Int J Clin Exp Med 2017;10(7):10683-10689
www.ijcem.com /ISSN:1940-5901/IJCEM0050944

Original Article

High-resolution computed tomography features of *Pneumocystis jirovecii* infection in patients with renal transplant

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Received February 15, 2017; Accepted May 19, 2017; Epub July 15, 2017; Published July 30, 2017

Abstract: Objective: To describe the radiological and clinical features of Pneumocystis jirovecii pneumonia (PJP) infection in patients who underwent renal transplantation. Subjects and methods: This retrospective analysis of 16 PJP infections in renal transplantation recipients was carried out at Anhui Provincial Hospital over a 5-year period. All patients underwent the same antimicrobial therapy. Between the onset of symptoms and the start of therapy, a series of early and late pulmonary high-resolution computed tomography (HRCT) scans were evaluated. Results: The most common clinical features included fever (12/16, 75%), cough (8/16, 50%), and shortness of breath (8/16, 50%). Common HRCT findings were bilateral diffuse ground-glass opacity that was mostly distributed in the lung apices, emphysema, lymphadenopathy, air bronchogram, and pleural thickening. Conclusion: Renal transplantation patients with PJP appear to have a different pattern of infection than similar patients with immunosuppression caused by HIV infection. Analysis of HRCT features can enable an early diagnosis to be made, which would enable treatment to be started promptly to maximize prognosis.

Keywords: *Pneumocystis jirovecii* pneumonia, renal transplantation, HRCT, early diagnosis

Introduction

Pneumocystis jirovecii is a fungus normally found in humans and a variety of animals. *P. jirovecii* pneumonia (PJP) is the most common opportunistic infection in patients with impaired immune function and is the causative pathogen of *Pneumocystis* pneumonia [1-4]. The clinical symptoms of renal transplantation patients with PJP are more severe and atypical than those of HIV-infected patients [5]. Moreover, a delay in the diagnosis of PJP is associated with a high mortality rate caused by severe respiratory failure [1, 6-8].

Gruden *et al.* [9] previously showed that high-resolution computed tomography (HRCT) is valuable in the evaluation and detection of clinically suspected PJP in AIDS patients with normal, equivocal, or nonspecific radiographic findings. However, to our knowledge, no data exist about the course, duration, and morphology of pulmonary changes depicted in HRCT in renal transplantation patients with PJP. This retrospective study therefore analyzed the clinical manifestations and HRCT characteristics of renal transplant recipients with PJP to better characterize their findings with the aim of providing an earlier correct diagnosis for a more effective treatment.

Materials and methods

Patients

We collected clinical data from 348 living donor renal allograft recipients treated at the Anhui Provincial Hospital Transplantation Center from 2010 to 2015. All patients received the same immunotherapy after renal transplantation. A total of 16 (4.6%) patients had pulmonary infections with *P. jirovecii*. None of the PJP patients received specific prophylaxis prior to the onset of symptoms. All clinical records and imaging data were reviewed.

Pathogenic diagnosis

P. jirovecii is not readily cultured in the laboratory, so was diagnosed using microscopic anal-

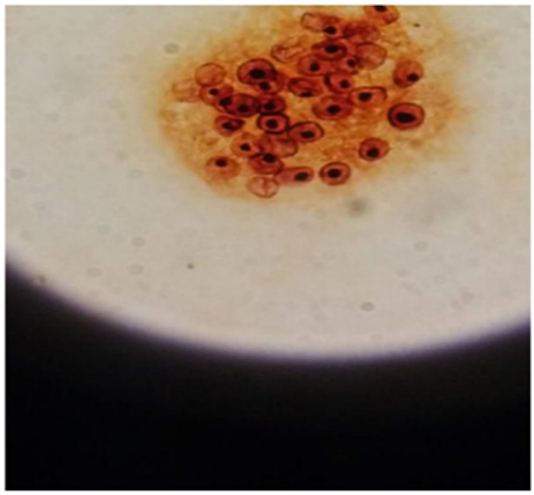

Figure 1. Gomori methenamine silver staining. Typical pneumocystis cyst in a bronchoalveolar lavage specimen stained with Gomori methenamine (brown to black staining, 100×). Thick cyst walls and some intracystic bodies are evident.

ysis of respiratory secretions. A standard sputum sample was initially obtained for examination. Sputum induction with hypertonic saline was performed if the initial specimen was negative for *P. jirovecii* (n = 6). Bronchoscopy with bronchoalveolar lavage was performed if the induced specimen was negative for *P. jirovecii* (n = 10) [4, 9]. Trophic and cystic forms of *P. jirovecii* were demonstrated using Gomori methenamine silver staining (**Figure 1**).

