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Pulmonary Infections in Renal Transplant Recipients*)

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ABSTRACTS

Pheumonia occurred in 8 cases of 70 renal transplant recipients. Infections appeared from 40 days to 30 months after renal transplantation, predominintly after 6 months (75%).

Three cases were caused by fungi (2 by Aspergillus, 1 by Cryptococcus). Another 6 cases had seversl episodes of rejections, but two cases had no episode. Severe interstitisl pneumonia occurred in 3 patients after the Pulse therapy to rejections and all of them died.

With regard to complications, liver dysfunction was presented in 2 cases, G-I troubles in 2 cases, and Cryptococcal menigitis in one case.

Therefore, critical care must be performed during Pulse therapy to prevent pulmonary infections and its complications.

INTRODUCTION

Infection, one of the most common complications encountered after renal transplantation, often results in a serious condition due to immunosuppressive therapy given before and after transplantation. Pathogenic organisms of pulmonary infections are diffucult to idendify, and so we frequently encounter numerous difficulties when diagnosing and treating pulmonary infection.

We studied the pulmonary infection cases we have encountered and reviewed some previous reports on this issue.

SUBJECTS

For the period from 1971 to 1984, we performed 70 renal transplantations (58 living and 12 cadaverous). 8 cases developed pulmonary infections.

Immunosuppressive therapy consisted mainly of Methylprednisoloe, Azathioprine, and Brednine, sometimes combined with ALG, Cyclophosphamide, and Cyclosporin A.

This study only includes cases of primary infection. Secondary pulmonary lesions resulting from Multiple Organ Failure are omitted.

PULMONARY INFECTION CASES

As shown in Table 1, the average age of the subjects was 27.4 years, ranging from 18 to 35. The subjects, four men and four women, developed pulmonary infection 15 months after transplantation on average, ranging from 40 days to 30 months. cases 2 and 4 developed the infection earlier, the remaining 6 cases developed 6 months after operation or later.

Pathogenic organisms were fungus in 3 cases, Mycoplasma in 2, Pheumocystis carinii (P. sarinii) in 1, and Tubercelosis in 1. One case is a suspected Cytomegalovirus infection.

6 cases showed rejection symptoms. 5 cases

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Table 1. Pulmonary Infections after Renal Transplantations

Case No.	Age	Sex	Onset after Transplant. (Months)	Chief Complaint	Pathogenic Organisms	No. of Rejections	Causative Factors	Complications	Prognosis
1	32	Male	20	Fever	Cryptococcus	0	—	Menigitis Liver dysfunction	Good
2	30	Female	1.5	Thore throat	Aspergillus	1	—	—	Good
3	35	Female	6	Dyspnea	Aspergillus	1	Pulse therapy	Gastric perforation	Died
4	28	Female	2	Dyspnea	Cytomegalovirus (?)	1	Pulse therapy	G-I bleeding Liver dysfunction	Died
5	28	Male	15	Dyspnea	Pneumocystis carinii	3	Pulse therapy	—	Died
6	21	Male	13	Cough Fever	Mycoplasma	1	—	—	Good
7	27	Female	29	Cough	Mycoplasma	1	—	—	Good
8	18	Male	30	Fever	Tuberculosis	0	—	—	Good

who developed pneumonia after the Pulse therapy for rejections were very serious, and 2 of them were complicated Gastro-Intestinal (G-I) troubles. The prognosis of these cases unfavorable. Another 2 cases were complicated with hepatic dysfunction, and one with Meningococcus meningitis. The 3 deseased cases complained mainly of serious dyspnea. Arterial blood gas analyses demonstrated a pattern of alveolar-capillary block and metabolic acidosis, and interstitial pneumonia was suspected.

CHEST RADIOGRAM

Table 2 shows chest radiographic findings, classified by Nelson[11]. Wide spread bilateral consolidation pattern was most frequently seen, that is, in the 3 cases who died. Cavitation was seen in 2 mycosis cases. Mycoplasma pneumonia in 2 cases was restricted to one side of the lung. Case 8 showed a radiogram typical of miliary tuberculosis. Fig. 1 is a chest radiogram of case 4 which shows translucency indicating interstitial pneumonia in both lung field.

