# Brain Parenchymal Infection in Bone Marrow Transplantation Patients: CT and MR Findings

William T. C. Yuh[1]
Hoang D. Nguyen[1]
Feng Gao[1]
E. Turgut Tali[1]
David J. Fisher[1]
Nina A. Mayr[1]
Donald P. Mueller[1]
Yutaka Sato[1]
Michael E. Trigg[2]
Roger Gingrich[3]

**OBJECTIVE. The purpose of this study was to assess the MR and CT appearances of brain infection after bone marrow transplantation and to correlate the appearances with laboratory and pathologic findings.**

**MATERIALS AND METHODS. We retrospectively reviewed the records of seven bone marrow transplant recipients with radiologic evidence of brain infection.**

**RESULTS. Forty-one lesions were detected in seven patients with proved infectious foci outside the brain before brain infection was suspected clinically. Six patients had low total WBC or lymphocyte counts and one patient had normal total WBC and lymphocyte counts. Most lesions in patients with low total WBC or lymphocyte counts showed no appreciable edema or contrast enhancement. However, all lesions detected in the patient with normal total WBC and lymphocyte counts showed marked vasogenic edema and ring enhancement.**

**CONCLUSION. Brain infection in bone marrow transplant recipients during immunosuppression exhibited MR characteristics different from those typically seen in immunocompetent patients. This appearance may be related to a diminished immunologic/inflammatory response.**

*AJR* **1994;162:425–430**

On MR images and CT scans, brain parenchymal infections in immunocompetent patients are usually characterized by marked vasogenic edema and intense enhancement after IV administration of contrast material [1–5]. Earlier CT studies of brain parenchymal infection in immunocompromised patients showed diminished contrast enhancement [6]. However, MR and CT findings of brain parenchymal infection in bone marrow transplant recipients have not been reported, particularly with regard to the level of vasogenic edema and the degree of contrast enhancement. Our purpose was to study the MR and CT findings of brain infection in bone marrow transplant recipients and to correlate these findings with clinical presentation and laboratory and pathologic results.

## Materials and Methods

MR and CT studies of 10 consecutive bone marrow transplant recipients who had clinical and radiologic findings suggestive of brain infection were reviewed retrospectively. In this study, the trend of low or normal total WBC or lymphocyte counts had to be consistent for at least 10 consecutive days before neuroimaging was performed. Three patients were excluded because the correlating laboratory trend could not be established. Thus, this retrospective study involved seven patients.

The four males and three females 3–45 years old (mean, 24 years) underwent bone marrow transplantation for acute lymphoblastic leukemia (two patients), chronic myelogenous leukemia (two patients), severe aplastic anemia (one patient), refractory anemia (one patient), and non-Hodgkin's lymphoma (one patient). Six patients had low total WBC or lymphocyte counts; the remaining patient had normal total WBC and lymphocyte counts. All patients had nonspecific signs and symptoms suggesting brain infection, including changes in mental status, hemiparesis, dysarthria, lethargy, urinary incontinence, and fever. All patients had evidence of systemic infection (five had aspergillosis proved by blood and spu-

Received March 18, 1993; accepted after revision October 8, 1993.

[1]Department of Radiology, 200 Hawkins Dr., The University of Iowa College of Medicine, Iowa City, Iowa 52242. Address reprint requests to W. T. C. Yuh.

[2]Department of Pediatrics, The University of Iowa College of Medicine, Iowa City, IA 52242.

[3]Department of Internal Medicine, The University of Iowa College of Medicine, Iowa City, IA 52242.

0361–803X/94/1622–0425
© American Roentgen Ray Society

Downloaded from www.ajronline.org by 193.140.39.39 on 03/07/22 from IP address 193.140.39.39. Copyright ARRS. For personal use only; all rights reserved

tum cultures or by skin/nasal mucosa biopsies, one had cytomegalovirus infection, and one had Epstein-Barr virus infection) before brain infection was suspected clinically.

