AIDS-Related CNS Cryptococcosis: Radiologic-Pathologic Correlation

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PURPOSE: This study evaluates the effectiveness of cranial CT and MR in detecting autopsy findings of AIDS-related CNS cryptococcosis. METHODS: Final imaging studies compared with pathology were CT in eight patients (five with contrast) and MR in five patients (all with Gd-DTPA). RESULTS: Neither modality effectively identified cryptococcal meningitis. Punctate hyperintensities were seen in all patients with MR and corresponded pathologically to both perivascular spaces dilated by cryptococcal infection and cryptococcomas. Pathologically, cryptococcomas were more common than dilated perivascular spaces. MR detected more cryptococcomas than did CT, but both modalities underestimated the number of lesions seen at autopsy. Contrast enhancement of cryptococcomas and cryptococcal meningitis was uncommon. CONCLUSIONS: CNS cryptococcosis was more effectively demonstrated by MR than by CT, but both modalities underestimated the pathologic extent of the disease. Cryptococcal lesion contrast enhancement was unusual possibly because of the immunocompromised state of our patients and the unique characteristics of the organism itself.

Index terms: Acquired immunodeficiency syndrome (AIDS); Brain, infection; Radiologic-pathologic correlations


Cryptococcus neoformans is the most common fungus to involve the central nervous system (CNS). This ubiquitous organism typically enters the body via the respiratory tract and then spreads hematogenously from the lungs to the CNS (1). Intracranial cryptococcosis primarily manifests itself as meningitis, although mass lesions can develop (2-11). CNS cryptococcosis is a particularly important neurologic problem in patients with the acquired immunodeficiency syndrome (AIDS) since Cryptococcus neoformans ranks as the third most frequent CNS pathogen in these patients following only the human immunodeficiency virus (HIV) and Toxoplasma gondi (12, 13). AIDS patients are not only at increased risk to develop cryptococcal infection, but they also tend to present with more disseminated forms of the infection (14).

Several reports have been written describing computed tomography (CT) and magnetic resonance imaging (MR) findings in patients with CNS cryptococcosis (6, 7, 9, 15-18). Two recent large series have presented CT (10) and CT and MR (11) features in 35 and 29 patients, respectively. However, only two reports of two patients each have directly compared the imaging and pathological findings (7, 17). This study compares cranial CT and MR with autopsy findings in 13 patients with AIDS-related CNS cryptococcosis, with particular emphasis on determining the effectiveness of CT and MR in detecting the pathologic changes.

Materials and Methods

The medical records of 66 patients with AIDS-related CNS cryptococcosis who had received consultation from the Department of Neurology at our institution from January 1, 1986 to December 31, 1990 were retrospectively evaluated. Of the 66 patients 13 patients who died near the time of their final brain imaging study and were sub-
sequentially autopsied are the focus of this study. One of the patients was included in a previous report (19). The interval between the last imaging study and death ranged from 4 hours to 28 days, with a mean duration of 8.5 days and median duration of 6 days. The study group consisted of 12 men and one woman, with ages ranging between 28 years and 56 years (mean age = 38 years). Risk factors for AIDS included homosexuality or bisexuality in eight patients, intravenous drug abuse in three patients, and heterosexual contact with an HIV-infected partner in one patient. No risk factor was identified in one patient. Seven of 13 patients had acute episodes of cryptococcal meningitis that directly contributed to their demise. Three patients experienced relapses of previously controlled cryptococcal meningitis that contributed to their deaths. Three patients had previous episodes of cryptococcal meningitis that clinically appeared to be adequately suppressed at the time of death.