Table 2. Chest X-P findings

X-P findigs	Case No.
Wide spread bilateral consolidation	3, 4, 5
Solitary cavity	1
Multiple cavity	2
Lobar or Segmental consolidation	6, 7
Ill-defined nodules	8

FUNGUS INFECTION

Post-transplant fungal infections are usually caused by Cryptococcus, Aspergillus, and Can-

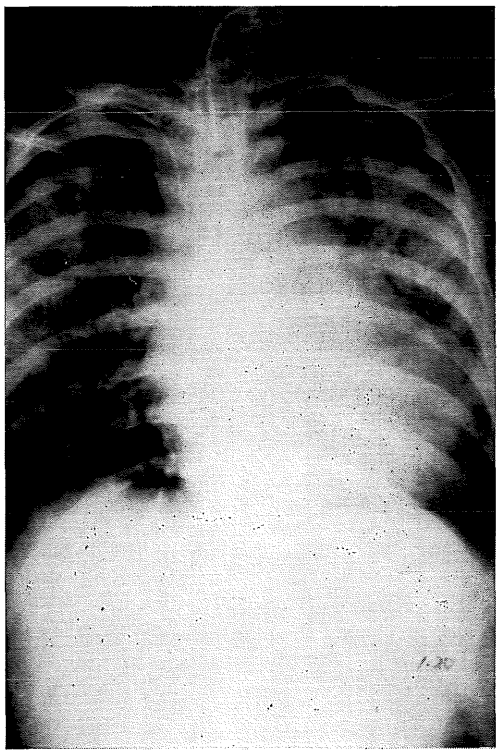

Fig. 1. Case 4. Bilateral interstitisl pneumonia was found, especially in the hilar region.

Table 3. Fungal Infections after Renal Transplantations

Case No.	Onset after Transplantation	Pathogenic Organisms	Affected Organs	X-P findings	Diagnosis	Therapy	Prognosis
1	20 months	Cryptococcus neoformans	Lung, Foot Meninges	Fungus ball (1.3×1.3 cm)	Spinal fluid	Amphotericin B i. v. Miconazole i. v. 5-FC p. o.	Good
2	1.5 months	Aspergillus fumigatus	Lung	Fungus ball (4×4.5, 3.5×2.5) cm	Sputum	Amphotericin B i. v. 5-FC p. o.	Good
3	6 months	Aspergillus	Lung	Wide spread bilateral consolidation	Autopsy	Amphotericin B p. o.	Good

dida. As shown in Table 3, two cases were caused by Aspergillus, one by Cryptococcus. The fungi detected in the spinal fiuid of case 1 and in the sputum of case 2. Autopsy revealed case 3 as having an Aspergillus infection.

Chest X-ray films of Case 1 and 2 revealed characteristic fungus ball formations and that of Case 3 showed wide spread bilateral consolidation pattern.

It has been reported that the incidence of fungal infection is significantly lower in cases prophylactically treated with oral anti-fungal agents as compared to a non-treated group[12]. We make it a rule to give oral Amphotericin B and Mycostatin prophylactically to all transplant recipients. And, we give cases diagnosed as having mycosis a combination therapy of intravenous Amphotericin B and oral 5-Fluorocytosine (5-FC). In addition, Miconazole was also administered to Case 1.

CASE REPORT

Aspergillus infection of Case 2 is shown. (Fig. 2). The patient complained a thore throat 38 days after the operation. On the 50th post operative day, Aspergillus was found in sputum. A chest film confirmed the presence of typical fungus balls on the 55th post-operative day. Azathioprine and Bredinine were immediately withdrawn, the dose of Methylprednisolone was reduced, and treatment with anti-fungal agents was begun. The initial intravenous dose of Amphotericin B was 2 mg which was gradually increased to 20 mg/day. Concomitantly, 4 g/day of 5-FC was administered orally.

Fig. 3 is a chest film before the treatment, which shows two clear fungus balls (4.5×4.0 cm and 3.5×2.5 cm), in the right lower lung field.

Fig. 4 is a chest film taken on the 41st day after Amphotericin B therapy. The funges balls have disappeared. The total amount of Amphotericin B to this patient was 522 mg.

DISCUSSION

Infection is the most common complication of renal transplantation, often taking a serious course. A report on registered cases of renal transplantation for 1982 in Japan showed that infection accounted for 35.7% (204 cases) of the 527 dead cases. Hida[5] also reported 76 out of 120 Autopsy cases after renal transplantation were due to infectious disease, including brochitis and pneumonia at a rate of 60%, indicating the significance of respiratory infection.