HRCT protocol

All patients underwent non-contrast HRCT imaging of the chest using Picker 6000 spiral CT (Philips Medical System, Best, the Netherlands), with a collimation of 2 or 5 mm. All images were viewed using standard mediastinal and lung windows. Every patient received follow-up HRCT imaging. All CT images were reviewed independently by two radiologists who were blinded to clinical data. Differences in CT reports were resolved by reviewer discussion.

Treatment protocol

All patients received sulfamethoxazole (SMZ) plus glucocorticoids after diagnosis [7, 10]. Third-generation cephalosporins were also administered to prevent bacterial infection.

Results

Clinical data

A total of 13 men and 3 women with a mean age of 33.1 ± 6.8 (SD) years (range: 25-48 years) were diagnosed with PJP (**Table 1**). Common clinical features included fever (temperature >38°C; 12/16, 75%), cough (8/16, 50%), and shortness of breath (8/16, 50%; **Table 1**). All patients received long-term immunosuppressive treatment after renal transplantation with CellCept and prednisone. Nine patients also received cyclosporine and seven received tacrolimus (**Table 2**). The mean time from transplantation to diagnosis of PJP was 180.7 ± 140.9 days (range: 33-515 days) for all patients. Patients treated with cyclosporine had a mean time to infection of 159.9 days (range: 33-515 days), while patients receiving tacrolimus had a mean time to infection of 207.4 days (range: 87-365 days).

Thirteen (81.3%) patients improved with treatment and recovered by 150 days after the start of treatment, while three others died. One of these patients developed severe pulmonary infection and sepsis 2 months after hospital admission. The use of a non-invasive ventilator failed to improve oxygenation and family members gave up treatment. The second patient had hepatitis B-based disease and developed liver failure, hepatic encephalopathy, and multiple organ failure. The third patient had diabetes that was poorly controlled and pulmonary infection of *Acinetobacter baumannii*. This infection became difficult to control, leading to respiratory failure.

All three women had received cyclosporine but no tacrolimus.

Other clinical observations included the fact that patients older than 36 years suffered shortness of breath more often than younger patients (4/4 vs. 4/11, Chi square test, $p = 0.029$). All patients with PJP diagnosed before 120 days after transplantation had a cough compared with none diagnosed later than this (8/8 vs. 0/7, Chi square test, $p < 0.0001$). Patients treated with cyclosporine showed a trend toward a less frequent development of cough than patients treated with tacrolimus (6/8 vs. 2/7, Chi square test, $p = 0.072$).

Table 1. Clinical data

#	Gender	Age (years)	Δ (days)	Cellcept	Prednisone	Cyclosporine	Tacrolimus	Fever	Cough	Shortness of breath
1	M	25	140	X	X		X	X		
2	M	41	81	X	X	X		X	X	X
3	M	31	340	X	X		X	X		X
4	F	48	515	X	X	X				X
5	M	30	348	X	X	X		X		
6	M	30	90	X	X		X	X	X	
7	F	25	114	X	X	X		X	X	
8	M	31	94	X	X	X			X	
9	M	35	89	X	X	X		X	X	X
10	F	36	73	X	X	X		X	X	
11	M	36	87	X	X		X	X	X	
12	M	26	92	X	X	X			X	X
13	M	42	365	X	X		X			X
14	M	39	160	X	X		X	X		X
15	M	27	33	X	X	X		X		
16	M	27	270	X	X		X	X		X

Δ (days) = days from transplantation; X = corresponding symptoms.