Eight patients had CT scans as their last brain imaging study and five of these were given intravenous iodinated contrast. Scans were performed with 4-mm section thickness through the posterior fossa, 8-mm section thickness through the rest of the brain, 20-cm field of view, and 512 × 512 matrix. In addition, two of these eight patients had recent MR scans without contrast administration. The five remaining patients had MR studies with Gd-DTPA administration as their last imaging study of the brain. Two of these five patients also had recent noncontrast-enhanced CT scans. MR was performed on a 1.5-T instrument using routine spin-echo imaging to obtain T1-weighted (600/20/1 TR/TE/excitations) and spin-density and T2-weighted (3000/30,100/1) images. Images were acquired with 5-mm section thickness, 2-mm intersection gap, 24-cm field of view, and 256 × 256 matrix. The CT and MR studies were evaluated for abnormalities that might suggest cryptococcal infection such as leptomeningeal thickening, punctate lesions representing dilated perivascular spaces, or intracranial masses. Presence or absence of abnormal contrast enhancement of any type was also noted. For each patient, the parenchymal lesions were counted and categorized as to whether they were less than or greater than 3 mm in size to correlate with pathologic specimens. Tien et al (11) did not state a specific measurement but assumed that in patients with CNS cryptococcosis tiny hyperintense foci on T2-weighted images represented dilated perivascular spaces, as originally reported by Wehn et al (17). While there has been, to our knowledge, no MR study of brain specimens affected by cryptococcosis, one group has found état criblé in four brain specimens imaged with MR. The perivascular spaces were usually 3 mm or less, although, in one specimen, 4-mm spaces were observed (20). We attempted to evaluate punctate hyperintense foci on MR by choosing a lesion size (<3 mm) based on material presented in the literature describing dilated perivascular spaces and hypothesized that small lesions less than 3 mm in size would be due to dilated perivascular spaces. Evaluation of the relative performance of CT and MR was done by examining how well each modality detected autopsy findings overall and not how effectively the two modalities performed in the same cases, since only four of the 13 patients had both studies near death.

Autopsies were performed on all patients within 36 hours after death. All brains were fixed in buffered formalin (10%) for at least 2 weeks. Brains were cut in coronal or horizontal sections and evaluated grossly. Histologic evaluation was performed on 5-micron thick sections stained with hematoxylineosin or with mucicarmine. Definitions of pathologic entities pertinent to this study were modified from Vinters and Anders (21). A perivascular space is actually a potential space that surrounds a parenchymal vessel and represents an extension of the subarachnoid space. A dilated perivascular space was defined histologically as a well-marginated circular space within the brain tissue with a vessel located inside the space (Fig. 1D). The diameter of a dilated perivascular space can vary from a few times to several times the diameter of the vessel it surrounds. When infected with cryptococci, the space contained mucinous material, inflammatory cells and organisms, and was associated with compression, but not invasion or destruction of the surrounding parenchyma. In this study, the term “dilated perivascular space” refers to one infected with cryptococci, unless specified otherwise. Parenchymal invasion by cryptococcal organisms, either by extension out of the perivascular space or by direct involvement unrelated to a vessel, was termed a cryptococcoma. Histologically, cryptococcomas were irregularly margined lesions which contained mucinous material, inflammatory cells, and organisms, and replaced brain parenchyma. They frequently were confluent (Fig. 2D). Cryptococcomas were counted and categorized as to whether they were less than or greater than 3 mm in size, to test the hypothesis stated above that tiny lesions on MR correspond to dilated perivascular spaces.

Results

Twelve of 13 patients had abnormal final imaging studies as described in Table 1. The most common abnormalities noted were punctate hyperintensities (<3 mm in size) seen on T2-weighted MR images in five patients. These lesions were primarily seen in the basal ganglia and midbrain, but could also be found throughout the brain. Pathologically, these imaging findings corresponded to either dilated perivascular spaces or small cryptococcomas. Cryptococcomas and dilated perivascular spaces were usually both present in the same areas within the specimens. Overall, cryptococcomas were seen more frequently than dilated perivascular spaces, although the more frequent lesion varied from one area to another.

Dilated perivascular spaces were present at autopsy in all 13 brains. Imaging studies showed lesions corresponding pathologically to dilated perivascular spaces in all patients who had MR...
as their final brain imaging study, but in no patient who had CT as their final brain imaging study. Grossly, there are usually several dilated spaces that are not individually resolved on MR, but instead are seen as single larger lesions (Fig. 1). Histologically, the dilated perivascular spaces were as described above, with the space around the vessel being several times the size of the vessel diameter. The vast majority of these lesions were less than 3 mm in size and were not detected by imaging. In one case, a 56-year-old man, some of the enlarged perivascular spaces seen with MR were not filled with organisms, but presumably were dilated in association with age- and/or HIV-related atrophy.

