CLINICAL INFECTIOUS DISEASE ARTICLES

Brain Abscess Following Marrow Transplantation: Experience at the Fred Hutchinson Cancer Research Center, 1984–1992

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The etiology of brain abscess in patients undergoing marrow transplantation at the Fred Hutchinson Cancer Research Center in Seattle was assessed in a retrospective review. Fifty-eight patients with histology- or culture-proven brain abscess diagnosed between January 1984 and March 1992 were identified. A fungus was isolated in 92% of cases. *Aspergillus* species were the most prevalent fungi (58% of cases), and *Candida* species were second in frequency (33%); sporadic cases were caused by *Rhizopus, Absidia, Scopulariopsis,* and *Pseudallescheria* species. Bacteria were involved in fewer than 10% of cases. There was no appreciable variation from year to year in the incidence of brain abscess over this period. Aspergillus brain abscess was associated with concomitant pulmonary disease (87% of cases), whereas candida brain abscess often occurred in association with fungemia (63% of cases) or neutropenia (63%). Mortality was high (97%); the risk of death was unrelated to etiology or therapeutic regimen. Since the etiology of brain abscess in patients undergoing marrow transplantation is primarily fungal, the development of better antifungal therapeutic and/or prophylactic modalities is warranted.

Marrow transplantation is effective for the treatment of many hematologic conditions, including aplastic anemia and leukemia. The use of aggressive conditioning regimens that result in prolonged neutropenia and of immune-modulating agents (to prevent graft-vs.-host disease, or GVHD) places patients at risk for opportunistic infection. Many infections following marrow transplantation occur at times that are predictable on the basis of the patient's immune status and the pace of immunologic recovery [1]. Recognition of these patterns among marrow transplant recipients has been helpful in the development of prophylactic antimicrobial regimens that have reduced the incidence and severity of viral, bacterial, and fungal infections [2–4].

The diagnosis and management of brain abscess can be challenging for the physician. Undiagnosed brain abscess is universally fatal [5]. Mortality has been significantly reduced (to 5%–20%) with the use of antimicrobial agents [6–12] and computerized tomography (CT) [13, 14]. Outside the setting of marrow transplantation, patients with brain abscess present with the triad of headache, fever, and neurological change [5]. Predisposing conditions include sinus disease, pulmonary infection, dental disease, infectious endocarditis, congenital heart disease, and immunosuppression [5, 6, 15]. The single pathogens found in 50%–70% of brain abscesses include streptococci, Enterobacteriaceae, and anaerobic bacteria [5, 16, 17]. Recommended treatment consists of the administration of parenteral antibiotics and (when feasible) surgical intervention [12, 18].

The etiology of brain abscess in some immunocompromised patients has been defined. *Toxoplasma gondii* and *Cryptococcus neoformans* are common causes of brain abscess in patients infected with human immunodeficiency virus (HIV) [19–21]. *Aspergillus* species and *C. neoformans* are the primary etiologic agents in kidney or liver transplant recipients [22–24]. Brain abscesses in heart and heart-lung transplant recipients are likely to be due to *Aspergillus* species or *T. gondii* [25–27]. Previous reviews of neurological complications of marrow transplantation have indicated that brain abscess is uncommon in this population [28–30]. However, these reviews have not gone into great detail concerning the etiology and incidence of brain abscess in these patients. The present report describes the etiology, presentation, predisposing conditions, and outcome of brain abscess

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in marrow transplant recipients at the Fred Hutchinson Cancer Research Center in Seattle from 1984 to 1992.

