The Incidence and Management of Pulmonary Mycosis in Renal Allograft Patients

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A retrospective analysis of 193 renal transplant recipients yielded 15 patients who developed pulmonary mycosis post-transplantation and one case in which mycotic lung infection existed at the time of transplant surgery. Agents responsible for infection included *Nocardia asteroides* in 8 cases, *Aspergillus flavus* in 5 cases, *Cryptococcus neoformans* in 4 patients and *Candida albicans* in 2 cases. Two cases had mixed mycotic infections. Ten patients died, of which 7 had diagnosis established antemortem. Two cases had diagnosis established by thoracotomy and 1 case by transtracheal aspiration. Problems in establishing accurate diagnosis are discussed with emphasis placed on the need for more frequent use of transtracheal aspiration and thoracotomy for precise diagnosis.

SEVERAL AUTHORS have documented a high incidence of fungal and nocardia infections complicating renal transplantation.[10,11,14,16,17] The earlier introduction of adrenal corticosteroids,[23] antibiotics[23,28] and cytotoxic drugs[6,12] has also been followed by a rise in mycotic infections.

Infection in renal transplant patients often follows rejection episodes and their treatment.[2] Diagnosis of mycotic infections in these patients is often made only at autopsy or terminally when therapy has been ineffective.

The purpose of this report is to describe experience with 16 pulmonary mycotic or nocardia infections following renal transplantation. There are 6 survivors. Of 10 deaths, 7 had diagnosis established antemortem.

Methods

A retrospective analysis of 193 patients undergoing renal transplantation at Duke and the Durham Veterans' Administration Hospital from February 26, 1965 through August 26, 1973, yielded 16 patients with pulmonary nocardia or mycotic infection. Criteria for selection included isolation of nocardia or fungus from pulmonary secretions or histological demonstration of fungus with or without cultural identification. Culture and antibiotic sensitivity determinations were performed using standard techniques.

Postoperative immunosuppression was similar in most cases and consisted of Azathioprine 100 mg/day beginning the day prior to transplantation, and Prednisone 20-60 mg/day in divided doses. Two patients received ALG. Episodes of threatened rejection were treated with intravenous Methylprednisone 1 gr/day, oral Prednisone 200 mg/day and local irradiation to the graft, 900 RADs over 5 days.

All patients were under the care of the Nephrology Staff in hospital clinics.

Results

Sixteen of 193 renal transplant patients developed pulmonary nocardia or fungal infections, an incidence of 8.3%.

Eight of 16 infections were in patients receiving cadaveric renal transplants, an incidence of 50%. There were 90 cadaveric transplanted kidneys in the series of 193 patients, an incidence of 47%. The remaining 8 pulmonary fungus infections occurred in patients with living related non-HL-A identical donor kidneys, an incidence of 50%. Living related, non-HL-A identical donors comprised 36.2% or 70 of the transplants performed in this period. None of the patients in the infected group had an HL-A identical donor, while 17% of the 193 renal transplants had an HL-A identical donor.

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TABLE 1.

Case	Age (yrs) & Sex	Primary Disease	Donor	Diabetic	Number of Rejection Episodes	Onset infect. Month post TP	Organism	Non Pulmonary Sites
1RH	34M	C-G-N	LRD* (2nd) Transplant	No	2	3	Nocardia	——
2JD	42M	Malignant Hypertension	LRD	No	1	27	Nocardia	——
3VD	21M	C-G-N	LRD	No	0	6	Nocardia	Brain
4JG	47M		Cad†	Yes	0	5	Nocardia Rhinosporosis	
5LW	20M	Nephrotic Syndrome 2° A-G-N	LRD 2nd plant	No	0	7	Nocardia	Brain
6JN	33M	C-G-N	LRD	Yes	1	2	Nocardia	——
							Aspergillus	——
7WC	49M	Malignant Hypertension	Cad	Yes	0	3	Aspergillus	——
8CB	46M	Systemic Beryllosis	Cad	No	0	4	Aspergillus	GI
9PED	23M	C-G-N	LRD	No	2	4	Aspergillus	
10FH	43M	Malignant Hypertension	Cad	No	2	1	Aspergillus Nocardia	——
11GB	56M	C-G-N	Cad 2nd plant	No	0	5	Cryptococcus Nocardia	Brain
12ED	30M	C-G-N	LRD	No	0	0	Cryptococcus	Brain
13TC	49M	C-G-N	Cad	No	0	61	Cryptococcus Chromomycosis	Brain Skin
14CG	35M	C-G-N	Cad	No	0	37	Cryptococcus	——
15GP	33M	WRM-H	LRD	No	3	0	Candida	——
16WP	26M	C-G-N	Cad	No	1	7	Candida	——

*Living Related Donor
†Cadaver

All patients in the infected group were male while in the entire series 70.4% of the patients were male.

Four deaths were from the group with living related donor transplants and 6 deaths occurred in the group of 8 infected patients with cadaveric transplants.

Table 1 summarizes pertinent clinical data as to type of infecting organism, number of rejection episodes, time of onset of the pulmonary infection after renal transplantation, symptoms, extrapulmonary sites of fungal infection, admission chest x-ray and laboratory data. Results are further analyzed according to type of fungal organism isolated. Table 2 summarizes the mode of diagnosis, treatment and outcome.

Nocardosis

Eight patients had nocardial pulmonary infections. Three of these had associated pulmonary mycoses, 1 having associated pulmonary aspergillus, 1 with pulmonary cryptococcosis and meningitis, and the third having pulmonary rhinosporosis. Five patients lived and 3 patients died.

Onset of the nocardial infections ranged from 1 to 27 months after transplantation. Seven patients gave a 1 to 7 day history of fever, cough, pleuritic chest pain and myalgia. The eighth patient was semi-comatose on admission. One patient developed mild transient right hemiparesis associated with abnormal brain scan; another had multiple nocardial brain abscesses demonstrated at autopsy.

Case Reports

Chest x-ray revealed pulmonary infiltrates in 7 pateints and cavitation in one. Pleural effusions were present in 2 cases. Pulmonary infiltrates progressed to cavitation in 5 cases.

Sputum gram stain or culture yielded the diagnosis in 5 cases, transtracheal aspiration in 1 and open lung biopsy in 1 case.

Case 2 had numerous bacterial pathogens demonstrated on repeated sputum specimens with nocardia being demonstrated only once. However, repeated transtracheal specimens consistantly yielded *Nocardia asteroides* and resulted in institution of triple sulfonamide and Ampicillin therapy with a favorable outcome. Prednisone was tapered from 60 mg/day to 20 mg/day and Imuran from 100 mg/day to 25 mg/day following diagnosis.

