Intracranial Infection in Cardiac Transplant Recipients

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Infections have produced most of the deaths in the Stanford cardiac transplant program. Of the first 182 transplant recipients, 27 developed nonviral intracranial infections: meningoencephalitis/abscess in 16 patients, meningitis in 9, and rhinocerebral phycomycoses in 2. The responsible organisms included aspergillus, toxoplasma, candida, klebsiella, cryptococcus, coccidioides, listeria, mucor, and rhizopus. Characteristically, the areas of meningoencephalitis and abscesses were multiple and deep seated. Intracranial infections were invariably associated with pulmonary or disseminated infection with the same organism.

Computed tomographic (CT) brain scans in patients with meningoencephalitis often showed minimal, nonspecific, low-density lesions which usually did not exhibit contrast enhancement. At surgery the lesions were found to differ from typical pyogenic abscesses in that capsules were not well developed, and the aspirate consisted of necrotic fragments of edematous white matter and inflammatory cells rather than liquefied pus.

Aspergillus infections of the central nervous system usually developed within the first three months after transplantation. Cases of meningitis occurred at variable times after transplantation, but approximately half appeared within 30 days after immunosuppressive therapy for treatment of rejection was increased. The prognosis for brain abscess depended on the causative organism. All patients with aspergillus infection died despite treatment with amphotericin B. The toxoplasma abscess responded to a combination of sulfadiazine and pyrimethamine. Meningitis was successfully suppressed or cured with appropriate treatment except for 1 patient with disseminated cryptococcosis.

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The problem of infection in immunosuppressed organ transplant recipients has been well documented [11, 14, 21, 22, 26, 29, 35, 37, 38, 39, 42, 46, 48]. Cardiac homotransplantation was initiated at Stanford Medical Center in January, 1968, and the single largest series of such patients has been accumulated at this institution [2]. As of January, 1980, 199 hearts had been transplanted into 182 patients. Of the 110 patients who died after transplantation, infection was the chief cause of death in 59 (53.6%) (Stinson EB: personal communication, 1980). Intracranial infection from nonviral agents occurred in 27 patients (13.6%). We report here the types of intracranial infections, their relationship to immunosuppressive therapy, and the diagnostic and therapeutic difficulties associated with these infections.

Immediately prior to cardiac transplantation, patients begin immunosuppressive therapy with a loading dose of azathioprine and one dose of antithymocyte globulin of rabbit origin (RATG). Following the transplant, immunosuppressive therapy consists of azathioprine, antithymocyte globulin, and corticosteroids (methylprednisolone and prednisone). Early signs of acute rejection are treated by increasing the dosage of corticosteroids, giving actinomycin D, and repeating the RATG injections. The specific details of immunosuppressive regimens are outlined in a recent review by Baumgartner et al [2].

The Intracranial Infections

Of the 27 patients with intracranial infection, brain abscess and nonviral meningoencephalitis occurred in 16. The responsible organisms included *Aspergillus* species, *Candida albicans*, *Klebsiella pneumoniae*, and *Toxoplasma gondii*. Meningitis occurred in 9 patients, with 1 having two separate attacks. The causative organisms were *Cryptococcus neoformans*, *Listeria monocytogenes*, and *Coccidioides immitis*. Rhinocerebral phycomycoses occurred in 2 patients due to rhizopus and mucor, respectively.

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Table 1. Meningoencephalitis and Brain Abscess in Heart Transplant Recipients

Case No.[a]	Transplant Date	Sex and Age (yr)	Onset/Survival[b] (days)	Organism	Means of Diagnosis	Neurological Symptoms and Signs
1	1/6/68	M, 54	13/15	Aspergillus	Autopsy	Terminal coma
18	9/14/69	M, 64	50/60	Aspergillus	Autopsy	Somnolence, confusion, disorientation; seizures, status epilepticus
34	8/18/71	M, 52	26/48	Aspergillus	Culture, pulmonary abscess	Confusion, disorientation leading to obtundation; R hemiparesis; terminal uncal herniation
61	8/21/73	M, 51	—/57	Aspergillus	Autopsy	No neurological symptoms present
68	3/19/74	M, 28	—/48	Aspergillus	Autopsy	Terminal neurological deterioration with disorientation leading to progressively decreasing level of consciousness
118	1/7/77	M, 48	48/54	Aspergillus, brain aspirate	Culture	Headache, nuchal regidity, R hemiparesis, R hemianopia, progressive obtundation leading to terminal coma
129	8/31/77	M, 48	—/201	Aspergillus	Autopsy	Cardiac arrest during pulmonary aspiration; seizures, no localizing findings; premortem diagnosis: anoxic encephalopathy
140	3/19/78	M, 46	—/101	Aspergillus	Culture, pulmonary aspergillus; positive CT scan	Acute onset of L hemiparesis 48 hr prior to death
144	6/4/78	M, 39	49/69	Aspergillus	Culture, brain aspirate	Confusion 7 wk posttransplant; R hemiparesis, dysphasia, R hemianopia starting 5 days later; terminal coma
172	7/4/79	M, 50	130/145	Aspergillus	Pulmonary aspergillus; positive CT scan	Headaches, lethargy progressing to terminal coma
24	5/14/78	M, 50	16/20	Candida	Autopsy	Progressive deterioration in level of consciousness thought secondary to pulmonary and renal failure
42	4/9/72	M, 45	—/65	Toxoplasma	Autopsy	None
123	4/2/77	F, 35	—/30	Toxoplasma	Autopsy	None
115	11/25/76	M, 48	301/628	Toxoplasma	Culture and smear from brain aspirate	3 wk history of increasing lethargy, disorientation; CT scan positive for three lesions (large abscess R frontal lobe)
143	4/29/78	F, 36	—/219	Toxoplasma	Autopsy	Terminal seizures thought secondary to lidocaine infusion for control of cardiac arrhythmia
102	4/29/76	M, 42	814/836	Klebsiella	Culture at autopsy; CT scan positive	Headache; blurred vision; incoordination of right upper extremity; nystagmus in right lateral gaze

[a]Refers to heart transplant series number.
[b]Day after transplant when symptoms first noted/total number of days of survival after cardiac transplant.
[c]Primary cause as determined by autopsy examination.