All seven patients had unenhanced MR examinations, and five of the seven had contrast-enhanced MR studies (two patients had studies before the availability of gadopentetate dimeglumine). One patient had five serial MR and/or CT examinations. MR examinations were performed with either a 0.5- or a 1.5-T superconductive scanner. All images were obtained with spin-echo sequences: axial and coronal T1-weighted images with 350–750/20–60 (TR/TE) and two to four excitations and axial and coronal T2-weighted images with 2000–2300/90–100 and one or two excitations. Contrast-enhanced images were obtained immediately after IV injection of gadopentetate dimeglumine (0.1 mmol/kg; Magnevist, Berlex, Wayne, NJ) by using the same parameters as for unenhanced T1-weighted images. Contrast-enhanced CT examinations (150 ml of iodinated contrast material, drip infusion) were performed in one patient on a Somatom DRH scanner (Siemens, Erlangen, Germany) with 8-mm contiguous axial slices and a 2-mm interslice gap.

All examinations were reviewed by four neuroradiologists with attention to the size, location, and number of lesions, the amount of edema (trend), and the degree of contrast enhancement. Vasogenic edema was defined as abnormal white matter signal intensity surrounding the lesion and extending along the white matter tract with fingerlike projections. Clinical findings and laboratory results at the time of each neuroimaging procedure also were reviewed with special attention to the clinical presentation, including fever, mental status, neurologic deficits, and laboratory results, especially the total WBC and differential counts. Additionally, all available pathologic records were reviewed.

## Results

A total of 41 lesions were detected in seven patients, with lesion diameters of 5–10 mm (nine lesions), 10–15 mm (five lesions), 15–20 mm (13 lesions), and greater than 20 mm (14 lesions). Three patients had cerebral aspergillosis abscess proved by stereotaxic biopsies or surgical resection (22 lesions). One patient had systemic aspergillosis with multiple CSF cultures growing aspergillosis (five lesions). Another had partial lung resection for aspergillosis (three lesions). This patient had rapid clinical deterioration and subsequently died. Owing to family wishes, no autopsy was performed. The patient with CNS cytomegalovirus and the one with Epstein-Barr virus were treated empirically for fungal infections (11 lesions) and improved clinically.

Thirty-five lesions were located in or near the corticomedullary junction (Figs. 1–5), five were in the basal ganglia, and one was in the deep white matter. Thirty-eight lesions were detected on MR images of patients with low total WBC or lymphocyte counts, and 28 of these lesions (four of six patients) were studied with contrast-enhanced MR imaging (Figs. 1–4). Relative to surrounding tissue, unenhanced MR studies of all 38 lesions showed hyperintensity on T2-weighted images (Figs. 1–4) and mild hypointensity (three lesions) or isointensity (35 lesions) on T1-weighted images. Thirty-seven of 38 lesions showed no significant vasogenic

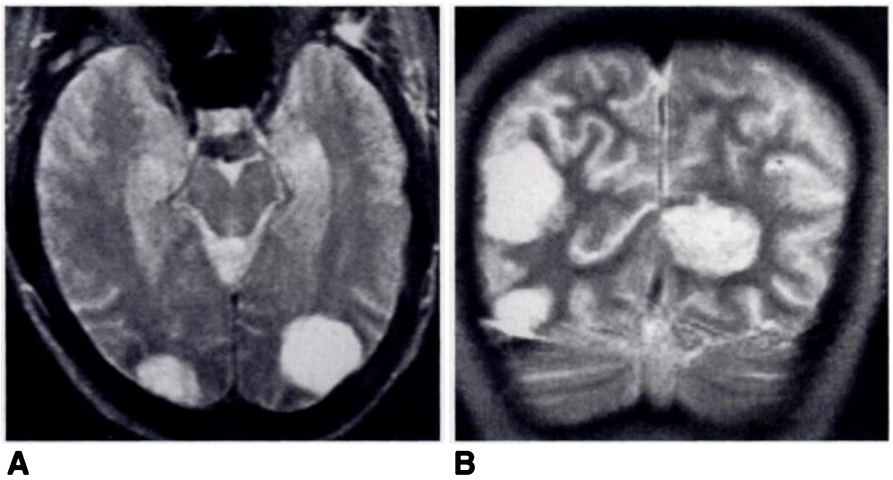



**Fig. 1.—Multiple lesions in corticomedullary junction with minimal edema in a patient with a low WBC count after bone marrow transplantation.**

