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Successful Empirical Treatment of Severe *Pneumocystis carinii* Pneumonia in Immunocompromised Children

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Abstract Immunocompromised patients are very prone to infection and sometimes result in death. *Pneumocystis carinii* pneumonia (PCP) is one of the opportunistic infections that affects lung. The frequency was high (80-88%). We reported 2 severe cases of PCP infection that remain survive. Case 1 is 8-year-old boy, post-liver transplantation, with PCP, pulmonary tuberculosis, cytomegalovirus infection, septic shock and severe malnutrition. Case 2 is 8-year-old girl, HIV positive, with PCP, respiratory failure, and severe malnutrition. These patients survived after adequate treatment of PCP and nutritional support. After 26 months of follow up, they are doing well with good nutritional status.

Keywords: *pneumocystis carinii, pneumonia, immunocompromised, children*

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1. Introduction

Pneumocystis carinii pneumonia (PCP) is an opportunistic infection that occurs in immunosuppressed populations, usually patients with advanced human immunodeficiency virus infection. [1] The term *Pneumocystis carinii* is widely used although the causative organism has been renamed *Pneumocystis jiroveci*. *P. carinii* is classified as fungi even though it could not be treated with antifungal regimen. [2]

P. carinii is found in the lung tissue of immunocompetent and immunocompromised hosts. It adheres specifically to the epithelium of the alveoli. Normal host has adequate immune response against *P. carinii*, therefore it does not cause infection. When the immune system is suppressed, the organism is able to proliferate. *P. carinii* binds to the type I pneumocytes and prevents gas to be exchanged between capillaries and the alveoli. Untreated inhibition of gas exchange in the host leads to poor oxygenation, hypoxemia and death. [3]

Although HIV-AIDS has been the most frequent cause of immunosuppression, other causes such as long-term steroid treatment, chemotherapy, transplant patient and cancer also have significant effect. The incidence of HIV-AIDS in children is decreasing in United Stated. It is related to universal screening in pregnant woman and good follow up of prevention mother to child transmission. In contrast, the incidence of HIV-AIDS in developing countries is increasing. In 2006, there were 150 HIV-AIDS patient under fifteen in Jakarta, Indonesia. In 2012, based on Ministry of Health Republic of Indonesia, there are 1969 children with HIV-AIDS in Indonesia. Frequency of PCP in immunocompromised patient was high (88% in lung transplant patient and 80% in HIV patient) and the rate is decreasing as the prophylaxis treatment widespread used. Infection of PCP increase mortality rate in HIV children with odds ratio 1.87.[4] This report presents two successful PCP cases with HIV-AIDS and post liver transplant.

2. Case Presentations

2.1. Case 1

An 8-year-old Javanese boy was admitted to the hospital due to prolonged fever. He underwent liver transplantation 2 years before admission due to autoimmune hepatitis. The patient received methylprednisolone and tacrolimus to prevent graft rejection. He was hospitalized for cytomegalovirus infection treatment. The diagnosis was made from the positive result of polymerase chain reaction (PCR) of urine sample. During hospitalization, he was dyspneic with oxygen saturation 70% in room air. He suffered productive cough with yellowish thick mucus. Patients had no response to third generation of cephalosporin, aminoglycosides, and beta-lactamase combination.

On examination, he was ill-looking, febrile, with respiratory rate 40 beats per minute and lower chest indrawing. His body weight was 14 kg (severe malnourished). He looked pale and icteric, with no palpable lymph nodes. Normal vesicular breath sound with no adventitious sounds was auscultated over the lungs.The liver was palpable 7 cm

below the right costal margin in tide midclavicular line; the spleen was palpable at Shuffner IV.

Investigations revealed hemoglobin concentration of 7.0 g/dl, total leucocyte count of 5430/cu mm, differential leukocyte count of band forms 0%, neutrophils 86%, lymphocytes 8% and monocytes 6%, and platelet count 39.000/cu mm. Blood culture was sterile. Arterial blood gas analysis revealed pH 7.487, $PaCO_2$ 28.3 mm Hg, and PaO_2 58.3 mm Hg. Serum IgG was 1023 mg/dL, Ig A was 170 mg/dL, Ig M was 71 mg/dL, and total IgE was 55.9 mg/dL. Immunity state showed decrease of CD4 count (85 cell/µL). Chest radiograph showed extensive patchy infiltrates in both lungs. Sputum examination was positive for *P. carinii* by Giemsa staining and positive for acid fast bacilli with Kinyon Gabet staining. The sputum culture showed positive for *Candida albicans*. Neither aspergillus nor cryptococcus was found.

