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Pneumocystis jirovecii pneumonia in pediatric patients: an analysis of 15 confirmed consecutive cases during 14 years

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Purpose: *Pneumocystis jirovecii* pneumonia occurs in various immunocompromised patients. Despite the prophylaxis strategies in clinical practice, certain patients develop *P. jirovecii* pneumonia. This study was performed to investigate pediatric cases with *P. jirovecii* pneumonia in a single center.

Methods: We identified pediatric patients younger than 19 years with microbiologically confirmed *P. jirovecii* pneumonia from January 2000 to February 2014. A retrospective chart review was performed.

Results: Fifteen episodes of *P. jirovecii* pneumonia in 14 patients were identified with median age of 8.3 years (range, 0.4–18.6 years). Among these patients, 11 patients had hematology-oncology diseases, 2 had primary immunodeficiency disorders (one with severe combined immunodeficiency and the other with Wiskott Aldrich syndrome), 1 had systemic lupus erythematosus and 1 received kidney transplant. Four patients were transplant recipients; 1 allogeneic and 2 autologous hematopoietic cell transplant and 1 with kidney transplant. The median absolute lymphocyte count at the diagnosis of *P. jirovecii* pneumonia was 5,156 cells/mm^3 (range, 20–5,111 cells/mm^3). In 13 episodes (13 of 15, 86.7%), patients were not receiving prophylaxis at the onset of *P. jirovecii* pneumonia. For treatment, trimethoprim/sulfamethoxazole was given as a main therapeutic agent in all 15 episodes. Steroid was given in 9 episodes (60%). Median treatment duration was 15 days (range, 4–33 days). Overall mortality at 60 days was 35.7% (5 of 14).

Conclusion: Majority of our patients developed *P. jirovecii* pneumonia while not on prophylaxis. Continuous efforts and more data are needed to identify high risk patients who may get benefit from *P. jirovecii* pneumonia prophylaxis.

Key words: Pneumocystis carinii, Pneumocystis jirovecii, Pneumocystis jirovecii pneumonia, Pediatrics, Immunocompromised host

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Introduction

Pneumocystis jirovecii is a common pathogen found worldwide in the lungs of mammals. In the 1980s, Pneumocystis rRNA and mitochondrial DNA had been analyzed, by which this organism was identified as a fungus[1]. *P. jirovecii* belongs to the genus of Pneumocystis and is a human specific pathogen[2]. Serologic surveys show that most humans are infected by 2–3 years old[3]. In the immunocompetent children, these infections are usually asymptomatic. However, *P. jirovecii* pneumonia (PCP) usually occurs in severely immunocompromised hosts[3,4]. Prematurity, malnutrition in infants, immunosuppressive treatment, transplantation, primary immunodeficiency disorders and human immunodeficiency virus (HIV) infection are well-known risk factors for PCP[5]. PCP in immunocompromised persons can be a life threatening infection. It has been reported that

up to 43% of children with cancer developed PCP before the era of trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis and nowadays its occurrence is much less with prophylaxis[3]. However, certain immunocompromised patients still develop PCP[5,6]. Therefore, we conducted this study to analyze pediatric cases with PCP in the Samsung Medical Center.

Materials and methods

A retrospective chart review was performed in pediatric patients with PCP at Samsung Medical Center, Seoul, Korea from January 2000 to February 2014. Over 2,000 pediatric immunocompromised patients were cared at our pediatric center. Patients with microbiologically confirmed PCP were identified. PCP was confirmed by direct fluorescent antibody from bronchial washing fluid or bronchoalveolar lavage (BAL) in patients who were suspected to have PCP with pertinent clinical manifestation. The Institutional Review Board of Samsung Medical Center approved this study (approval number: 2015-02-067).

Results

Fifteen episodes of PCP were diagnosed in 14 patients. Among them 1 patient with severe aplastic anemia developed PCP twice at the age of 6 years and 16 years old.