Methods

Case selection. A retrospective review of marrow transplant recipients at the Fred Hutchinson Cancer Research Center was conducted. Ninety-one patients with possible brain abscess diagnosed between January 1984 and March 1992 were identified by review of all brain biopsy reports, all autopsy reports, and all records of patients with a discharge diagnosis code indicating brain abscess or other brain pathology. A case of brain abscess was defined by histologic results of a brain biopsy or autopsy that were diagnostic of brain abscess and clinical data suggesting onset after marrow transplantation. On the basis of these criteria, 58 of the 91 patients initially identified were included in the study. The other 33 patients were excluded for the following reasons: 6 patients did not undergo marrow transplantation, 2 patients had brain lesions before marrow transplantation, 4 patients underwent a limited autopsy or brain biopsy—or none at all—and were only presumed to have brain abscess, and 21 patients had other types of brain pathology (encephalitis in 6 cases, meningitis in 4, stroke in 3, subdural hematoma in 2, intracerebral hemorrhage in 2, Ommaya reservoir dysfunction in 1, CNS malignancy in 1, hematopoiesis in 1, and gliosis in 1).

Definitions and data collection. The demographic data evaluated included those on underlying disease, HLA match, and GVHD. The potential risk factors assessed were conditioning regimen, presence of endocarditis, intrathecal therapy, presence of an Ommaya shunt, maximal dose of steroids, and use of prophylactic systemic antibiotics, laminar airflow rooms, and colony-stimulating factors. The date of diagnosis was defined as the date of onset of symptoms or—if there were no symptoms—the date of positive findings in an imaging study or at autopsy. The laboratory values reported were those documented on the date of diagnosis.

In most cases the etiology of brain abscess was determined by culture of tissue obtained at biopsy or autopsy. In cases with negative culture results, the infecting organism was identified by its histologic appearance.

Patients with macroscopic disease had evidence of brain abscess on radiological evaluation; patients with microscopic disease had no such evidence. Patients who did not undergo radiological evaluation were not included in this subset analysis.

The cumulative dose of antibiotics (including amphotericin B) was determined, and the amounts given before and after diagnosis were ascertained. The number of days until death was counted from the date of diagnosis. Statistical analyses were conducted by means of the χ^2 and Wilcoxon two-sample tests.

Table 1. Etiology of brain abscess, following marrow transplantation.

Organism	No. of patients*
Fungi	57
Aspergillus	33
fumigatus	19
flavus	3
terreus	1
Species unknown	10
Candida	19
albicans	15
tropicalis	2
Species unknown	2
Rhizopus species	2
Absidia species	1
Pseudallescheria boydii	1
Scopulariopsis species	1
Bacteria	4
Clostridium species	1
Enterobacter cloacae	1
Pseudomonas aeruginosa	1
Xanthomonas maltophilia	1
Parasites	1
Toxoplasma gondii	1
Total	62

* Four patients had abscesses caused by two organisms (*Aspergillus* and *Candida*, three patients; *Enterobacter* and *Candida*, one patient).

Results

Etiology. Sixty-two pathogens were identified in the 58 cases of brain abscess (table 1). Fungal pathogens accounted for the majority of isolates (57 of 62; 92%). *Aspergillus* and *Candida* species, the most common fungi, were isolated from 53% and 31% of all cases, respectively. Other fungi isolated included *Rhizopus* species (two cases) and *Absidia* species, *Pseudallescheria boydii*, and *Scopulariopsis* species (one case each). Four patients had bacteria isolated from the brain abscess: *Pseudomonas aeruginosa*, *Xanthomonas maltophilia*, *Enterobacter cloacae*, and *Clostridium* species were isolated from one case each. One patient had brain abscess caused by the parasite *T. gondii*. A single pathogen was identified in 54 cases, whereas two organisms were found in the remaining four cases.

Demographic characteristics and risk factors. The demographic characteristics of the 58 patients with brain abscess are outlined in table 2. Because of the high incidence of brain abscess due to *Aspergillus* and *Candida*, data on the subgroups of patients infected with these organisms are presented separately. There were no apparent differences among groups in terms of age, underlying disease, HLA compatibility, or time of onset or diagnosis of infection relative to transplantation. In general, brain abscess developed later than the more common fungal diseases that follow marrow transplantation [31]. This later onset may reflect a need for

Table 2. Demographic characteristics of patients with brain abscess following marrow transplantation.