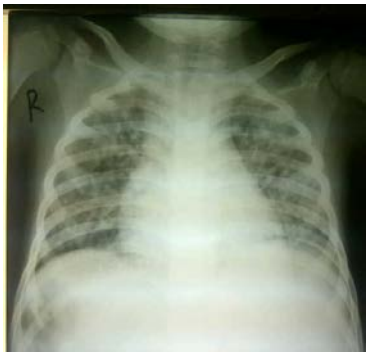

Figure 1a. Patient's chest x-ray showed diffuse bilateral and pathcy infiltrate

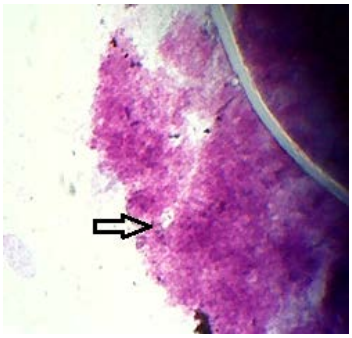

Figure 1b. *P. Carinii* cyst , thropic form (100x magnification)

During hospitalization, he was admitted to the intensive care because of septic shock. Continuous inotropic agent (dobutamine, dopamine) was infused for a week. Patient was treated by co-trimoxazole peroral 5 mg/kg/dose 6 hourly, mikafungin and antituberculosis (rifampicin/ isoniazid/ pyrazinamide/ ethambutol). During the treatment, the symptoms were getting improved. One week later, patient was discharged from hospital. Co-trimoxazole was given until 3 weeks and antituberculosis for 6 months. After completed the treatment, sputum examination was repeated and the result was negative for *P. carinii.* On 26 months of follow up, he was doing well with no opportunistic infection. Isoniazid and co-trimoxazole were still given as prophylaxis. His nutritional status was improving (his body weight was 21 kg).

2.2. Case 2

An 8-year-old girl with fourteen kilograms body weight had progressive dyspnea since two months before admission. Tachypnea and severe chest indrawing were seen. Peripheral saturation with 2 liter per minute oxygen was only 70%. The vesicular sound was decrease on left lung and crackles were heard in all parts of the lungs. HIV antibody analysis was positive with CD3 count 436 cells/µL (93%) and CD4 10 cells/µL (1%). The chest radiograph showed wide diffuse infiltrate on both lungs, and only small part of aerasion on right paracardial. The patient was treated with wide spectrum of antibiotics (cefotaxime, clarithromycin), and co-trimoxazole due to PCP suspected. Blood and sputum specimen for smear and culture were taken previously. On the sixth day of admission, the patient life got threatened with $PaCO_2$ 65.8 mmHg and PaO_2 43.1 mmHg and needed mechanical ventilation. However, the family decided not to receive any resuscitation.

On the eighth day of admission, the laboratory reported that several cysts of *P. carinii* were seen on sputum stained Giemsa. At the same time, the patient kept improving. The co-trimoxazole was continued until 21 days and she was discharged after 32 days admission. On 26 months follow-up clinic visit, she was doing well with good nutritional state (24 kg of body weight). She is still on antiretroviral treatment.

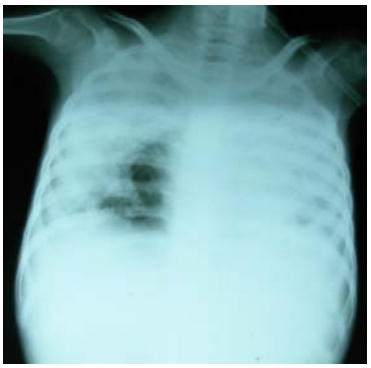

Figure 2a. First chest x-ray on admission showed wide diffuse infiltrate on both lungs

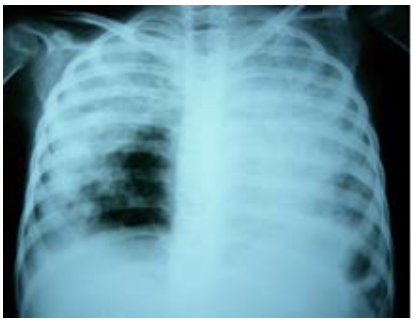

Figure 2b. Chext x-ray showed improvement on fifth day of admission

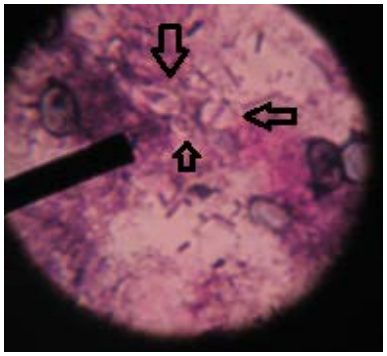

Figure 2c. *P. carinii* cyst , thropic form (100x magnification)

3. Discussion

This report describes two children who present with PCP. Both of them had immunodeficiency problem with different etiology. Definitive diagnosis of PCP in pediatric is difficult to establish because specimen collection is hard to obtain. The diagnostic was usually made by clinical criteria. The clinical criterias consist of presence of diffuse pneumonia which is unresponsive to common antibiotics, hypoxemia, HIV infection or risk of HIV infection, and low CD4 count. [5] This clinical criteria is not fit with patient case 1 because the risk factor in this patient is liver transplantation. Severe malnutrition in these cases played important role to severity of illness.