At autopsy, 12 of 13 brains had cryptococcomas within brain parenchyma. In six of these 12, the cryptococcomas measured greater than 3 mm and presumably could have been seen on imaging studies. The number of cryptococcomas greater than 3 mm in these six specimens ranged from one to 14 or more (in some cases the confluent cryptococcomas were difficult to identify separately). The basal ganglia, thalamus, and midbrain were the most frequent locations of the larger cryptococcomas, although lesions greater than 3 mm were also present in the cerebellum, pons, corpus callosum, and cortex. In all six of these patients, the final imaging studies (three MRs, three CTs) showed abnormalities consistent with cryptococcomas (hyperintense on long TR images, hypointense on short TR images, hypodense or isodense mass on CT; Figs. 2 and 3). However, the number of lesions seen on the final imaging studies was less than the actual number of cryptococcomas greater than 3 mm detected pathologically by an average of 55% (range = 0–100%, standard deviation = 35%) (Table 2). In three cases in which both recent MR and CT studies could be compared, MR demonstrated

Fig. 1. Dilated perivascular spaces in a patient with cryptococcal meningoencephalitis.

A, T2-weighted MR image (3000/100) showed punctate hyperintensities in the midbrain bilaterally.

B, CT scan without iodinated contrast performed the same day as the MR does not show any midbrain abnormalities.

C, Gross specimen of the midbrain shows multiple small pseudocysts (arrowheads).

D, Photomicrograph (hematoxylineosin, X260) of a midbrain lesion demonstrates a dilated perivascular space with cryptococci (arrows) and leukocytes surrounding a vessel (V).
Fig. 2. Right basal ganglia cryptococcomas in a patient with CNS cryptococcosis.

A, CT scan without iodinated contrast shows mass effect on the frontal horn of the right lateral ventricle without a discrete abnormality of attenuation.

B, Gd-DTPA-enhanced T1-weighted MR image (600/20) demonstrates nonenhancing hypointense masses within the right caudate and lentiform nuclei.

C, T2-weighted MR image (3000/100) (degraded by motion artifact) shows hyperintense lesions in both lentiform nuclei and in the right caudate nucleus.

D, Horizontally sectioned autopsy specimen of the right cerebral hemisphere reveals that the right lentiform nucleus mass is composed of many confluent pseudocysts. The caudate nucleus lesion is of similar composition as seen on an adjacent section.

E, Photomicrograph (hematoxylineosin, X40) demonstrates multiple confluent cryptococcomas in the right basal ganglia.

more lesions than CT in each case. MR detected lesions in the basal ganglia, caudate, cerebellum, and brain stem better than CT, but both modalities were equally poor in detecting cortical cryptococcomas present at autopsy. None of the cryptococcomas greater than 3 mm showed con-


inflammatory cells (lymphocytes and occasional meningeal inflammatory reaction was usually histiocytes) were seen histologically within the subarachnoid spaces and leptomeninges. The most common mass lesions detected by CT (Fig. 3) was not given contrast.

The enhancing mass was found to be primary CNS lymphoma at autopsy and not a cryptococcoma. One patient had a contrast-enhanced CT and another had a Gd-DTPA-enhanced MR (Fig. 2) showing no contrast enhancement of their masses. One patient with multiple masses seen on CT (Fig. 3) was not given contrast. Pathologically, the masses in these latter three patients were found to be multiple confluent cryptococcomas in the basal ganglia.

All 13 patients had cryptococcal meningitis as manifested grossly by opacification of the meninges and the presence of mucoid material produced by the cryptococcal organisms within the subarachnoid space. Cryptococcal organisms and inflammatory cells (lymphocytes and occasional histiocytes) were seen histologically within the subarachnoid spaces and leptomeninges. The meningeal inflammatory reaction was usually mild. Abnormal meningeal contrast enhancement was seen in one of five enhanced MR studies and none of the five enhanced CT scans. The patient who demonstrated gyriform enhancement (Fig. 4) pathologically was found to have a focal bacterial cerebritis related to Nocardia septicemia, with severe vascular congestion near the area of enhancement. The cryptococcal meningitis in this patient was no more severe pathologically than that seen in the other nonenhancing cases and probably did not account for the contrast enhancement.

Atrophy was a common finding both on imaging studies and at autopsy. Five of 13 patients (three on CT, two on MR) exhibited subjective imaging evidence of cerebral atrophy. Since the presence of atrophy was not a primary focus of this study, no quantitative evaluation of brain volume was performed.