Characteristic	Value for indicated group		
	Total (n = 58)	*Aspergillus* (n = 33)	*Candida* (n = 19)
Age in y: mean (range)	31 (6–65)	30 (6–55)	29 (8–56)
Sex: M/F	36/22	17/16	15/4
Underlying disease: no. (%)			
ALL	13 (22)	6 (18)	5 (26)
AML	23 (40)	14 (42)	8 (42)
CML	11 (19)	6 (18)	3 (16)
Lymphoma	3 (5)	1 (3)	3 (16)
Multiple myeloma	2 (3)	0 (. . .)	0 (. . .)
Aplastic anemia	3 (5)	3 (9)	0 (. . .)
Other	3 (5)	3 (9)	0 (. . .)
HLA match: no. (%)			
Autologous graft	2 (3)	1 (3)	0 (. . .)
Matched graft	33 (57)	18 (55)	10 (53)
Unrelated donor	11 (19)	7 (21)	2 (11)
Mismatched donor	12 (21)	7 (21)	7 (37)
Acute GVHD: no. (%)			
Present	34 (59)	21 (64)	11 (58)
Not present	24 (41)	12 (36)	8 (42)
Days from transplantation to onset of symptoms or diagnosis: mean (range)	78 (3–502)	77 (6–300)	63 (10–270)

NOTE. ALL = acute lymphocytic leukemia; AML = acute myelocytic leukemia; CML = chronic myelocytic leukemia; GVHD = graft-vs.-host disease.

additional time for the development of a deep CNS infection. There was no apparent relation between the etiology of brain abscess and the conditioning regimen or the steroid dose used. Neither was a relation evident between etiology and the presence of infectious endocarditis, the use of intrathecal methotrexate, the presence of an Ommaya shunt, the use of prophylactic systemic antibiotics, the use of laminar airflow rooms, or treatment with colony-stimulating factors.

Sites of infection at diagnosis. Nine patients with brain abscess underwent brain biopsy. Histologic studies resulted in the diagnosis and the identification of the etiologic agent in all of these cases. *Aspergillus* species was identified in seven cases, *Rhizopus* species in one, and *T. gondii* in one. Cultures of two biopsy specimens were positive—one for *Aspergillus fumigatus* and one for *Rhizopus* species.

Of the 10 lumbar punctures performed, five revealed neutrophilic pleocytosis (4–999 white blood cells/mm^3); findings for the other five CSF samples were within normal limits. One patient with candidal brain abscess had a CSF culture that was positive for *Candida albicans*.

Twelve of the 19 patients with candidal brain abscess were fungemic at the time of diagnosis. No other patients had blood cultures positive for the same pathogen found in the brain abscess. Sputum culture revealed the etiology of the brain abscess in eight cases—seven due to *Aspergillus* species and one due to *Candida* species. Sinus cultures yielded *Candida* in one case and *Rhizopus* in one, with the same organism found in the brain abscess. Other infected sites at the time of diagnosis included the lungs (three cases), the skin (two), the chest-tube drainage (one), and the eye (one) for *Aspergillus* species; the skin for *Candida* and *Absidia* species (one case each); and the lungs for *P. boydii* (one case). In summary, before death 33% of patients with aspergillus brain abscess also had *Aspergillus* detected in the lungs, and 63% of patients with brain abscess due to *Candida* species were fungemic.

Sites of infection at autopsy. An autopsy was performed in 54 cases (93%), and a detailed neuropathological report was prepared in most instances (table 3). Patients had multiple abscesses throughout the brain parenchyma. *Aspergillus* was cultured from brain tissue in more than 50% of cases and was frequently found (by histologic examination) in other organs, such as the lungs (87% of cases), the heart (37%), and the kidney (35%). The majority of brain abscesses due to *Candida* species were associated with involvement at wide-

Table 3. Autopsy findings in 54 cases of brain abscess following marrow transplantation.