***A* and *B*, Axial (*A*) and coronal (*B*) T2-weighted MR images (2000/100, one excitation) show multiple hyperintense occipital lesions. Note relatively well defined margins of these lesions, lack of associated vasogenic edema, and normal appearance of subcortical white matter (U fiber).**

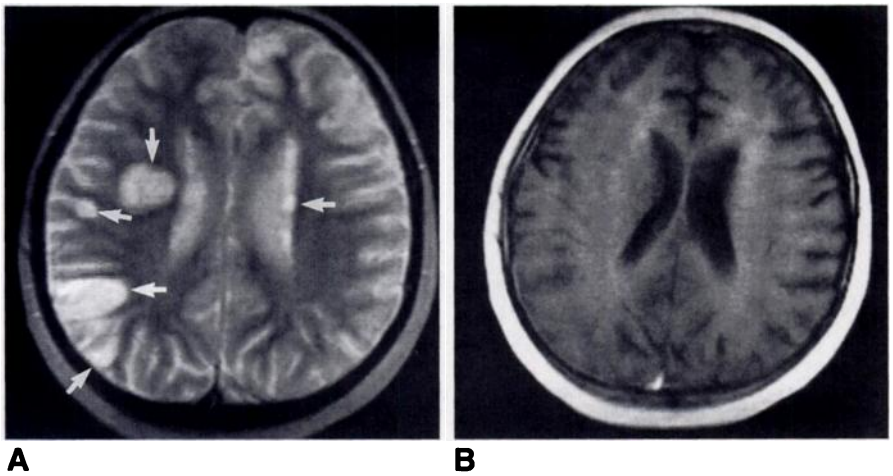



**Fig. 2.—Absence of vasogenic edema and contrast enhancement in a patient with a low WBC count after bone marrow transplantation.**

***A*, Unenhanced axial T2-weighted MR image (2000/100, one excitation) shows multiple hyperintense lesions (*arrows*) in corticomedullary junction and in body of left caudate nucleus. No significant abnormal signal changes are seen in white matter, particularly in subcortical region. Stereotaxic biopsies of three of these lesions revealed aspergillosis.**

***B*, Contrast-enhanced axial T1-weighted MR image (350/20, one excitation) shows no apparent enhancement of these lesions, despite motion artifact.**

Downloaded from www.ajronline.org by 193.140.39.39 on 03/07/22 from IP address 193.140.39.39. Copyright ARRS. For personal use only; all rights reserved

Downloaded from www.ajronline.org by 193.140.39.39 on 03/07/22 from IP address 193.140.39.39. Copyright ARRS. For personal use only; all rights reserved

