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AJNR Am J Neuroradiol 1994, 15 (10) 1885-1894
http://www.ajnr.org/content/15/10/1885

Use of Thallium-201 Brain SPECT to Differentiate Cerebral Lymphoma from Toxoplasma Encephalitis in AIDS Patients

Armando Ruiz, William I. Ganz, M. Judith Donovan Post, Armando Camp, Howard Landy, William Mallin, and George N. Sfakianakis

PURPOSE: To determine whether thallium-201 brain single-photon emission CT could be used to make the distinction between central nervous system lymphoma and toxoplasma encephalitis, which may not be possible by routine MR and CT. **METHODS:** A total of 37 patients with acquired immunodeficiency syndrome who had intracranial mass lesions found during a 9-month prospective study by either MR or CT underwent further evaluation with Tl-201 brain single-photon emission CT. **RESULTS:** Twelve patients had increased intense focal Tl-201 uptake. All of these patients had either biopsy- or autopsy-proven lymphoma. Twenty-five of the patients studied had no Tl-201 brain uptake in the lesion(s); 24 of these patients had toxoplasma encephalitis on clinical follow-up. One patient with no Tl-201 uptake was found by cerebrospinal fluid analysis to have mycobacterium tuberculosis abscess. **CONCLUSION:** Patients with acquired immunodeficiency syndrome who have intracranial mass lesions on MR or CT may benefit from Tl-201 brain single-photon emission CT because it can help distinguish between lymphoma and infectious lesions such as toxoplasma encephalitis.

Index terms: Lymphoma; Encephalitis; Toxoplasmosis; Single-photon emission computed tomography (SPECT); Acquired immunodeficiency syndrome (AIDS); Brain neoplasms, computed tomography

AJNR Am J Neuroradiol 15:1885–1894, Nov 1994

The diagnosis of brain lymphoma is especially difficult with human immunodeficiency virus (HIV) infection, particularly because lymphoma and toxoplasma encephalitis may have similar computed tomography (CT) and/or magnetic resonance (MR) characteristics. Patients with acquired immunodeficiency syndrome (AIDS) who present with a contrast-enhancing central nervous system (CNS) mass lesion are often, in many institutions, treated empirically for toxoplasma encephalitis and followed by CT or MR for response. If the patients do not respond to medical treatment, stereotactic biopsy is often required to exclude other causes, including lymphoma.

To our knowledge, since the initial mention by Ganz et al (1) and Vanarthos et al (2) of the value of thallium-201 brain single-photon emission CT (SPECT) imaging for differentiating CNS lymphoma from infectious processes such as toxoplasma encephalitis in AIDS patients, a systematic routine application of this technique for this purpose has not become widespread. We therefore performed a prospective study to determine whether Tl-201 brain SPECT could be routinely used to differentiate CNS lymphoma from inflammatory lesions in HIV-positive persons.

Subjects and Method

In a prospective study of 37 AIDS patients, in which a plain and contrast-enhanced CT and/or MR exam demonstrated CNS mass lesions, a Tl-201 brain SPECT study was performed. The first 5 patients in the study presented with CNS masses that were not responding to conventional

Received October 22, 1993; accepted after revision March 10, 1994.

Presented in part at the 31st Annual Meeting of the American Society of Neuroradiology, May 1993, Vancouver, Canada.

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AJNR 15:1885–1894, Nov 1994 0195-6108/94/1510–1885

antitoxoplasmosis medical therapy. The rest (32 patients) were evaluated consecutively with Tl-201 brain SPECT soon after the demonstration of CNS mass lesions by CT and/or MR.

A triple-head camera was used with three general all-purpose collimators, and 80- and 150-keV dual peaks, with 15% windows. Five minutes after the intravenous injection of 5 mCi of Tl-201, a 5-minute planar acquisition was obtained with all three heads (120° separated). In the planar image, one head was selected to obtain an anterior or posterior projection to be closest to the patient's intracranial lesion. The SPECT was performed in a "step and shoot" mode using a circular orbit and 2.0 magnification. Each head underwent 30 stops lasting 40 seconds per stop at 4° increments for each head. A 64 × 64 matrix filtered back projection reconstruction provided transaxial, coronal, and sagittal images of the 90 views. Reconstruction was performed with attenuation correction and a 1.4-cycle per centimeter order and 0.90-cycle per centimeter cut-off frequency hamming filter (mathematical algorithm applied to the image data to increase the signal-to-noise ratio). At the conclusion of the Tl-201 SPECT acquisition, the thallium planar images were acquired again for 5 minutes. Each lesion was analyzed visually to obtain the average and maximal ratio of the lesion to the contralateral soft tissues on the planar studies and on the 1.1-cm transaxial sections demonstrating the tumor. If necessary, quantitation was performed. A SPECT scan was considered normal when the intracranial activity was equal to or less than the activity of the contralateral scalp. Active tumor was considered when a focus of increased intracranial activity was greater than the activity of the contralateral scalp (ratio > 1.0).

A high-resolution plain CT scan, followed by a 45-minute to 1-hour delayed double-dose contrast study of the brain (using approximately 78 g of iodinated intravenous contrast medium), was taken in each of the 37 patients. Standard axial 5- and 10-mm cuts were obtained through the posterior fossa and supratentorial regions, respectively.