Finding	No. (%) of cases with finding in indicated group*		
	Total: 54 (93)	*Aspergillus*: 31 (94)	*Candida*: 19 (100)
No. of lesions			
1	17	5	9
2	5	4	1
3	6	5	2
>3	26	17	7
Location of lesions			
Frontal	30	20	8
Parietal	37	25	10
Temporal	21	12	6
Occipital	27	19	6
Basal ganglial	24	12	10
Cerebellar	17	10	0
Other infected sites†			
Brain			
Histology	48 (89)	29 (94)	14 (74)
Culture	37 (69)	17 (55)	12 (63)
Lung	47 (87)	27 (87)	15 (79)
Kidney	25 (46)	11 (35)	13 (68)
Heart	26 (48)	12 (39)	12 (63)
Spleen	17 (31)	4 (13)	11 (58)
Liver	13 (24)	3 (10)	9 (47)
Intestine	13 (24)	6 (19)	4 (21)
Sinus	7 (13)	5 (16)	0 (. . .)
Skin	3 (6)	1 (3)	2 (11)

* Numbers following group designations indicate numbers of autopsies (percentage of all cases).

† Additional sites of aspergillus infection were the thyroid (2 cases), the eyes (2), and the thymus (1). Additional sites of candidal infection were the bone marrow and the thymus (1 case each).

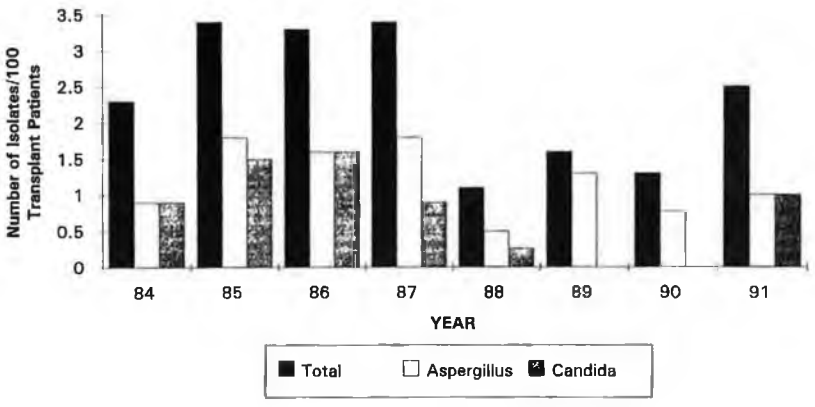

Figure 1. Incidence of brain abscess at the Fred Hutchinson Cancer Research Center from 1984 through 1991.

spread sites, including the lungs, kidney, heart, spleen, and liver. In the two cases of brain abscess due to *Rhizopus*, adjacent sinus disease was documented. Bacterial brain abscess was associated with disseminated disease (due to *E. cloacae* or *Clostridium* species) or with pulmonary infections (due to *P. aeruginosa* or *X. maltophilia*).

Incidence. The annual number of brain abscesses ranged from 4 in 1984 to 10 in both 1987 and 1991; the number of transplantations performed annually increased from 219 in 1984 to 396 in 1991. Brain abscess developed in ~1 of every 49 transplant recipients, with no significant change in incidence over the study period. No cases of brain abscess due to *Candida* species occurred in 1989–1990; in contrast, the incidence of brain abscess due to *Aspergillus* species did not vary substantially over the study period (figure 1).

Clinical features (table 4). The most prevalent physical finding was fever (83% of cases), with an average temperature of 39.2°C (range, 37.1°C–42.2°C) at presentation. Altered mental status, cranial nerve abnormality, and hemiparesis were the most common neurological findings at presentation. Headache, nausea, and vomiting were uncommon. Nearly one-third of patients with brain abscess due to *Candida* had no signs or symptoms; these infections were diagnosed post-mortem. Sixty-five percent of patients with neurological symptoms had brain abscess due to *Aspergillus*. Patients with brain abscess due to *Candida* tended to have slightly higher serum levels of creatinine than the study population as a whole (3.0 vs. 2.0 mg/dL; $P = .0014$); moreover, patients with candidal abscesses were more likely to be neutropenic than those infected with *Aspergillus* (63% vs. 30%; $P = .02$). Patients with other causes of brain abscess had no unique clinical or laboratory features.

Table 4. Presenting signs and symptoms of patients with brain abscess following marrow transplantation.

