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BRIEF REPORT

Lymphocyte surge as a marker for immunorestitution disease due to *Pneumocystis jiroveci* pneumonia in HIV-negative immunosuppressed hosts

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Pneumocystis jiroveci (previously known as *Pneumocystis carinii* f. sp. *hominis*) pneumonia (PjP) [1] is a well-known opportunistic infection affecting immunocompromised hosts, especially patients infected with HIV. However, with the rising number of patients receiving immunosuppressive therapy, PjP is being increasingly recognised in immunosuppressed hosts who are not infected with HIV [2]. For instance, one previous study found PjP in 3.4--43% of solid organ transplant recipients not infected with HIV, with an especially high incidence among patients on long-term steroid therapy [3]. Though the exact pathogenesis of PjP remains obscure, it has been suggested that immunorestitution disease (IRD) contributes to the manifestation of

PjP [4]. Reported here are seven cases of PjP manifesting as IRD in HIV-negative immunosuppressed hosts.

Between July 1995 and June 2003, 35 patients were diagnosed with PjP at the Queen Mary and United Christian Hospitals in Hong Kong based on the presence of radiologically proven pulmonary infiltrations, the presence of *Pneumocystis jiroveci* in bronchoalveolar lavage fluid, and symptoms consistent with the clinical picture of PjP infection, such as fever, cough, and dyspnoea. Twenty-five of the patients were HIV positive; 19 of these patients were newly diagnosed and had not begun highly active antiretroviral therapy at the time of presentation. The remaining 10 patients were HIV-negative immunosuppressed subjects with renal diseases (glomerulonephritis in 2, renal transplantation in 1), haematological conditions (immune thrombocytopenic purpura in 2), autoimmune diseases (bullous pemphigoid in 1, pemphigus vulgaris in 1, juvenile rheumatoid arthritis in 1), and solid organ tumour (thymoma in 1). The case of one patient with Cushing's disease was reported previously [4]. The immunosuppressive therapy administered to these patients consisted of an endogenous steroid in one, steroid therapy in three, and a combination of steroids and cytotoxic treatment in five.

Altogether there were 22 male and 13 female patients, and their ages ranged from 7 to 75 years (mean±SD, 43.3±13.9 years). Thirty of them were ethnic Chinese, four were Thai and one was Filipino. The most common clinical presentations of PjP were dyspnoea (80%), fever (80%), non-productive cough (54.3%), and productive cough with clear sputum (31.4%). A minority of the patients presented with chest pain (8.6%), general malaise (8.6%), anorexia (8.6%), dizziness (5.7%), sore throat (5.7%), and diarrhoea (5.7%). Oxygen desaturation with SaO_2 <90% while on ambient air occurred in three of the patients. Chest radiographs revealed bilateral lesions in 30 patients, whereas five patients had unilateral involvement. An alveolar pattern of radiographic lesions was shown in 19 patients, whereas interstitial radiographic lesions were found in the

remaining 16 patients. Unilateral pleural effusion was noted in one patient upon admission. Pneumothorax was not observed in any of our patients on presentation. None of the 35 patients had received prior chemoprophylaxis for PjP. High-dose intravenous co-trimoxazole was given to 30 patients, and intravenous pentamidine was initiated in the remaining five patients.

We defined IRD as an acute symptomatic presentation of PjP temporally related to the recovery of the immune system (as evidenced by an increase in the absolute lymphocyte count), which resulted in immunopathological damage associated with reversal of immunosuppressive processes, such as a reduction in the corticosteroid dose or a reduction in HIV viral load by HAART. Seven of the 35 patients fulfilled the case definition of IRD, with an upsurge of absolute lymphocyte counts being noted from the reduction of immunosuppression (median, 300/μl; range, 290--740/μl) to the onset of IRD (median, 1,500/μl; range, 600--5,620/μl). The demographic characteristics of patients with and without reversal of immunosuppression before the clinical manifestation of PjP are listed in **Table 1**.

