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Pulmonary Infection in Patients with Cyclosporine, Azathioprine, and Corticosteroids after Cardiac Transplantation
Clinical and Radiographic Assessment

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サイクロポリン，アザチオプリン，ステロイドの三剤併用の免疫抑制剤を投与した心臓移植後患者の肺感染症：
臨床及び放射線学的評価

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サイクロスポリン，アザチオプリン，ステロイドの三剤併用の免疫抑制療法を施行した49例の心臓移植後患者の肺感染症を臨床的及び放射線学的に検討した．21病変の肺感染症（14例）を認めた．肺感染症の起因病原体は9病変で同定されたが，最も多く見られた起因病原体はサイトメガロウイルスであった．他にニューモシスチスカリニー，アスペルギルス，緑膿菌，大腸菌，インフルエンザ菌，ヘルペスウイルスが起因病原体として認められた．アスペルギルスによる肺感染症1例が唯一の肺感染症による死亡例であった．12病変の起因病原体が不明の肺感染症では，死亡にいたった例は認められなかった．これらは通常の抗生物質投与に速やかに反応したため，細菌感染と考えられた．これら起因菌不明の肺感染症は，移植後13.2月＋3.2月（平均＋標準偏差）で発生しており，起因病原体が判明した9病変の肺感染症の移植後発生までの期間3.3月＋1.0月とは有意な相違を認めた．肺感染症の低罹患率，低死亡率はサイクロスポリン，アザチオプリン，ステロイドの三剤併用の免疫抑制療法によるものと考えられた．胸部単純X線像によるパターンは，4型に分類された．すなわち，(1) サイトメガロウイルス，ニューモシスチスカリニー，インフルエンザ菌による肺感染症に見られる間質性陰影，(2) 細菌性肺炎における斑状影，区域や肺葉のコンソリデーション像，(3) アスペルギルス感染症に見られる限局した結節陰影，(4) ヘルペスウイルス肺感染症による多発性の斑状影やその融合像の4型である．間質性陰影を呈した1例のインフルエンザ菌肺感染症，及び4例の起因病原体不明の肺感染症はサイトメガロウイルス肺感染症との鑑別が困難であり，臨床上注意が必要と思われた．

Heart transplantation has become well-established as therapy for patients with end-stage cardiac disease, since the introduction of cyclosporine immunosuppression in 1980[1)2)]. The survival rate for cardiac transplant recipients treated with cyclosporine has increased because the leading causes of mortality, infection and cardiac rejection, have decreased[1)~5)].

Radiological descriptions of respiratory infections occurring after cardiac transplantation have been limited, especially after the introduction of cyclosporine[6)~10)]. This study updates the clinical and radiologic findings of pulmonary infections in patients treated with cyclosporine, azathioprine, and corticosteroids after cardiac transplantation.

Materials and Methods

Between November, 1985, and November, 1989, 54 patients underwent 55 cardiac transplants (One patient underwent reoperation). Five patients died intraoperatively or within one week of transplantation. The other 49 patients followed-up for at least 5 months constitute the subjects for this series.

Ages ranged from 16 to 61 years (mean, 44.8 years). Ten patients were female and 39 male. The preoperative diagnoses were end-stage ischemic heart disease (n=24), idiopathic cardiomyopathy (n=23), familial cardiomyopathy (n=1), and postpartum cardiomyopathy (n=1).

Triple drug immunosuppression consisting of cyclosporine, azathioprine, and prednisolone was administered to all patients. Oral cyclosporine was adjusted to achieve whole blood high power liquid chromatography (HPLC) levels of 200~300 ng/ml for the first month after transplant, and the level was allowed to drop to a maintenance of 125~200 ng/ml. Azathioprine was combined at 2 mg/kg/day, adjusted for white blood cell count. Prednisolone was maintained at 0.2 mg/kg/day.

Episodes of cardiac graft rejection, diagnosed by endomyocardial biopsy, were treated with pulse intravenous methylprednizolone (1 g/day) within the first 2 months after transplant; Thereafter, rejection was treated with oral prednisolone (100 mg/day followed by a 2 week taper to maintenance). Steroid-unresponsive rejection was treated with rabbit antithymocyte serum or OKT3.