MR was performed in 6 of 37 patients in 1.0- or 1.5-T units consisting of T1-weighted coronal or sagittal images (700/20/2-4 [repetition time/echo time/excitations]), T2-weighted axial images (2400/20,80/1), and axial, coronal, or sagittal T1-weighted images (600/30/2) after the intravenous administration of 0.1 mmol/kg of gadopentetate dimeglumine. Section thickness was 5 mm.

The brain CT and MR studies were evaluated for the presence of enhancing intraaxial mass lesions, abnormal ependymal or leptomeningeal enhancement, areas of abnormal high or low density, or signal abnormalities in the cases with MR studies.

Results

Of our 37 AIDS patients, 29 were men and 8 women. Ages ranged from 26 to 46 years with a mean of 34 years.

TABLE 1: Imaging results of 37 AIDS patients with intracranial mass lesions

	Positive Tl-201 CNS Uptake (Lymphoma) (12 patients)[a]	Negative Tl-201 CNS Uptake (Non-lymphoma) (25 patients)[b]
Pattern of enhancement on CT/MR		
Thin ring	0	16
Thick ring	11	0
Homogeneous	0	9
Inhomogeneous	1	0
Lesion location on CT/MR		
Cerebral cortex	2	0
Cortical-white matter junction	5	18
Basal ganglia	3	15
Thalamus	0	5
Periventricular	3	0
Cerebellar	2	7

[a] Five patients with more than one CNS lesion.
[b] Nineteen patients with two or more CNS lesions.

The patients' clinical presentations varied from focal symptoms (sensory/motor deficit) in 19 to nonfocal symptoms (headaches, altered mental status, nausea, vomiting, and seizures) in 18. We could not differentiate clinically between infectious or neoplastic cause.

Serial serum antitoxoplasmosis IgG antibodies were obtained in all the patients, being positive in 24 (titers ≥ 2.5) patients with proved toxoplasma encephalitis and negative in 13 (titer ≤ 1.0) patients (12 cases of proved lymphoma and one case of posterior fossa mycobacterium tuberculosis abscess).

Only 5 of the 36 patients, specifically those with the smallest lesions and no significant mass effect, underwent spinal tap for cerebrospinal fluid analysis. One patient had cerebrospinal fluid cultures positive for mycobacterium tuberculosis; the other 4 patients had routine laboratory findings of the cerebrospinal fluid that were nonspecific (ie, culture negative, mild elevation of protein, and a pleocytosis).

Based on our results, we divided our patients into two major groups (Table 1). The first group was composed of 12 patients with negative serial serum antitoxoplasmosis IgG antibodies and increased Tl-201 uptake. The areas of increased Tl-201 uptake in every case matched the location and size of the lesions seen on CT and/or MR. The lesion size ranged from 6 mm to

6 cm. Seven patients had a single brain parenchymal lesion (Figs 1A, B, and C; 2A and B; and 3A and B). Five patients had more than one parenchymal lesion (Fig 4A, B, C, and D). The most common pattern of enhancement on CT and/or MR was thick irregular rings surrounded by vasogenic edema, although solid enhancement was also seen. The biopsies and results of autopsy were positive for primary brain lymphoma (immunoblastic type) in each case (Figs 1E and F, and 2C).

A second group of 25 patients had no brain Tl-201 uptake. Six patients had a single CNS lesions. Nineteen patients had 2 or more CNS lesions. Serial serum antitoxoplasmosis IgG antibodies were positive in all the patients except in 1 whose culture was positive for mycobacterium tuberculosis by cerebrospinal fluid analysis. The number of lesions in this group ranged from 1 to 14. Most of the lesions had thin ring enhancement and surrounding vasogenic edema, but solid nodular enhancement was also seen. Except for the patient with CNS tuberculosis, all the patients improved on antitoxoplasmosis medication and the lesions resolved on serial CT follow-up studies within 2 to 6 weeks (Fig 5A, B, and C).