Sign/symptom	No. (%) of patients with manifestation in indicated group		
	Total ($n = 58$)	*Aspergillus* ($n = 33$)	*Candida* ($n = 19$)
Fever (>38.5°C)	48 (83)	28 (85)	16 (84)
Altered mental status	29 (50)	17 (52)	8 (42)
Cranial nerve abnormality	18 (31)	9 (27)	5 (26)
Hemiplegia	15 (26)	11 (33)	2 (11)
Seizure	13 (22)	10 (30)	3 (16)
Headache	4 (7)	2 (6)	1 (5)
Papilledema	2 (3)	1 (3)	1 (5)
Nausea/vomiting	1 (2)	1 (3)	0 (. . .)
None	9 (16)	1 (3)	6 (32)

Radiological findings. CT of the head was performed in 37 cases and yielded abnormal findings in 26 (70%) of these cases. Magnetic resonance imaging (MRI) of the head was conducted in nine cases, with abnormal results in eight. MRI generally detected more abnormal foci than CT; in one case, a single lesion visible by MRI had not been evident on prior CT. The majority of patients with brain abscess due to *Aspergillus* had at least one abnormal scan (26 of 31 cases, or 84%). Aspergillus brain abscesses were typically multifocal, hypodense, and nonenhancing, with little mass effect (figure 2). The majority of patients with brain abscess due to *Candida* had normal scans (6 of 10 cases, or 60%). Further radiological features of brain abscess in marrow transplant recipients have been reviewed elsewhere [32].

Patients with macroscopic disease—i.e., abnormal scans—presented later after transplantation (mean, 98 days; range, 6–300 days) than did those with microscopic disease —i.e., normal scans (mean, 38 days; range, 10–113 days). These two groups of patients presented with similar signs and symptoms and had similar clinical courses. In all nine cases in which the patient presented with seizures and had a radiological scan, the scan showed evidence of macroscopic disease due to *Aspergillus*.

Outcome. The outcome of brain abscess following marrow transplantation was poor. Fifty-six of 58 patients died shortly after diagnosis (mean, 4.2 days; range, 0–15 days). One patient with brain abscess due to *T. gondii* survived for 126 days after treatment with pyrimethamine and sulfadiazine but then had a relapse of acute myelocytic leukemia and died. The other survivor had candidal brain ab-

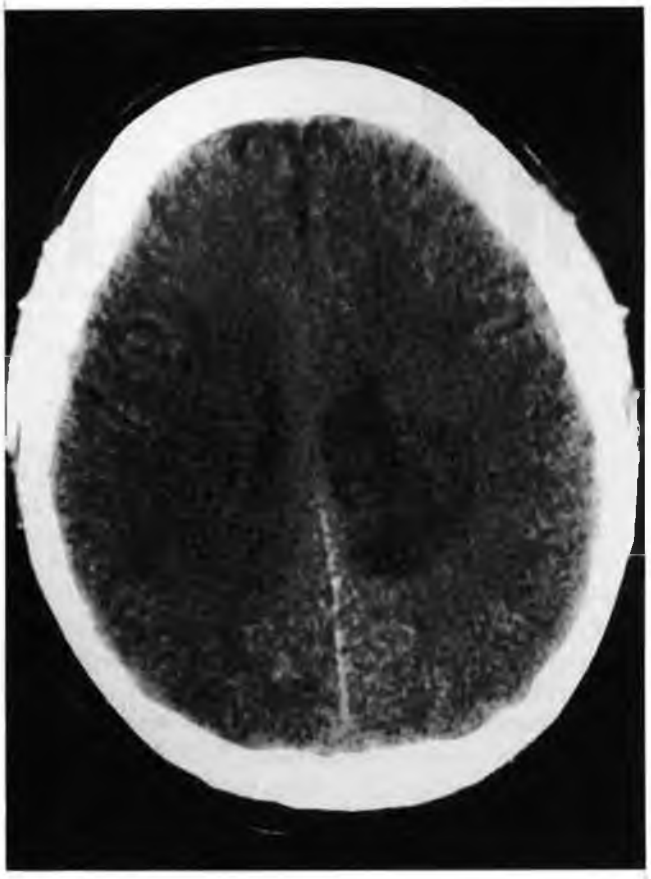

Figure 2. CT of the brain of a typical patient with aspergillus brain abscess. A large hypodense lesion is evident in the parieto-temporal region.

scess and was treated with 1 g of amphotericin B. This patient survived for 38 days before dying of congestive heart failure. Autopsy of the brain revealed hyphal elements consistent with candidal brain abscess, but a culture was negative. It is not clear whether these findings represented active or resolving disease.

