.org/0000-0001-5748-0015
Ji-Man Kang
https://orcid.org/0000-0002-0678-4964

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ABSTRACT

The effectiveness of corticosteroids in preventing immune reconstitution inflammatory syndrome in non-human immunodeficiency viruses *Pneumocystis carinii* pneumonia (PCP) patients, such as severe combined immunodeficiency (SCID) patients, is controversial. We experienced a paradoxical reaction during severe PCP treatment in a SCID infant, which responded well to adjuvant corticosteroids.

Keywords: Severe combined immunodeficiency; Immune reconstitution inflammatory syndrome; *Pneumocystis pneumonia*; Steroid

INTRODUCTION

Immunosuppressed patients with human immunodeficiency viruses (HIV) infection or taking immunosuppressant after organ transplantation may experience an excessive inflammatory response which leads to further exacerbation after receiving anti-retroviral therapy or stop the immunosuppressant and the rebuild of immune function by recovered CD4+ T cell. This phenomenon is called "immune reconstitution inflammatory syndrome (IRIS)".[1)]

IRIS refers to a worsening of clinical symptoms in HIV patients caused by an inflammatory response to a preexisting infection as CD4+ T cells are recovered after the initiation of antiretroviral therapy.[2)] Standard guidelines recommend the use of adjunctive corticosteroids with anti-PCP therapy for treating moderate to severe cases of *Pneumocystis jirovecii* pneumonia (formerly called *Pneumocystis carinii* pneumonia or PCP), a representative opportunistic infection in HIV patients.[3,4)] However, the effectiveness of adjuvant corticosteroids in other immunocompromised individuals remains controversial.[5)] Here, we discuss our experience using adjuvant corticosteroids to treat an infant with PCP and severe combined immunodeficiency (SCID), who theoretically could not develop IRIS due to the absence of T cells.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Authors Contributions

Conceptualization: Kang JM; Formal analysis & Investigation: Lin CY, Lim SM; Visualization and Writing: Lin CY, Kang JM; Supervision: Kang JM, Kim SY, Hahn SM, Ahn JG; Writing–review & editing: Lin CY, Lim SM, Kim SY, Hahn SM, Ahn JG, Kang JM.

CASE

A six-month-old male infant with progressive respiratory distress was transferred to our emergency room (ER). He was born full-term to non-consanguineous Korean parents and was given routine immunizations, including live vaccines. Two days before admission, he showed coughing and tachypnea, and was diagnosed with community-acquired pneumonia at a local hospital.

Symptoms progressed and patient needed O_2 supplement to maintain oxygen saturation. On examination, the patient appeared acutely ill, with a blood pressure of 100/63 mmHg, heart rate of 136 beats/min, respiratory rate of 36 beats/min, body temperature of 36.5°C, shallow breathing, and rales throughout the lung fields. Multiple nodular rashes were observed without lymphadenopathy or hepatosplenomegaly. An examination of family history revealed infant deaths of two brothers of the patient's mother from unknown causes (**Supplementary Fig. 1**). For initial blood testing results at ER, see **Table 1**. Additional data are presented in **Fig. 1A** and **Table 2**. Chest radiography showed a mild increase in interstitial markings of the lung field; thymic shadow was not visible (**Fig. 1B**). Based on family history, clinical features and study including lab findings and imaging studies, SCID was suspected from the time of admission to the ER.