Discussion

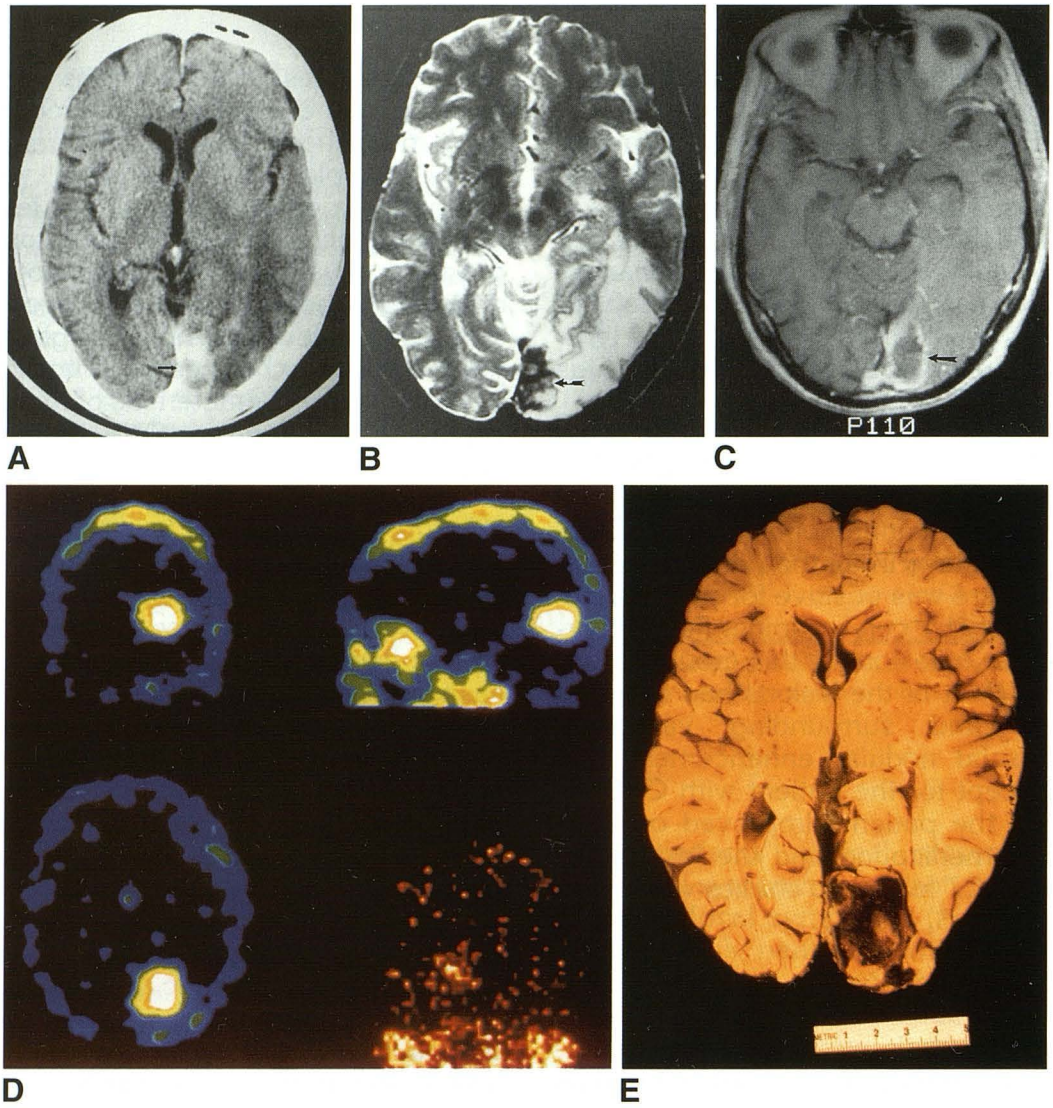
It has been estimated that in 1992, 2 million people in the United States had HIV (3–5). Of the subgroup of HIV-positive patients in whom AIDS or AIDS-related complex developed, about 40% will develop CNS disease related to the HIV virus, opportunistic infection, or neoplasm (6).

Malignant neoplasms associated with AIDS patients are primary CNS lymphoma, presenting in 2% to 6% of neurologically symptomatic patients (7, 8); metastatic lymphoma, estimated to occur in 1% to 5% of the patients (invading the meninges with leptomeningeal and epidural spread and rare mass lesions) and Kaposi sarcoma, which rarely involves the CNS. On the other hand, a wide variety of infectious organisms may affect the CNS in AIDS patients. The most common CNS opportunistic infection is toxoplasma encephalitis caused by the parasite *Toxoplasma gondii*, occurring in up to 33% of neurologically symptomatic AIDS patients.

When an AIDS patient is found to have a CNS mass lesion, it is crucial to establish whether the cause of the lesion is infectious or neoplastic, because of the significant differences in treatment modalities. The major differential diagnosis is toxoplasma encephalitis versus lymphoma, with other inflammatory lesions being less common. The clinical symptoms and the patient's physical findings are not enough to distinguish these causes (9), because symptoms such as fever, drenching night sweats, and weight loss may be present in both entities.

The imaging characteristic of toxoplasma encephalitis and primary CNS lymphoma have been well described (10–16) on CT and MR. There are some diagnostic imaging clues, but absolute differentiation is not possible. On CT and MR, both lymphoma and toxoplasma encephalitis may appear as a focal ring and/or nodular enhancing mass lesions in the brain surrounded by edema. The lesions in either disease process may be single or multiple and may be superficial (eg, at the corticomedullary junction) and/or deep (eg, in the basal ganglia, thalamus). Although the cerebral hemispheres are most commonly affected, the brain stem and cerebellum can also be involved. On MR, both lymphoma and toxoplasma encephalitis can appear as focal mass lesions isointense to gray matter on T2-weighted images. Even when the lymphomas are necrotic (which is reported to occur more frequently in patients with lymphoma who are HIV-positive), the rim of the lesions still appear isointense to gray matter on T2-weighted images, while the center is hyperintense.

Because of these shared imaging characteristics an absolute differentiation on initial CT or MR between lymphoma and toxoplasma encephalitis is not possible. However, there are some imaging clues on CT and MR that may be helpful in ordering the differential diagnosis. Lymphoma can be favored in the differential when the lesions involve the corpus callosum, subependymal, and/or periventricular location (17, 18) (Figs 4 and 6), and when the enhancement pattern is that of a thick irregular and/or nodular type (Figs 1B and C and 3A) (Swischuk JL, Post MJD, "Imaging Findings in HIV-Positive Individuals with Biopsy and/or Autopsy Proved CNS Lymphoma," presented at the 31st Annual Meeting of the ASNR, May 16–20, 1993, Vancouver, Canada). On plain CT, lymphomas often have a hyperdense appearance. Rapid progression of imaging findings on short-time-interval studies also favors lymphoma in the