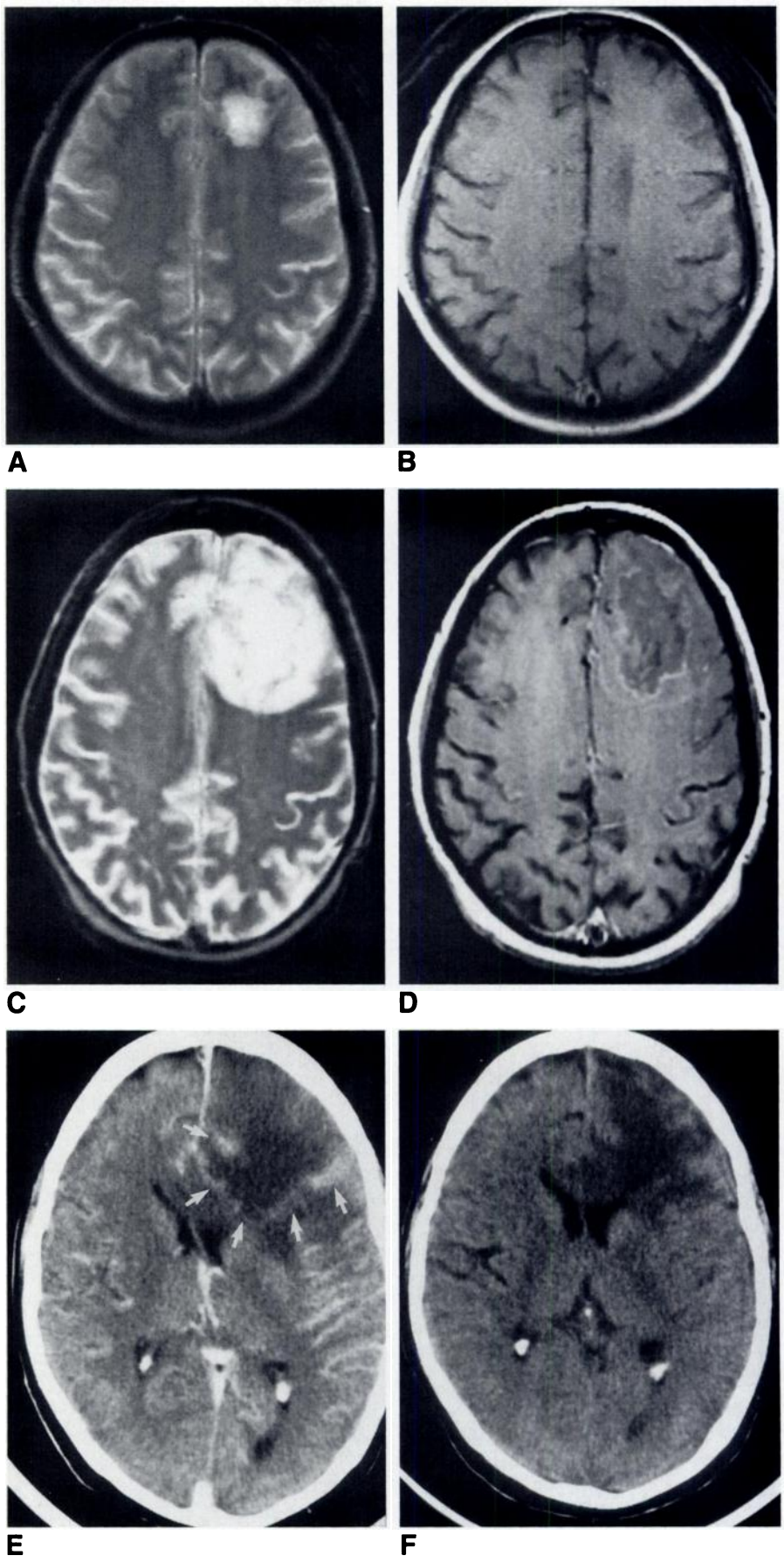



**Fig. 3.—Progressive development of vasogenic edema and contrast enhancement while WBC count returns to normal in a patient who had bone marrow transplantation.**

***A*, Axial T2-weighted MR image (2000/100, one excitation) 35 days after bone marrow transplantation shows lesion in left frontal lobe that is hyperintense relative to surrounding tissue. No apparent vasogenic edema is noted while total WBC or lymphocyte count is low.**

***B*, Contrast-enhanced T1-weighted MR image (350/20, one excitation) shows no enhancement of lesion, but enhancement is noted in sagittal sinus.**

***C* and *D*, Unenhanced axial T2-weighted (*C*) and contrast-enhanced axial T1-weighted (*D*) MR images 43 days after transplantation, as total WBC or lymphocyte count returns to low-normal level. Unenhanced image (*C*) shows development of mass effect and evidence of edema (abnormal signal in subcortical white matter and relatively intact cortex) associated with left frontal lesion. Mild peripheral enhancement is seen after administration of contrast material (*D*).**