Case 3 (Fig. 1) had multiple sputum cultures showing other bacterial pathogens and obscuring correct diagnosis. Prednisone was reduced from 60 mg/day to 35 mg alternate days and Imuran reduced from 100 mg/day to 25 mg/day. Diagnosis and treatment of nocardiosis was made only after one week of hospitalization and did not prevent death from disseminated nocardiosis despite Gantrisin therapy. Early lung biopsy may have been valuable in this case.

Case 4 developed cough and pleuritic right chest pain while hospitalized for treatment of a bacterial pyarthrosis of the right hand. Chest

TABLE 1. *(continued).*

Symptoms	Chest X-Ray	At Infection Onset WBC	Prednisone	Imuran	BUN	CR	Creatinine Clearance ml/min
4d cough, chest pain, fever	RLL infiltrate R pleural effusion	6,700	40	25	63	6.3	——
3d chest pain, malaise	RUL infiltrate R&L pleural effusions	9,200	60	100	36	1.9	43
4d fever, cough, yellow sputum	LLL infiltrate	9,500	60	100	25	1.8	37
1d fever, semicomatose	RUL cavity	25,800	40	75	28	0.8	71
3d fever, cough, headache 7d cough,	R lung abscess	10,000	75	30	22	1.1	43
fever, R chest pain	RLL infiltrate	9,300	860	100	18	1.3	80
30d fever, cough, yellow sputum	LUL infiltrate	9,800	45	50/75	53	1.2	——
hemoptysis x 14 months	LL bilateral infiltrates	7,800	25	50	20	0.7	——
3 wk. fever, cough	bilateral infiltrates	16,000	80	100	130	2.6	42
1d cough, pleuritic chest pain	L hilar cavitation RLL abscess	13,000	40	75	44	2.5	——
fever, cough, chest pain	RLL infiltrate LLL cavitation	16,700	100	75	41	1.5	46
1 wk. fever, headache, blurred vision	bil. infiltrates	7,200	120	100	31	1.2	67
lassitude	RUL infiltrate & nodule	10,100	20	100	26	0.5	——
cough, yellow sputum, headache, nausea vomiting	LLL mass	8,900	25	100	11	1	——
——	RLL cavitation	12,500	——	——	——	——	——
——	RLL infiltrate	500	45	100	53	2.2	20

x-ray revealed a right upper lobe infiltrate, right pleural effusion and some haziness in the left lower lung field. Multiple cultures of sputum, CSF, urine, blood and pleural fluid were negative. The hand infection resolved uneventfully after drainage cultured *E. coli* and klebsiella; Keflin and Kanamycin were administered. Serial chest x-rays revealed clearing of the right pleural effusion with cavitation of the right upper lobe infiltrate (Fig. 2). Prednisone was maintained at 40 mg/day and Cyclophosphamide 50 mg/day was substituted for Imuran due to concern over the possibility of Imuran hepatotoxicity. Five months after this hospitalization and 10 months after renal transplantation, the patient was found to be febrile and semi-comatose at home. Neurological examination revealed no localizing or lateralizing signs. The patient responded only to noxious stimuli. WBC was 28,500, hemoglobin 13.2 gr%, BUN 23; arterial blood gases showed a P_{O_2} of 75, P_{CO_2} of 16 and a pH of 7.57. EKG showed no significant changes. Chest x-ray showed the previously described right upper lobe lung abscess. Lumbar puncture was normal. With the impression that the patient had septicemia, he was treated with fluids, antibiotics and high dose steroids. However, he pursued a rapid downhill course and died 12 hours after admission. Autopsy revealed massive nocardia bronchopneumonia and a 3 x 3 cm abscess in the right lung containing nocardia and rhinosporosis. The abscess extended into the main pulmonary artery.

Comment: Persistent undiagnosed pulmonary cavitation 5 months after renal transplantation progressed to massive nocardial bronchopneumonia and death at 10 months. Surgical diagnosis was required here at an early stage.

Case 5 received a cadaveric renal transplant at the age of 18, but rejection required transplant nephrectomy 2 months later. Five months after nephrectomy he received a renal transplant from his sister. Immunosuppression consisted of Prednisone 30 mg/day and Imuran 75 mg/day. Seven months post-transplant, surgical drainage and antibiotic treatment were required for a large left flank abscess which cultured *E. coli, Enterobacter aerogenes* and *Salmonella typhimurium. S. typhimurium* was also found in blood culture. A large right lower lobe lung abscess was noted on admission chest x-ray, however, no etiology was determined. Keflin and Gentamycin were administered for 14 days and he was discharged on Ampicillin. Immunosuppression was continued unchanged. One month later complaints of nonproductive cough, fever, headache and dizziness resulted in readmission. Purulent material was draining from the abdominal wound. Chest x-ray revealed the previously described right lung abscess as well as several new small cavitary lesions in the left lung. The flank abscess grew *Nocardia asteriodes, S. typhimurium, E. coli, Staphylococcal aureus* and *Bacteriodes oralis.* Five days after admission right thoracotomy with resection of the right middle lobe abscess was performed. Culture of the lung abscesses revealed *Nocardia asteroides* and *S. typhimurium.* Azathioprine was stopped and triple sulfonamides, Ampicillin, Clindamycin and Gentamycin were administered. Prednisone was maintained at 30 mg/day. A right transverse colostomy was performed because of feculent drainage in the left flank abscess. Postoperatively, transient mild right hemiparesis developed associated with increased left occipital tracer uptake on brain scan. Cerebral arteriogram, electroencephlogram and lumbar puncture were normal. Persistance of fever resulted in stoppage of all antibiotics except Ampicillin and sulfa. Fever gradually resolved and 3 months after admission he was discharged with a grossly normal chest x-ray.

Comment: Diagnostic thoracotomy was invaluable in this patient's management. Multiple bacterial pathogens in sputum cultures obscured