As shown in Table 4, the incidence of pulmonary infection is 10 to 20% in post-renal transplantation cases, which is consistent with our finding of 11.2%. The mortality rate is, however, considerably high, suggesting that pul-

Table 4. Frequency and Prognosis of Post-Transplant Pulmonary Infections

Author		Frequency (%)	Mortality (%)
Simmons	(1972)	38/212 (18.0)	18/38 (47.3)
Huertas	(1976)	33/266 (12.4)	17/33 (51.5)
Sakagami	(1977)	4/15 (26.6)	1/4 (25.0)
Munda	(1978)	41/168 (24.4)	17/41 (41.5)
Yamamoto	(1980)	18/93 (19.4)	6/18 (33.3)
Oka	(1983)	33/179 (18.4)	6/33 (18.2)
Enomoto	(1984)	13/103 (12.6)	10/13 (76.2)
Our Laboratory	(1984)	8/70 (11.4)	3/8 (37.5)

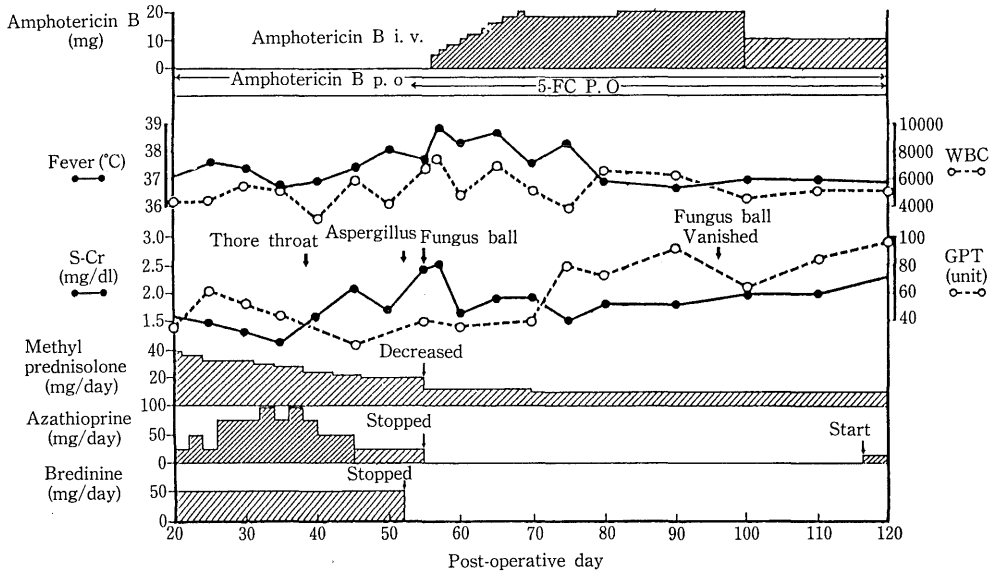

Fig. 2. Clinical course of Case 2. Aspergillus was found in sputum at the 50th day. Immediately lmmunosupressive drugs were decressed and administration of Amphotericin B and 5-FC was started for 40 days. Chest fungal balls were vanished at 96th day.

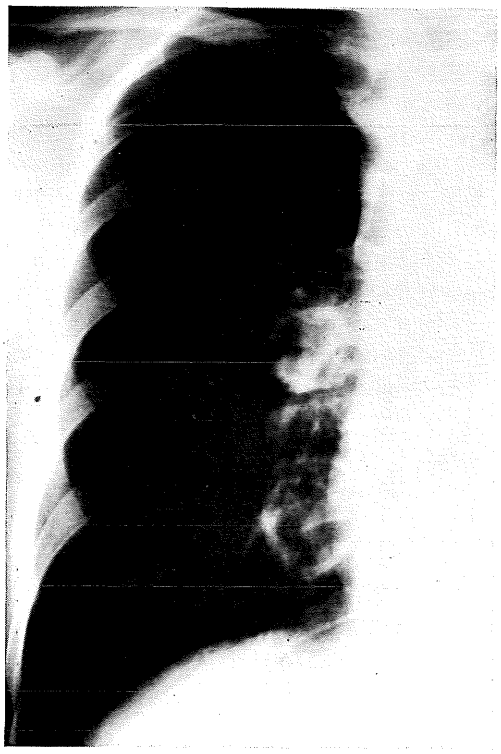

Fig. 3. Case 2. Pulmonary Aspergillus infection. 2 fungal balls were found in the right hilar region.