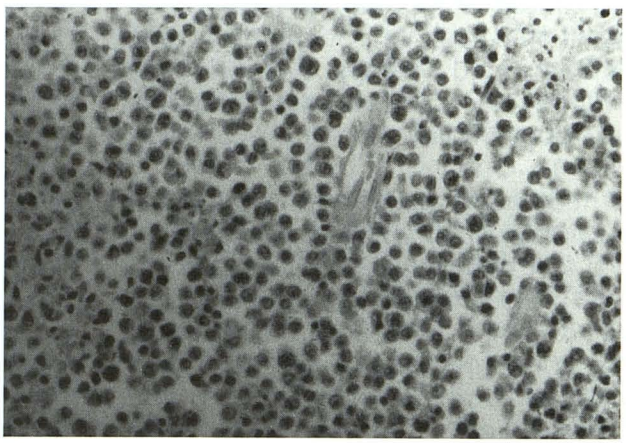


Fig 1. Autopsy-proved primary brain lymphoma in an AIDS patient.

A, Nonenhanced brain CT shows a hemorrhagic mass lesion in the left occipital lobe cortex (*black arrow*).

B, Axial T2-weighted image of the brain obtained 2 weeks after *A* demonstrates a mass lesion in the left occipital cortex (*black arrow*), with areas of hemosiderin deposition and surrounding vasogenic edema.

C, Axial gadopentetate dimeglumine T1-weighted image of the brain obtained 2 weeks after *A* demonstrates a peripherally enhancing mass lesion (*black arrow*) in the left occipital lobe. Peripheral areas of hemorrhage were obscured by the contrast material.

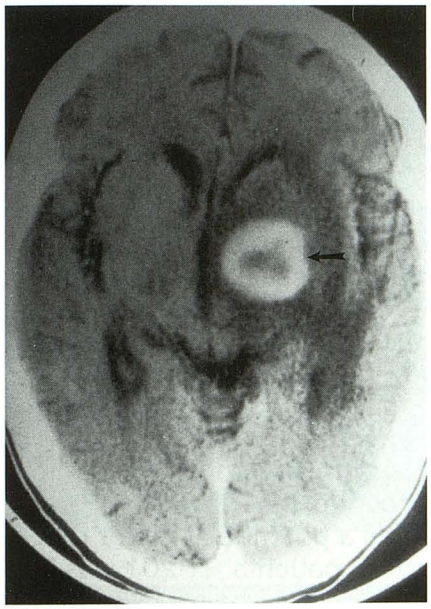
D, Coronal, sagittal, and axial Tl-201 SPECT images of the brain show focal, intense Tl-201 uptake in the left occipital lobe. The lower right image represents 1 of 90 projection stops used to reconstruct the SPECT image (single-step projection) used to detect motion artifacts in the image.

E, Postmortem axial section of the brain showing a hemorrhagic mass lesion in the left occipital lobe with leptomeningeal invasion, taken 1 week after images *B*, *C*, and *D*.

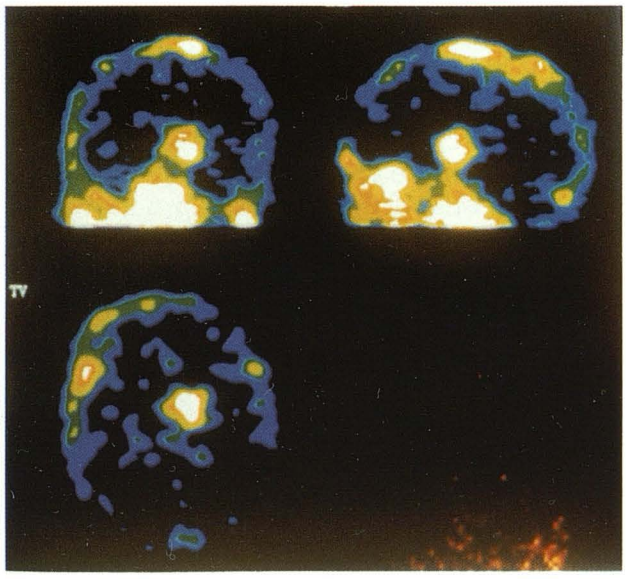
F, Photomicrograph of the left occipital lobe mass lesion demonstrates perivascular collection of atypical lymphoreticular cells (hematoxylin and eosin, magnification ×360) that were positive for leukocyte common antigen using immunoperoxidase technique and consistent with primary brain lymphoma.

diagnosis. In contrast, lesions caused by *Toxoplasma gondii* (which are located at the corticomedullary junction most commonly, followed by the basal ganglia) improve over time when the patient is receiving adequate medication (eg, pyrimethamine and sulfadiazine) (Fig 5A and B). A continuing decrease in the size and number of enhancing lesions as well as a decrease in the edema and mass effect will be seen over a period of 2 to 4 weeks with antibiotic therapy. With continued medication, the lesions will eventually resolve or leave residual sites of encephalomalacia, calcification, and/or focal atrophy.