TABLE 2. *Mode of Diagnosis, Treatment and Outcome*

Case	Diagnosis Mode of	RX	Outcome	Cause of Death
1RH	Sputum	Gantrisin Ampicillin	Died	1. Diffuse bilateral nocardia pneumonia 2. Subarachnoid hemorrhage 3. Pneumococcal septicemia
2JD	Sputum	Ampicillin Triple Sulfa	Alive 3 years Post infection	
3VD	Sputum	Keflin, Kanamycin, Gantricin	Died	1. Diffuse bilateral nocardia pneumonia 2. Nocardia brain abscess
4JG	Bronchial Washings	Keflin, Kanamycin	Died	1. Right lung abscess (nocardia) extending into pulmonary artery. 2. Massive nocardia broncho-pneumonia
5LW	Sputum	Triple Sulfa, Ampicillin, Gentamycin, Cleocin	Alive.	
6JN	Sputum	Sulfadiazide Erythromycin Gentamycin Carbenicillin	Died	1. Fungal pneumonia 2. Gram-ve septicemia
7WC	Autopsy	———	Died	1. Acute MI 2° LAD thrombosis 2. Necrotising aspergillus pneumonitis
8CB	Sputum	Ampicillin, Keflin Kanamycin, Gentamycin	Died	Aspergillus pneumonia
9PED	Sputum	Amphotericin	Alive	
10FH	Sputum	Amphotericin Minocycline Septra	Alive	
11GB	CSF Sputum	Amphotericin	Died	Renal failure 2° chronic rejection and Amphotericin
12ED	CSF Sputum	Amphotericin 5-Fluorocytosine	Alive	
13TC	CSF	Penicillin, Keflin, Gentamycin	Died	1. Cryptococcal meningitis pneumonia 2. RUL cryptococcal abscess
14EG	Surgery	5-Fluorocytosine	Alive	
15GP	Autopsy	Gentamycin Carbenicillin	Died	1. Gram-ve septicemia 2. Candida pneumonia
16WP	Autopsy	Keflin, Gentamycin	Died	1. Candida bronchopneumonia 2. Pyelonephritis, gram-ve septicemia

and delayed diagnosis. Central nervous system involvement was presumed.

Case 10 had been treated for pulmonary aspergillosis (Fig. 3b) with intravenous Amphotericin B which was discontinued due to development of renal tubular acidosis. Two months later new pulmonary infiltrates and cavitation appeared (Fig. 3c). Gram stain and culture of bronchial washings revealed *Nocardia asteroides*. Treatment with triple sulfonamides was instituted. Imuran was discontinued while Prednisone was maintained at 40 mg/day. However, the lung lesions increased in size and open lung biopsy was performed. Biopsy specimens showed the nocardia to be resistant to triple sulfonamides, but sensitive to Septra and Minocycline. Therapy with these agents was successful with clearing of both chest x-ray and sputum (Fig. 3d). Imuran was then restarted at 25 mg/day.

Of the 5 deaths, 1 patient died following Amphotericin B treatment for cryptococcal meningitis and did not receive therapy for nocardiosis. Two other patients died 12 hours and 6 days respectively after admission without adequate therapy. The 2 remaining patients had nocardia diagnosed by sputum on the second and third hospital days respectively, and were treated with sulfonomides and Ampicillin or Erythromycin as well as cessation of Imuran and tapering of Prednisone, but showed progression of their pulmonary disease throughout their hospital course until their deaths.

Aspergillosis

Five patients had pulmonary aspergillosis and 2 of these patients had mixed infections with nocardia. One patient had aspergillosis located in the GI tract. All patients gave a 1 to 30 day history of fever, cough (often productive) and pleuritic chest pain. One patient had several episodes of hemoptysis 12 months prior to his final admission. His case is discussed below.

Case Reports

Onset of infection ranged from 1 to 4 months after renal transplantation. Chest x-ray showed infiltrates in 4 patients and left hilar cavitation in a fifth.

Diagnosis was made by sputum examination in 4 patients. In 1 patient diagnosis was made at autopsy. The patient died from myocardial

infarction 12 hours after admission. Sputum specimens in this case were negative.

Two patients survived. Case 9 developed pulmonary aspergillosis while hospitalized for treatment of threatened rejection (Fig. 4). Rapid diagnosis of aspergillosis by sputum examination was followed by a decrease in Prednisone to 50 mg/day and Imuran was discontinued. Treatment with intravenous Amphotericin B cleared both sputum and chest x-ray. However, transplant nephrectomy was required as a result of both the rejection episode and Amphotericin B therapy. Subsequently, he has undergone a second renal transplant and is now well 37 months after cessation of Amphotericin therapy. Case 10 (Fig. 3a) also had rapid sputum diagnosis and treatment with Amphotericin B. Immunosuppression was continued at previous levels. Amphotericin B was stopped when renal tubular acidosis developed. At that time the chest x-ray (Fig. 3b) had largely cleared but aspergillosis is still present in sputum. This patient is well 6 months after stoppage of Amphotericin B.

Three patients died and none received Amphotericin B. Case 7 died of a myocardial infarction as presented above. Case 8, a 47-year-old Caucasian man, underwent cadaveric renal transplantation in October of 1970 for chronic renal insufficiency secondary to systemic berylliosis. The patient had also suffered from respiratory insufficiency secondary to systemic berylliosis prior to his renal transplantation. Four months post renal transplantation, the patient had one episode of recurrent hemoptysis. Chest x-ray at that time revealed no active disease. Aspergillus was obtained on 8 occasions from the sputum culture. The patient received no treatment for this episode, which was felt at the time to be endobronchial aspergillosis. At the time of his final admission, 17 months post renal transplantation, the patient was receiving immunosuppression consisting of Imuran 50 mg/day and Prednisone 25 mg/day. Three weeks prior to his last hospital admission, the patient developed progressive dyspnea with cough productive of a thick yellowish, rusty sputum. This cough was accompanied by several episodes of shaking chills with temperatures of 99.5 to 101 F. The patient saw his local medical doctor for this cough and was placed on Ampicillin which he continued to take for the ensuing 3 weeks prior to his last hospital admission. The Ampicillin treatment did not improve his respiratory difficulty, and led to the patient's referral to Duke. On admission, the patient was moderately dyspneic. The temperature was 37.5 C. Blood gases revealed an arterial P_{O_2} of 28 with a P_{CO_2} of 27. The creatinine was 0.7 mg% and the bilirubin 2.1 mg%. Chest x-ray revealed bilateral lower lobe infiltrates. The patient's hospital course initially consisted of oxygen therapy and bronchial toilet. Because the diagnosis of pneumocystis was initially entertained, the patient was placed on Pentamidine. In addition, pending the arrival of culture results, the patient received Keflin and Kanamycin. The patient's sputum grew out Aspergillus. Sputum for pneumocystis was negative. The urine was negative for cytomegalovirus, bacteria and fungus. Multiple serological tests for histoplasma, blastomycosis and coccidioidomycosis were negative. The patient's hospital course consisted of gradual but progressive deterioration with increasing jaundice accompanied by failure of his pulmonary infiltrates to respond to his Keflin and Kanamycin therapy. Antibiotics were later changed to Gentamycin and Carbenicillin. Imuran and, later, Prednisone were discontinued. Pentamidine was discontinued after 7 days of therapy. Terminally, the patient's course was complicated with upper and lower GI

