Pneumocystis jiroveci pneumonia in non-HIV immunocompromised Taiwanese children

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Background: **Pneumocystis pneumonia (PCP) has been a common opportunistic infection in patients infected with human immunodeficiency virus (HIV). Up to the present, the burden of HIV infections predisposing to PCP is not a major concern in Taiwanese children. This paper describes our experience in dealing with 5 children with PCP in a tertiary children's center in northern Taiwan.**

Methods: **We retrospectively reviewed cases by computer search of our hospital records with a diagnosis of PCP by microbiological or histological evidence of *Pneumocystis jiroveci* infection in patients younger than 18 years of age between January 1996 and December 2005 in the Chang Gung Children's Hospital.**

Results: **A total of 5 patients with PCP were identified. Their ages ranged from 2 months to 14 years. The major underlying diseases were acute lymphoblastic leukemia (1 patient), severe combined immunodeficiency (SCID) (2), Langerhans cell histiocytosis (1), and systemic lupus erythematosis (1). None of the patients received regular chemoprophylaxis, 4 patients survived but 1 died from respiratory failure.**

Conclusions: **From 1996 to 2005, PCP infections in Taiwanese children were commonly seen in primary immunodeficiency diseases, leukemia, or malignancies receiving cytotoxic and corticosteroid therapy. PCP in susceptible patients suggests non-compliance or under-prescription of PCP chemoprophylaxis by the patients or in-charge physicians respectively.**

World J Pediatr 2007;3(3):200-202

Key words: ***Pneumocystis jiroveci*** **pneumonia; non-HIV immunocompromised; immunodeficiency**

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Introduction

Pneumocystis pneumonia (PCP) has been a common opportunistic infection in patients infected with human immunodeficiency virus (HIV).[1,2] However, the prevalence of HIV infection in Taiwan remains low with a sero-prevalence of 12.3 per 100 000 in the years before 2000.[3] For non-HIV patients with PCP, predisposing factors include congenital immunodeficiency syndromes,[4] administration of corticosteroids or cytotoxic agents in hematological malignancies, bone marrow or organ transplantations. Despite rarity, PCP remains an important cause of morbidity in children because of its potential lethality.[5] This article describes our experience in dealing with 5 children with PCP in a tertiary children's center in northern Taiwan.

Methods

We retrospectively reviewed cases by computer search of the hospital records with a diagnosis of PCP in patients younger than 18 years of age between January 1996 and December 2005 in Chang Gung Children's Hospital. PCP was proven by microbiological, cytological or histological findings of *Pneumocystis jiroveci*: identification of cysts of *P. jiroveci* from induced sputum or bronchoalveolar fluid (BALF) using Gomori-methenamine silver stains or histological documentation of cysts or trophozoites of *P. jiroveci* in lung biopsy tissue. The patients with a presumptive diagnosis of PCP who did not meet the criteria were excluded. Five children were identified, and their demographic data, clinical features and treatment outcome were reviewed and analyzed.

Results

The 5 patients found by computer search during a 10-year-period (1996-2005) consisted of 3 boys and 2 girls. Their ages ranged from 2 months to 14 years. All the patients were immunocompromised (Table). None of them received regular trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis. Three

patients received prednisolone therapy with doses ranging from 1 mg/kg to 2 mg/kg per day before the onset of pneumocystis infection, and the other 2 patients received no corticosteroid therapy. All patients were presented with dyspnea and cough, among them 4 developed fever. Leukopenia was found only in 1 patient, but all of them had absolute lymphocytes <1000/mm^3. Chest radiography revealed interstitial infiltrates in 4 patients and alveolar consolidation in 1. The polymerase chain reaction (PCR) for detection of *P. jiroveci* either from sputum or BALF was positive in 4 of them. A 14-year-old adolescent girl with systemic lupus erythematosis (SLE) had concurrent *P. jiroveci* and cytomegalovirus (CMV) infection that required an open lung biopsy for diagnosis. All patients received TMP-SMX therapy after diagnosis; 4 patients survived but 1 died from respiratory failure.

Discussion

In 1909, Chagas[6] originally described the organism that caused human PCP was protozoa in nature. With the advance of DNA analysis, pneumocystis organism is now reclassified of fungus origin.[7] In recent years, true infections of *P. carinii* occurred in rats only, while *P. jiroveci* are exclusively found in humans.[8,9] The acronym PCP which was formerly used to describe human *P. carinii* pneumonia should refer to Pneumocystis pneumonia by its up-to-date usage.