CMV = cytomegalovirus; IT = intrathecal.

Treatment	Pathological Findings	Microscopic Findings	Related Pathology	Cause of Death[c]
None	Abscesses in both frontal and R parietal lobes; subarachnoid hemorrhage, L temporal lobe	Necrotizing meningoencephalitis	Aspergillus in heart	Disseminated aspergillus
None	Multiple abscesses: L frontal, L frontoparietal, R frontal, and R occipital lobe, L cerebellum	Necrotizing aspergillus meningoencephalitis	Aspergillus in heart, lung, kidney, pancreas	Disseminated aspergillus
Amphotericin B IV, IT	Large abscesses: L cerebellum, R frontal and occipital lobes; hematoma, L cerebellum with intraventricular extension	Necrotizing aspergillus meningoencephalitis	Aspergillus in lungs; pulmonary CMV	Disseminated aspergillus
None	Abscesses: R and L frontal lobes, R cerebellum, L caudate, R pons	Necrotizing aspergillus meningoencephalitis; microglial nodules	Pulmonary aspergillus; acute rejection	Disseminated aspergillus; acute cardiac rejection
None	Multiple hemorrhagic lesions: both frontal, R temporal, both parietal, and R occipital lobes; cerebellum	Necrotizing aspergillus meningoencephalitis	Candida in heart, lungs, kidneys	Disseminated fungal infections
Burr hole aspiration for diagnosis	Hemorrhagic necrotic lesion: L basal ganglia, L occipital and R temporal lobes	Necrotizing aspergillus meningoencephalitis	Aspergillus in lungs	Disseminated aspergillus
Amphotericin B IV 4 days prior to death	Multiple necrotic hemorrhagic lesions: R internal capsule, caudate, and putamen	Necrotizing aspergillus meningoencephalitis	Aspergillus in lungs, heart, stomach, kidney	Disseminated aspergillus
Amphotericin B IV 1 mo prior to death	Large necrotic lesions of R parietooccipital lobes	Necrotizing aspergillus meningoencephalitis	Aspergillus in lungs	Disseminated aspergillus
Burr hole aspiration for diagnosis; amphotericin B 20 days prior to death	Hemorrhagic necrotic lesions: L parietooccipital lobes, L internal capsule	Necrotizing meningoencephalitis	Aspergillus in lungs, thyroid; sepsis	Disseminated aspergillus
Amphotericin B IV	Multiple abscesses throughout both hemispheres, cerebellum, and brainstem	Necrotizing meningoencephalitis	Aspergillus in lungs, heart, liver, thyroid	Disseminated aspergillus
None	Small, red, annular lesions throughout	Focal candida encephalitis; chronic meningitis; microglial nodules	Pulmonary CMV	Disseminated candida; rejection; bleeding diathesis
None	Normal	Disseminated toxoplasma cysts in CNS; microglial nodules	Severe acute rejection; pulmonary aspergillus; positive CMV titer	Acute rejection
None	Normal	Disseminated toxoplasma cysts in CNS; changes ranging from microglial nodules to foci of necrosis	Toxoplasma in heart, lungs, liver, pancreas, bone marrow	Disseminated toxoplasma
Aspiration of R frontal abscess; sulfadiazine and pyrimethamine	Small R frontal abscess; infarct L putamen/globus pallidus	Well-encapsulated abscess consisting of central area of necrosis surrounded by fibroblastic and inflammatory reaction; no organisms seen	Chronic and acute rejection	Cardiac rejection
None	Normal	Acute toxoplasma infection associated with microglial nodules	Acute rejection	Acute rejection
Penicillin, chloramphenicol, sulfamethoxazole, amphotericin B, 5-fluorouracil, pyrimethamine	1 cm abscess, right cerebellar peduncle	Encapsulated brain abscess	Pulmonary cryptococcosis; atherosclerosis in coronary arteries	Bronchopneumonia