Cefuroxime and either Nafcillin or Vancomycin were given as perioperative antibiotic prophilaxis for 48 hours. Beginning with the second month after transplant and extending through the sixth, Trimethoprim-sulfamethoxazole was given twice weekly as *Pneumocystis carnii* prophilaxis. Serum immunoglobulin was given per protocol once weekly for 5 weeks after transplant to all but one Cytomegalovirus (CMV) negative recipients with a seropositive donor. Also many seropositive recipients with seropositive or seronegative donors received the immune globulin protocol treatment.

Aciclovir was used to treat clinically evident herpes simplex viral (HSV) infection but was not used prophilactically. Clotrimezole was used for Candida prophilaxis.

Chest radiographs were reviewed in all patients. Radiographs were obtained immediately after heart transplant and at least daily before discharge. After discharge, chest radiographs were obtained as indicated by the patient's clinical status. Immediately after surgery, anteroposterior (AP) portable radiographs were performed in the intensive care unit, but posteroanterior (PA) and lateral radiographs were obtained once the patient was discharged from the unit.

The diagnosis of pneumonia was based on the presence of a new intrathoracic radiographic opacity with either (a) culture, serologic, cytologic, or histopathologic evidence of a specific organism or (b) clinical course in which pulmonary infection appeared highly likely. CMV pneumonia was diagnosed by culture or spin amplified plate cultures[11)] from bronchoalveolar lavage or transbronchial biopsy.

Radiographic interpretation was based on prospective review of the radiographs by two authors (J.D.G., S.I.M.) and retrospective review of the radiographs by two authors (S.M., J.I.). All four reviewers were aware of relevant clinical data.

Results

Of the 49 patients, 4 patients had died as of April 30, 1990. Follow-up periods of all patients are classified on Table 1. Death was caused by infection (n=1), and cardiac rejection (n=2), and primary lung cancer (n=1).

Pulmonary infection after transplantation developed on 21 occasions in 14 (29%) of the 49 patients. Six of the 49 patients had multiple separate episodes of pneumonia. Radiographic patterns and clinical data are summarized on Table 2.

Causative organisms were identified for 9 (43%) of the 22 episodes of pulmonary infections, with multiple organisms found in 2 episodes (CMV plus *P. carinii*, and CMV plus *P. carinii* plus *Pseudomonous*

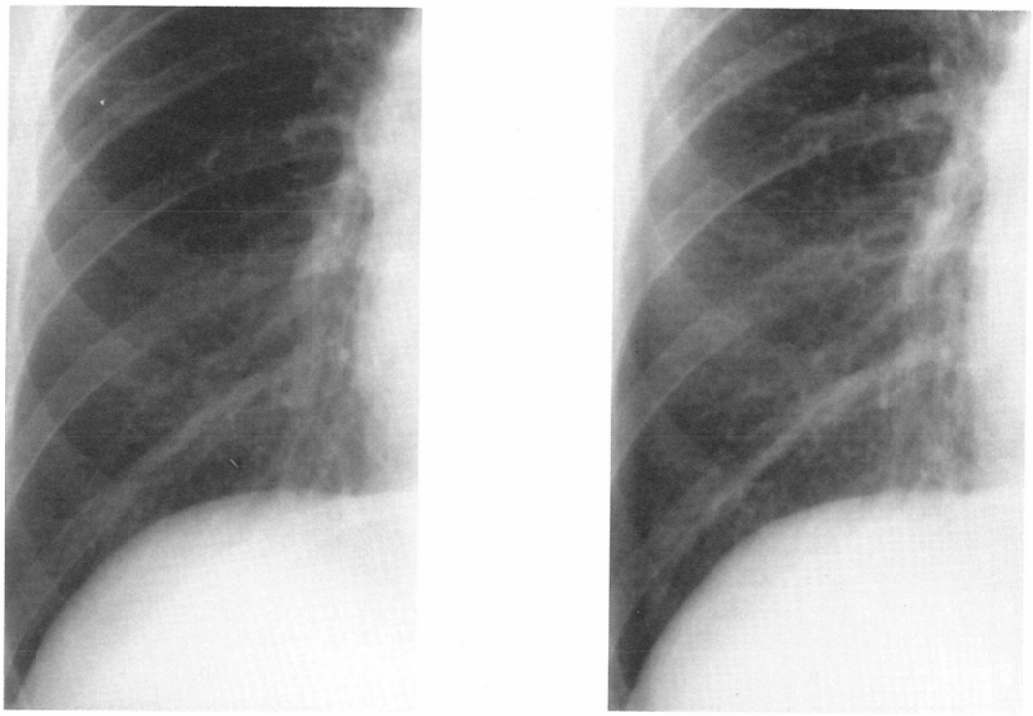
Table 1 Follow-up Time (months) After Cardiac Translantation