Treatment. Multiple therapeutic modalities were used in these cases, including the administration of antibacterial and antifungal agents as well as surgical procedures. Antimicrobial treatment was appropriate (as judged by the susceptibility of the isolate) in the majority of cases (93%), although such treatment did not alter outcome. Seven patients developed CNS disease while receiving appropriate therapy. These patients all had evidence of disseminated fungal disease (due to *Aspergillus* in four instances and *Candida* in three); they were treated for a mean of 36 days (range, 20–48 days) before the development of CNS symptoms or death. Since the timing of initial seeding of a brain abscess is not known, it is unclear whether these cases represented the inevitable natural history of brain abscess or the unusual progression of disease despite appropriate therapy.

Amphotericin B was administered to the majority (81%) of patients. Those treated with amphotericin B after diagnosis survived slightly longer (from 4.2 to 6.4 days) than those who did not receive this agent, and survival was further prolonged (i.e., to a mean of 10.8 days) among patients given >500 mg. Other antifungal regimens included intrathecal amphotericin B (one case), amphotericin colloidal dispersion (two cases), fluconazole (one case), itraconazole (one case), flucytosine (two cases), and rifampin (two cases). None of these agents offered any apparent benefit. Attempts to augment the immune response with macrophage colony-stimulating factor (two cases) or granulocyte-macrophage colony-stimulating factor (one case) had no impact on survival. Surgical procedures (biopsy, drainage, or excision) were performed in 11 instances. A slight prolongation of survival (from 4.2 to 7.2 days) was noted; this effect was even more marked among patients who were also treated with amphotericin B (mean, 8.6 days). No bleeding complications of surgery were noted.

Discussion

Brain abscesses in immunocompetent individuals are usually due to bacterial pathogens [5, 15, 16]. In this study the majority (92%) of cases of brain abscess in marrow transplant recipients were due to a single fungal pathogen. Davis, Patchell, and colleagues [28, 29] found *Aspergillus* to be the most common cause of brain abscesses in marrow transplant recipients. The low rate of involvement of bacterial pathogens in such abscesses may be due to routine prophylaxis during episodes of neutropenia with antibacterial agents that penetrate the CNS to at least a limited extent.

Lung abscess, infectious endocarditis, dental disease, sinusitis, and otic infection predispose to the development of brain abscess in immunocompetent individuals [5]. In this study patients with aspergillus brain abscess were found to have evidence of coexisting aspergillus pulmonary infection either at autopsy (87% of cases) or on culture of sputum, lung tissue obtained at biopsy, or chest-tube drainage (33%). Brain abscess due to *Candida* was often seen in conjunction with fungemia; presumably these cases involved the hematogenous seeding of multiple organs, including the brain. Similarly, candidal brain abscess in solid-organ transplant recipients usually reflects disseminated disease [22, 25]. Both patients with brain abscess due to *Rhizopus* had contiguous sinus infection with direct invasion of the brain. No cases of brain abscess were thought to be due to dental disease; a thorough dental examination was routinely performed before transplantation.

Headache, fever, and neurological alteration are the most common presenting features of brain abscess in immunocompetent patients [11–17]. Likewise, solid-organ transplant recipients and HIV-infected individuals often present with fever and headache [20, 22]. Although in this study fever was common among marrow recipients (83%), head-

ache was reported by only 7% of these patients. Neurological abnormalities, such as altered mental status, cranial nerve abnormality, and hemiparesis, were more prevalent. Brain abscess was discovered at autopsy in nine cases, six of which were due to *Candida* species.