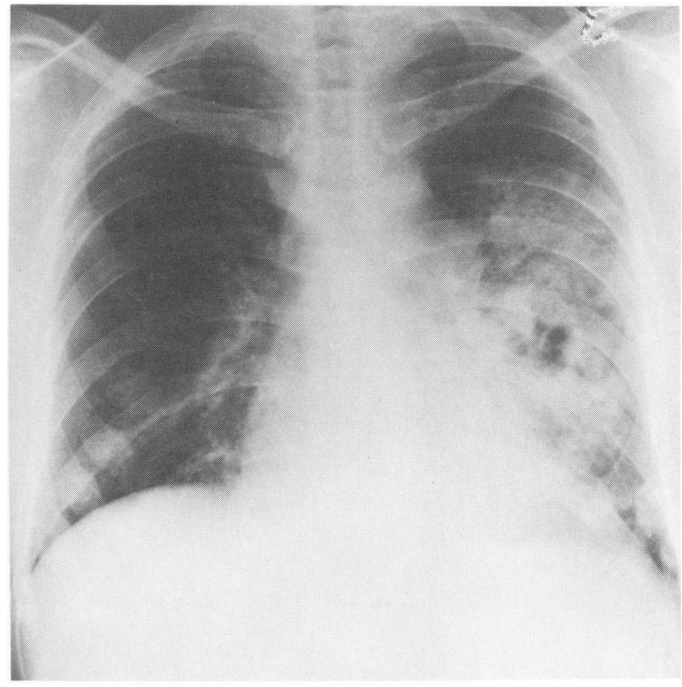

FIG. 1. Film is representative of Case 3 demonstrating pulmonary abscesses 2° to nocardia. Autopsy revealed diffuse pulmonary nocardiosis and two nocardial brain abscesses.

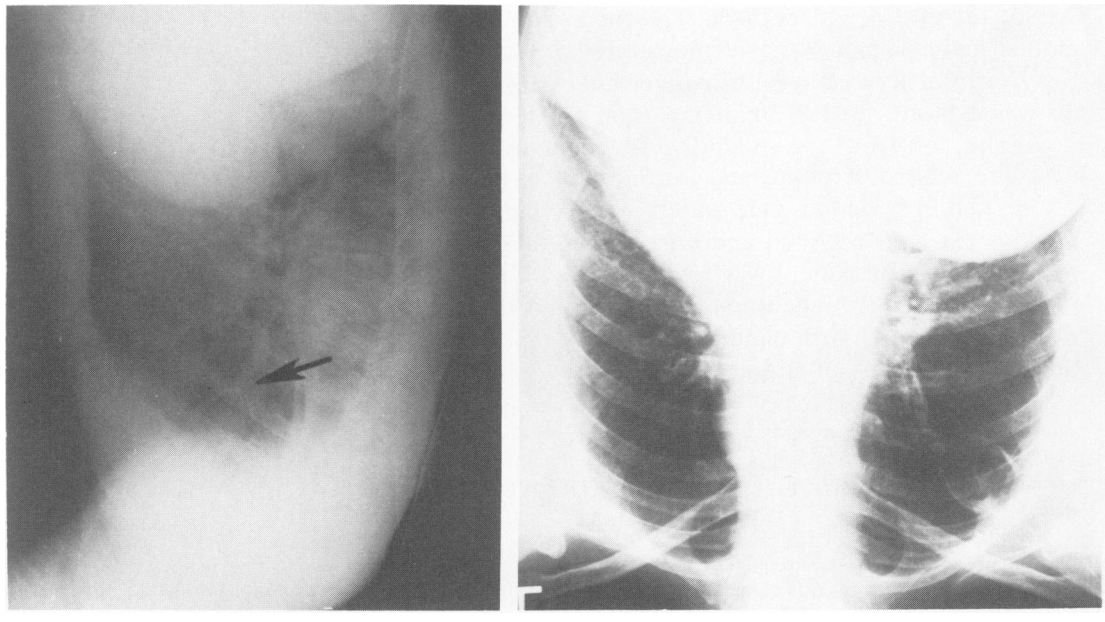

FIG. 2. X-ray film from Case 4 demonstrates a right upper lobe cavity of undiagnosed etiology. Five months later this abscess progressed to massive bilateral nocardial pneumonia and resulted in the patient's death.

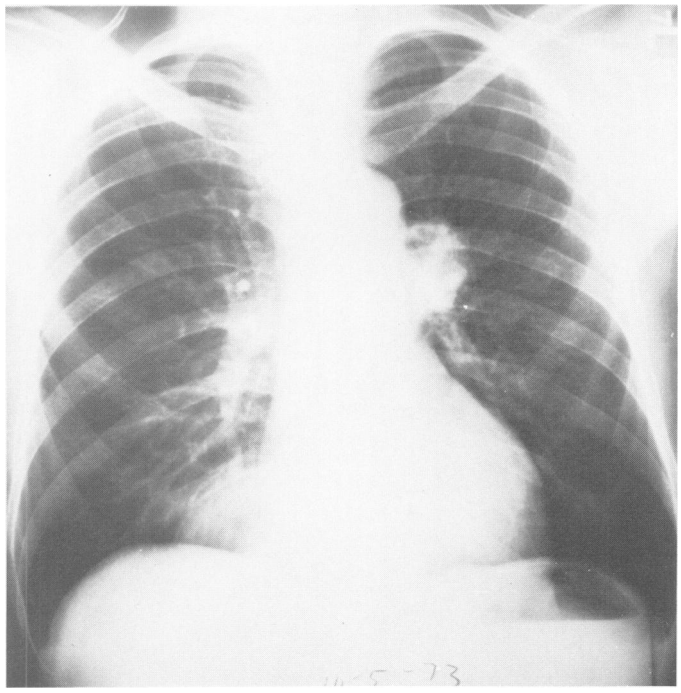

FIG. 3a. (Case 10) Chest film demonstrating a 5 cm diameter left, hilar lesion with areas of cavitation. Aspergillus was cultured from this patient's sputum.

bleeding peripheral vascular insufficiency and ischemic necrosis of his distal extremities. Renal function fell progressively. The patient suffered a respiratory arrest on April 4, 1972. Autopsy revealed aspergillosis in both his lungs and GI tract. Microscopic examination of the lungs in addition revealed multiple microscopic pulmonary vessel thrombosis, diffuse interstital fibrosis, edema and granuloma formation with intra-alveolar hemorrhage.

Comment: Endobronchial aspergillosis 3 months after renal transplantation was followed by disseminated aspergillosis 17 months after transplantation. Isolation of aspergillosis in sputum was not followed by Amphotericin B therapy.

Cryptococcosis

Four patients had pulmonary cryptococcal infections. One of these also had nocardia present in sputum and another had chromomycosis demonstrated in skin at autopsy. Central nervous system involvement by cryptococcus was demonstrated in 3 patients. Symptoms included headache, blurred vision and a fever in one, and headache, nausea, vomiting and cough productive of yellow sputum in a second. One patient was asymptomatic initially, but later relapsed and experienced fatigue and lassitude. A fourth patient was asymptomatic. The onset of infection was 5, 37, and 61 months post-transplantation in 3 patients. The fourth patient was found to have been infected at the time of surgery.