	<6.0	6.1-12.0	12.1-24.1	24.1-36.0	>36.0
Alive (n=45)	2	5	15	12	10
Dead (n=4)	0	2	0	1	1

Table 2 Clinical and Radiographic Data

Case	Age/Sex	Organism	Diagnostic Procedure	Onset (M)	Radigraphic Patterns
1	53M	CMV	throat culture	1.9	subtle diffuse interstitial prominenc
2	48M	CMV	BAL	1.6	diffuse interstitial prominenc
		unidentified	N/A	14.0	bibasilar interstitial opacities
3	52F	P carinii + CMV	TBLB	2.0	diffuse interstitial prominence leading to diffuse air space shadow
4	57M	CMV +P carinii +P aeruginosa	BAL TBLB sputum culture	3.0	diffuse interstitial prominence leading to lobar air space shadow
5	51M	E coli	pleural fluid culture	1.1	LLL consolidation with left pleural effusion, leading to empyema
		Aspergillus	TBLB	7.3	a round nudule leading to multiple cavitary round nodules
6	50M	H flu	BAL	10.5	bibasilar interstitial opacities
7	48M	HSV	BAL	0.5	diffuse patchy and confluent opacities
		CMV	throat culture	2.0	unidentified
		unidentified	N/A	3.5	bibasilar interstitial opacities
8	31M	unidentified	N/A	0.2	a focal patchy opacity
9	47M	unidentified	N/A	14.1	right basal interstitial opacities
10	53M	unidentified	N/A	2.3	left basal interstitial opacities
		unidentified	N/A	14.3	left basal patchy opacities
11	29M	unidentified	N/A	19.5	left basal patchy opacities
		unidentified	N/A	25.0	LLL consolidation
12	35M	unidentified	N/A	3.8	both basal patchy opacities
13	44M	unidentified	N/A	0.4	right basal patchy opacities
14	50M	unidentified	N/A	28.4	right basal patchy opacities
		unidentified	N/A	33.4	right middle lobe consolidation

BAL=bronchoalveolar lavage, TBLB=transbronchial lung biopsy, N/A=not applicable, LLL=left lower lobe



a　　b

Fig. 1　(Case 1) CMV pneumonitis. PA radiograph 1.9 months after cardiac transplantation shows prominent interstitial opacities (b), compared to the normal chest radiograph 5 days before (a).