***E* and *F*, Enhanced (*E*) and unenhanced (*F*) CT scans obtained 55 days after initial study, when total WBC or lymphocyte count was normal, again show increased mass effect, vasogenic edema, and contrast enhancement (*arrows*). This was proved by surgery to be aspergillosis abscess.**

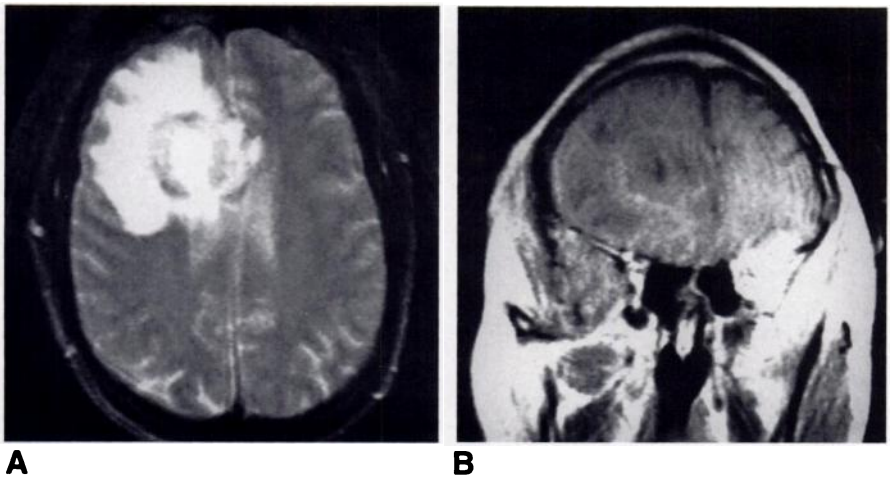



**Fig. 4.—Extensive vasogenic edema and mild contrast enhancement in a patient with low WBC count after bone marrow transplantation.**

***A*, Unenhanced axial T2-weighted MR image (2000/100, one excitation) shows massive vasogenic edema.**

***B*, Coronal T1-weighted MR image (450/20, two excitations) after administration of contrast administration shows mild ring enhancement. This patient had four additional lesions that showed no evidence of vasogenic edema or enhancement.**

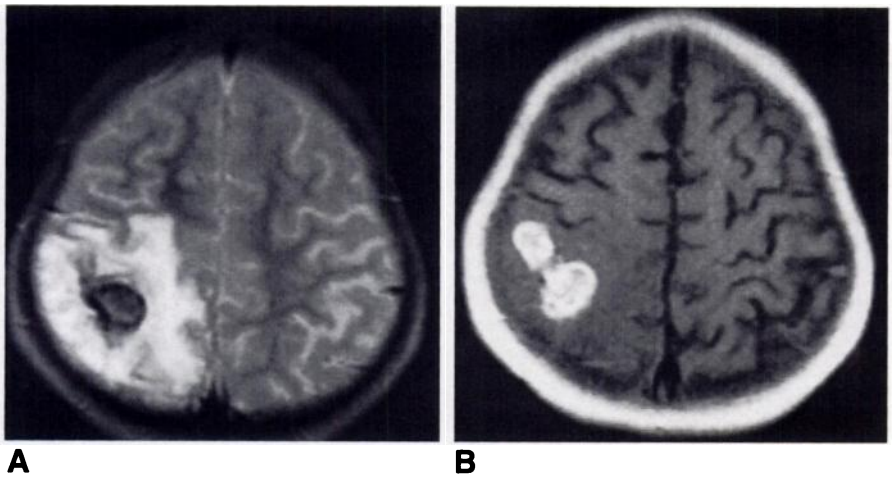



**Fig. 5.—Extensive vasogenic edema and intense contrast enhancement in a patient with normal WBC count after bone marrow transplantation.**

***A*, Unenhanced axial T2-weighted MR image (2000/100, one excitation) shows a right parietal abscess with vasogenic edema and evidence of hemorrhage.**