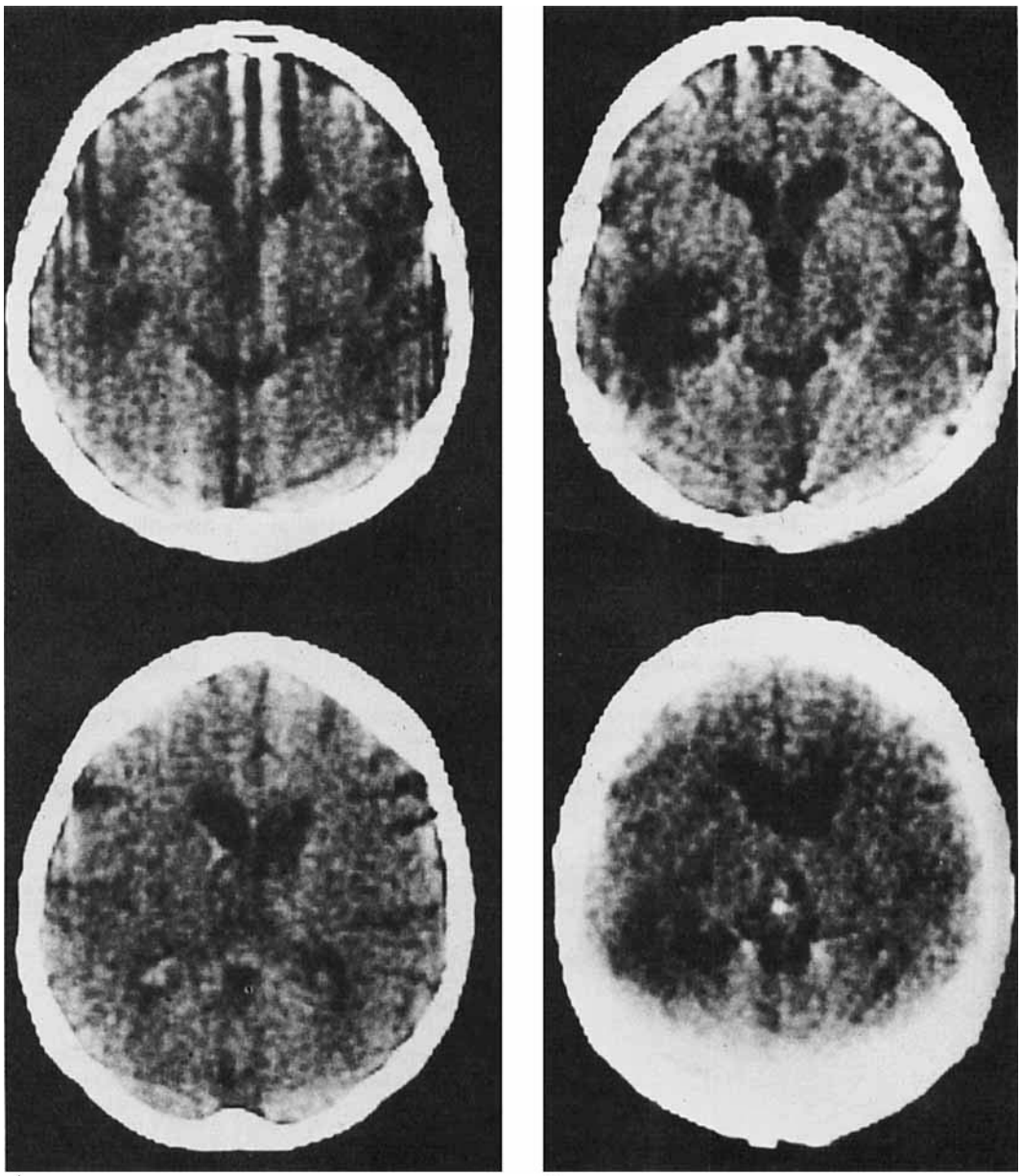


Fig 1. (Case 118) (A) Initial CT scan in a cardiac transplant patient with right hemiparesis, hemianopia, and nuchal rigidity shows a small area of decreased density in the left temporal lobe on the precontrast scan (top). *A small linear hemorrhage is present adjacent to the left frontal horn* (bottom). *(B) Repeat CT scan three days later with contrast infusion shows a dramatic increase in the size of the left temporal lobe lesion but no contrast enhancement.*

Brain Abscess/Meningoencephalitis

ASPERGILLUS. *Aspergillus* species were responsible for 10 cases of necrotizing meningoencephalitis (Table 1). Invariably, the organisms disseminated from a pulmonary focus. The onset of clinically apparent disease occurred early after the transplant. In all except Cases 129 and 172, the aspergillus infection disseminated within the first three months following the transplant (range, 13 to 201 days). Neurologically, these patients presented with disorientation and confusion and progressed to obtundation and terminal coma. Four patients had a subacute course with focal neurological findings (hemiparesis, hemianopia, and dysphasia) (Table 1).

The diagnosis of aspergillus meningoencephalitis was difficult to make antemortem. CT brain scans were performed in 5 patients and demonstrated nonspecific findings. The scans in 2 patients were characterized by multiple low-density lesions with minimal, irregular contrast enhancement (Figs 1, 2). In 3 patients, only low-density lesions without any contrast enhancement were present. The size of such

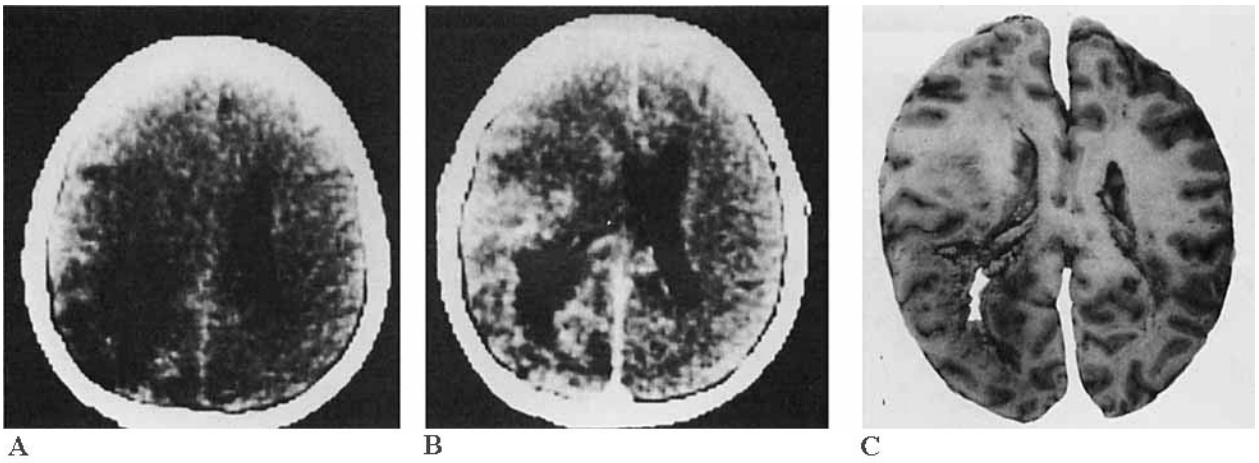


Fig 2. (Case 144) (A) CT scan of a 39-year-old transplant patient with right hemiparesis, dysphasia, right hemianopia, and confusion reveals an abnormal area of low density in the left parietal lobe. (B) After contrast infusion a poorly demarcated area of enhancement is noted at the periphery of this low-density lesion. The enhancement extends across the midline at the splenium of the corpus callosum. (C) At autopsy a 5 × 7 cm necrotic lesion was present in the left parietoocipital lobe, as seen in a slice of the fixed brain cut in the CT plane.

lesions increased substantially within a few days (Fig 1)—scans at short intervals are important in following the condition of an immunosuppressed host with progressive neurological symptoms and signs.