The relative risk of PCP infections corresponds to the level of lymphopenia and immuno-suppression caused by corticosteroids.[4,10] In our study, the 5 patients showed absolute lymphocyte counts lower than 1000/mm^3. Hypoxemia in HIV-patients with PCP tends to develop insidiously for 1 to 2 weeks, comparing to non-HIV patients with rapid deterioration.[11,12] In this study, most patients presented with acute onset of dyspnea, cough and fever. Interstitial infiltration was seen in 4 children, and alveolar consolidation in 1.

The cysts of *P. jiroveci* were typically stained by toluidine blue or Gomori-methenamine silver staining, whilst monoclonal immunofluorescence antibody staining was capable of demonstrating both cystic form and trophozoites of *P. jiroveci* with a sensitivity of 85%. Molecular diagnosis of *P. jiroveci* infection using PCR with induced sputum or BALF was positive in 4 of the 5 patients in this study. Nonetheless, an open lung biopsy was required in a 14-year-old girl to prove PCP infection associated with concomitant pulmonary CMV infection.

PCP is typically seen in patients with T cell immunodeficiency and those with severe combined immunodeficiency. PCP tends to occur in patients with lymphoproliferative malignancies in higher frequency than in those with localized solid tumors because more intensive immunosuppressive therapy is required for lymphoproliferative neoplasms. About 22%-45% of children with acute lymphoblastic leukemia develop PCP if chemoprophylaxis is not given regularly. However, isolated cases of agammaglobulinemia,[13,14] X-linked hyper IgM with CD40L deficiency, also have been reported.[15] In this study, 2 patients with severe combined immunodeficiency (SCID) had PCP, both of them were not known to be immunodeficient before PCP was diagnosed. For those children who are unable to thrive with frequent and unusually severe infections, the possibility of primary immunodeficiency should be highly suspected and complete immunological examination is mandatory.

The indications for anti-pneumocystis prophylaxis in patients with HIV have been clearly defined.[1] The period of susceptibility to *P. jiroveci* infection can be predicted by the peripheral CD4 cell counts below 200/mm^3. However, no laboratory markers are available for predicting the susceptibility of PCP in non-HIV patients.[16,17] Sepkowitz[18] suggested chemoprophylaxis for PCP in patients receiving chemotherapy, radiotherapy or those receiving prednisolone ≥20 mg/day (or its equivalent) for ≥4 weeks. The routine use of chemoprophylaxis can decrease the incidence of PCP. TMP-SMX had been prescribed in patient 3 but the patient did not take the medication. In contrast, TMP-SMX was withheld temporarily in patient 4 because of the low white blood counts observed by the attending physician.

Table. Clinical features of 5 patients with pneumocystis pneumonia

Age	Sex	Underlying diseases	*Pneumocystis jiroveci*				WBC/mm^3	ALC/mm^3	Outcome
			BALF-PCR	BALF-cytology	Sputum PCR	Lung biopsy			
2 months	F	Langerhans cell histiocytosis	+	+	ND	ND	4600	92	Survived
5 months	M	SCID	+	-	ND	ND	9900	297	Survived
1 year	M	SCID	+	+	ND	ND	11500	920	Died
5 years	M	ALL	ND	+	+	ND	1300	637	Survived
14 years	F	SLE	-	-	-	+	8300	415	Survived

BALF: broncho-alveolar lavage fluid; PCR: polymerase chain reaction; WBC: white blood cells; ALC: absolute lymphocyte count; SCID: severe combined immunodeficiency; ND: not done; ALL: acute lymphoblastic leukemia; SLE: systemic lupus erythematosus.

One patient with SLE had pulmonary involvement of *P. jiroveci*. Literature review showed that PCP occurs in only 1%-2% of patients with rheumatologic disorders with/without immunosuppressive therapy.[19,20] However, due to the high risk of mortality in patients with connective tissure disorders with PCP, the routine use of anti-pneumocystis prophylaxis remains controversial.[21]

In conclusion, in an area with a low prevalence of HIV infection, PCP is commonly seen in patients with primary immunodeficiency diseases. Patients with leukemia, SLE or malignancies who require cytotoxic or corticosteroid therapy are predisposing to PCP. PCP in susceptible patients suggests under-utilization of chemoprophylaxis either by the physician or due to non-compliant patients. Respiratory specimens using induced sputum or BALF and special silver stains have a high probability of detection of PCP, but open lung biopsy remains the gold standard of diagnosis in difficult cases.

Funding: None.
Ethical approval: Not needed.
Competing interest: None declared.
Contributors: Wong KS wrote the first draft of this paper. All authors contributed to the intellectual content and approved the final version.

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Received May 11, 2007
Accepted after revision June 25, 2007