For the most part, laboratory data were not helpful in diagnosing brain abscess. However, several parameters may be helpful in predicting the etiology of a brain abscess. Patients with brain abscesses due to *Candida* species tended to be neutropenic (63%) and fungemic (63%) and to have normal results in CNS imaging studies (60%), possibly because of a microscopic miliary pattern too small to be seen on CT. In contrast, many patients with brain abscess due to *Aspergillus* were engrafted (70%), had evidence of pulmonary disease (48%), and had abnormal results in CNS imaging studies (84%), with large single or multiple lesions [31]. The fact that no patients with aspergillus brain abscesses were found to be fungemic likely reflects an inability to identify this organism in the blood.

The outcome of brain abscess following marrow transplantation is poor. In our study survival tended to be prolonged by treatment with amphotericin B, but antifungal therapy had no clinically relevant impact on outcome. At autopsy, the majority of infected tissues that had been identified histologically were culture-positive. This observation suggests that either amphotericin B did not reach fungicidal levels at the infected site or patients did not live long enough for the drug to work. The slight increase in the duration of survival among patients undergoing surgical treatment and among those treated with amphotericin B may have been due to the degree of life support used rather than to therapy. Few patients with aspergillus brain abscess survive [32], and most of those who do are immunocompetent. One liver transplant recipient and one renal transplant recipient are among the reported survivors. Survivors of aspergillus brain abscess have been treated aggressively with surgical excision of the abscess cavity and extensive administration of amphotericin B. Surgical treatment of marrow transplant recipients is not likely to be effective because multifocal disease is the norm. Whether early and aggressive treatment of brain abscess following marrow transplantation can result in long-term survival is not yet known.

Seven patients with disseminated fungal infection developed CNS disease despite appropriate treatment. This phenomenon may represent the expected clinical course of a deep-seated CNS infection in this population. On the other hand, resistant fungal strains may have developed during treatment; unfortunately, the fungal isolates that grew in culture were not tested for drug susceptibility. Finally, these cases may indicate that existing regimens for the treatment of disseminated fungal disease are not adequate.

This retrospective study examined the experience with brain abscess following marrow transplantation at the Fred Hutchinson Cancer Research Center. Although a thorough search was conducted in an effort to identify all cases of brain abscess during the period from January 1984 through March 1992, it is possible that some cases were not discovered—e.g., mild cases in which no brain biopsy or autopsy was conducted and infection resolved with empirical therapy. Thus, both incidence and survival may have been underestimated.

In summary, brain abscess following marrow transplantation at this institution is caused mainly by fungi, the most common of which are *Aspergillus* and *Candida* species. These data imply that, while the results of brain biopsy are being awaited, aggressive antifungal therapy for suspected brain abscess in marrow transplant recipients may be of benefit. The continuing high mortality from brain abscess of all causes in this setting, despite the routine use of amphotericin B, underscores the need for better antifungal treatment or prophylaxis in marrow transplantation.