Results of cerebrospinal fluid (CSF) examination were not helpful in establishing the diagnosis of aspergillus infection. Cell counts ranged from 0 to 498 white blood cells (WBC) per cubic millimeter (see Table 3). Protein was elevated (68 to 152 mg/dl) in all but 1 case. Stain preparations and cultures of CSF were performed in 6 patients and did not reveal aspergillus in any of them. Serological tests for aspergillus were performed in initial cases and did not prove to be of diagnostic reliability; we no longer order them in suspected cases.

The definitive diagnosis was made by direct needle aspiration of suspected intracranial lesions in only 2 patients. In neither was there evidence of capsule formation (i.e., no resistance was encountered to the passage of a Cone ventricular needle through the brain). The aspirated fluid in both cases was watery and contained fragmented white matter, and communication with the ventricle was suspected. Potassium hydroxide preparations and cultures revealed aspergillus. Speciation was not performed.

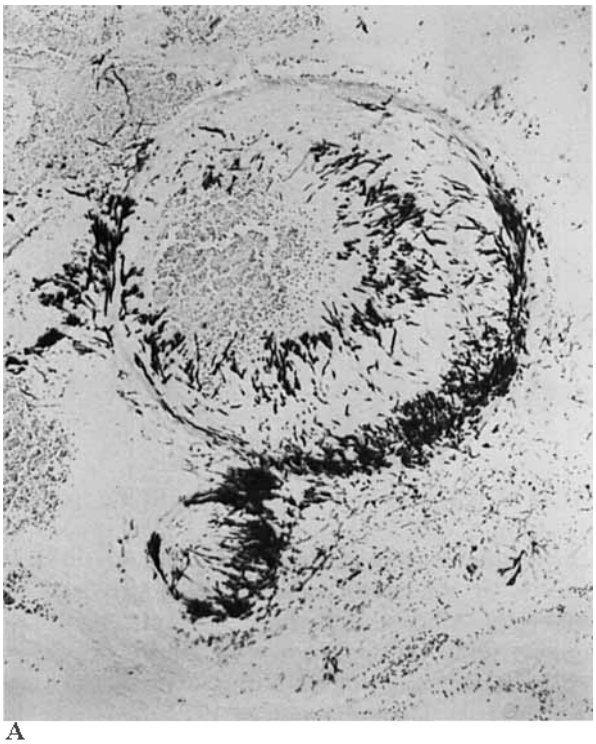
In 3 cases the diagnosis was strongly suspected, and amphotericin B therapy for aspergillus in the lungs had either been started or was in progress at the time neurological symptoms and signs began. In 5 patients aspergillus infection in the central nervous system (CNS) was not suspected until autopsy examination.

Five patients were treated with amphotericin B. In Case 34 it was given both intravenously and intrathecally. All cases ended fatally despite aggressive therapy. In all but 1 patient, aspergillus was present in other organs at autopsy, most commonly the lungs (see Table 1). Dissemination of the fungus was the cause of death in all patients except 1, in whom acute rejection was a contributing factor.

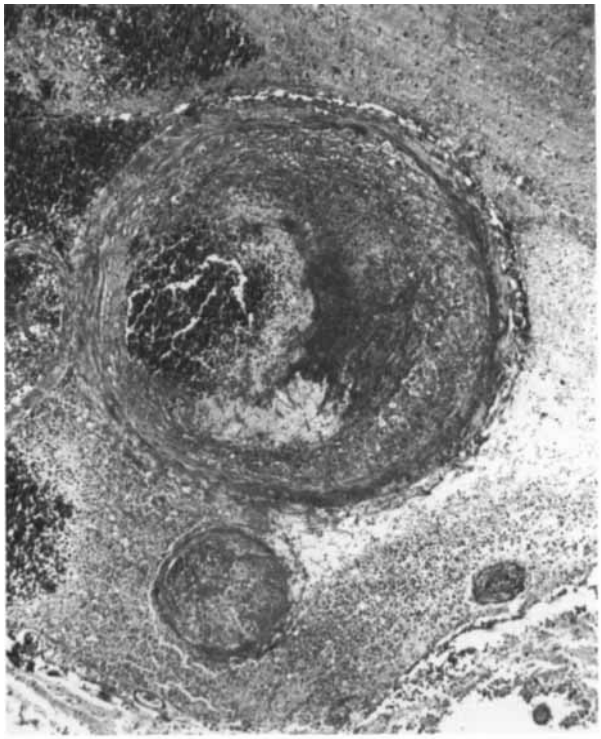
At autopsy there was gross evidence of multiple necrotic and hemorrhagic lesions throughout the brains. The pathological findings were more extensive than CT scans had suggested antemortem. Microscopically, the process was characterized by vascular invasion by aspergillus leading to secondary thrombosis and cerebral infarction, often hemorrhagic (Fig 3). There was a variable degree of inflammatory response, but it was often minimal, considering the extent of involvement by the fungus. There was evidence of astrogliotic reaction around some of the lesions.

CANDIDA ALBICANS. One patient (Case 24) developed progressive deterioration in level of consciousness on the sixteenth postoperative day. The changes were considered secondary to deteriorating pulmonary status and renal failure. At autopsy, candida encephalitis with multiple focal lesions was seen microscopically in areas of small, red, annular lesions throughout the brain.