Of the seven patients who died during their first episode of CNS cryptococcosis, three had both small (<3 mm) and large (>3 mm) cryptococcomas pathologically, while four had only small cryptococcomas. All three of the patients who died during relapses of previously controlled cryptococcosis had both small and large cryptococcomas. One of the three patients who died with clinically suppressed CNS cryptococcosis had no cryptococcomas, while the other two had only small cryptococcomas.

### Discussion

CNS cryptococcosis is an important clinical problem in patients with AIDS ranking as the third most frequent cause of CNS infection in AIDS (12, 13) and presenting more often as a disseminated infection in these patients than in other patients (14). The diagnosis of cryptococcal meningitis in AIDS patients is complicated by the fact that cerebrospinal fluid cell count, protein, and glucose may be normal or only mildly abnormal in comparison to the nearly always abnormal laboratory values in HIV-negative patients with cryptococcal meningitis. The presence of fever and headache in a patient with AIDS or at risk for AIDS should prompt an investigation for CNS cryptococcal disease. CT and MR are important diagnostic techniques in any patient with HIV infection or AIDS and neurologic dysfunction since intracranial mass lesions are frequent (22). The most common mass lesions detected by CT are due to toxoplasmosis, although lymphoma and less common infectious processes such as

### Table 1: Findings on final imaging study before autopsy in 13 patients with CNS cryptococcosis

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<thead>
<tr>
<th>Finding</th>
<th>CT</th>
<th>MR</th>
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<tr>
<td>Normal</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Atrophy</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Punctate lesions (&lt;3 mm)</td>
<td>0</td>
<td>5</td>
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<td>Masses (&gt;1 cm):</td>
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<tr>
<td>Enhancing</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Nonenhancing</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No contrast</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal meningeal enhancement</td>
<td>0</td>
<td>1*</td>
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*Pathologically found to be primary CNS lymphoma.
*This patient had focal cerebritis and adjacent vascular congestion as discussed in the text.
cryptococcosis must be considered (23–25). Of concern in patients with cryptococcosis is the report that 20% of patients with mass lesions and meningitis and 10% of patients with mass lesions without meningitis had no signs or symptoms suggesting CNS disease (5).

The typical pathologic findings of CNS cryptococcosis in our series were meningitis, dilated perivascular spaces, and cryptococcomas. Cryptococcal meningitis is the most common neurologic manifestation of cryptococcosis and often has an insidious chronic course (1, 22). In response to the host immune system’s attack on the organisms, the cryptococci will produce a mucoid material (26). When the meningeal disease involves the extensions of the subarachnoid space that accompany perforating arteries into the parenchyma, the production of voluminous mucoid material may enlarge these perivascular spaces (17). Cryptococcomas, which, by our definition, represent a collection of organisms, inflammatory cells, and gelatinous mucoid material
within brain parenchyma, can develop when the organisms have extended directly from the perivascular spaces into the parenchyma (26) or, possibly, when they have invaded the parenchyma from other meningeal or ependymal surfaces.

In the detection of meningeal disease due to cryptococcosis, imaging techniques were not sensitive, since only one of 10 studies with contrast administration was positive. The meningeal contrast enhancement in this one MR case was more likely due to a superimposed bacterial cerebritis and its associated vascular congestion than due to cryptococcosis, since the severity of cryptococcal meningitis present was not significantly different than that seen in the cases without contrast enhancement. Gd-DTPA-enhanced MR has been shown to be more effective than contrast-enhanced CT in detecting meningeal enhancement in bacterial and tuberculous meningitis (27, 28). Cryptococcal meningitis was associated with meningeal enhancement on Gd-DTPA-enhanced MR in one of four cases (11) and neither of two cases (28) in two other clinical studies. Gyriform enhancement on CT examinations of cryptococcal meningitis has been reported (6, 9), although it is not commonly seen (10, 11). An obvious pitfall in these clinical studies without pathologic correlation is that other conditions, in particular, infarction, can cause gyriform cortical and meningeal enhancement (29). Our results indicate that AIDS-related cryptococcal meningitis does not typically produce meningeal enhancement on CT or MR.