Despite these helpful imaging clues, it must be emphasized that at initial presentation the CT and MR findings are not pathognomonic and lymphoma cannot be differentiated totally from toxoplasma encephalitis or from other infectious processes that may occur in the HIV-infected patient (eg, candida albicans, nocardia, etc). Indeed, in AIDS patients, the appearance of primary CNS lymphoma resembles an abscess of toxoplasmosis in up to 50% to 80% of



A



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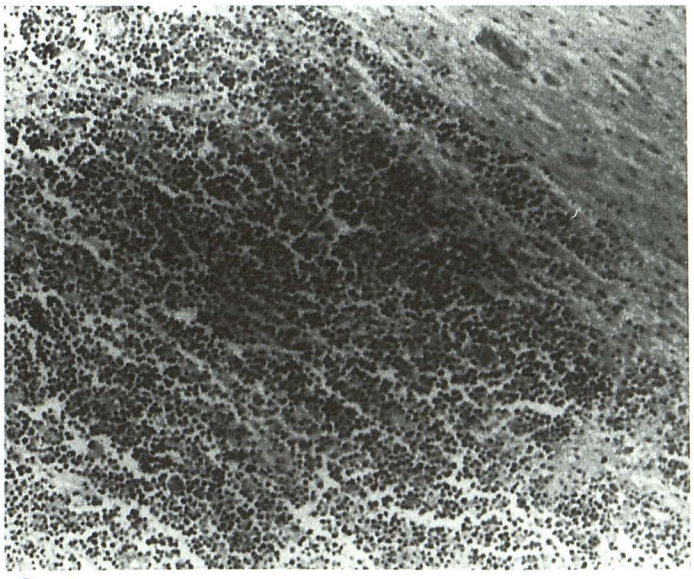


C

Fig 2. AIDS patient with biopsy-proved primary brain lymphoma of the left basal ganglia.

A, Contrast-enhanced CT of the brain (double dose delayed technique) shows a thick ring-enhancing (*black arrow*) left basal ganglia mass lesion with surrounding vasogenic edema.

B, Coronal, sagittal, and axial Tl-201 brain SPECT images show intense abnormal uptake in the left basal ganglionic region. The lower right image represents a single-step projection used to detect motion artifacts and determine the quality of the images.

C, Photomicrograph of a biopsy sample obtained from the left basal ganglionic lesion shows atypical lymphoreticular cells compatible with primary brain lymphoma (hematoxylin and eosin, magnification ×100), confirmed by a positive leukocyte common antigen using immunoperoxidase technique.

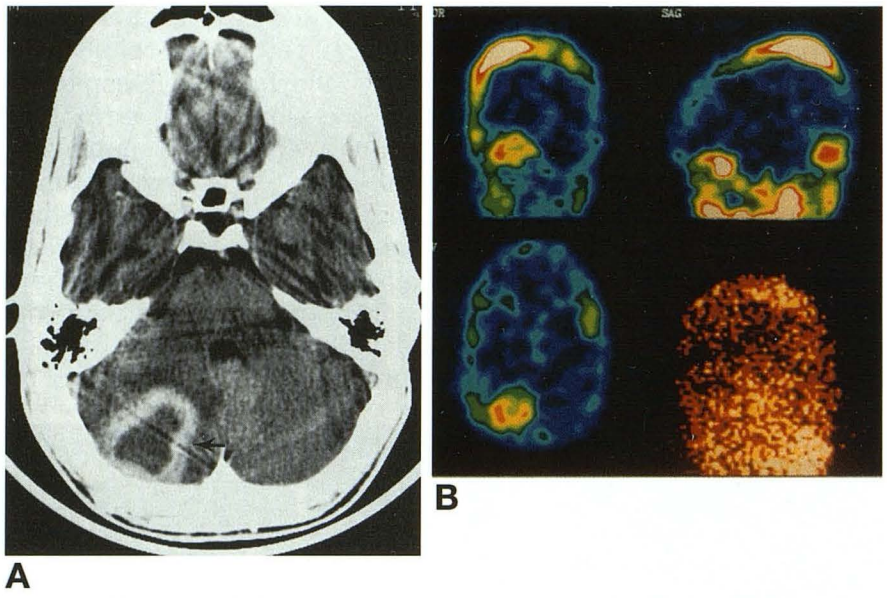


Fig 3. AIDS patient with biopsy-proved right cerebellar lymphoma.

A, Contrast-enhanced CT (double dose delayed technique) shows a thick ring-enhancing mass lesion in the right cerebellar hemisphere.

B, Coronal, sagittal, and axial Tl-201 brain SPECT demonstrates abnormal intense uptake in the right cerebellum. The lower right image represents the single-step projection used to detect motion artifacts and determine the quality of the images.

the cases reported (19–21). These figures are comparable to our own experience. Clinically neurologic deterioration can proceed rapidly if the patient actually has CNS lymphoma, yet is being treated empirically for toxoplasma encephalitis, a fact that shows the importance of obtaining a Tl-201 scan immediately after MR or CT when a focal mass in an HIV-positive patient is evident (Swischuk and Post, "Imaging Findings").