HRCT of the chest

HRCT of the chest identified three stages (**Figure 2**). Early-stage infection consisted of bilateral diffuse ground-glass opacities (GGO), typically in the apex of the upper lobe (n = 12) (**Figure 3**). Consolidation, represented by air bronchograms, was an uncommon manifestation (n = 1). Pleural effusion, cystic changes, and pneumothorax were not typically observed. Some patients had enlarged mediastinal lymph nodes (n = 4) or pleural thickening (n = 7; **Table 2**). Patients treated with trimethoprim-sulfamethoxazole (TMP-SMZ) for at least 2 weeks showed markedly fewer GGO. Follow-up 1 month after the completion of treatment showed the complete resolution of lung findings with few residual fibrosis or cyst-like lesions.

Discussion

Pneumocystis pneumonia is a serious cause of sickness and death in immunocompromised individuals. Most reports of PJP have been in patients with HIV [4, 11-13]. However, patients undergoing solid organ transplantation are immunosuppressed by different mechanisms so have different clinical manifestations of PJP from those found in HIV patients [11, 14].

HRCT patterns in non-AIDS immunocompromised patients [12] were divided into three patterns. Early infections showed bilateral diffuse GGO, mid-stage had bilateral diffuse GGO and patchy consolidation, and late-stage had bilateral diffuse consolidations. Other manifestations included pleural effusions, small nodules, pneumothorax, pneumomediastinum, pneumohypoderma, cystic lesions, and thickened lobular septa, consistent with previous reports [9, 12].

Common imaging findings of individuals with HIV-associated PJP were previously shown to include perihilar haze or GGO, scattered thin-walled lung cysts, and spontaneous pneumothorax. Uncommon manifestations include focal nodules or masses, focal consolidation, pleural effusion and organizing pneumonia [2, 8, 11].

The 16 treated patients could be divided into three stages on HRCT findings. The early stage was characterized by bilateral diffuse GGO, mainly in the mid and upper lobe distribution. Almost all patients had apex of the upper lobe involvement. Consolidation seen as air bronchograms was typical, but pleural effusion, cystic changes, and pneumothorax were rarely seen. A small number of patients had mediastinal lymph nodes or pleural thickening. The mid-

