นิพนธ์ต้นฉบับ

Complications and causes of death in intrathoracic organ transplantation

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Objective : *To study the complications and causes of death in heart, heart-lung and lung transplant patients*

Design : *Retrospective study*

Setting : *Departments of Pathology, Medicine, Surgery: Faculty of Medicine: Chulalongkorn University*

Subjects : *23 heart transplants, 7 heart-lung, and 6 lung transplant patients who died after transplant operation at Chulalongkorn Hospital*

Methods : *Biopsy, necropsy and autopsy materials as well as clinical findings were studied and reviewed*

Results : *Bacterial pneumonia was the most common complication and cause of death in intrathoracic organ transplantation. Aspergillosis and cytomegalovirus (CMV) infection were also seen in a number of patients. Rejection is more common in heart transplants over 6 months after operation*

Conclusion : *Infection is the most common complication and cause of death in intrathoracic organ transplantation. Acute rejection is less common. Except in heart transplants over 6 months after operation.*

Key words : *Intrathoracic organ transplantation, Infection, Rejections.*

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วัตถุประสงค์ : *เพื่อศึกษาภาวะแทรกซ้อนและสาเหตุตายในผู้ป่วยเปลี่ยนอวัยวะ หัวใจ หัวใจ-ปอด และปอด*

รูปแบบการวิจัย : *การศึกษาแบบย้อนหลัง*

สถาบันการศึกษา : *ภาควิชาพยาธิวิทยา ภาควิชาอายุรศาสตร์ และภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

ผู้เข้าร่วมการศึกษา : *ผู้ป่วยผ่าตัดเปลี่ยนหัวใจที่เสียชีวิต 23 ราย เปลี่ยนหัวใจและปอด 7 ราย เปลี่ยนปอด 6 ราย*

ผลการวิจัย : *การติดเชื้อจากแบคทีเรียในปอด เป็นสาเหตุการตายที่พบบ่อยที่สุด รองลงมาเป็นเชื้อราและเชื้อไวรัส cytomegalovirus (CMV) ตามลำดับ*

วิจารณ์และสรุป : *การติดเชื้อเป็นภาวะแทรกซ้อนและสาเหตุตายในระยะ 6 เดือนแรก ภายหลังการผ่าตัดเปลี่ยนอวัยวะมากกว่าการสลัดกราฟท์ (Rejection)*

Following the introduction of cyclosporine as a major immunosuppressive drug, There has been a marked increase in the types and numbers of intra-thoracic organ transplantations. The patients outcome after the transplantations are probably related to multiple factors such as improved selection of candidates; improved clinical experience at all levels of the surgical, pathological and medical staff; better regulation of immunosuppression; and effective therapy for infections. The most common cause of death after transplants in most series has been infections. Most infections occur within 6 months after transplantation. Infection, as well as acute and chronic rejection, are major complications and causes of death in solid organ transplantation.[1,2] We therefore studied the occurrence of infection and rejection among heart, heart-lung and lung transplant patients at Chulalongkorn Hospital.

Materials and Methods

Materials

All heart, heart-lung and lung transplant patients at Chulalongkorn Hospital who died after successful transplantation were included in this study. Endomyocardial biopsy was routinely used for monitoring rejection and infection after heart transplantation.[3] Transbronchial lung biopsy and sometimes open lung biopsy were used for detection of rejection and infection in heart-lung and lung transplantation.[4]

Methods

Clinical findings, microbiologic laboratory results, imaging reports, cytology, biopsy, necropsy and autopsy materials were reviewed and studied.

Routine as well as special histochemistry stainings were used for pathologic study. Immunohistochemistry for T cell, B cell, histiocytes and cytomegalovirus were done.[5,6] Special stain for bacteria, nocardia, acid-fast bacili and fungi were also performed.

Etiologic diagnosis of pneumonia was based on histopathology, stainings and or cultures.

Survival period after transplantation was classified as early and late, within 6 months and after.

Result

Heart transplant patients

Forty heart transplants had been performed since December, 1987. Twenty-three of the 39 successful heart transplant recipients had complications and died, as shown in Table 1. Of 5 patients who died within one month after operation, 4 were due to bacterial infections and one from acute rejection. The common cause of death that occurred 1-6 months after operation was still infection, six out of nine. However, the causative agents were gram negative bacteria in only 3 cases, the other three were pulmonary aspergillosis, tuberculosis and nocardia brain abscess.

Figure 1. Nocardia brain abscess in a heart transplant patient who died 4 months after transplantation. (Arrows)

Table 1. Clinical features in 23 heart transplant patients.