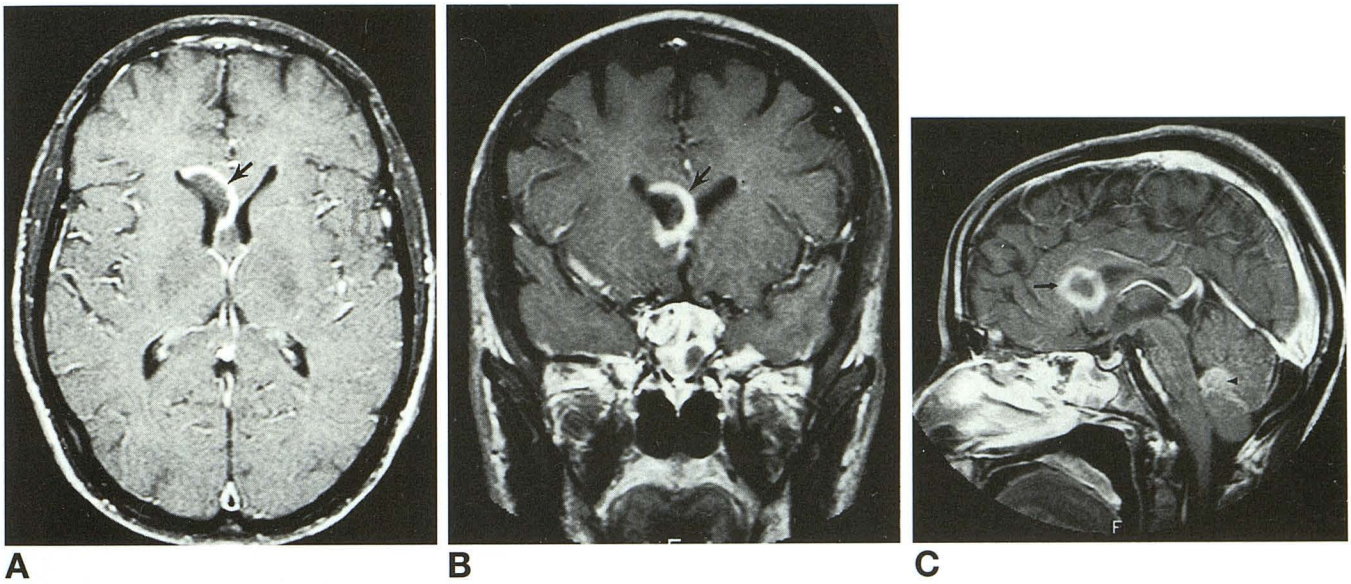
Laboratory studies are often not conclusive. The toxoplasmosis serum antibody IgG test, although helpful, is a quantitative assay that when positive indicates past or recent exposure to the agent and does not exclude a different or coexistent CNS lesion. Although a recent publication (22) states that up to 22% of the patients with toxoplasma encephalitis do not have detectable antitoxoplasmosis IgG antibodies, a single or serial of negative serum antoxoplasmosis IgG antibody titer in the presence of a CNS mass lesion is valuable in alerting the clinicians of the need to search for other possible causes (23, 24). The CSF analysis of AIDS patients is often not specific either. For example, in those with primary CNS lymphoma, cytologic examination only occasionally reveals malignant lymphoma cells (25). Additionally, in the presence of a focal mass lesion, a spinal puncture would be contraindicated.

Not uncommonly, despite the information provided by CT, MR, and laboratory tests, a straightforward etiological clinical diagnosis of CNS mass lesions in AIDS patients is often difficult and the clinicians usually use empiric antitoxoplasmosis medication. However, because early CNS radiotherapy can improve the survival of primary CNS lymphoma patients, early brain biopsy, particularly of ring-enhancing and single lesions, has been advocated by some authors (22, 26).

Because of the uncertainty of the diagnosis in many cases and the desire to avoid a brain biopsy in AIDS patients with CNS masses, Tl-201 brain SPECT has a potentially major role in the evaluation of these patients. Tl-201 was first used by Kawan et al (27) to obtain a myocardial image. Tl-201 is currently used to distinguish viable from nonviable myocardium; to study renal ischemia; to follow musculoskeletal cancer; to detect ocular melanoma; and to detect and follow breast, pulmonary, thyroid, and cerebral neoplasms (28–31). Tl-201 is a cyclotron-produced radionuclide that decays by electron capture, with a half-life of approximately 73 hours. It emits photons of the daughter product mercury 201, with an energy range of 69 to 81 keV (95% abundance). Smaller numbers of gamma rays at energies of 167 and 135 keV are also produced (30). Tl-201 behaves very similarly to potassium in its biodistribution. After the intravenous administration of Tl-201, it rapidly disappears from the blood. Normal increased activity is seen in the orbits, base of the skull, scalp, and nasopharyngeal regions. Normally, there is absence of Tl-201 uptake in the brain. SPECT, rather than planar imaging, provides improved lesion contrast, and accurate three-

dimensional location and multiplanar images that are comparable to CT and MR (27, 29).

The potential clinical utility of Tl-201 for the diagnosis of CNS lymphoma in AIDS patients rests on a mechanism of improved location similar to that already described for other primary CNS neoplasms and metastatic lesions. The main mechanism of uptake by the CNS lymphoma probably is active transport of Tl-201 (similar to potassium) into the tumor cells promoted by an adenosine triphosphate cell membrane active pump such as that present in active, growing, dividing cells. Other possible but less attractive explanations for the abnormal Tl-201 uptake in CNS lymphoma would include increased regional vascular flow and less likely alterations in the blood-brain barrier (26, 28, 30). In our series, the high-grade immunoblastic nature of primary CNS lymphoma (cell type commonly seen in the AIDS population) probably explains the highly intense Tl-201 brain uptake as opposed to low or no uptake in other low-grade tumors (gliomas). Tl-201 has been