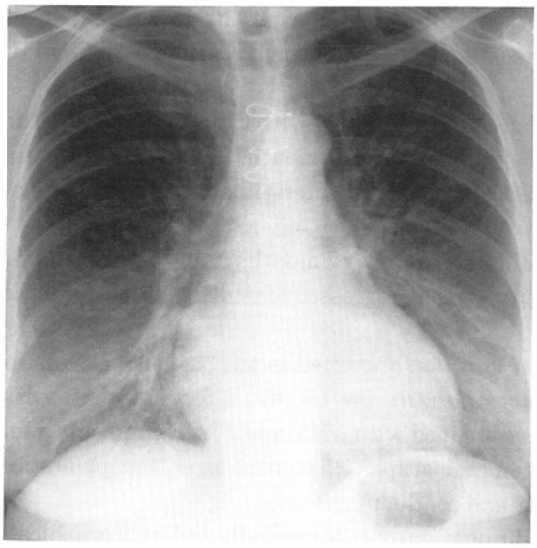
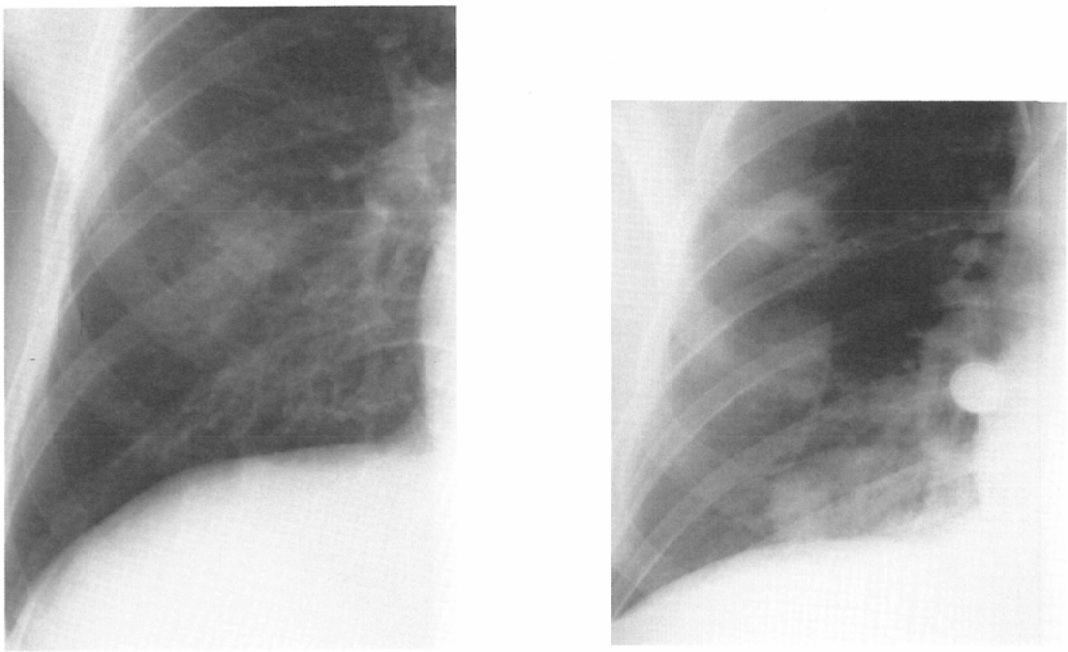


Fig. 2　(Case 3) *P carinii* pneumonia. PA chest radiograph 2.0 months after cardiac transplantation shows diffuse air space shadowing overlying on the diffuse interstitial opacities.



a b

Fig. 3 (Case 5) Aspergillus infection. PA chest radiograph 7.3 months after cardiac transplantation shows a focal round nodule in the right lower lung (a), leading to multiple cavitary nodules on a AP portable chest radiograph in a week (b).

aeruginosa). Death occurred in one case with aspergillosis.

CMV was the most commonly identified organism in this study (5 episodes). CMV pneumonitis was initially seen radiographically from 1.6 to 3.0 months. Radiographic patterns of the 4 episodes of CMV associated infection were diffuse interstitial prominence (n=4) with focal pulmonary haziness (n=2). In one case, diffuse interstitial prominence was subtle (Fig. 1). In one episode, patchy and confluent opacities due to remote HSV infection obscured the CMV infection.

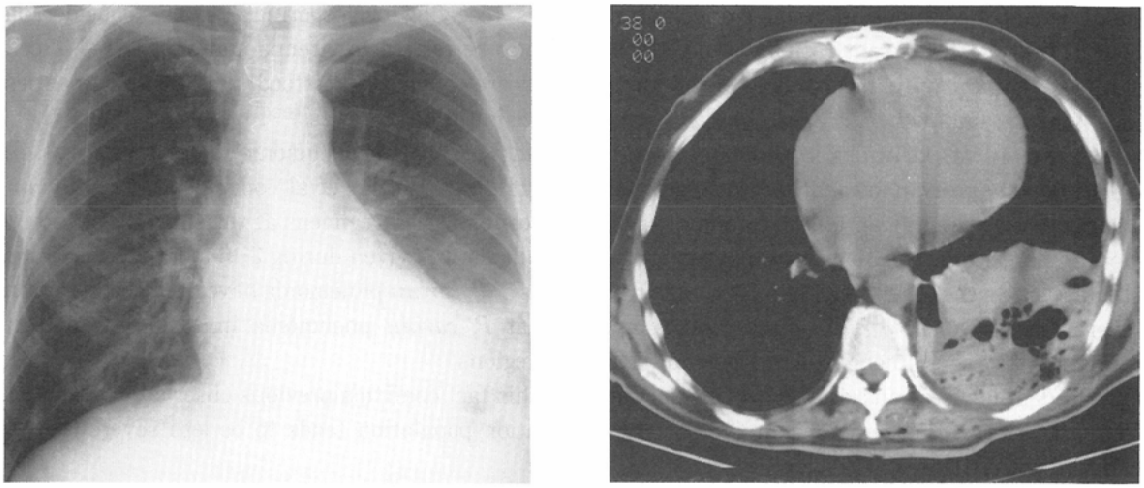
P. carinii was found in 2 episodes of infection and both were combined with CMV infection. Neither episode was fatal. *P. carinii* pneumonia was seen radiographically at 2.0 months and 3.0 months after transplantation, and the radiographic patterns in both cases were diffuse interstitial prominence with air space shadowing (Fig. 2).