Table 2. Clinical symptoms and HRCT features

Patient number/ sex/age (in yrs)	Clinical symptoms	Interval between transplantation and onset (days)	Immunosuppressive agents	Microscopic examination/ sample	Chest HRCT
1/M/25	Fever for 1 day	140	Tacrolimus, CellCept, Prednisone	BALF	Bilateral diffuse ground-glass attenuation that was mostly distributed in the upper lobe
2/M/41	Fever, cough and dyspnea for 7 days	81	Cyclosporine, CellCept, Prednisone	BALF	Bilateral diffuse ground-glass attenuation that was mostly distributed in the right apex, combined with emphysema, consolidation in the left lower lobe, mediastinal lymphadenopathy, and pleural thickening
3/M/31	Fever and dyspnea for 1 day	340	Tacrolimus, CellCept, Prednisone	BALF	Bilateral diffuse ground-glass attenuation, patchy consolidation in the right middle lobe; air bronchogram, pleural thickening, lesions resolved on follow-up CT scans
4/F/48	Cough and exertional dyspnea for more than 1 month	515	Cyclosporine, CellCept, Prednisone	BALF	Bilateral diffuse ground-glass attenuation that was mostly distributed in the right upper lobe
5/M/30	Fever for 3 days	90	Cyclosporine, CellCept, Prednisone	BALF	Bilateral diffuse foggy shadow, ground-glass attenuation in apexes and more severe in the left lung, mediastinal lymphadenopathy; pleural thickening, large patchy consolidation on follow-up CT scans
6/M/30	Fever for 2 days, cough and expectoration for 10 days	348	Tacrolimus, CellCept, Prednisone	Induced sputum	Bilateral diffuse ground-glass attenuation that was mostly distributed in the right upper lobe, combined with emphysema, consolidation in the right middle lobe, mediastinal lymphadenopathy
7/F/25	Fever for 1 day, cough for 4 days	114	Cyclosporine, CellCept, Prednisone	Induced sputum	Bilateral diffuse ground-glass attenuation that was mostly distributed in the apexes, consolidation in the left lingular lobe and lower lobe; patchy consolidation on follow-up CT scans
8/M/31	Cough and nonproductive cough for 1 day	94	Cyclosporine, CellCept, Prednisone	Induced sputum	Ground-glass attenuation in apexes, linear or reticular shadows in lower lobes
9/M/35	Fever, nonproductive cough and dyspnea for 3 days	89	Cyclosporine, CellCept, Prednisone	BALF	Bilateral diffuse patchy shadow and ground-glass attenuation that were mostly distributed in apexes; lesions resolved on follow-up CT scans
10/F/36	Fever and nonproductive cough for 10 days	73	Cyclosporine, CellCept, Prednisone	Induced sputum	Bilateral diffuse linear or reticular, patchy shadow and ground-glass attenuation that were mostly distributed in the right apex;pleural thickening, mediastinal lymph nodes and lesions resolved on follow-up CT scans
11/M/36	Fever and cough for 5 days	87	Tacrolimus, CellCept, Prednisone	Induced sputum	Bilateral diffuse ground-glass attenuation that was mostly distributed in the upper lobes
12/M/26	Nonproductive cough, dyspnea and fatigue for 5 days	92	Cyclosporine, CellCept, Prednisone	BALF	Bilateral diffuse foggy shadow and ground-glass attenuation, linear or reticular shadows in left lower lobes
13/M/42	Dyspnea for 3 days	365	Tacrolimus, CellCept, Prednisone	BALF	Bilateral diffuse ground-glass attenuation that was mostly distributed in the upper lobes, pleural thickening in left lung, mediastinal lymphadenopathy
14/M/39	Fever for 3 days, dyspnea and fatigue for 10 days	160	Tacrolimus, CellCept, Prednisone	BALF	Bilateral diffuse patchy shadow and ground-glass attenuation, combined with emphysema; pleural thickening, lesions resolved on follow-up CT scans
15/M/27	Fever for 5 days	33	Cyclosporine, CellCept, Prednisone	BALF	Bilateral sporadic patchy shadow, sporadic ground-glass attenuation in apexes; lesions resolved on follow-up CT scans
16/M/27	Fever, dyspnea and fatigue for 7 days	270	Tacrolimus, CellCept, Prednisone	Induced sputum	Bilateral diffuse patchy shadow and ground-glass attenuation, lymphadenopathy in lower lobes.

ALF: bronchoalveolar lavage fluid.