Patient No	Age	Sex	Underlying disease	Survival period	Complications and cause of death
1*	52	F	GCM	11 months	moderate acute rejection with heart failure
2**	12	M	VHD (RHD)	17 weeks	moderate acute rejection with heart failure
3*	31	M	DCM	1 year 8 months	chronic rejection (accelerated atherosclerosis) with heart failure
4*	43	F	IHD	6 years	severe bacterial pneumonia and aspergillosis
5*	21	M	DCM	4 months	nocardia brain abscess (Fig. 1)
6*	39	M	DCM	6 months	moderate acute rejection & focal pneumonia
7	58	M	IHD	2 years	sudden death (? acute rejection)
8	30	F	VHD (RHD)	2 years 2 months	sudden death (? acute rejection)
9	47	M	DCM	1 month	sudden death (? acute rejection)
10*	52	M	DCM	2 months	acute aortitis with abscess and dissecting hematoma
11**	60	M	DCM	11 months	right coronary artery - right atrium fistula, severe acute cellular rejection
12	55	M	IHD	2 years 10 months	acute renal failure with heart failure
13	60	M	IHD + DM	1 year 10 monts	acute renal failure with heart failure
14*	55	M	IHD	2 months	Bilateral tension pneumothora with penumonia and enterocolitis
15*	35	M	DCM	12 days	post operative bleeding with infected surgical wound
16	50	F	IHD	2 month	bacterial pneumonia with aspergillosis
17	25	F	IHD	1 months 12 days	bacterial pneumonia
18*	42	M	DCM	4 months	myocarditis
19*	41	M	DCM	3 month 14 days	severe acute cellular rejection (Fig .2)
20	53	M	IHD	5 months	Herpes encephalitis, pulmonary T.B.
21*	45	M	IHD	11 days	Pneumonia
22*	50	M	DCM	1 month	Pneumonia
23*	63	M	DCM	16 days	Pneumonia

* Autopsy performed
** Heart-lung necropsy performed
GCM - giant cell myocarditis
VHD - valvular heart diseae
RHD - rheumatic heart disease
DCM - dilated cardiomyopathy
IHD - ischemic heart disease

The most common cause of death after 6 months of operation was graft versus host reaction or rejection, eight out of nine death. Severe acute cellular reejection was the cause of death in two patients (patient No 11, 19).

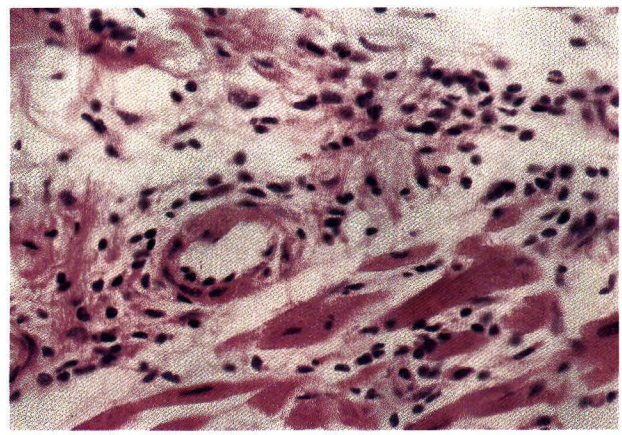

Figure 2. Perivascular mononuclear infiltrate with myocyte damage in acute cellular rejection. H&E x 400

The other 5 patients died from mild to moderate acute cellular rejection with heart failure. And one patient had chronic rejection (accelerated atherosclerosis) with associated heart failure.

Heart-lung transplant patients

Fifteen heart-lung transplants had been performed since October 18, 1992. Of the 15 patients, 7 had complications and died, as shown in Table 2. One patient had obliterative bronchiolitis which may represent chronic rejection, (patient No 3), survived 5 months after operation, and finally died of bacterial and CMV pneumonia. Most death, 6 out of 7, occured within. 6 months after operation, all had pneumonia due to mixed organisms, gram negative bacteria with aspergillus in 2, bacteria and CMV in one and 1 patient had severe pneumonia due to gram negative bacteria, aspergillus and CMV.

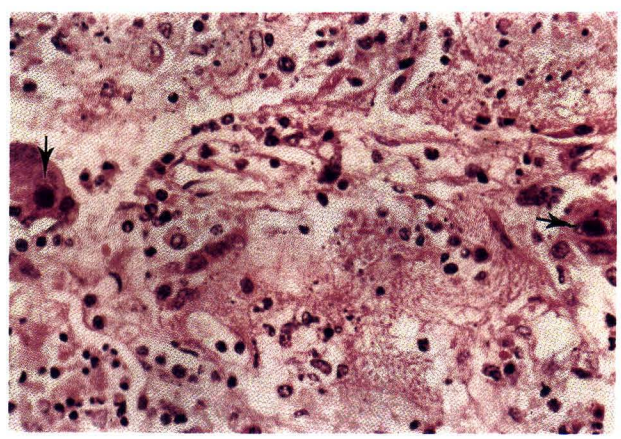

Figure 3. Polymorphonuclear and mononuclear infiltrates with intranuclear inclusion bodies in cytomegalovirus infection in the lung. (Arrows) H&E x 400

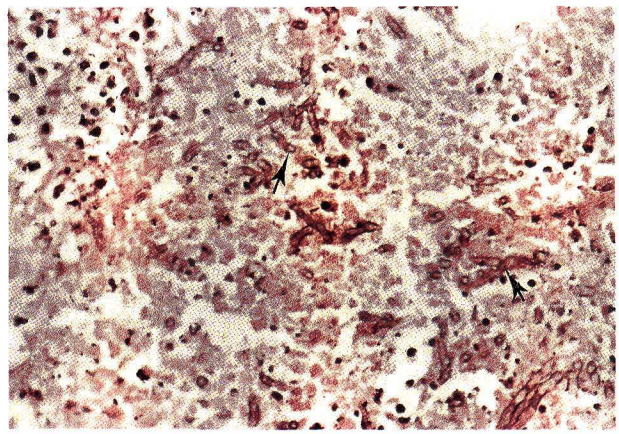

Figure 4. Septate hyphae with PMNS infiltration and necrotic tissue in the lung. H&E x 400

Table 2. Clinical features in 7 heart-lung transplant patients.