Several ways to obtain sputum collection from children are bronchoalveolar lavage and induced sputum. Bronchoscopy is very high risk procedure in children due to general anesthesia effect. In these cases, sputum was obtained from coughing without induction. Even though sputum is the best sample to identify PCP, only 10-11% showed positive. [6,7] It was contrast with post mortem evaluation that PCP accounted in 52% HIV children who died due to respiratory illness. Since PCP is difficult to find in sputum collection, presumptive treatment is very important and often life-saving. [8,9] In these cases, treatment has been initiated before the sputum evaluation was made. Some studies review serum indicator to detect PCP infection in early stage. Four serum markers have been evaluated included lactate dehydrongenase (LDH), beta D-glucan, KL-6 and C-reactive protein. Beta D-glucan and LDH concentrations were helpful to establish the diagnosis of PCP for early treatment. [10,11] Unfortunately, we could not perform beta D-glucan and LDH measurement due to the limitation of laboratory resources. Therefore, clinical assessment is very important. Another diagnostic tool for PCP is PCR of nasopharyngeal aspirate. The sensitivity, specificity, positive predictive value, and negative predictive value are 86%, 95%, 96% and 85%, respectively. [12] We did not performed PCR of these patients because sputum specimen showed positive result. Sputum specimen is gold standard for PCP diagnostic. Chest x-ray is not specific to diagnose PCP especially in case 1 where there are multiple lung infections. Chest x-ray should be made to evaluate how much lung parenchyma is involved.

Prophylaxis of PCP is considered when CD4 count is less than 100 cell/µL. It contributed to significant reduction of PCP incidence in developed countries. [13,14] In case 1, PCP prophylaxis was given after respiratory symptoms occurred but the case 2, prophylaxis was given after PCP established. Monitoring CD4 count is difficult to be done in our countries because there are few laboratories available. After 3 weeks of full dose treatment, prophylaxis is continued with co-trimoxazole.

Co-trimoxazole oral still has a good response in these two cases. Reference [15] described increasing of PCP resistance to sulfametoxazole. It becomes obvious that new drugs must be identified. Sulfa-resistant in PCP is associated with dihydropteroate synthase mutation. We can consider the DPHS mutation if there is no improvement in 5 days of co-trimoxazole therapy. [16] Unfortunately, PCP does not response to antifungal treatment due to different sterol metabolism. Pentamidine, atovaquone, clindamycin, and primaquine have successfully reduced the number of deaths attributed to PCP infection. [17]

Co-infection in PCP patients is higher in developing countries than in industrialized countries. The most common pathogen is *Mycobacterium tuberculosis.* In case 1, *M. tuberculosis* was found in sputum examination. *M. tuberculosis* is present in almost 66% cases of PCP. The other pathogen such cytomegalovirus was found in 44-68% PCP patients. The risk factors of co-infection are low of CD4 (less than 22 cell/µL) and steroid use. [18,19] Patient case 1 had more opportunistic infections (fungal pneumonia, cytometalovirus infection, pulmonary tuberculosis and PCP) than patient case 2 (only PCP). It could be related to immunosuppressant use. Even though patient in case 2 has immunodeficiency, antiretroviral therapy can improve her immunity.

Several studies had described the prognostic factors in HIV patient with PCP. Albumin, oxygenation status, and CD4 level are significant contributing factor. [20,21,22,23] In case 2, oxygen saturation was maintained with adequate oxygen supplementation, albumin level within the normal limit, and CD4 count was improving during antiretroviral treatment.

The two success stories of severe PCP with bad prognosis are supported by early treatment, nutritional support, adequate oxygen supplementation, and good management of co-infection. From these cases, we suggest several things to remember in management of immunocompromised patients at limited resources. First, in immunocompromised patient with respiratory symptoms, PCP treatment could be initiated even though definitive diagnosis has not been established. Second, we must think about multiple infections in immunocompromised patient therefore, it is important to investigate all opportunistic infections such as tuberculosis, fungal infection, cytomegalovirus, and PCP. Finally, optimalizing oxygenation state with high supplementation oxygen should be maintained to get better prognosis.

4. Conclusion

In immunocompromised patient with respiratory illness, PCP should be considered. Early treatment should be started even though definitive diagnosis has not been made. Oral co-trimoxazole has a good response to PCP. Other co-infection should be evaluated to get a better outcome. PCP prophylaxis should be given in immunocompromised patient.

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