References

1. Meyers JD. Infections in marrow transplant recipients. In: Mandell GL, Douglas RG Jr, Bennett JE, eds. Principles and practice of infectious diseases. 3rd ed. New York: Churchill Livingstone, 1990:2291–4.
2. Pizzo PA, Commers J, Cotton D, et al. Approaching the controversies in antibacterial management of cancer patients. Am J Med 1984;76:436–48.
3. Goodrich JM, Mori M, Gleaves CA, et al. Early treatment with ganciclovir to prevent cytomegalovirus disease after allogeneic bone marrow transplantation. N Engl J Med 1991;325:1601–7.
4. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med 1992;326:845–51.
5. Chun CH, Johnson JD, Hofstetter M, Raff MJ. Brain abscess. A study of 45 consecutive cases. Medicine 1986;65:415–31.
6. Brewer NS, MacCarty CS, Wellman WE. Brain abscess: a review of recent experience. Ann Intern Med 1975;82:571–6.
7. Samson DS, Clark K. A current review of brain abscess. Am J Med 1973;54:201–10.
8. Alderson D, Strong AJ, Ingham HR, Selkon JB. Fifteen-year review of the mortality of brain abscess. Neurosurgery 1981;8:1–6.
9. Ingham MR, Selkon JB, Roxby CM. Bacteriological study of otogenic cerebral abscesses: chemotherapeutic role of metronidazole. Br Med J 1977;2:991–3.
10. Seydoux C, Francioli P. Bacterial brain abscesses: factors influencing mortality and sequelae. Clin Infect Dis 1992;15:394–401.
11. Kaplan K. Brain abscess. Med Clin North Am 1985;69:345–60.
12. Mampalam TJ, Rosenblum ML. Trends in the management of bacterial brain abscess: a review of 102 cases over 17 years. Neurosurgery 1988;23:451–8.
13. Rosenblum ML, Hoff JT, Norman D, Weinstein PR, Pitts L. Decreased mortality from brain abscesses since the advent of computerized tomography. J Neurosurg 1978;59:658–68.
14. Whelan MA, Hilal SK. Computed tomography as a guide in the diagnosis and follow-up of brain abscesses. Radiology 1980;135:663–71.
15. Mathisen GE, Meyer RD, George WL, Citron DM, Finegold SM. Brain abscess and cerebritis. Rev Infect Dis 1984;6(suppl 1):S101–6.
16. Richards J, Sisson PR, Hickman JE, Ingham HR, Selkon JB. Microbiology, chemotherapy and mortality of brain abscess in Newcastle-upon-Tyne between 1979 and 1988. Scand J Infect Dis 1990;22:511–8.

17. Wispelwey B, Scheld WM. Brain abscess. Clin Neuropharmacol 1987;10:483–510.
18. Leys D, Christiaens JL, Derambure P, et al. Management of focal intracranial infections: is medical treatment better than surgery? J Neurol Neurosurg Psychiatry 1990;53:472–5.
19. Snow RB, Lavyne MH. Intracranial space-occupying lesions in acquired immune deficiency syndrome patients. Neurosurgery 1985;16:148–53.
20. Levy RM, Bredesen DE, Rosenblum ML, Davis RL. Central nervous system disorders in AIDS. Immunol Ser 1989;44:371–401.
21. de Gans J, Portegies P. Neurological complications of infection with human immunodeficiency virus type 1. A review of literature and 241 cases. Clin Neurol Neurosurg 1989;91:199–219.
22. Conti DJ, Rubin RH. Infection of the central nervous system in organ transplant recipients. Neurol Clin 1988;6:241–60.
23. Bruno A, Adams HP Jr. Neurologic problems in renal transplant recipients. Neurol Clin 1988;6:305–25.
24. Martinez AJ, Estol C, Faris AA. Neurologic complications of liver transplantation. Neurol Clin 1988;6:327–48.
25. Hotson JR, Enzmann DR. Neurologic complications of cardiac transplantation. Neurol Clin 1988;6:349–65.
26. Green M, Wald ER, Tzakis A, Todo S, Starzl TE. Aspergillosis of the CNS in a pediatric liver transplant recipient: case report and review. Rev Infect Dis 1991;13:653–7.
27. Hall WA, Martinez AJ, Dummer JS, et al. Central nervous system infections in heart and heart-lung transplant recipients. Arch Neurol 1989;46:173–7.
28. Davis DG, Patchell RA. Neurologic complications of bone marrow transplantation. Neurol Clin 1988;6:377–87.
29. Patchell RA, White CL III, Clark AW, Berchorner WE, Santos GW. Neurologic complications of bone marrow transplantation. Neurology 1985;35:300–6.
30. Wiznitzer M, Packer RJ, August CS, Burkey ED. Neurological complications of bone marrow transplantation in childhood. Ann Neurol 1984;16:569–76.
31. Meyers JD. Fungal infections in bone marrow transplant patients. Semin Oncol 1990;17(suppl 6):10–3.
32. Hagensee M, Kjos B, Bauwens JE. Radiological manifestations of *Aspergillus* brain abscess in bone marrow transplant (BMT) patients [abstract no 1498]. In: Program and abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, 1992:360.