***B*, Contrast-enhanced T1-weighted MR image (350/20, two excitations) shows intense enhancement. These findings of brain abscess in a patient with normal WBC counts after bone marrow transplantation are the same as those in immunocompetent patients. This was proved by surgical resection to be aspergillosis abscess.**

edema (Figs. 1–3) on the unenhanced studies, and 27 of the 28 lesions studied with contrast-enhanced MR imaging showed no apparent contrast enhancement (Figs. 2B and 3B). Only one of 28 lesions showed vasogenic edema and mild contrast enhancement (Fig. 4). This patient had four other lesions that showed no significant vasogenic edema or contrast enhancement. The one patient (Fig. 3) with five serial MR and CT examinations initially had no evidence of vasogenic edema or contrast enhancement, but subsequently had progressive vasogenic edema and peripheral enhancement that correlated with the recovery of WBC counts, especially the lymphocyte count, to normal levels. Contrast-enhanced CT scans showed massive vasogenic edema, mass effect, and ring-enhancing lesions with necrotic centers. This was proved to be an aspergillosis abscess by surgical resection. This patient eventually died of brain herniation caused by massive vasogenic edema after the WBC count had completely returned to a normal level. This mechanism was suspected clinically because the patient was responding to the antifungal medications and no progression was evident clinically prior to the time of death.

A total of three lesions were detected in the one patient with normal total WBC and lymphocyte counts. Unenhanced MR studies of one lesion showed areas with hyperintensity on T1-weighted images and hypointensity on T2-weighted images, suggestive of hemorrhage (Fig. 5). In addition, all three lesions had marked vasogenic edema and intense contrast enhancement, similar to those found in immunocompetent patients. These lesions were proved by stereotaxic biopsy to be aspergillosis abscesses.

## Discussion

MR and CT have been reported to be effective imaging techniques for the diagnosis of brain infection [1, 2, 7–10]. Brain parenchymal infection usually begins as a focal area of cerebritis that may progress to form an abscess. Some investigators consider these two entities to be a continuum, both stages of an abscess, with cerebritis as the early stage and the capsular form as the late stage [11]. Most agree that, by definition, brain abscess is characterized by an area of liquefaction necrosis containing purulent material that occurs in a region of cerebritis. Because cerebritis and abscess can coexist, it is not always possible to distinguish these two related entities with imaging. For example, microabscesses can be detected by histopathologic techniques but not

Downloaded from www.ajronline.org by 193.140.39.39 on 03/07/22 from IP address 193.140.39.39. Copyright ARRS. For personal use only; all rights reserved

Downloaded from www.ajronline.org by 193.140.39.39 on 03/07/22 from IP address 193.140.39.39. Copyright ARRS. For personal use only; all rights reserved

always with imaging. Nevertheless, on MR and CT images of immunocompetent patients, both cerebritis and abscess stages are characterized by abnormal enhancement associated with vasogenic edema. Cerebritis has homogeneous enhancement, whereas brain abscess (capsular stage) has ring enhancement with a necrotic/purulent center [1–5]. The mechanisms for these changes shown on MR images and CT scans are unknown; however, they are thought to be related to a breakdown of the blood-brain barrier caused by an inflammatory response to the infection within the brain parenchyma [1–5].

The blood-brain barrier is analogous to a selectively permeable membrane that restricts the exchange of certain solutes and contrast agents between the blood plasma and the brain extracellular fluid [12, 13]. This unique barrier may be compromised when an infectious pathogen invades the brain, because it typically elicits an inflammatory response from an immunocompetent host, resulting in breakdown of the blood-brain barrier [3, 14–16]. The integrity of the blood-brain barrier of the tissue surrounding the infection is interrupted, allowing protein and other substances (such as contrast material) to cross the blood-brain barrier into the brain extracellular spaces. Therefore, vasogenic edema and contrast enhancement of the brain abscess are typical MR and CT findings in immunocompetent patients.