Broad-spectrum antimicrobials including trimethoprim-sulfamethoxazole (TMP/SMX) for PCP, ganciclovir for cytomegalovirus (CMV) and a combination of isoniazid, rifampin, and levofloxacin for *Mycobacterium bovis* (with the addition of ethambutol after confirmation through Korean Tuberculosis Research Institute by in-house polymerase chain reaction [PCR] testing) were initiated to address potential X-linked SCID and opportunistic respiratory and skin infections. PCR tests for multiplex respiratory viral and bacterial pathogens and for severe acute respiratory syndrome coronavirus 2 were negative. High-flow nasal cannula oxygen therapy was utilized to support respiration; however, on hospital days (HD) 2, tachypnea and hypoxia progressed and mechanical ventilator support was initiated (**Fig. 1C**). Immunological values were: CD3+ 28/μL, CD4+ 7/μL, CD8+ 21/μL, CD19+ 3,469/μL, and CD56+ 17/μL (**Table 2**, HD2). PCR tests detected *P. jirovecii* in tracheal aspirate specimens, rotavirus in a stool specimen, and *M. bovis* in a gastric aspirate specimen. On HD6, CMV PCR was confirmed negative and ganciclovir was changed to acyclovir. The respiratory condition gradually improved in a wax-and-wane pattern, but on HD12, fever recurred, reaching 38.5°C and O_2 requirements increased with a $PaCO_2$ retention of up to 65 mmHg (**Fig. 1A**). Chest radiography showed a worsening of pneumonia (**Fig. 1D**). However, other infections, skin lesion aggravation, and maternal cell engraftment were not evident. Subsequent lymphocyte subtests showed almost negligible T and NK cells (**Table 2**, HD12). We contemplated the possibility of TMP/SMX failure in the treatment of PCP or IRIS-like reaction in the absence of T cells. On HD14, we administered corticosteroid (methylprednisolone, 2-mg/kg/day) intravenously, under the suspicion of IRIS-like reaction. As a result, the patient's respiratory

Table 1. Initial blood test result at ER

Laboratory parameter	Normal	ER
WBC	6,000–14,000, μL^{-1}	19,920
ALC	1,500–3,000, μL^{-1}	6,573
Hb	10.5–14.0, $g \cdot dL^{-1}$	13.1
PLT	150–400, $\times 10^3\ \mu L^{-1}$	559
CRP	0–8, $mg \cdot dL^{-1}$	0.3

Abbreviations: ER, emergency room; WBC, white blood cell; ALC, absolute lymphocyte count; Hb, hemoglobin; PLT, platelet count; CRP, C-reactive protein.

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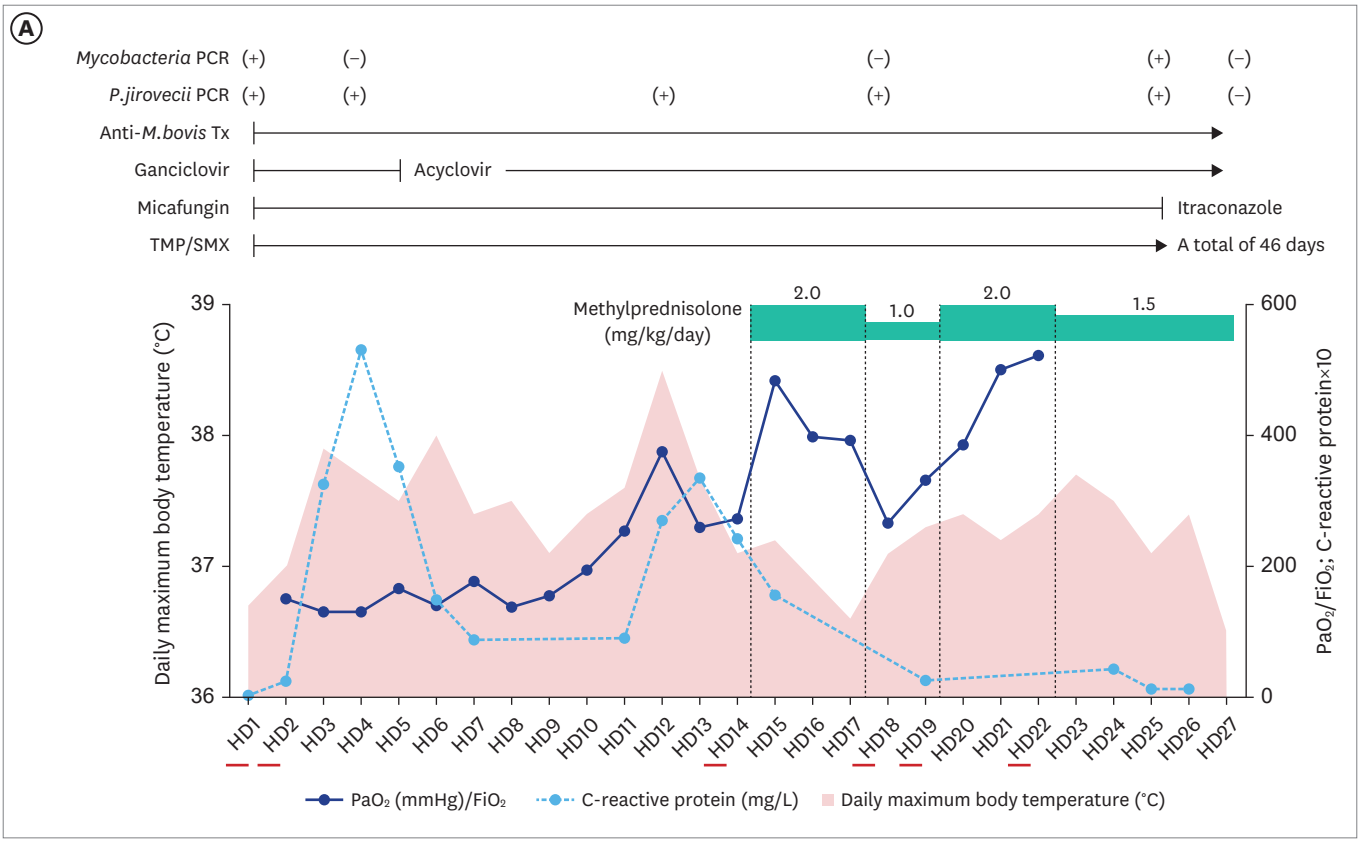