Aspergillus was found in one episode leading to death, developing at 7 months after transplantation. The initial radiographic pattern was a focal nodular opacity, which progressed to multiple patchy opacities (Fig. 3).

Three episodes of bacterial infection occurred. *E. coli* infection presented as left basilar consolidation and pleural effusion leading to empyema (Fig. 4). *Hemophilia influenza* (*H. flu*) infection presented as bibasilar interstitial opacities (Fig. 5). *Ps. aeruginosa* was combined with CMV and *P. carinii* pneumonia.

HSV was found in one patient. It was first apparent on radiographs 0.5 months after transplantation. The radiographic pattern was diffuse, ill-defined, nodular and confluent opacities (Fig 6).

No causative organisms were identified in twelve additional episodes of clinically and radiographically diagnosed pneumonia. These episodes resolved after empiric antibiotic therapy. They developed 13.2 months + 3.2 months (mean + standard deviation), which is significantly different from the mean of 3.3



a　　b

Fig. 4　(Case 5) *E coli* infection. (a) PA chest radiograph 1.1 months after cardiac transplantation shows a left lower lobe consolidation and left pleural effusion. (b) Noncontrast CT of the chest 2 months after (a) shows an empyema in the left thorax.

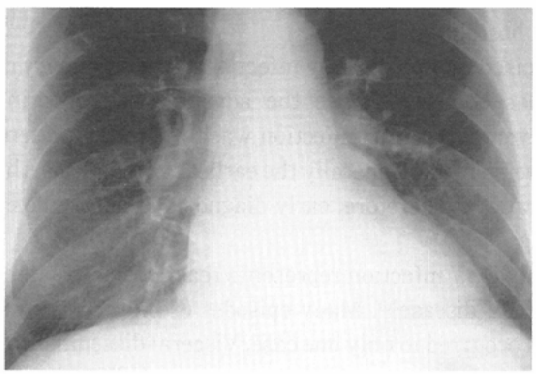


Fig. 5　(Case 6) *H flu* infection. PA chest radiograph 10.5 months after cardiac transplantation shows subtle interstitial opacities in both bases.

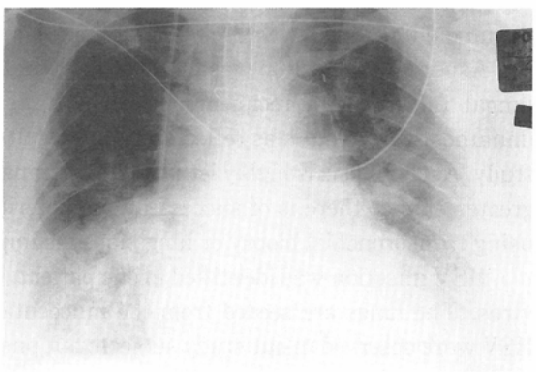


Fig. 6　(Case 7) HSV infection. AP portable chest radiograph 0.5 months after cardiac transplantation shows diffuse patchy and confluent opacities.

months + 1.0 month in the 9 episodes of pneumonia with identified organisms. Radiographic patterns were focal patchy opacities or lobar consolidation (n=8) and interstitial opacities (n=4).