Median age of the first PCP episode was 8.3 years (range, 0.4–18.6 years). Among these 14 patients, 10 patients (71.4%) had hematology-oncology diseases and two had primary immunodeficiency disorders (severe combined immunodeficiency and Wiskott Aldrich syndrome). One patient had systemic lupus erythematosus and the other received solid organ transplant. Four patients (26.7%) were transplant recipients; 1 allogeneic and 2 autologous hematopoietic cell transplant (HCT) recipients and one kidney transplantation recipient (Table 1). The main symptoms and radiology findings were shown in Table 2. Fever and dyspnea were the most common symptoms. Bilateral diffuse opacities were the most prominent radiologic finding (Table 2).

In 13 cases (13 of 15, 86.7%), patients were not receiving PCP prophylaxis within 1 month from the onset of PCP development. Median duration of last PCP prophylaxis to disease was 161.5 days (range, 1–493 days). Two patients developed PCP despite of prophylaxis. One patient with relapsed acute lymphoblastic leukemia (ALL) received PCP prophylaxis of pentamidine inhalation (TMP, 300 mg/dose) every month. The other patient with ALL received TMP/SMX prophylaxis (TMP, 120 mg/m^2/day) on 2 consecutive days every week.

For treatment, TMP/SMX was given as a main therapeutic agent in all 15 episodes. Three patients were treated with pentamidine and TMP/SMX combination therapy and one patient was treated with caspofungin and TMP/SMX combination therapy. Steroid was given in 9 episodes (60%) (Table 3).

Overall mortality at 60 days was 35.7% (5 of 14) (Table 4). The first patient died 41 days after the diagnosis of PCP despite aggressive antimicrobial treatment and ventilator care in an intensive care unit (ICU). He also had coinfection with *Acinetobacter baumanii* pneumonia. The second patient was diagnosed with PCP twice in 2004 and 2014, respectively. He did not receive any prophylaxis before both episodes of PCP. The patient was recovered from the first episode of PCP after TMP/SMX and pentamidine combination therapy with steroid. Ten years later, he developed the second episode of PCP and was treated with TMP/SMX and caspofungin combination therapy with steroid. However, during this 2nd episode, the patient also had probable

Table 1. Characteristics of patients of 15 cases with PCP

Characteristic	Value
Male sex	11 (73.3)
Age (yr)	8.3* (18.6–0.4)
Underlying diseases	
Hematology-oncology	11 (73.3)
Primary immunodeficiency	2 (13.3)
SLE	1 (6.7)
KT	1 (6.7)
Transplant recipients	4 (26.7)
HCT	3
Allogeneic HCT	1
Autologous HCT	2
KT	1

Values are presented as number (%) or median (range).
PCP, *Pneumocystis jirovecii* pneumonia; SLE, systemic lupus erythematosus; KT, kidney transplant; HCT, hematopoietic cell transplantation.
*Fifteen episodes occurred among 14 patients. Among these patients, 1 with severe aplastic anemia patient had 2 episodes of PCP at the age of 6 and 16.

Table 2. Clinical symptoms and image features of PCP patients

Variable	No. (%)
Symptoms (n=15)	
Fever	9 (60.0)
Dyspnea	8 (53.3)
Tachypnea	6 (40.0)
Cough	5 (33.3)
Simple chest x-ray (n=15)	
Bilateral diffuse opacities	14 (93.3)
Pleural effusion	2 (13.3)
Chest CT (n=13)	
GGO	12 (92.3)
Pleural effusion	1 (7.9)

PCP, *Pneumocystis jirovecii* pneumonia; CT, computed tomography; GGO, ground glass opacities.