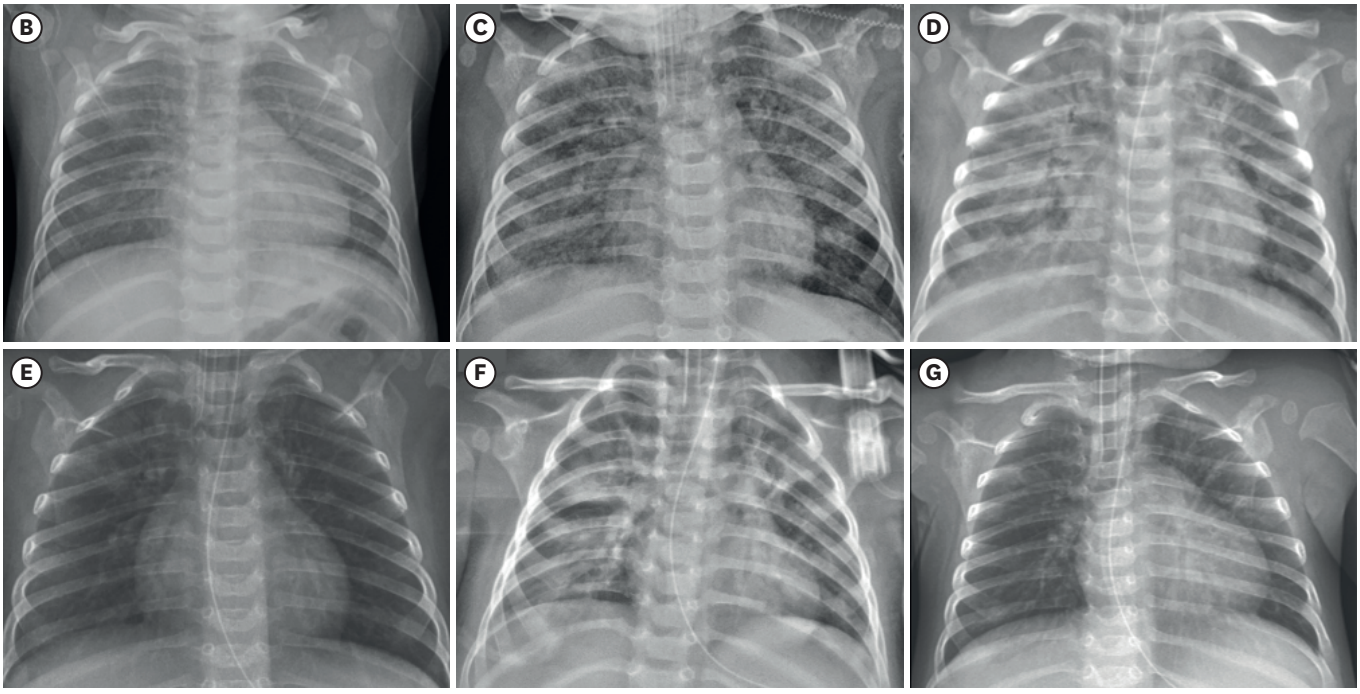

Fig. 1. Clinical course and chest radiographic findings at the time of PCP treatment of a patient with severe combined immunodeficiency. (A) changes in body temperature, PaO_2/FiO_2, and inflammatory markers over time during hospitalization owing to PCP. (B-G) show chest radiographies according to HD. (B) first emergency room visit (HD1). (C) immediately after airway intubation in the intensive care unit due to PCP progression (HD2). (D) a state in which pneumonia eventually progressed despite TMP/SMX treatment (HD14). (E) improvement after adjuvant steroid treatment (HD18). (F) worsened condition of patient a day after the adjuvant corticosteroid dose was reduced by half (HD19). (G) improved condition of patient after the adjuvant corticosteroid dose was increased again (HD22). The corresponding HDs are indicated by a red line in (A).
Abbreviations: PCR, polymerase chain reaction; TMP/SMX, trimethoprim-sulfamethoxazole; HD, hospital days; PCP, *Pneumocystis jirovecii* pneumonia.

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Table 2. Clinical features and laboratory data of the patient at initial admission

Laboratory parameter	Normal	HD1	HD2	HD12	HD14	HD17	HD19	HD22
Vitals								
BP	mmHg	85/53	88/49	-	117/67	109/56	-	114/54
PR	/min	130	132	156	105	84	126	94
BT	℃	36.7	37	38.5	37.1	36.6	37.3	36.2
Lab								
WBC	6,000–14,000, μL^{-1}	16,860	18,590	5,460	6,870	4,810	4,040	4,730
ALC	1,500–3,000, μL^{-1}	3,450	3,400	2,160	3,050	3,100	2,240	2,420
Hb	10.5–14.0, $g \cdot dL^{-1}$	13.1	12.2	8.1	9.9	9.1	9.0	8.6
PLT	150–400, $\times 10^3 \mu L^{-1}$	647	533	347	406	508	445	348
CRP	0–8, $mg \cdot dL^{-1}$	0.4	2.6	27.0	24.2	-	2.6	-
TB	0.2–0.8, $mg \cdot dL^{-1}$	0.3	0.4	-	0.2	0.2	<0.15	-
AST	13–34, $IU \cdot L^{-1}$	36	49	-	33	30	29	-
ALT	5–46, $IU \cdot L^{-1}$	36	31	-	5	9	13	-
$CD3^+$	51–77%	-	0.7	0.7	-	-	-	-
$CD4^+$	35–56%	-	0.2	0.1	-	-	-	-
$CD8^+$	12–23%	-	0.6	0.5	-	-	-	-
$CD19^+$	11–41%	-	99.1	-	-	-	-	-
$CD56^+$	3–14%	-	0.5	0.3	-	-	-	-
ABGA								
pH	7.32–7.38	7.335	7.103	7.395	7.339	7.372	7.295	7.378
PaO_2	30–50 mmHg	76.8	66	112.5	109.3	117.5	116.3	55.9
$PaCO_2$	38–50 mmHg	39.9	85.6	40.6	50.3	38.9	53.3	31.6

Abbreviations: HD, hospital days; BP, blood pressure; PR, purse rate; BT, body temperature; WBC, white blood cell; ALC, absolute lymphocyte count; Hb, hemoglobin; PLT, platelet count; CRP, C-reactive protein; TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ABGA, arterial blood gas analysis.