KLEBSIELLA PNEUMONIAE. Only 1 patient presented with a bacterial brain abscess. Three years after cardiac transplantation he presented with a 2-day history of headache, unsteady gait, diplopia, and gross dysmetria on the right side. A CT scan demonstrated a 2 cm contrast-enhancing ring lesion in the right superior cerebellar peduncle consistent with an abscess. The patient had a coexistent lung le-



A



B

C

Fig 3. Neurohistological findings in aspergillus meningoencephalitis. Characteristic invasion of the aspergillus organisms (A) leading to secondary thrombosis (B) of cerebral blood vessels. Morphologically the organisms are characterized by multiple branching of septate hyphae (C). (A, Grocott's methenamine silver, ×75; B, H&E, ×75; C, Grocott's methenamine silver, ×480. All before 15% reduction.)

sion that was aspirated and grew cryptococcus. The brain lesion was not aspirated because of its location adjacent to the brainstem. Treatment with Decadron was begun, and his neurological status improved. He was started on antibiotic therapy including amphotericin B to cover possible etiological agents of the brain lesion. Radiation therapy to the posterior fossa was begun because of the possibility that the lesion represented a microglioma. Eighteen days after hospitalization he developed a necrotizing staphylococcal pneumonia and died. At autopsy the brain lesion was aspirated, and cultures of the pus grew *Klebsiella pneumoniae.* The brain lesion was not considered a contributing factor in the patient's death.

TOXOPLASMA GONDII. There were 4 cases of toxoplasma infection of the CNS. Three of the 4 patients showed microscopic evidence of diffuse encephalitis, with toxoplasma cysts often associated with formation of microglial nodules. The diagnosis in these 3 cases was made at autopsy (see Table 1). There was nothing from the history or physical examination to suggest CNS infection except seizures in 1 patient, which probably were secondary to large infusions of lidocaine given to control cardiac arrhythmias. In 1 patient, disseminated toxoplasma infection affecting the heart, lungs, liver, pancreas, and bone marrow was the principal cause of death [41]. In the other 2, acute rejection was responsible for death.

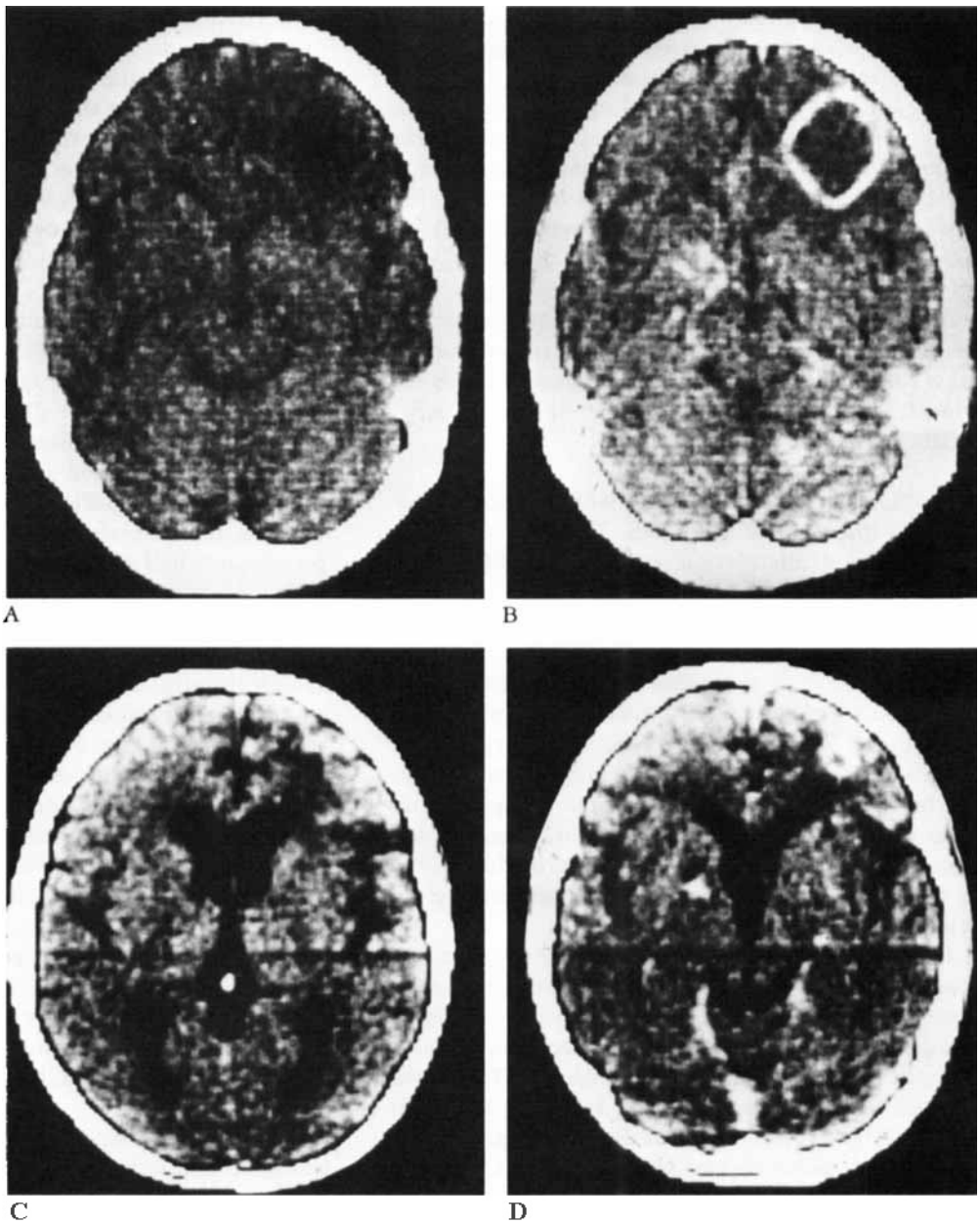
The fourth patient had abscess formation in the brain [30]. The patient was a 48-year-old man who developed a 3-week history of increasing lethargy and disorientation 10 months after transplantation. A CT scan (Fig 4A,B) showed three lesions. There was a large, contrast-enhancing ring lesion in the right frontal lobe typical of a sizable abscess. Smaller contrast-enhancing lesions were present in both the left basal ganglia and the right cerebellar hemisphere. A right frontal burr hole was placed. Toxoplasma cysts and tachyzoites were seen extracellularly and intracellularly within inflammatory cells on preparations of the aspirate stained with Wright-Giemsa and with hematoxylin and eosin. The patient was treated with sulfadiazine and pyrimethamine. His mental status improved. At the time of his last examination he still had decreased recent and long-term memory and a right superior visual defect. A CT scan performed 33 weeks after surgery showed resolution of the small lesions in the left basal ganglia and right cerebellar hemisphere. The abscess in the right frontal lobe was much smaller (Fig 4C,D). The patient died slightly more than a year later from graft rejection. The brain showed a small residual abscess in the right frontal region consisting of a central area of necrosis surrounded by a fibroblastic and inflammatory reaction. No organisms were seen. A residual infarct involved the region of the left basal ganglia. This case illustrates the value of aspirating suspected areas of intracranial infection, since the diagnosis was made on smear preparation of the aspirated material and appropriate therapy was instituted promptly with good neurological improvement.