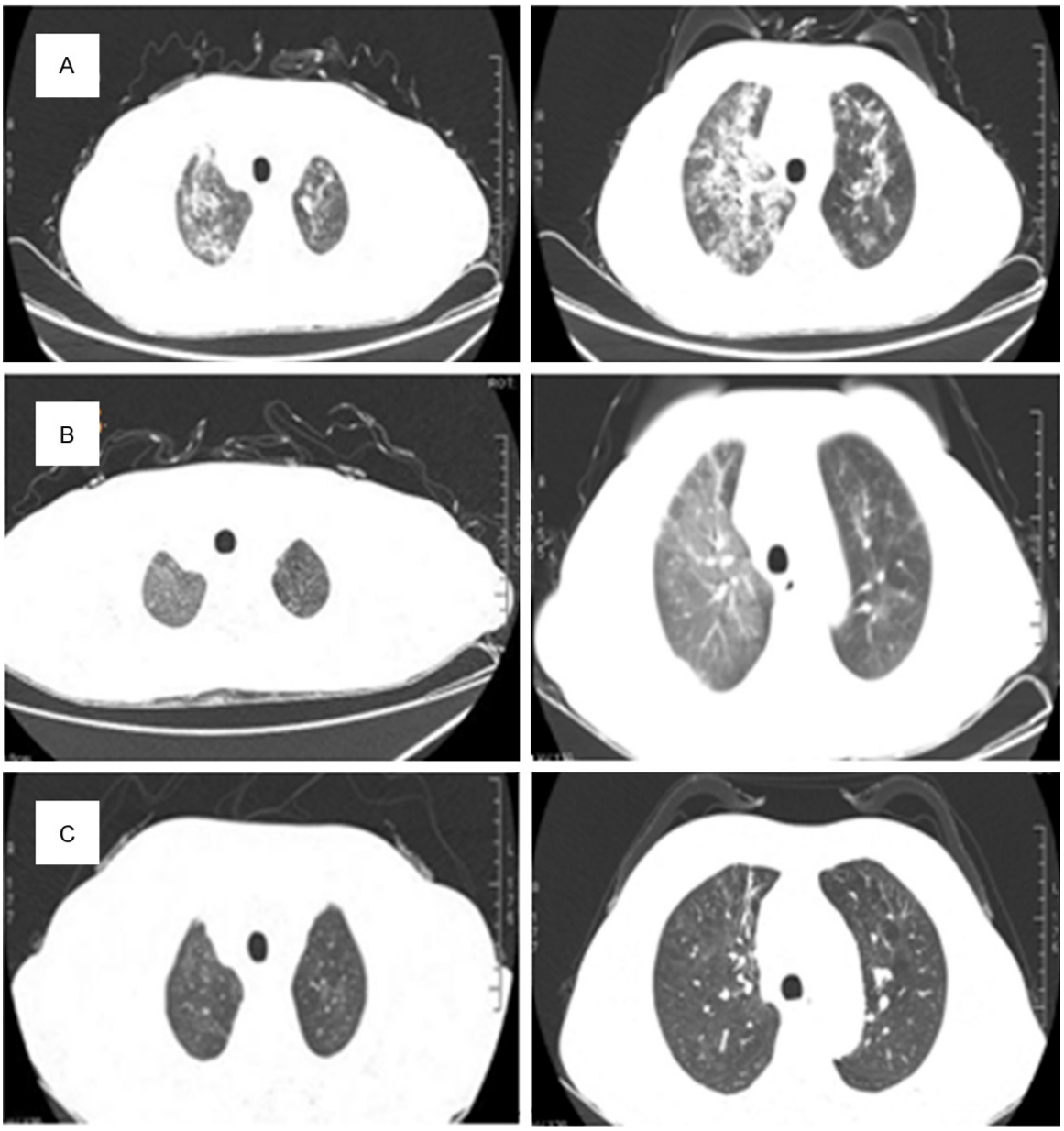

Figure 2. Serial chest CT imaging in a 36-year-old female patient with PJP 73 days after renal transplantation. A: Ten days after the onset of symptoms, CT shows diffuse ground-glass opacities in the upper lobe, mostly in the right apex. B: After 2 weeks of treatment, CT shows an obvious improvement in ground-glass opacity lesions. C: One month after treatment, CT shows that ground-glass opacities have been completely absorbed. Only residual fibrosis and a few cyst-like lesions remain.

dle stage was seen after 2 weeks of TMP-SMZ treatment, and was associated with markedly fewer GGO. After about 1 month of treatment, the HRCT lesions were generally resolved with no residual pulmonary fibrosis or cyst-like lesions.

PJP usually occurs in immunocompromised patients. Immune responses directed against PJP involve complex interactions between CD4+ T lymphocytes, CD8+ T lymphocytes, alveolar macrophages, neutrophils, and soluble mediators that facilitate the clearance of infection. The activity of CD4+ T cells is pivotal in the host's defense against PJP, and PJP usually occurs when the CD4+ count is below 200 cells/mm^3 in HIV patients [2, 4, 8, 11, 13, 14]. Patients with HIV and CD4+ counts below 200