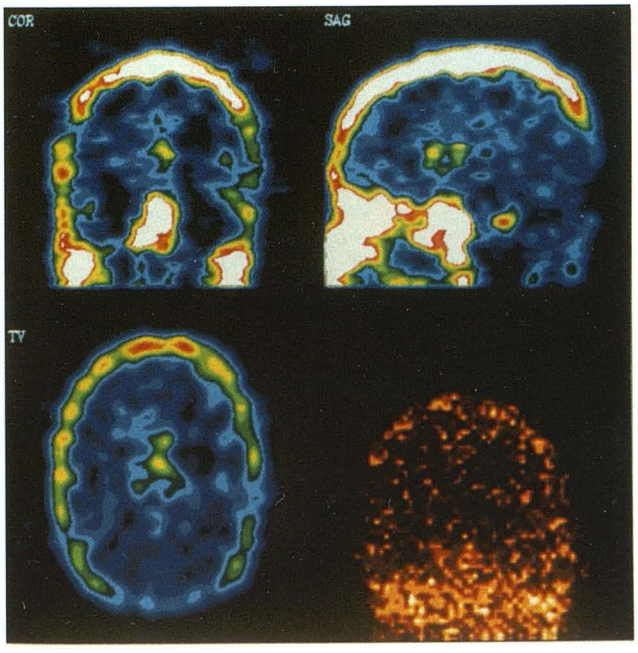


Fig 4. Biopsy-proved primary brain lymphoma in an AIDS patient.

A and *B*, Postgadolinium axial and coronal T1-weighted images show a ring-enhancing mass lesion in the region of the genu of the corpus callosum (*black arrow*).

C, Postgadolinium sagittal T1-weighted image shows ring- and solid-enhancing lesions in the genu of the corpus callosum (*large black arrow*) and adjacent to the fourth ventricle, respectively (*black arrowhead*).

D, Coronal, sagittal, and axial Tl-201 brain SPECT images show abnormal, intense uptake in the region of the genu of the corpus callosum and adjacent to the fourth ventricle. The lower right image represents a single-step projection used to detect motion artifacts and determine the quality of the images.

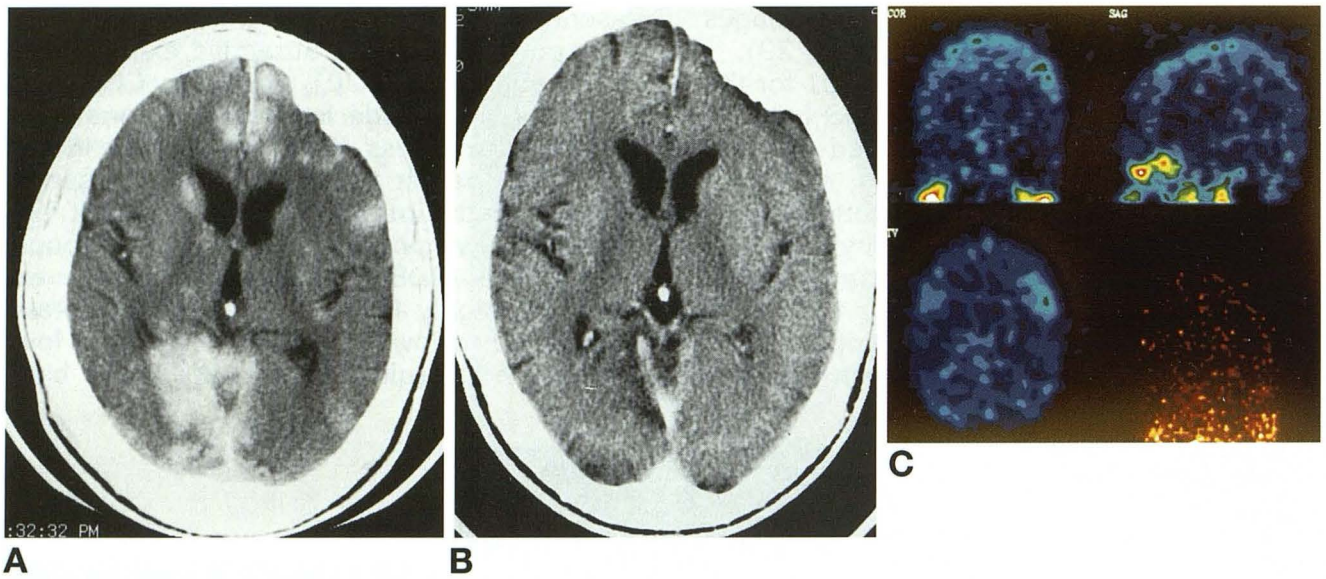


Fig 5. AIDS patient with clinically proved toxoplasma encephalitis.

A, Axial contrast-enhanced CT (double dose delayed technique) demonstrates multiple bihemispheric nodular deep and superficial enhancing lesions.

B, Axial contrast-enhanced CT (double dose delayed technique) obtained 2 weeks after medical treatment for toxoplasma encephalitis demonstrates resolution of the lesions in *A*.

C, Coronal, sagittal, and axial Tl-201 brain SPECT images obtained no more than 2 days after *A* are negative for areas of abnormal intracranial uptake. The lower right image represents a single-step projection used to detect motion artifacts and determine the quality of the images.

Fig 6. Biopsy-proved multicentric lymphoma.

A, Postcontrast enhanced CT axial (double dose delayed technique) images show ring-enhancing lesions in the region of the corpus callosum with surrounding vasogenic edema (*long black arrow*) and also thick ring-enhancing lesions in the right frontoparietal lobe and in the region of the hippocampal formation (*short black arrow*).