Chest x-ray revealed pulmonary infiltrates in 3 patients, pulmonary nodules in 2, and cavitation in one.

Diagnosis was made by culture or from stain of sputum and India ink examination of CSF in 2 patients, CSF alone in 1 and by surgery in the fourth.

Two patients survived. The first, Case 14, is a 35-year-old Caucasian man who underwent cadaveric renal transplantation in October of 1970. Postoperatively the patient was maintained on Imuran 100 mg/day and Prednisone 25 mg/day. Routine follow-up chest x-ray 37 months post-transplantation revealed a solitary lung mass in the left lower lung field (Fig. 5). Tomograms showed the lesion to be non-calcified and multinodular.

The patient complained of no respiratory symptoms. He was afebrile and examination of the chest was normal. Laboratory values showed a WBC of 8,900, BUN of 11, and creatinine of 10. Sputum and urine cultures for bacteria and fungus were negative. Thoractomy with wedge resection of the lesion was performed. Biopsy revealed a granuloma containing cryptococcus. Lumbar puncture was within normal limits. Prednisone and Imuran were continued at preoperative levels throughout the hospital course. He received a 6 week course of 5-Fluorocytosine and has remained well at followup 6 months later.

Comment: An asymptomatic lung lesion was diagnosed 37 months post-transplantation and required surgical diagnosis.

The second survivor, Case 12, was found to have had pulmonary cryptococcosis at the time of transplantation and received 2 courses of Amphotericin B and 1 course of 5-Fluorocytosine. Prednisone was tapered from 120 mg/day to 10 mg/day and Imuran was discontinued. He remains well with a clear chest x-ray 28 months after discontinuation of Amphotericin B therapy.

Two patients died; the first of whom (Case 11) had cryptococcus diagnosed by India ink preparation and spinal fluid culture soon after admission. Immunosuppression consisted of Prednisone 100 mg/day and Imuran 75 mg/day. A right lower lobe infiltrate was also present on admission and sputum culture was positive for cryptococcus. Treatment consisted of 1500 mg of intravenous Amphotericin B over 10 weeks as well as tapering of Prednisone to 20 mg/day and discontinuation of Imuran. The right lower lobe infiltrate resolved; however, an abscess cavity appeared in the left upper lobe (Fig. 6). Serial chest x-rays showed clearing of this cavity and discharge chest x-ray revealed only minimal residual infiltrate. Discharge lumbar puncture was within normal limits and sputum culture was negative for cryptococcus. However, renal function showed progressive decline with a discharge creatinine clearance of 21 cc/min. Over the 2 weeks following discharge,

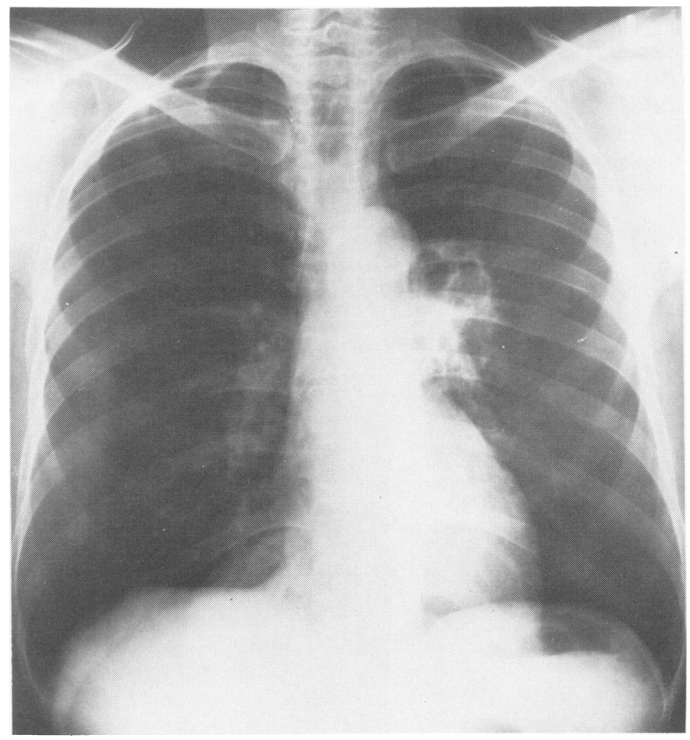

FIG. 3b. Followup film after treatment with Amphotericin B (405 mg). Marked clearing of the left hilar lesion is noted. Renal tubular acidosis forced discontinuation of Amphotericin treatment.

he became progressively weaker, stuperous and experienced nausea and vomiting. Readmission showed a clear chest x-ray and CSF within normal limits. BUN was 196 mg% and serum creatinine 4.5 mg% with a creatinine clearance of 10 cc/min. Prednisone was increased to 40 mg/day. The patient deteriorated rapidly, dying soon after admission. Autopsy was not obtained. Death was probably a result of chronic rejection and the nephrotoxic effects of Amphotericin B therapy.

The second death was Case 13, a 49-year-old man who received a cadaveric renal transplant in July 1967. Since that time he had been maintained on Imuran 100 mg/day and Prednisone 20 mg/day. Five years after transplantation, during evaluation of facial squamous cell carcinoma, routine chest x-ray revealed a right upper lobe lung infiltrate. He admitted to a 6 day history of cough productive of a yellow purulent sputum but denied chills or fever. Sputum culture revealed staphylococcus coagulase positive. Penicillin therapy resulted in marked clearing of the infiltrate and resolution of symptoms. However, a 1 x 1 cm right upper lobe nodule had been unmasked with a resolution of the infiltrate (Fig. 7). Sputum and gastric washings were negative for fungus. The patient was discharged on Penicillin; Imuran and Prednisone were continued unchanged. One month following discharge the right upper lobe nodule persisted unchanged in size and Penicillin therapy was discontinued. Two months following discharge he developed headache, nausea, vomiting and mild confusion resulting in readmission. Lumbar puncture revealed cryptococcus by India ink preparation and culture. Imuran was decreased to 25 mg/day and intravenous Amphotericin B therapy started. Prednisone was continued unchanged. Shortly after admission he became hypotensive. Blood and urine culture revealed *E. coli*. Keflin and Gentamycin therapy was started. Rapid deterioration in clinical condition ensued with dysuria and hypotension persisting. Death occurred on the seventh hospital day.

Autopsy revealed cryptococcal meningitis of the cerebellum and spine with cryptococcal invasion and necrosis of the cerebellar cortex. Budding yeast forms were present indicating failure of Amphotericin B therapy. Examination of the lung revealed that the right upper lobe nodule previously seen on chest x-ray consisted of demarcated but non-encapsulated area of necrosis with many cryptococci present within the lesion and adjacent alveoli. No objective evidence for *E. coli* septicemia was found.