Our limited retrospective review of bone marrow transplant recipients, including patients with normal and abnormal WBC counts, showed that most parenchymal infections failed to demonstrate vasogenic edema (37 of 41, 90%) and abnormal contrast enhancement (27 of 31, 87%) on MR images. The mechanism of this phenomenon is unknown and requires further study. One possible explanation is related to the low WBC count resulting in a relatively intact blood-brain barrier around the infection in bone marrow transplant recipients because their immunocompromised status may not enable them to generate an inflammatory response.

After bone marrow transplantation, the body's defense systems are compromised because of damaged oral and gastrointestinal mucosal barriers, loss of integrity of the integument by iatrogenic procedures, impairment of neutrophilic functions, diminished and dysregulated cellular and humoral immune responses, poor opsonization of the pathogen, loss of splenic reticuloendothelial functions, irradiation, and immunosuppression by drugs used against tissue rejection [17]. Therefore, bone marrow transplant recipients are not only susceptible to infection but also lack the normal inflammatory response to combat infection. This is supported by the observation that all but one brain lesion (3%) in patients with low total WBC or lymphocyte counts showed no significant vasogenic edema or contrast enhancement, whereas all lesions in the patient with normal total WBC and lymphocyte counts showed marked vasogenic edema and striking contrast enhancement. This hypothesis may be supported further by the one patient in whom progressive vasogenic edema and abnormal parenchymal enhancement developed during recovery phases of the total WBC and lymphocyte counts (Fig. 3). In addition, the increase in the level of vasogenic edema and intensity of abnormal enhancement appeared to correlate with the total WBC and lymphocyte counts. Furthermore, the presence of abnormal enhancement and vasogenic edema did not relate to the size of the lesion or to the amount of mass effect, but rather to the WBC counts, particularly the lymphocyte counts. This suggests that the development of edema and enhancement may be related predominantly to the immune status of the patients.

Enzmann et al. [6] found that immunosuppressed patients whose brain abscesses showed typical ring enhancement on CT scans survived, whereas patients who had no typical contrast enhancement died. Enhancement of the lesions again suggested a relatively vigorous immunologic response to isolate or encapsulate the offending organisms, resulting in breakdown of the blood-brain barrier, compared with lesions with minimal contrast enhancement [6]. In our study, four of the six patients who had no evidence of enhancement on the initial studies subsequently died, whereas the one patient with vasogenic edema and ring enhancement on the initial studies survived. One of the six patients in whom the WBC count returned to normal and progressive vasogenic edema and minimal ring enhancement developed on follow-up studies subsequently died from cerebral herniation rather than infection (the patient was clinically responding to antifungal medications), possibly because of the improved inflammatory response. This, again, may support the hypothesis that patients with the typical ring enhancement of brain abscesses have a better immune status.

Typically, recovery of the immune system takes at least 4 months after successful bone marrow transplantation. A variety of factors, including the conditioning regimens and graft-vs-host disease or its prophylaxis, can delay this recovery [18]. During the period of profound leukopenia (which may or may not be within the first 4 months), bone marrow transplantation patients may not have classic signs and symptoms of inflammation and characteristic radiologic findings. In our study, six patients had evidence of brain infection within 4 months after transplantation (five had low total WBC or lymphocyte counts and one had normal total WBC and lymphocyte counts). However, one patient with low total WBC and lymphocyte counts had one lesion (out of five lesions) that showed extensive vasogenic edema or mild peripheral enhancement (Fig. 4). The other four lesions in the same patient had no vasogenic edema or enhancement, as seen in other transplantation patients with low WBC counts. The reason for the discrepancy is unclear, but it may relate to the breakdown of the blood-brain barrier due to tissue necrosis.

Although it is true that the malignant tumors of the patients in this series have been reported to metastasize to the brain, the enhancement characteristics observed and the rapid clinical progression (days or weeks) in our patients make it unlikely that these lesions were metastases. Furthermore, brain metastases from non-CNS primaries do not have the blood-brain barrier and should enhance homogeneously regardless of immunologic status.