B, Coronal, sagittal, and axial Tl-201 brain SPECT images show abnormal increased uptake in the pericallosal region, left medial temporal lobe, and right frontoparietal lobe regions, corresponding in location to the enhancing lesions in *A*. The lower right image represents a single-step projection used to detect motion artifacts and determine the quality of the images.

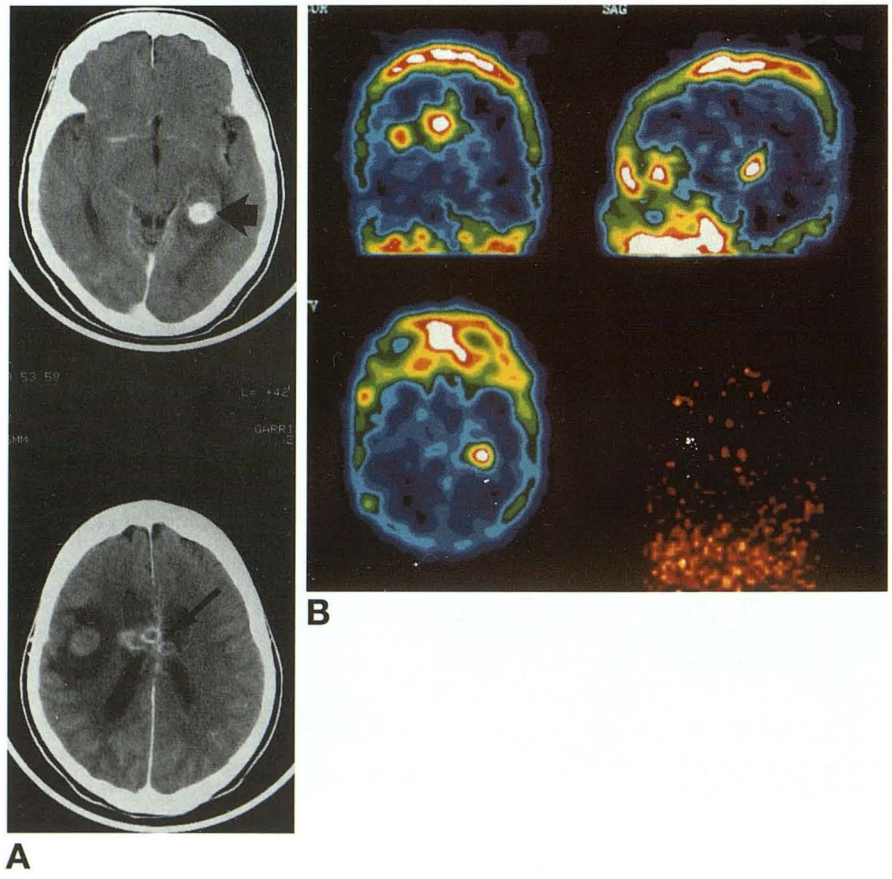


TABLE 2: Results of Tc 99m hexamethyl-propylenamine oxine perfusion brain SPECT patterns in 37 AIDS patients with CNS masses

	Lymphoma, n	Nonlymphoma, n
Increased	2	1
Normal	3	12
Decreased	7	10
Mixed	0	2

localized in the nuclear, mitochondrial, and microsomal fractions of neoplastic tissue (31-33).

In our study there was no CNS uptake in cases of toxoplasma encephalitis and in the case of CNS tuberculosis, making it unlikely that alteration of the brain-blood barrier is of importance as an explanation for the Tl-201 CNS uptake. Even though in our series we had no false-positive or false-negative results for primary CNS lymphoma, potential false-negative results in cases of CNS lymphoma may occur when the size of the lesion falls below the resolution of the SPECT gamma camera (in our study, less than 6 to 8 mm), in small infratentorial or supratentorial lesions close to the base of the skull and calvarium that are obscured by the normal high activity of the adjacent soft tissue (scalp), and also in instances of subtle subependymal and nonfocal leptomeningeal spread of lymphoma.

In our institution, technetium 99m hexamethyl-propylenamine oxine brain SPECT frequently accompanies and follows Tl-201 brain SPECT. Tc 99m hexamethyl-propylenamine oxine is a radiopharmaceutical that is useful in the imaging of regional cerebral blood perfusion. Local variations in flow are associated with brain diseases such as stroke, epilepsy, tumors, and psychiatric disorders including HIV dementia (34). Its role is limited to the location of the CNS lesion (which was already known from CT and MR) by demonstrating areas of abnormal perfusion. We did not find a characteristic pattern of abnormal perfusion for toxoplasma encephalitis or CNS lymphoma (Table 2), a fact that suggests Tc 99m hexamethyl-propylenamine oxine is probably unnecessary in the evaluation of these two entities.

In conclusion, we believe that the application of Tl-201 brain SPECT in AIDS patients with CNS mass lesions is helpful not only to confirm or exclude the presence of lymphoma, but also to orient the neurosurgeons to specific sites for biopsy in patients in whom lymphomas are coexistent with other, nonneoplastic lesions. With early diagnosis of CNS lymphoma, whole-brain radiation therapy can be started in hopes of improving the patient's survival and decreasing medical costs by reducing unnecessary hospitalization time while awaiting response to empiric antitoxoplasmosis medication.

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