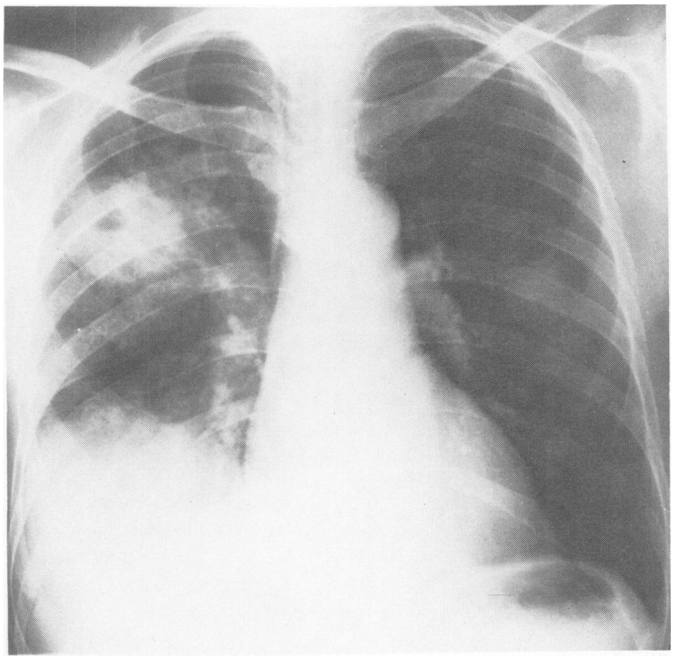

FIG. 3c. Reappearance of new pulmonary infiltrates and cavitation. Bronchial washings revealed nocardia asteroides which proved refractory to triple sulfonamide treatment and led to open biopsy allowing specific antibiotic sensitivities to be obtained.

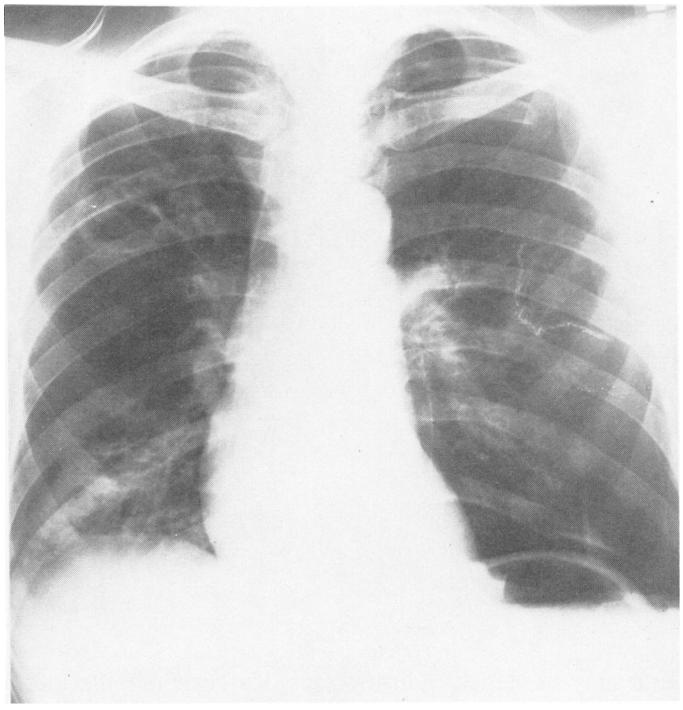

FIG. 3d. After two months treatment with Septra and Minocycline there is marked clearing of chest x-ray and sputum is now negative for nocardia.

Candida

Two patients had pulmonary candidiasis and both died. In each patient, candida was demonstrated only at autopsy. Case 15 developed right lower lobe cavitation while undergoing treatment for threatened rejection with massive doses of Prednisone, Imuran 50 mg/day and local graft irradiation within the first postoperative month. Autopsy revealed extensive candida bronchopneumonia which developed during treatment for a misdiagnosed rejection episode. Autopsy revealed an *E. coli* pyelonephritis as the cause of the deterioriation in renal function. No evidence of rejection was seen. Gram negative septicemia complicated each patients' terminal course.

Discussion

Rapid, accurate diagnosis of the responsible organism combined with determination of its antibiotic sensitivities is the cornerstone of management of any infection. This principle assumes added importance in the infected immunosuppressed renal transplant recipient.

Many of the same factors which render the renal transplant recipient susceptible to infection by opportunistic fungi are the same ones responsible for altering the clinical course and systemic response in the infected patient. These factors include antibiotic, steroid, and cytotoxic therapy as well as abnormal phagocytic activity, alterations in cellular and humoral immunity and the catabolism and acidosis of renal failure.[1,3,12,13]

Delayed cutaneous hypersensitivity is attenuated by both uremia and immunosuppression. Skin testing is not available for many of the fungal infections encountered

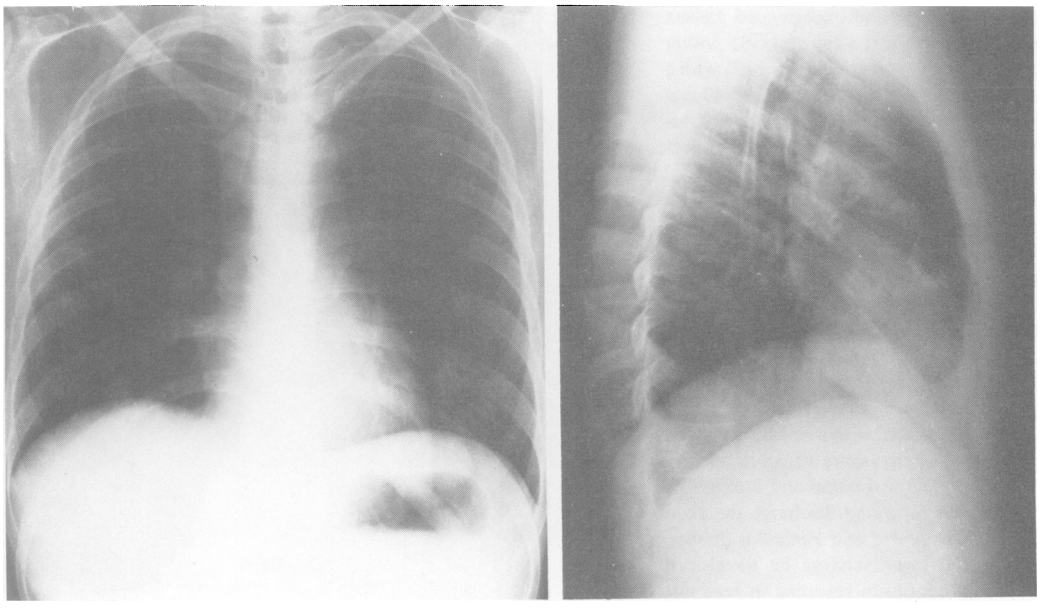

FIG. 4. (Case 9) Multiple pulmonary abscesses and cavities are present, best seen in lateral x-ray. Rapid diagnosis of aspergillosis by sputum culture allowed successful treatment with Amphotericin B.

and may be negative in the face of overwhelming infection.