Table 3. Clinical features of PCP patients

Variable	Value
Prophylaxis	
Within 18 months before PCP	8 (53.3)
Within 1 month before PCP	2 (13.3)
Absolute lymphocyte count (cells/mm^3)	515 (20–5,111)
CD4 count* (cells/mm^3)	250 (0–880)
ICU stay	13 (86.7)
Mechanical ventilation	11 (73.3)
Antimicrobial treatment (n=15)	
TMP/SMX only	6 (40)
TMP/SMX, Methyl PD	5 (31.3)
TMP/SMX, Methyl PD, pentamidine	3 (33.3)
TMP/SMX, Methyl PD, caspofungin	1 (6.7)

Values are presented as number (%) or median (range).
PCP, *Pneumocystis jirovecii* pneumonia; ICU, Intensive care unit; TMP/SMX, trimethoprim/sulfamethoxazole; Methyl PD, methylprednisolone.
*CD4 counts were available in 8 patients (46.7%).

Table 4. Mortality of PCP patients

Mortality	No. (%)
Overall mortality	5/14 (35.7)
PCP only	2
Coinfection with PCP	3
VRE sepsis	1
Acinetobacter pneumonia	1
Invasive aspergillosis	1*

PCP, *Pneumocystis jirovecii* pneumonia; VRE, vancomycin resistant enterococci; Acinetobacter pneumonia, Acinetobacter baumanii pneumonia.
*Among 15 cases, 1 patient had 2 episodes of PCP at the age of 6 and 16. He died at the 2nd episode of PCP.

invasive pulmonary aspergillosis (IPA) and died of progressing respiratory failure. The third patient developed PCP 104 days after the 2nd allogeneic HCT despite prophylaxis. Unfortunately, he also had bacteremia due to vancomycin resistant enterococci (VRE). He was treated with broad-spectrum antibiotics for VRE bacteremia and also for PCP but died. The forth patient was an infant with neuroblastoma. The patient was not receiving PCP prophylaxis according to the protocol. She developed persistent tachypnea with low oxygen saturation for which PCP was suspected later and she received empiric treatment for PCP with TMP/SMX. She received TMP/SMX and pentamidine combination therapy with steroid. However, her condition became deteriorated and she died 28 days after PCP confirmation from the lung tissue. The last patient had a hemophagocytic lymphohistiocytosis. He was developed a PCP despite of prophylaxis. He died of respiratory failure after 8 days of TMP/SMX monotherapy.

Discussion

This study analyzed 15 episodes of PCP in 14 pediatric immunocompromised hosts that occurred in a single center where over 2,000 of pediatric immunocompromised patients have been cared during these 14 consecutive years. Although PCP cases are rare events nowadays due to prophylaxis strategy, there is still a handful of patients who may develop PCP due to various reasons. Our data showed that in over 86.7% of cases (13 of 15), patients were not receiving PCP prophylaxis within 1 months from the onset of PCP development. Our study confirms that prophylaxis is the most important strategy in PCP prevention and suggests that clinicians should be vigilant in suspecting PCP.

In our study, we analyzed the reasons why prophylaxis was not performed in patients who developed PCP. Firstly, there were 2 patients with solid tumor who developed PCP during chemotherapy in which prophylaxis are not typically recommended. Secondly, there was 1 patient who developed PCP before the engraftment after HCT and did not have a chance to start PCP prophylaxis. Thirdly, there was one patient who developed PCP after the termination of recommended PCP prophylaxis period. Fourthly, in cases of primary immunodeficiency disorders, the 2 patients presented with PCP as one of the initial manifestations before being diagnosed with primary immunodeficiency disorders. Finally, there were patients who started PCP prophylaxis but stopped transiently with any reason, and did not resume prophylaxis properly even though the risk still existed.

It has been reported that non-HIV immunocompromised patients had more acute respiratory symptoms and needed more mechanical ventilator support than with those with acquired immunodeficiency syndrome[7]. Severe respiratory failure patients who needed the mechanical ventilator increased mortality rate up to 60% to 75%. Steroid is frequently used in PCP cases. However, unlike HIV patients in whom steroid use appeared beneficial[8], there have been conflicting reports on steroid use in non-HIV patients with PCP[9]. Nine (9 of 15, 60%) of our patients also received steroid and all of the patients who needed ICU cared received steroid. Among the 9 patients treated with steroid, 3 patients (33.3%) died. In our study, due to the small number of PCP cases, we could not further investigate the effect of steroid in detail.