condition dramatically improved (**Fig. 1E**). But when we reduced the corticosteroid dose to 1-mg/kg/day (HD17); chest radiography subsequently worsened and CO_2 retention recurred (**Fig. 1F**). The corticosteroid dose was back to 2-mg/kg/day (HD19). After that, we were slowly tapering the corticosteroid dose and extubated on HD27 (**Fig. 1G**). On HD41, novel missense mutation in *IL2RG* (c.340G>A) was confirmed by next-generation sequencing. Anti-*M. bovis* treatment was continued and acyclovir, TMP/SMX, and fluconazole prophylaxis were begun. Corticosteroids were administered for a total of 22 days until HD35, and TMP/SMX was administered as a treatment for a total of 46 days. At eight months of age, the patient underwent a fully matched and unrelated hematopoietic cell transplantation, and neutrophil engraftment was achieved at day 17. On Day 13, fever, multiple rashes, swelling of the Bacillus Calmette–Guérin (BCG) vaccine site, and an increased C-reactive protein (up to 198 mg/L) were observed and the patient was diagnosed with BCG-related IRIS-like reaction, which was improved with corticosteroids (**Supplementary Fig. 2**). At two and six months post-transplantation, the patient was hospitalized with fever and soft tissue abscess formation (**Supplementary Fig. 3**). Acid-fast staining for bacteria in pus-aspirated fluid was positive, but improved after corticosteroid administration. Currently, approximately 13 months post-transplantation, the patient receives a low-dose steroid (0.1-mg/kg/day) and anti-*M. bovis* medications.

We obtained informed consent from both parents in advance for this case report and for primary immunodeficiency disease research. These process and information were reviewed and approved by the Institutional Review Board of Severance Hospital (No. 4-2020-0220).

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DISCUSSION

To our knowledge, this is the first study to observe responses before and after treatment with adjuvant corticosteroids for severe PCP in SCID patients. A case series on PCP examined steroid use in 21 SCID patients, but did not include the effects pre- and post-steroid application.[6] Our report detailed the effects before and after steroid usage in an SCID infant with PCP. Several studies have reported the benefits of steroid use for HIV patients.[3] However, the benefits of steroid use in non-HIV patients with PCP are controversial.[7] According to the European Conference on Infections in Leukemia guidelines published by Maschmeye et al.,[5] a high dosage of TMP/SMX is preferred for PCP treatment in patients with non-HIV-infected hematology, while steroid use should be determined on a case-by-case basis.

IRIS is a state of dysregulated, hyper-inflammatory response against opportunistic infections after the improvement in CD4 cell count and immune response. In this patients, CD+4 T cells are excessively activated and stimulate to release cytokines. Cytokine levels are markedly elevated such as interleukin (IL)-2, IL-4, IL-8, IL-10, and IL-13. Symptoms also vary depending on the type of cytokine with high levels.[1] Although no definitive diagnostic criteria for IRIS have been set, IRIS-like reaction were noticed in this SCID infant without T cells.[1] We hypothesize that even in the absence of T cells, other immune cells that are not deficient in SCID patients, specifically tissue macrophages of innate immunity, may be activated due to the huge pathogen burden, which was lessened by TMP/SMX treatment.[8] The absence of regulatory T cells to control this hyper-inflammatory response may be another possible reason.[2,3] This phenomenon was not observed in the case of BCG infection at initial presentation, which appeared as typical BCG-IRIS, as T cells recovered after transplantation. Further studies are necessary to clarify the difference between these two opportunistic infections.

We report a positive response to adjuvant corticosteroid usage in SCID patients with severe PCP. We also report that paradoxical reaction may occur even in the absence of T cells. However, lung infection can be caused not only by PCP but also by *M. bovis*, and the fact that this cannot be completely excluded can be said to be a limitation of this case. This finding requires further attention.

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We wish to thank the patient and his family for their participation in this study.

SUPPLEMENTARY MATERIALS

Supplementary Fig. 1
Pedigree of this patient.

Supplementary Fig. 2
Skin lesions on post-transplantation day 13.

Supplementary Fig. 3
Skin abscess lesion six months after transplantation.

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요약

인체면역결핍바이러스 감염자의 폐포자충폐렴 치료에 있어 보조적 스테로이드 치료의 효용성은 잘 알려진데 반해, 비인체면역결핍바이러스 면역저하자에서의 폐포자충폐렴 치료에 있어서의 보조적 스테로이드 치료의 효용성은 논란의 여지가 있다. 본 연구자들은 비인체면역결핍바이러스 면역저하자인 중증복합면역결핍증 영아에서 이환된 중증 폐포자충폐렴를 치료하던 중 면역재구성염증증후군 유사현상을 관찰하였으며, 보조적 스테로이드 치료에 잘 반응하였기에 이를 보고하는 바이다.