Meningitis

Ten episodes of meningitis occurred in 9 patients. The causative organisms were *Cryptococcus neoformans* in 5, *Coccidioides immitis* in 1, and *Listeria monocytogenes* in 4 (Table 2). In contrast to the cases of fungal abscess and meningoencephalitis, in which the organism disseminated to the CNS relatively early following transplantation, meningitis appeared to develop at any time after the transplant. However, approximately half of the cases occurred within 30 days after immunosuppressive therapy for treatment of rejection was increased. Two of the cases due to listeria (Nos. 72 and 96) arose 4 and 18 days, respectively, after treatment for rejection. Two of the 5 cases due to cryptococcus (Nos. 67 and 96) occurred shortly after therapy for rejection in 1 case and immediately following a second heart transplant in the other. In the latter patient, a single colony of cryptococcus grew from the preoperative sputum culture at the time of the second heart transplant. Since the patient had no demonstrable focus of infection and was asymptomatic, amphotericin B was not started. The patient died 35 days postoperatively from disseminated cryptococcosis. Another patient (Case 77) was receiving antithymocyte globulin on a chronic basis in addition to the usual regimen of immunosuppressive therapy when he developed cryptococcal meningitis.

The patients most commonly presented with headache and lethargy. Fever was the most frequent sign. In 4 patients, focal neurological deficits were present in the form of hemiparesis. A CT scan performed in a patient with listeria meningitis with an evolving left hemiparesis revealed a contrast-enhancing ring lesion suggestive of an abscess. The lesion was aspirated through a burr hole at another institution and yielded no pus. The patient improved on antibiotic therapy alone, and a repeat CT scan a year later showed only a small residual area of low density.

Examination of CSF was helpful in establishing the diagnosis of meningitis (Table 3). In the patients with cryptococcal meningitis the pleocytosis was modest, with WBC counts ranging from 4 to 13 WBC/mm^3. The majority of cells were mononuclear. There was a slight to moderate elevation of protein (53 to 132 mg/dl). CSF glucose was low compared with serum



values drawn at approximately the same time. India-ink preparation and gram stains showed budding yeast organisms. Cultures were uniformly positive for *Cryptococcus neoformans*. Cryptococcal antigen was positive in the CSF in 3 cases in which it was tested.

The patients with listeria infection had marked CSF pleocytosis, with cell counts ranging from 68 to 2,100 WBC/mm^3. Both polymorphonuclear leukocytes and mononuclear cells were present. Protein was elevated (125 to 348 mg/dl), and CSF glucose was depressed in relation to serum glucose when comparison could be made. Although gram stains of

Fig 4. CT appearance of a Toxoplasma gondii *brain abscess. The preinfusion scan (A) shows a low-density region in the right frontal lobe, which demonstrates characteristic ring enhancement after intravenous contrast infusion (B). In addition, two smaller contrast-enhancing lesions are seen in the left basal ganglia and right cerebellar hemisphere (B). Eight months after treatment with sulfadiazine and pyrimethamine the noncontrast scan (C) shows only a small low-density area in the right frontal lobe and a smaller ring of enhancement (D) after contrast infusion.*

Table 2. Cases of Meningitis in Heart Transplant Recipients

Case No.[a]	Transplant Date	Sex and Age (yr)	Onset/ Survival[b]	Organism	Neurological Symptoms/Signs	Primary Infection Site	Treatment	Outcome	Cause of Death[c]
67	3/2/74	M, 46	117/146	Crypto-coccus	Increasing headache over 2 wk	...	Amphotericin B IV	Died 6 days after diagnosis	Pneumonia
77	10/19/74	M, 38	378/alive	Crypto-coccus	Headache 2 wk	Lung	Amphotericin B IV, IT; 5-FC	Erad.	Survived
92	9/17/75	M, 54	759/alive	Crypto-coccus	Headaches 3 mo; mild R hemiparesis; fever	Lung	Amphotericin B IV; 5-FC	Erad.	Survived
95	11/21/75	M, 50	955/alive	Crypto-coccus	Fever, weakness, anorexia	Lung	Amphotericin B IV	Erad.	Survived
127	7/29/77	M, 49	48/alive	Coccidi-oides	Transient L hemiparesis and blindness; headache	Lung	Miconazole IV; amphotericin B IV, IT	Erad.	Survived
20	1/16/70	M, 49	1,204/1,996	Listeria	Headache, disorientation, fever, meningismus, L hemiparesis, status epilepticus	Septi-cemia	Penicillin IV	Erad.	Pneumonia
72	6/24/74	M, 43	73/293	Listeria	Lethargy, headache, fever	...	Penicillin IV	Erad.	Survived
96	12/8/75	M, 32	50/1,269	Listeria	Lethargy, fever	...	Penicillin, chloramphen-icol IV	Erad.	Survived
	4/27/79			Crypto-coccus	(Autopsy: died of massive GI hemorrhage secondary to cryptococcal invasion of GI walls)	...		Died	Disseminated cryptococcus
66	12/12/73	M, 23	1,099/1,521	Listeria	Headache, lethargy, evolving L hemiparesis; contrast-enhancing ring lesion, R frontoparietal lobe; burr hole aspiration negative for pus	Septi-cemia	Ampicillin, gentamicin IV	Erad.	Cardiac arrhythmia

[a]Refers to heart transplant series.
[b]Day after transplant when symptoms first noted/total number of days of survival after cardiac transplant.
[c]As determined by autopsy examination.