All seven patients who developed symptomatic PjP during reversal of immunosuppression tested negative for HIV. Five of them had received chronic steroid therapy for more than 3 months. They had a higher mean age (53.1 vs 40.9 years, P=0.04) and a shorter mean duration of symptoms preceding admission (2.0 vs 19.9 days, P<0.01). They tended to be more hypoxemic (pO_2 7.8 vs 10.9 kPa on ambient air, P=0.06), and they had a significantly higher mean lymphocyte count (1,918 vs 641/μl, P<0.01). When compared with those patients without reduction of immunosuppression, a significantly higher proportion of patients with IRD required steroid therapy as adjunctive treatment (100% vs 60.7%, P=0.04), and patients with IRD suffered more frequent opportunistic infections (57.1% vs 17.9%, P=0.03). Interestingly, steroid therapy was initiated after a median delay of 1.5 days following high-dose intravenous co-trimoxazole for PjP in four of the patients without IRD. Compared with patients without IRD, a higher proportion

of IRD patients was admitted to the intensive care unit (100% vs 53.6%, *P*=0.02), received mechanical ventilation (85.7% vs 32.1%, *P*=0.01), had a longer mean duration of hospital stay (37.3 vs 18.4 days, *P*<0.01), and died (42.9% vs 10.7%, *P*=0.04).

The clinical manifestation of PjP as a form of IRD is not a rare phenomenon. In our study, the seven patients with this condition represented 20% of all patients with microbiological evidence of *Pneumocystis jiroveci* infection and 70% of the HIV-negative immunosuppressed patients with PjP. As seen in these patients, PjP occurring in the context of IRD is acute and fulminant, often associated with nonspecific findings on initial chest radiographs, and often associated with a high absolute lymphocyte count resulting from the tapering of immunosuppressive therapy or reversal of immunosuppressed status. All of our patients with IRD required steroid therapy adjunctive to antimicrobial treatment, and more than 80% of them required ventilatory support for acute respiratory failure. Unfortunately, the diagnosis of PjP was usually delayed in these patients because of its atypical presentation in this clinical setting. Mortality was significantly higher among the patients with IRD.

Acute respiratory failure following HAART initiated during the treatment of PjP has been clearly documented as an IRD in HIV-infected patients [5, 6]. In three patients treated with HAART early after the diagnosis of PjP (i.e., 1--16 days), acute respiratory distress occurred shortly after HAART introduction (i.e., 7--17 days) [5], when the CD4+ lymphocyte count increased along with a concomitant reduction in viral load. Similar experience has been reported in another three patients [6]. All of these patients had severe respiratory distress as evidenced by PaO_2 of less than 70 mmHg, and they required the administration of steroids as anti-inflammatory therapy. Either HAART was given too early during the course of PjP disease (1--16 days), or the steroid was stopped too early (<15 days). The phenomenon of IRD in HIV-positive patients with PjP infection has been further substantiated by examination of the lungs and transbronchial biopsy

specimens, with histopathologic examination revealing mixed inflammatory infiltrates including macrophages, neutrophils, lymphocytes, and plasma cells. Almost all infiltrating lymphocytes were in T-cell lineage as assessed by immunophenotyping, and CD4+ and CD8+ lymphocyte subsets were equally represented in the tissue level [5].

In fact, rapid reduction of immunosuppressive therapy, such as steroid treatment, has been implicated as a predisposing factor for the development of PjP in HIV-negative patients [2, 7--9]. However, these cases were not all analyzed from a perspective of IRD. Serial changes of absolute lymphocyte counts were not noted or reported [2, 7--9]. It has been suggested that an upsurge of the absolute lymphocyte count, especially CD4+ lymphocyte counts in HIV-positive patients, can act as a surrogate marker for immunopathological damage during IRD in both HIV-negative and HIV-positive patients [4]. In each of our seven HIV-negative immunosuppressed patients, a consistent rise in the absolute lymphocyte count was observed from the time reduction of immunosuppression occurred to the onset of IRD. A similar trend of increasing CD4+ lymphocyte counts was also found in other HIV-positive cases before and during IRD [5, 6]. An upsurge in absolute lymphocyte counts at the time of IRD has been previously reported in patients with viral infections, such as polyomavirus and influenza A virus [10] as well as paradoxical deterioration of tuberculosis during anti-tuberculous therapy [11]. However, it must be emphasized that the number of circulating lymphocytes detected may not always represent the number in the affected tissues or their in vivo functional activity. For instance, in a case of PjP associated with steroid withdrawal that we reported previously, the lymphocyte count surged to a very high level, then rapidly decreased to a low level within 1 day. This was likely due to extremely severe immunorestitution, in which all of the lymphocytes migrated into the site of restitution to produce severe damage [4].