Leukopenia, hyperglycemia, and moderate to severe renal failure were found by Adderson[1] to be consistently present among patients with fatal infections. Only one of our infections was associated with leukopenia at its onset. Three of the 18 patients in this series were receiving insulin at the time of infection. Leukocyte levels often relate more to the level of immunosuppressive drugs rather than the presence of inflammatory disease.

Interpretation of sputum cultures and their correlation with the clinical situation may be difficult at best. The organism isolated from the sputum may be the pathogen responsible for the clinical situation or it may represent only saphrophytic colonization of the respiratory tract.[24,26] This dilemma is illustrated by Case 8 in which investigation of hemoptysis 4 months post-transplantation resulted in isolation of aspergillus from sputum. In the face of an unchanged chest x-ray this was felt to represent saphrophytic colonization and was untreated. Sixteen months post-transplantation the patient developed fatal aspergillus pneumonia.

Stinson et al.[20] in a review of infectious complications following cardiac transplantation stated: "Because of the frequency with which mixed flora were cultured from sputum samples, the most valuable procedure in establishing the etiologic agent of pulmonary infections was percutaneous transtracheal aspiration." They also employed direct needle aspiration biopsy of pulmonary lesions in 3 patients in whom transtracheal aspiration failed to yield an etiologic agent. Two of 3 cases were diagnosed successfully in this manner before subsequent sputum and transtracheal culture yielded the offending organism. Transtracheal aspiration was responsible for yielding the etiologic agent in 1 of our cases (Case 2). Its more frequent use would appear to be indicated.

Several authors have emphasized the value of surgical diagnosis as a part of the aggressive work-up of these potentially fatal infections. Williams et al.[27] documented 3 patients in whom early extirpative therapy was both diagnostic and curative. Others have also excised localized areas of pulmonary fungal involvement in moribund patients with dramatic improvement.[4] All of our pulmonary fungal infections occurred in males. This

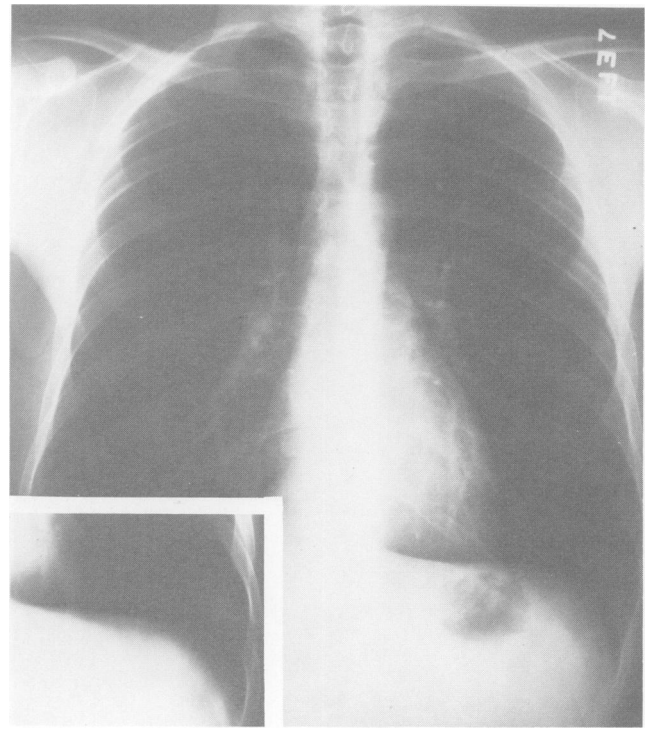

FIG. 5. (Case 14) Followup chest x-ray after transplantation demonstrated this solitary mass in the left lower lung field in an otherwise asymptomatic patient. At thoracotomy a cryptococcal granuloma was excised and appropriate therapy instituted.

sex predisposition has been noted by others.[9,16] No pulmonary fungal infections occurred in the HL-A identical group of renal transplants.

Many authors have noted that steroid and broad spectrum antibiotic therapy in man also increases susceptability to fungal infections.[3,12,13]

Steroid therapy increases susceptability of laboratory animals to fungal bronchopneumonias. The effects of cortisone on mice exposed to brief aerosols of aspergillus flavus spores included decreased peribronchial leukocytic infiltrate and early spore germination in comparison with non-cortisone treated controls.[7] Bach et al.[30] found that the frequency of fungal and nocardial infection increased linearly with the number of rejection episodes and their associated therapy. However, 8 of our 16 patients had no documented episodes of threatened rejections.

Cryptococcal pulmonary infections represented 5 of our 16 patients. This is a higher incidence than other series.[15,16,20,29,30] The reasons for this are not immediately apparent. Campbell[5] reviewed 60 normal hosts with untreated pulmonary cryptococcosis, and documented dissemination to the central nervous system in 7 of them. Two of our 4 patients had dissemination of cryptococcus from the lungs to central nervous system. In a third, both cryptococcal lung infiltrates and central nervous system involvement were documented simultaneously. Dissemination of this disease is more common in debilitating diseases[5,19] and has followed therapy with corticosteroids.[8,25]

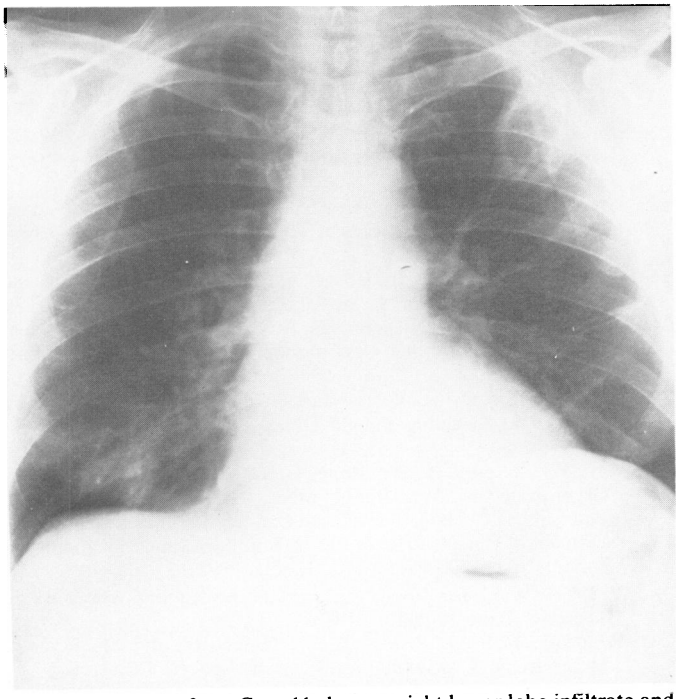

FIG. 6. Chest x-ray from Case 11 shows a right lower lobe infiltrate and an abscess cavity in the left upper lobe. The etiologic agent, cryptococcus responded to Amphotericin B with resolution of pulmonary pathology.