IV = intravenous; IT = intrathecal; 5FC = flucytosine; Erad. = eradicated infection.

the CSF were uniformly negative, all cultures grew out colonies of listeria.

The diagnosis in the single case of coccidioidomycosis was made indirectly. The patient had coccidioides in both sputum and urine at a time when he presented with headaches, a transient left hemiparesis, and blindness. A CT scan was negative. CSF analysis showed 2 mononuclear cells/mm^3, a protein of 87 mg/dl, and a normal glucose level. India-ink preparation of the CSF and culture were both negative. Complement-fixation test of the CSF was positive in a dilution of 1:24 (at its highest value) and established the diagnosis.

Treatment of the meningitis resulted in eradication or suppression of the infection in all but 1 patient. Case 96 had disseminated terminal cryptococcosis shortly after his second cardiac transplant. Cryptococcal meningitis was treated in this series of patients with intravenous amphotericin B; prior to 1975, amphotericin was used intrathecally and intracisternally in addition. The single case of coccidioides meningitis was treated using both intravenous and intrathecal amphotericin B and intravenous miconazole. Listeria meningitis was treated with penicillin or ampicillin.

Rhinocerebral Phycomycoses

Two patients developed rhinocerebritis due to rhizopus and mucor, respectively. Case 9 developed periorbital swelling on his twentieth postoperative day. Within a short time he had palsies of the right third, fourth, and fifth nerves. In addition, there was progressive aseptic necrosis of the right paranasal structures. Cultures grew rhizopus. He was given amphotericin B intravenously and improved over the course of 2 months with his only residual neurological abnormality being a fourth nerve paresis. He died of chronic graft rejection 100 days after transplantation. Permission was denied for postmortem examination of the brain.

Shortly before death, Case 37 developed a conjunctivitis that spread to involve the periorbital

Table 3. Cerebrospinal Fluid Findings in Cases of Intracranial Infections in Heart Transplant Recipients

Case No.	Organism	Opening Pressure (mm H_2O)	WBC (/mm^3)	Differential Count	RBC (/mm^3)	Protein (mg/dl)	CSF (Serum) Glucose (mg/dl)	Gram Stain, India Ink	Culture
67	Cryptococcus	140	4	100% monos		53	50 (137)	Yeast	Positive
77	Cryptococcus	170	5	100% monos	13	78	36 (102)	Yeast	Positive
92	Cryptococcus		13	85% monos, 15% polys		132	113	Yeast	Positive
127	Coccidioides		2	100% monos	5	87	244	Negative	Negative
20	Listeria	390	68	73% monos, 27% polys		267	45 (150–300)	Negative	Rare listeria
72	Listeria	300	2,100	99% polys, 1% monos	300	125	86	Negative	Rare listeria
96	Listeria		253	54% polys, 46% monos	22	348	27 (85)	Negative	Rare listeria
18	Aspergillus		7	57% polys, 43% monos		123	70	Negative	Negative
34	Aspergillus	120	0			29	90	Negative	Negative
118	Aspergillus		498	98% polys, 2% monos		106	34	Negative	Negative
129	Aspergillus	330	0			68	77	Negative	Negative
140	Aspergillus		14		2	136	92	Negative	Negative
172	Aspergillus		0		0	152	92 (287)	Negative	Negative
115	Toxoplasma	100	1	100% monos		141	137	Negative	Negative

WBC = white blood cells; RBC = red blood cells; monos = mononuclear leukocytes; polys = polymorphonuclear leukocytes.

structures bilaterally. He was comatose terminally. Postmortem examination showed necrosis of the olfactory bulbs and supraorbital gyri bilaterally. There was a necrotizing meningoencephalitis involving both frontal lobes. The process was characterized by marked vascular invasion by numerous fungi having nonseptate hyphae characteristic of mucor and resulting in secondary infarction. Microscopic examination of the eyes showed invasion of the same organism. The patient died of severe acute rejection, although meningoencephalitis may have contributed to his death.

Discussion

The high incidence (13.6%) of nonviral intracranial infections in these cardiac transplant patients reflects their altered immune status. Each of the agents used to combat allograft rejection (corticosteroids, azathioprine, antithymocyte globulin) depresses the humoral and cell-mediated immune systems [19, 20]. Noteworthy was the limited number of pathogenic organisms. Aspergillus accounted for 10 of 16 cases of meningoencephalitis and brain abscess. *Toxoplasma gondii* accounted for 4 cases. Meningitis was caused by only three organisms: cryptococcus, listeria, and coccidioides. The epidemiology, particularly with regard to aspergillus, toxoplasma, cryptococcus, and listeria, deserves inquiry. Thus far, no common source of infection for these organisms has been identified.