With a better understanding of the IRD phenomenon in cases of *Pneumocystis jiroveci* infection, we may be able to prevent the occurrence of IRD in HIV-positive patients by delaying the initiation of HAART. However, it is even more important to recognise the atypical manifestation of IRD in HIV-negative immunosuppressed patients because the consequences are worse. Very often, a diagnosis cannot be achieved based on clinical and/or radiological features alone. Analysis of absolute lymphocyte counts taken serially from the time of reduction of immunosuppression to the time of presentation can alert clinicians to the possibility of IRD associated with occult pathogens such as *Pneumocystis jiroveci*, if an upsurge of lymphocyte counts is detected.

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Table 1 Comparison of demographic characteristics of patients with or without immunosuppression reversal (IR) before the clinical manifestation of *Pneumocystis jiroveci* pneumonia (PjP)

Characteristic	With IR (*n*=7)	Without IR (*n*=28)	P value
Mean age in years (SD)	53.1 (13.6)	40.9 (13.1)	0.04
Male:female ratio	4:3	18:10	0.73
Proven HIV infection	0	25 (89.3%)	<0.01
Presence of immunosuppressive conditions other than HIV	7 (100%)[a]	4 (14.3%)[b]	<0.01
Presence of other co-morbidities	1 (14.3%)[c]	7 (25%)[d]	0.55
Chronic steroid therapy for more than 3 months	5 (71.4%)	1 (3.6%)	<0.01
Mean duration of symptoms to admission in days (SD)	2.0 (2.9)	19.9 (15.5)	<0.01
Classic interstitial infiltrates on initial chest radiograph	2 (28.6%)	14 (50%)	0.31
Mean PaO_2 (kPa) in ambient air (SD)	7.8 (1.3)	10.9 (3.6)	0.06
Mean lymphocyte count in μl at presentation (SD)	1918 (1753)	641 (362)	<0.01
Clinical suspicion of PjP on admission	0	10 (35.7%)	0.03
Mean days of anti-PjP therapy after onset of symptoms (SD)	8.1 (4.3)	24.5 (17.0)	0.02
Steroids as adjunctive anti-PjP therapy at acute phase	7 (100%)	17 (60.7%)	0.04
Delayed use of steroids after initiation of anti-PjP therapy	0	4 (14.3%)	0.29
Coinfection by other opportunistic pathogen(s)	4 (57.1%)[e]	5 (17.9%)[f]	0.03
Mean length of stay in days (SD)	37.3 (28.2)	18.4 (10.3)	<0.01
Intensive care admission	7 (100%)	15 (53.6%)	0.02
Mechanical ventilation	6 (85.7%)	9 (32.1%)	0.01
Overall mortality	3 (42.9%)	3 (10.7%)	0.04

[a]Immune thrombocytopenic purpura (2), glomerulonephritis (2), bullous pemphigoid (1), endogenous Cushing's disease (1), renal transplantation (1)

[b]Pemphigus vulgaris (1), juvenile rheumatoid arthritis (1), thymoma (1), diffuse large cell lymphoma (1)

[c]Chronic hepatitis C (1)

[d]Old tuberculosis (3), chronic hepatitis B (3), pregnancy at 12 weeks of gestation (1)

[e]CMV antigenaemia (3), CMV hepatitis (1)

[f]Varicella zoster virus reactivation (1), cytomegalovius (CMV) pneumonitis (1), cryptococcal meningitis (1), CMV antigenaemia & cryptococcal meningitis (1), and CMV retinitis & disseminated *Penicillium marneffei* (1).CXR, chest radiograph; HAART, highly active antiretroviral therapy