Discussion

Clinical Findings

In this study, opportunistic pathogens were the most commonly identified organisms causing pulmonary infection. These results are comparable to those in previous reports[6)7)12)-21)]. The most frequent organism in our series was CMV, appearing in 5 (56%) of 9 episodes of posttransplantation pulmonary infection with a documented organism. Overall, the frequency of CMV pneumonitis in our series was 10%, which is comparable to the previous report[13)]. CMV has been also described as the most common organism

found in infected lungs in renal transplant recipients receiving cyclosporine[14)15)]. The considerable susceptibility of transplant recipients to CMV appeared to be related to viremia and suppressed T cell-mediated immunity, but mechanisms of this susceptibility are not well understood[12)13)16)17)22)]. In our series, CMV was not fatal, which is different from the experience in the other series[7)8)13)].

P. carinii was identified in two cases and the overall frequency of pneumonia in our series was 4%. This low frequency is compatible with previous reports[16)21)23)]. Hofflin et al concluded that *P. carinii* pneumonia was significantly less common with immunosuppressive regimens at the same institution[16)]. More importantly, trimethoprimsulfamethoxazole prophilaxis was given during 2~6 months after transplantation. On the other hand, relatively high frequencies of *P. carinii* pnuemonia have been reported from several institutions[8)24)]. This discrepancy suggests that *P. carinii* pneumonia in cardiac transplant recipients may vary among institutions and geographic regions.

No deaths were caused by *P. carinii* pneumonia. This fact confirms previous observations that the course of *P. carinii* pneumonia in the posttransplantation population tends to be less severe than in patients with AIDS[18)].

The frequency of identified bacterial infection was 3 (14%) of the 21 episodes of the posttransplantation pulmonary infections. Three episodes of pneumonia were caused by *E. coli, H. flu*, and *Ps. aeruginosa*. This fact confirms the previous reports that aerobic gram-negative rods are the predominant bacterial organisms after cardiac transplantation[8)16)22)].

Two episodes of mixed pulmonary infections, CMV plus *P. carinii*, and CMV plus *P. carinii* plus *Ps. aeruginosa*, were identified. *P. carinii* and *Ps. aeruginosa* have been the most common organisms detected in the mixed infections with CMV in immunocompromised hosts[12)].

Aspergillus infection was found in 1 (5%) of the 21 episodes of pulmonary infections. The frequency of fungal infections in recipients of heart transplant has decreased since the advent of cyclosporine immunosuppression[16)], as reflected in our results. However, aspergillus infection was fatal in the present study. Aspergillosis is highly lethal in heart transplant recipients[16)]. Generally the earlier the diagnosis, the greater chance there is of successful amphotericin therapy[25)]. Therefore, early diagnosis of aspergillosis using transbronchial biopsy or lung biopsy is important.

HSV infection was identified in one patient. Generally HSV infection represents reactivation of latent virus. The lungs are seeded from the mucocutaneous HSV disease[26)]. Many episodes of mucocutaneous HSV were observed in our study subjects but pneumonia occurred in only one case. Visceral dissemination of HSV has been reported to be uncommon despite high frequency of mucocutaneous HSV in organ transplant recipients[26)].

Pulmonary infections with documented organisms were initially seen at 0.5~3.0 months after transplantation with the exception of a case of Aspergillus infection and a case of *H. flu* infection.

CMV has been described as the infecting agents found most frequently between 1 and 6.5 months after heart transplant[8)13)]. In our study, CMV pneumonitis was found between 1.6 and 3.0 months and confirms that CMV pneumonitis occurs in the early period after heart transplant.

P. carinii pneumonia has been reported to develop within 2~11 months after heart transplant[8)], and within 2~6 months after transplantation in renal transplant recipients[11)14)]. In our study, *P. carinii* pneumonia occurred 2.0 and 3.0 months after transplantation in two cases.

Aspergillus infection has been also described as an infecting agent in the early period after transplantation, but in our study, one Aspergillus infection occurred 7.3 months after transplantation.

HSV infection was found very early after heart transplant (0.5 month) in our study. HSV infection in the other reports occurred at 1.5, 4.2, and 10.7 months after heart transplant[6)8)]. Twelve episodes of clinically diagnosed pulmonary infections caused by unidentified organisms were encountered. In these

cases, rapid favorable response to the infection to empiric antimicrobial therapy was obtained. This fact suggests that these episodes were bacterial infections. Seven (54%) of 13 such episodes occurred more than 1 year after transplantation, which is similar to the experience in the previous report[8].