Patient No.	Sex	Age (yr)	Underlying disease	Survival period	Complications and cause of death
1*	M	46	PPH	1 month 6 days	Pneumonia with aspergillosis post op. bleeding with acute renal failure
2*	F	31	ASD with bidirectional shunt	3 years	Pneumonia with aspergillosis and CMV (Fig .3)
3	F	9	TGA with Eisenmenger syndrome	5 months	Pneumonia with CMV, obliterative bronchiolitis
4	F	43	PPH	1 month 12 days	Pneumonia with aspergillosis and CMV
5	M	37	VSD with PHT	15 days	Pneumonia with abscess and aspergilosis
6	F	53	VSD with Eisenmengers	3 months	Clinical acute rejection with pneumonia
7	M	16	PPH	14 days	Acute liver failure caused?

* Autopsy performed
PPH - primary pulmonary hypertension
ASD - atrial septal defect
TGA - transposition of great arteries
VSD - ventricular septal defect
PHT - pulmonay hypertension
CMV- cytomegalovirus

Lung transplant patients

Eight lung transplantations had been performed since July 7, 1994. One patient had primary graft failure and died shortly after the operation. Six of the 7 successful transplantations died as shown in Table 3. Most death died from bacterial pneumonia, regardless of survival period. Only mild acute rejection was seen in few patients, this was probably due to inadequacy of transbronchial biopsied tissue (usually 1-2 tiny pieces).

Table 3. Clinical features in 6 lung transplant patients.

Patient No.	Sex	Age (yr)	Underlying disease	Survival period	Complications and cause of death
1	M	63	Emphysema	3 monts 12 days	Pneumonia
2	F	19	Pulmonary tuberculosis with diffuse fibrosis	2 years 4 months	Severe pneumonia
3*	F	40	Connective tissue disease with pulmonary fibrosis	8 months	Pnuemonia
4*	M	35	Emphysema	18 days	Pneumonia with pericarditis
5	M	69	Pnuemoconiosis	4 months	Pneumonia with abscess and aspergillosis (Fig. 4)
6	F	19	Paraquat poisoning	2 months 24 days	Bronchovascular fistula

* Autopsy performed

Discussion

Early infections (within 1 month after operation) are often caused by bacteria that colonize or originate in surgical wound or anastomotic sites or other body sites.[7] After 1 month, (early-recent) risk of infections is due to suppression of cell-mediated immunity and therfore common etiologic agents are bacteria and intracellular organisms such as fungi, herpes and cytomegalovirus (CMV). Morbidity and mortality due to CMV infection has been reported in recipients of heart and heart-lung transplants.[8-10] Incidence and mortality of CMV pneumonia is even higher in heart lung transplants than any organ as also reported in our series. Aspergillosis is also commonly seen after 1 month of heart-lung transplantation.[11]

Among all intrathoracic organ transplantation, infections are most common in lung transplantaion.[12,13] Bacterial pneumonia is the most common cause of death in most series as also seen in our cases. Most pulmonary infections developed in the contralateral native lung. Single lung transplant recipients were significiently more likely to develop pulmonry infection than double lung transplant recipients. It was proposed that structural and functional abnormalities of the native lung may predispose to the reactivation of pre-existing colonization or easier progression of hospital gram-negative bacteria and fungus to the diseased lung.

Effective treatment of infectious diseases in organ-transplant recipients, remains problematic. The diagnostic yield, however, remains a challenge. Test for rapid and reliable detection of infectious diseases are continuting to evolve and have important implications for effective treatment. A significant higher numbers of bacteria, particularly same bacteria from many cultures, are often associated with infection. Strategies for antibiotic prophylaxis, however remains controversial, and must comprise approches that are not

only efficacious but also minimize the emergene of antibiotic resistance. Invasive fungal infections particulary aspergillosis, remains one of the most challenging opportunistic infection after transplantation; their treatment remains unsatisfactory probably due to delayed or inappropriate antifungal drug administration

The prevention of a number of infections after transplantation is proving to be increasingly successful, particularly in the area of viral infections, such as cytomegalovirus and herpevirus. The prevention of bacterial infection, however, remains controversial and problematic because of the crisis in antibiotic resistance, particularly multiple resistant gram negativebacteria.

Conclusion

Cause of death in heart-lung and lung transplantation were infections regardless of survival period. The causative agents were mostly bacteria, with CMV and aspergillus in some cases. In heart transplant recipients, common cause of death within 6 months after operation was also infection. However, the most common cause of death afterward was rejection.

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