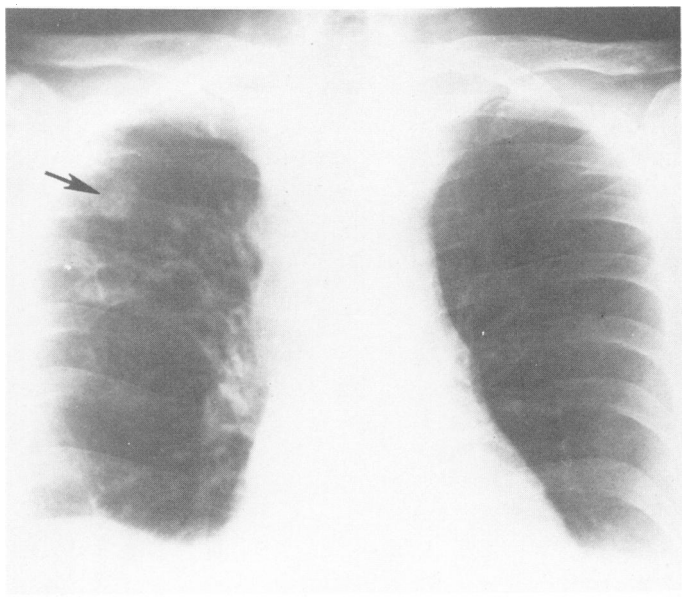

FIG. 7. PA chest x-ray demonstrating a 1 x 1 cm right upper lobe nodule. Two months later cryptococcal meningitis resulted in death. At autopsy, the pulmonary lesion proved to be a cryptococcal granuloma (Case 13).

Only 2 of our patients had candidiasis, a lower incidence than reported by others.[10,16,18] The routine prophylactic administration of oral Mycostatin in our hospitals may have played an important preventative role. The oral administration of Nystatin prevents candida overgrowth in the intestinal tract.[21] This may represent the organism's major point of entry. Stone[22] has recently presented evidence that thrice daily administration of oral Nystatin is uniformly effective in preventing evolution of Candida sepsis in a prospective randomized study of 243 burn patients.

Three patients (Cases 7, 15 and 16) in our series had no fungal organisms demonstrated prior to death. In 2 of these, early surgical diagnosis would have been of value in establishing the correct diagnosis and institution of appropriate therapy. The third patient died of myocardial infarction within 24 hours of admission. Sputum cultures were negative in this case.

Thoracotomy with lung biopsy was invaluable in determination of the pathogenic organism in 2 cases and in determining correct antibiotic sensitivity in a third case.

In the remaining 12 cases the organism responsible for the clinical situation was isolated from sputum of CSF. However, in 4 of these a significant delay in diagnosis occurred. Early surgical diagnosis in this group might have been of great benefit.

A high degree of suspicion is an important factor in the early diagnosis of these virulent fungal and nocardia infections. It should be emphasized that the symptomatic patient requires a greater sense of urgency than the asymptomatic patient with chest x-ray nodules or infiltrates. Failure of gram stain and culture of sputum for bacteria and fungus to reveal a pathogenetic organism or

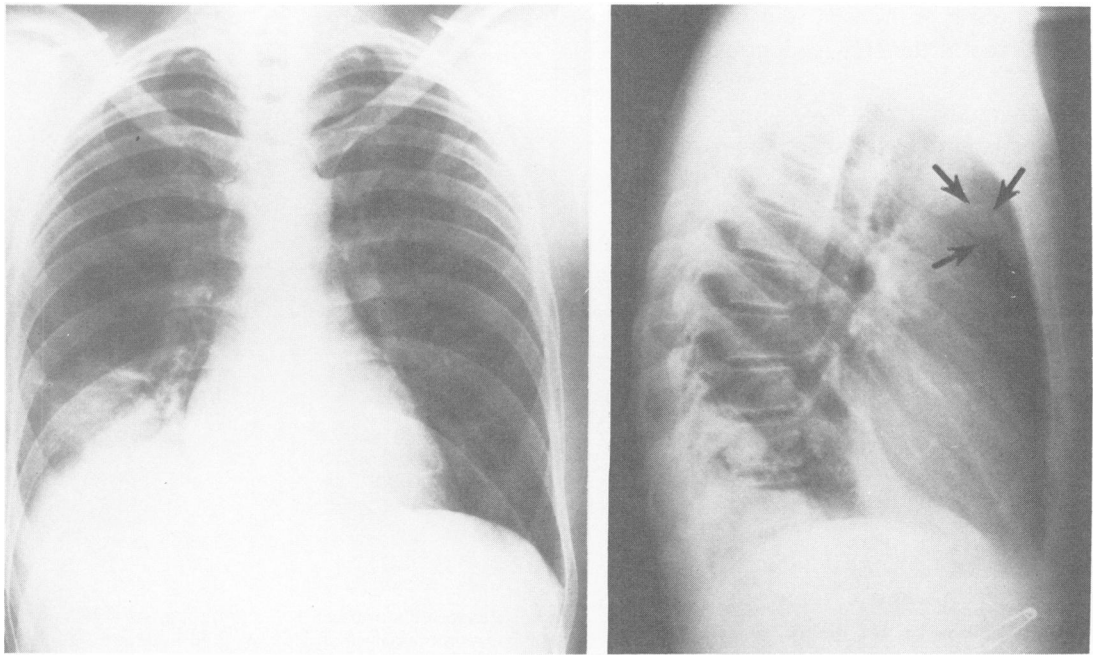

FIG. 8. Chest film from Case 6 demonstrating right lower lobe infiltrate and left upper lobe abscess. Nocardia and aspergillus were cultured from sputum. Death resulted from fungal pneumonia and gram negative septicemia.

failure to respond rapidly to indicated treatment should be followed by transtracheal aspiration and bronchoscopy for further specimen collection. Needle biopsy or thoracotomy should be performed if these tests are nonproductive. In both groups Imuran should be stopped and Prednisone tapered. Blood levels of appropriate antibiotics should be monitored.

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