In summary, our study of brain infection in a limited population of immunocompromised or immune-suppressed bone marrow transplant recipients showed diminished vasogenic edema and contrast enhancement. The cause of this is

unknown but may be related to a diminished immunologic or inflammatory response and a relatively intact blood-brain barrier in these patients. In one patient who had pancytopenia at the initial study but whose total WBC and lymphocyte counts subsequently returned to normal, suggestive of the recovery of the immunologic/inflammatory response, the abscesses exhibited vasogenic edema and contrast enhancement typically seen in immunocompetent patients.

## REFERENCES


1. Grossman RI, Joseph PM, Wolf G, et al. Experimental intracranial septic infarction: magnetic resonance enhancement. *Radiology* **1985**;155:649–653
2. Runge VM, Clanton JA, Price AC, et al. Evaluation of contrast enhanced MR imaging in a brain abscess model. *AJNR* **1985**;6:139–147
3. Wallenfang T, Bohl J, Kretzschmar K. Evolution of brain abscess in cats: formation of capsule and resolution of brain edema. *Neurosurg Rev* **1980**;3:101–111
4. Hossmann K-A, Bothe H-W, Bodsch W, Paschen W. Pathophysiological aspects of blood-brain barrier disturbances in experimental brain tumors and brain abscesses. *Acta Neuropathol* (Berl) **1983**;45[suppl 8]:89–102
5. Greenwood J. Mechanisms of blood-brain barrier breakdown. *Neuroradiology* **1991**;33:95–100
6. Enzmann DR, Brant-Zawadzki M, Britt RH. CT of central nervous system infections in immunocompromised patients. *AJR* **1980**;135:263–267
7. Enzmann DR, Britt RH, Yeager AS. Experimental brain abscess evolution: computed tomographic and neuropathologic correlation. *Radiology* **1979**;133:113–122
8. Brant-Zawadzki M, Enzmann DR, Placone RC Jr, et al. NMR imaging of experimental brain abscess: comparison with CT. *AJNR* **1983**;4:250–253
9. Haimes AB, Zimmerman RD, Morgello S, et al. MR imaging of brain abscesses. *AJNR* **1989**;10:279–291
10. Grossman RI, Wolf G, Biery D, et al. Gadolinium enhanced nuclear magnetic resonance images of experimental brain abscess. *J Comput Assist Tomogr* **1984**;8:204–207
11. Britt RH, Enzmann DR, Yeager AS. Neuropathological and computerized tomographic findings in experimental brain abscess. *J Neurosurg* **1981**; 55:590–603
12. Oldendorf WH. The blood-brain barrier. *Exp Eye Res* **1977**;25[suppl]:177–190
13. Sage MR. Blood-brain barrier: phenomenon of increasing importance to the imaging clinician. *AJNR* **1982**;3:127–138
14. Frank E, Pulver M, de Tribolet N. Expression of class II major histocompatibility antigens on reactive astrocytes and endothelial cells within the gliosis surrounding metastases and abscesses. *J Neuroimmunol* **1986**;12:29–36
15. Austen KF. Disorders due to hypersensitivity and altered immune response. In: Wintrobe MM, Thorn GW, Adams RD, et al., eds. *Harrison's principles of internal medicine*. New York: McGraw-Hill, **1970**:342–348
16. Waksman BH. Delayed hypersensitive reactions: a growing class of immunologic phenomena. *J Allergy Clin Immunol* **1960**;31:468–475
17. Wingard JR. Advances in the management of infectious complications after bone marrow transplantation. *Bone Marrow Transplant* **1990**;6:371–383
18. Lin K-H, Lee M-J, Hwang K-C, Lin K-S, Lee C-Y, Lui LT. Infections in marrow transplant recipients. *J Formos Med Assoc* **1988**;87:721–727


Downloaded from www.ajronline.org by 193.140.39.39 on 03/07/22 from IP address 193.140.39.39. Copyright ARRS. For personal use only; all rights reserved