There are reports on efficacy of caspofungin for treating PCP cases[10]. In this study, 1 patient developed 2 episodes of PCP. For the first episode, he received TMP/SMX and pentamidine combination therapy with steroid and successfully recovered from the infection. For the second episode, he received TMP/SMX and caspofungin combination therapy with steroid but failed to recover from the infection and died of respiratory failure aggravation. It is not clear whether caspofungin was not efficacious in treating PCP in this patient because he also had IPA. In patients with a very serious condition who are failing on

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traditional medication, newer option would be needed. Therefore, the role of caspofungin in PCP should be further investigated.

There are some limitations in this study. Because of the retrospective nature of the study, it was not readily available to know patients' compliance of PCP prophylaxis. In addition, it was not clear whether the patients were prescribed for PCP prophylaxis medication at the health care facility nearby home. In addition, this is a single center study and the included numbers were small. However, because of routine prophylaxis practices in the clinical field, it is not easy to have enough numbers of pediatric PCP cases. Yet, we tried to analyze the 15 pediatric PCP cases identified from a center where a large number of pediatric immunocompromised patients over 2,000 were cared during 14 consecutive years.

In conclusion, our data demonstrated that a subset of certain immunocompromised patients still developed PCP and most of them were not receiving PCP prophylaxis within 1 month from the onset of PCP. Overall mortality at two month was 35.7% (5 of 14). PCP is still a threat to certain immunocompromised children and vigilant monitoring is needed.

Conflict of interest

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

References

1. Edman JC, Kovacs JA, Masur H, Santi DV, Elwood HJ, Sogin ML. Ribosomal RNA sequence shows Pneumocystis carinii to be a member of the fungi. Nature 1988;334:519-22.
2. Gigliotti F. Pneumocystis carinii: has the name really been changed? Clin Infect Dis 2005;41:1752-5.
3. Caselli D, Petris MG, Rondelli R, Carraro F, Colombini A, Muggeo P, et al. Single-day trimethoprim/sulfamethoxazole prophylaxis for Pneumocystis pneumonia in children with cancer. J Pediatr 2014;164:389-92.e1.
4. Gilroy SA, Bennett NJ. Pneumocystis pneumonia. Semin Respir Crit Care Med 2011;32:775-82.
5. Morris A, Norris KA. Colonization by Pneumocystis jirovecii and its role in disease. Clin Microbiol Rev 2012;25:297-317.
6. Hughes WT, Kuhn S, Chaudhary S, Feldman S, Verzosa M, Aur RJ, et al. Successful chemoprophylaxis for Pneumocystis carinii pneumonitis. N Engl J Med 1977;297:1419-26.
7. Bollee G, Sarfati C, Thiery G, Bergeron A, de Miranda S, Menotti J, et al. Clinical picture of Pneumocystis jiroveci pneumonia in cancer patients. Chest 2007;132:1305-10.
8. Briel M, Bucher HC, Boscacci R, Furrer H. Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV-infection. Cochrane Database Syst Rev 2006;(3):CD006150.
9. Lemiale V, Debrumetz A, Delannoy A, Alberti C, Azoulay E. Adjunctive steroid in HIV-negative patients with severe Pneumocystis pneumonia. Respir Res 2013;14:87.
10. Beltz K, Kramm CM, Laws HJ, Schroten H, Wessalowski R, Gobel U. Combined trimethoprim and caspofungin treatment for severe Pneumocystis jiroveci pneumonia in a five year old boy with acute lymphoblastic leukemia. Klin Padiatr 2006;218:177-9.