MR was more effective than CT in demonstrating abnormalities due to dilated perivascular spaces but, instead, represent several spaces in close proximity to each other. We also found that these punctate MR abnormalities were more often due to small intraparenchymal cryptococcomas that likely developed as a progression of cryptococcosis involving perivascular spaces and, therefore, are located in the same areas as dilated perivascular spaces. However, dilated perivascular spaces and small cryptococcomas can result in an identical imaging appearance. In one of our patients, enlarged perivascular spaces were not uniformly a consequence of cryptococcosis but, instead, were probably at least partially due to age- or HIV-related atrophy. Generalized atrophy has been reported to be common in AIDS patients (30, 31) and, specifically, those with cryptococcosis (10). HIV infection itself may be the cause of this parenchymal loss, although no correlation has been found between the degree of atrophy and the severity of HIV infection (31). Since atrophy may enlarge the perivascular spaces to the extent that they are visible on MR, the observation of punctate hyperintensities is not specific for CNS cryptococcosis in patients with AIDS. However, this finding should raise the suspicion of cryptococcal disease, especially if other signs of diffuse atrophy such as ventricular and sulcal enlargement are not present or the patient has clinical signs or symptoms of meningitis.

MR was more effective than CT not only in identifying pathologic changes due to dilated perivascular spaces but also in demonstrating more cryptococcomas in each of the patients that had both studies performed near the time of death. In the detection of cryptococcomas greater than 3 mm, imaging techniques were sensitive in detecting abnormal cases, since every patient with these lesions had an abnormal imaging study. However, imaging was not sensitive in detecting individual lesions, since the actual number of lesions present pathologically was underestimated by more than 50%. Volume averaging of small lesions with normal brain or lack of radiographic contrast between some cryptococcomas and surrounding parenchyma are two possible reasons that many lesions cannot be seen retrospectively on imaging studies.

Some authors have called the larger lesions composed of organisms and mucoid material "gelatinous pseudocysts" (7, 10) which is an accurate description of the pathologic and CT appearances of these lesions, but also causes con-
Fig. 4. Superficial gyriform enhancement in a patient with cryptococcal meningitis.

A and B, T1-weighted MR images (600/20) before (A) and after (B) injection of Gd-DTPA shows superficial gyriform enhancement (arrowheads) in the right occipital and temporal lobes.

C, T2-weighted MR image (3000/100) demonstrates abnormal hyperintensity in the right occipital lobe (solid arrow). Note that the right thalamic lesion (open arrow) and two of the smaller punctate hyperintensities in the basal ganglia (arrowheads) corresponded pathologically to intraparenchymal cryptococcomas. Other punctate hyperintensities seen corresponded to dilated perivascular spaces.

D, Horizontal gross specimen of the occipital lobes shows bilateral leptomeningeal thickening (arrowheads) and right occipital lobe discoloration in the area of signal abnormality in C. This discoloration proved histologically to be severe vascular congestion secondary to bacterial cerebritis.

E, Photomicrograph (hematoxylineosin, ×150) of cryptococcal meningitis shows interstitial debris with a moderate inflammatory response as evident by the number of dark staining leukocytes (arrowheads).

fusion regarding cryptococcal disease. In our experience, "gelatinous pseudocysts" are the typical lesions that occur pathologically when the cryptococcal organisms cause a mass lesion in the brain. In other words, gelatinous pseudocysts and cryptococcomas are equivalent terms. In some cases, the relative amounts of mucoid material, inflammatory cells, and organisms result in x-ray attenuation that causes the appearance of the low-density gelatinous pseudocysts described by others (Fig. 3A). In other cases, the constituents are such that greater x-ray attenuation occurs and the lesions are nearly isodense to brain tissue (Figs. 2A and 3B). However, on gross pathological evaluation in both situations, the lesions have the same appearance of pseudocystic areas filled with mucoid material.

Contrast enhancement of cryptococcomas, similar to meningitis as mentioned above, is uncommon in AIDS-related CNS cryptococcosis based on the results of our study. This observation is probably due to the fact that only mild
vascular spaces and cryptococcomas. Both imaging modalities, however, underestimated the actual number of lesions identified pathologically and failed to detect cryptococcal meningitis. Contrast enhancement of cryptococcomas or cryptococcal meningitis was uncommon probably because of the immunocompromised state of these patients and the unique characteristics of the organism itself.

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**References**