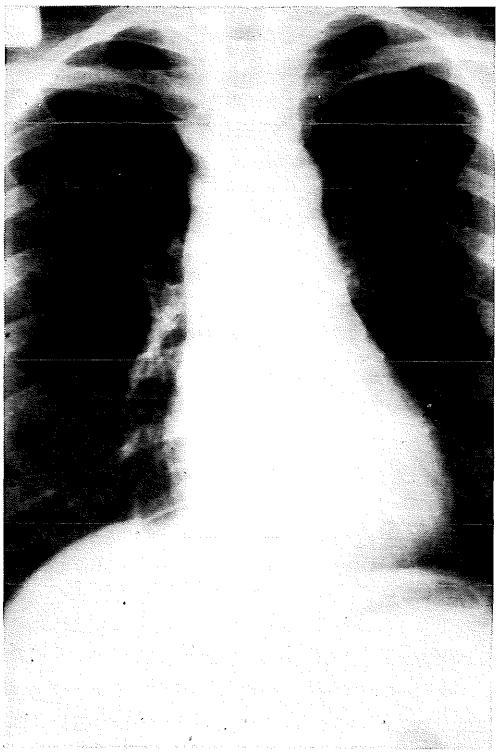

Fig. 4. Case 2. After administration of Amphotericin B, fungal balls were vanished.

monary infection is very serious.

Munda et al.[9] demonstrate that infection is likely to develop within four months after transplantation, but others report later development[3,14]. 6 out of our 8 cases developed infection at 6 months or later.

Anderson[1] raises three factors cacusing infection; leucocytopenia, hyperglycemia, and renal dysfunction due to rejections. He attributes these conditions to the long-term treatment of rejection with large doses of Azathioprine and Prednisone. However, Munda[9] reports that there is no correlation between the incidence of infection and the frequency of rejection or the dose of Steroids, but that infection cases tend to have higher levels of serum creatinine. They also report that the incidence of pulmonary infection in cadaver renal transplants was twice that of living renal transplant recipients.

With regard to rejections, 6 cases had several episodes of rejections. After the Pulse therapy for rejections, three cases developed pneumonia and all of them died. These reselts bring attention to the need for protection agaist infection after the Pulse therapy.

We routinely perform sputum culture and antibody titration for Virus before and after transplantation. However, we have difficulties in identifying the pathogenic organisms because of combined infections, particulary P. carinii, fungi, and Viruses.

Most cases of interstitial pneumonia caused by Cytomegalovirus (CMV) and P. carinii are difficult to differentiate and are often combined infestions. Cases with increased CMV antibody titer before transplantation were known to develop CMV infection at higher rates, 81% by Marker[7], and 85% by Glenn[4]. It is known that the risk of CMV infection becomes higher with an increase in the donor's antibody titer, suggesting the necessity of periodical tests of antibody titer.

In Japan, mycosis following surgical operations are mainly caused by Aspergillus, Candida, and Cryptococcus. Bach[2] reported that 11 cases of Aspergillus infection all died and Mills[8] revealed that 67% of pulmonary mycosis cases died. Generally, we treat pulmonary mycosis with Amphotericin B and 5-FC. However, strong side effects cause difficulties in the case of long-term treatment or large doses. It is reported that Miconazole therapy against Cryptococcal meningitis is effective[10]. Miconazole was administered for Case 1, and some effect was found.

Pulmonary infections following renal transplantations are often combined infections and thereby considerable time is ruquired for identifying the pathogenic organisms. As recommended by Enomoto[3] to use Multi-drug therapy such as antibiotics, gamma-globulin, Miconazole, Sulfamethoxazole-Trimethoprim (SMX-TMP), and Interferon or Cyclocytidine is effective. Since there is no specific drug with few side effects, we often administer large doses of various drugs concomitantly which is liable to result in hepatic dysfunction. And in the case of respiratory failure, G-I troubles due to stress are often occurred. These factors have a great effect on the prognosis, and so careful and adequate management folowing renal transplantation is essential.

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