Aspergillus was the most common cause of meningoencephalitis in our series and has previously been recognized as a frequent problem in recipients of both cardiac [17] and renal [6, 26, 32, 38] transplants as well as in other immunologically suppressed patients [24, 56]. Although it has been possible to cure the pulmonary infection in some cardiac transplant recipients [17], once the CNS was involved, aspergillus infection was uniformly fatal in our series. However, the literature reports patients with probable aspergillus infections of the CNS who recovered with amphotericin B therapy [6, 9]. These reports and our untoward experience with this infection stress the need for early diagnosis [1]. CNS aspergillus should be suspected when, in the context of known lung involvement, a patient develops subtle changes in mental status or focal neurological findings. CT scan reveals the CNS lesions, but unfortunately they are nonspecific, low-density lesions with minimal contrast enhancement [10]. Examination of CSF, in our cases as in others [31, 56], was not helpful in establishing the diagnosis. CSF protein was usually elevated and a variable pleocytosis was present; cultures did not grow out the organisms. Serological testing for invasive aspergillus has not been useful [55]. Our experience suggests that definitive premortem diag-

nosis requires direct needle aspiration of a cerebral lesion demonstrated on CT scan.

Toxoplasma has a particular predisposition for destruction of the central nervous system in a compromised host [7, 8, 13, 16, 37, 38, 51]. *Toxoplasma gondii* was the second most common cause of meningoencephalitis and brain abscess in this series of immunosuppressed transplant recipients. With toxoplasma, one probable source is transmission by latent infection from the donor heart [41]. Two heart transplant recipients (Cases 115 and 123 in Table 1) had negative serological tests for toxoplasma prior to transplantation and developed acute toxoplasmosis shortly after surgery. It is known that the myocardium can be infected during both the acute and chronic stages of the infection [49]. Furthermore, administration of the wide variety of immunosuppressive agents, including corticosteroids, cyclophosphamide, whole-body irradiation, and antithymocyte globulin [13, 47], has been shown to activate latent infection in experimental animals, and it is likely that this can occur in humans as well. Although toxoplasma cysts can be transmitted by transfusion of whole blood cells [44] and by oocysts [12], the role of these routes is not known.

Ruskin and Remington [40] reviewed 81 cases of *Toxoplasma gondii* in immunologically impaired hosts. Only one-fourth of the patients had their disease recognized before death. Clinically, the patients with toxoplasma CNS involvement had neurological signs consistent with diffuse encephalopathy with or without seizures, meningoencephalitis, or a progressively enlarging mass lesion [40, 51]. In the patient who presented with a contrast-enhancing ring lesion, the classic CT appearance of a brain abscess, the diagnosis was made by demonstration of extracellular and intracellular tachyzoites and cysts in a stained smear preparation of aspirated material obtained at surgery. In cases of toxoplasma encephalitis, serological diagnosis can be facilitated by having a preoperative serum determination against which to compare results from serum obtained during illness [34, 36]. Of the various serological assays available, the hemagglutination test should not be used, as rising titers may be delayed [54]. Effective treatment is possible with use of the combination of sulfadiazine (or trisulfapyrimidine) and pyrimethamine. Both compounds are known to cross the blood-brain barrier and have been shown to be effective against the potentially lethal meningoencephalitic form of infection [40] as well as toxoplasma brain abscess [30]. In the series reviewed by Ruskin and Remington [40], 80% of the patients who were treated had marked clinical improvement or complete remission of their symptoms and signs.

Meningitis was most commonly caused by either cryptococcus or listeria and occurred as a secondary site of infection. The primary focus was pulmonary for cryptococcus and a coexisting bacteremia for listeria. Listeria meningitis has also been a major postoperative complication in renal transplants [15, 25, 43, 53] and often follows high-dose corticosteroid treatment for graft rejection [25]. Such an association was seen in 2 of our patients. Establishing the diagnosis of meningitis was less difficult compared with the cases of meningoencephalitis. Examination of CSF was essential. Cryptococcus was demonstrated on India-ink preparations and also grew in culture. However, it is possible that cryptococcus infection of the CNS in compromised hosts may not be detected by either India-ink preparation or culture. In such cases an elevation in the CSF cryptococcal antigen has been diagnostic [45]. Listeria elicited a marked pleocytosis in the CSF of our patients; however, gram stain was negative in all instances. This has been the experience of other investigators as well [27, 50]. Cultures of CSF established the diagnosis in each of our patients.

Appropriate treatment of meningitis in this series led to cure or suppression of the disease process in all except 1 case of disseminated cryptococcosis. In addition to amphotericin B, 5-fluorocytosine [3–5, 52] is now used in the treatment of cryptococcal meningitis, as the combination of these two agents produces fewer failures or relapses, more rapid sterilization of CSF, and less nephrotoxicity than treatment with amphotericin B alone [4]. Ampicillin has now become the drug of choice for treatment of listeria meningitis [27, 28], although both ampicillin and penicillin were used in this series to successfully eradicate the organism.

Rhinocerebral phycomycoses occurred in 2 patients from mucor and rhizopus, respectively. The majority of reported patients with phycomycosis had uncontrolled diabetes or neoplastic disease, particularly lymphoma and leukemia [23, 33]. Transplant recipients are also at risk [18]. This infection begins in the nose and sinuses and progresses to invade the orbit and CNS secondarily. Unfortunately, the diagnosis often is not possible until after a serious complication such as vascular occlusion is detected. A recent report of 13 cases [33] suggests that aggressive surgical therapy with repeated debridement, in combination with intravenous amphotericin B, leads to a fairly high cure rate. Our experience with treatment of this entity in cardiac transplant recipients is limited.

A variety of opportunistic infectious agents invade the CNS of a compromised host. Diagnosis of the etiological agent can be difficult. Early aggressive in-

vestigation of suspected CNS infection is warranted since the wide variety of causative organisms requires precise diagnosis for optimal treatment. Serological testing may be useful in establishing the diagnosis of coccidioidomycosis, cryptococcosis, and toxoplasmosis, but not aspergillosis. Although the CT scan can be helpful, findings may be minimal early in the course of the disease. However, with continued neurological deterioration, CT abnormalities become more marked. New technical advances in CT diagnosis are needed so that early detection of CNS infections, particularly aspergillosis, can be made. Aspergillus was the major cause of morbidity and mortality due to disseminated fungal infections in our cardiac transplant patients and accounted for more deaths from CNS involvement than any other cause.

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