Other well-known opportunistic infectious organisms such as *Legionella pneumophilia, Cryptococcus neoformans, Nocardia asteroides*, and *Mycobacterium tuberculosis* were not identified in this study. Overall, the frequency and the mortality of pulmonary infections were remarkably low compared to the experience before cyclosporine immunosuppression. The interval between transplantation and onset of pneumonia was similar to the results of the previous reports for each organism with the exception of aspergillosis, which occurred 4 months later than in previous reports.

Radiologic Findings

Pulmonary infection in an immunosuppressed host generally has one of four radiographic patterns: interstitial prominence or opacities, as in CMV or *P. carinii* pneumonia; patchy segmental or subsegmental opacities, or lobar consolidation as in bacterial infection; a focal nodule or nodules, sometimes cavitary, as in fungal infection or septic emboli; multiple patchy and confluent opacities, as in HSV or Varicella-Zoster viral infection[28].

Interstitial prominence or opacities were the most common pattern in this series, including all episodes of CMV and *P. carinii* pneumonia, and an *H. flu* infection. "Interstitial prominence" means diffuse interstitial opacities in this study. Four episodes of non-specific (presumed bacterial) infection showed the pattern of intestitial opacities. The diffuse interstitial prominence as seen in Case 1 is a common pattern of CMV pneumonitis and uncommon in *P. carinii* pneumonia. Radiologists must be attuned to the subtlety of the interstitial change that may occur with CMV pneumonitis in a cardiac trasnplant patient. On the other hand, rapid progression of air space shadowing beginning with an interstitial pattern is common in *P. carinii* pnuemonia and uncommon in CMV pneumonitis[28][29]. In the present two episodes of *P. carinii* pneumonia, both were mixed with CMV infection, but radiographic patterns were most consistent with P. carinii pneumonia. *Ps. aeruginosa* was also detected in the mixed infections with *P. carinii* and CMV but lobar or segmental consolidation, a characteristic radiograph pattern for *Ps. aeruginosa*[28][29] was not observed.

One episode of *H. flu* and four non-specific infections with interstitial opacities pattern in either or both basal lungs were initially suspected to represent CMV pneumonitis radiographically because interstitial changes of a CMV pneumonitis typically begins in the bases. However, results of serological studies, throat cultures, bronchoalveolar lavage, or transbronchial throat cultures excluded CMV infection. Empiric antibiotic therapy cleared the disease rapidly and also suggested non-CMV infection. Johnson et al reported[10] bacterial pneumonia among 62 episodes of interstitial patterns occurring in patients who had undergone renal and liver transplantation[14]. We found that a confirmed *H. flu* bronchitis in our study resembled initial changes of CMV pneumonitis. The important difference between these episodes and the episodes of CMV pneumonitis is that three of non-CMV infections with an interstitial pattern were seen more than 10 months after transplantation, which is unlikely for the CMV pneumonitis after organ transplantation[8][12]~[14].

Focal patchy opacities or consolidation occurred in *E. coli* and the other non-specific (presumed bacterial) infections. *E. coli* pneumonia showed consolidation and pleural effusion leading to empyema.

A case of aspergillus pulmonary infection showed a round opacity, which is one of typical patterns of aspergillus infection[28][29].

Focla pneumonitis is another manifestation of CMV infection. Bronchoalveloar lavage is reported to be useful for detection of the focal CMV pneumonitis[7][8], but no focal CMV infection was observed in our study.

The diffuse patchy and confluent opacities pattern occurring in our single case of HSV pneumonitis is one of the typical radiographical patterns of an HSV infection[25)27)28)]. HSV pneumonia has been described as more commonly focal than generalized[30)]. In general, diffuse viral pneumonia is thought to represent a manifestation of hematogenous dissemination of the virus, whereas focal viral infection in the lung is thought to represent contiguous spread of infection within the respiratory tract[8)30)].

To summarize the radiographic findings, most episodes of pneumonia presented as expected patterns for each organism. Newly observed were one episode of *H. flu* and four by unidentified organisms in which interstitial opacities in either or both lung bases were identical to those of CMV pneumonitis.

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