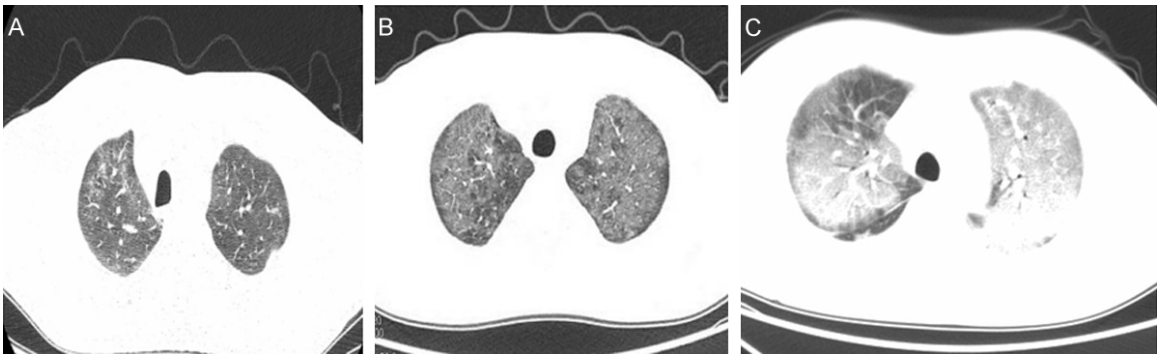

Figure 3. *Pneumocystis jirovecii* pneumonia (PJP) in different renal transplant recipients. HRCT of different patients (A-C) shows diffuse ground-glass opacities typically in the apex of the upper lobe.

Table 3. CD4+ and neutrophil counts

CD4%	N%	N# 10^9/L
49.7	75	5.15
55.9	83.7	8.6
46.8	87.5	6.5
46.3	68.4	5.17
38.1	84.5	5.78
/	74.8	2.95
48.5	62	3.72
21.8	84	7.95
55	80.3	10.02
44.8	83.6	6
42.8	84.9	3.3
27.9	82.91	10.08
30.2	84.1	8.82
52.6	72.7	3.35
42.2	/	/

Normal Range: CD4% (28.5, 60.5), N% (50, 70), N# (2, 7). CD4%: percentage of CD4+ T cells. N%: percentage of neutrophils; N#: absolute value of neutrophils.

cells/mm^3 generally experience reconstitution of their immune system with highly active antiretroviral therapy. The CD4+ and neutrophil counts of patients we treated were within the normal range (**Table 3**). The CD4+ count decreased when TMP-SMZ was discontinued, but gradually normalized.

Therefore, we hypothesized that PJP after renal transplantation is associated with severe inflammatory responses known as immune reconstitution inflammatory syndrome (IRIS) [13, 15]. However, the development of IRIScan result in substantial pulmonary impairment. Renal transplant recipients experience a similar immune system reconstitution during engraftment [4, 13], but those infected with PJP develop an intense T-cell-mediated inflammatory pulmonary response when immune reconstitution occurs [1, 4, 5, 16]. The biologic basis of IRIS in solid organ transplant recipients is believed to involve the change of anti-inflammatory responses into pro-inflammatory responses, which occurs with the withdrawal or reduction of immunosuppression. These findings are frequently observed in patients receiving immunosuppressive treatment consisting of tacrolimus, CellCept, and prednisone [13].

Because of the more rapid progression of PJP in non-AIDS immunosuppressed hosts, it is important to confirm the diagnosis of PJP at an early stage and begin specific anti-PJP therapy as soon as possible to reduce mortality and improve prognosis.

We identified several factors in the present study that appeared to alter clinical presentation and may aid in the evaluation of PJP. Patients we treated that were aged over 36 years more frequently showed shortness of breath than younger patients, while all patients diagnosed with PJP before 120 days after transplantation had a cough, compared with none who were diagnosed later. The choice of cyclosporine or tacrolimus as an anti-suppressant may also affect the clinical presentation. This study was limited by the small number of patients with PJP.

Conclusions

High-resolution computed tomography is the first method of choice to diagnose PJP because of its high sensitivity, especially in lesions of the apex of the upper lobes. Imaging features

can help achieve an early diagnosis and modify treatment. Different clinical parameters may affect the clinical presentation. Corroboration of these findings is needed in a larger group of patients.

Acknowledgements

This research was supported by grants from Anhui Provincial Natural Science Foundation (no.1608085MH216). We are grateful to Xiaoling Ma for help in preparing this manuscript and thank the numerous individuals who participated in this study. We also acknowledge the editors and reviewers for their insightful suggestions on this work.

Disclosure of conflict of interest

None.

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