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# Thallium-201 Brain SPECT of Lymphoma in AIDS Patients: Pitfalls and Technique Optimization

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**PURPOSE:** Our aim was to examine the  $^{201}\text{Tl}$ -SPECT scans in AIDS patients with focal CNS lesions to identify those studies with a false-positive or false-negative result to determine any potential pitfalls in interpretation as well as to suggest methods for technique optimization.

**METHODS:** We retrospectively reviewed the charts of 162 AIDS patients with cerebral mass lesions on  $^{201}\text{Tl}$ -SPECT studies. One hundred sixty-one patients had CT examinations, of which 50 also had MR studies. One patient had MR imaging without CT. Those patients in whom the diagnosis by  $^{201}\text{Tl}$ -SPECT did not correspond with the known pathologic or clinically proved diagnosis were then singled out and their CT, MR, and  $^{201}\text{Tl}$ -SPECT studies were reviewed, including blinded interpretation of the  $^{201}\text{Tl}$ -SPECT scans alone and alongside the corresponding CT and MR examinations. Studies were examined for lesion morphology, size, location, enhancement pattern, and presence of necrosis. The review of the  $^{201}\text{Tl}$ -SPECT studies included both a qualitative approach (subjective analysis of the scans for areas of abnormally increased uptake) and a quantitative approach (comparison of lesion activity versus activity within a reference standard, such as the scalp).

**RESULTS:** Sensitivity and specificity of  $^{201}\text{Tl}$ -SPECT in depicting lymphoma were 100% and 93%, respectively, based on the initial qualitative analysis. Fifty-one patients had positive  $^{201}\text{Tl}$ -SPECT results, of whom 43 were determined to have lymphoma (four by biopsy/autopsy, 39 by clinical and radiologic findings). Upon reevaluation with both a quantitative and qualitative approach, those studies initially interpreted as positive in patients without lymphoma (false positives) were found to be negative.

**CONCLUSION:** Brain  $^{201}\text{Tl}$ -SPECT is an effective study in the diagnosis of CNS lymphoma in AIDS patients. Specificity can be increased by routinely performing a quantitative analysis of all lesions.

Differentiating toxoplasmosis from lymphoma in AIDS patients can be difficult, as these disease processes possess similar features both clinically and on CT and MR imaging studies. While certain features—such as location; subependymal, periventricular, or corpus callosal involvement; nature of enhancement; increased density on plain CT and other studies—have been noted to be helpful in differentiating features, none is pathognomonic (1). This distinction is of vital clinical importance, as AIDS patients with primary CNS lymphoma benefit from brain irradiation

(XRT), with a more than fourfold increase in survival rates over those who do not receive appropriate therapy. Furthermore, the benefit of XRT is diminished if it is delayed, which is often the case when patients undergo an empirical trial of antitoxoplasmosis therapy to help make the diagnosis (2). Several studies have described the use of tumor-specific imaging techniques, most notably thallium-201 single-photon emission CT ( $^{201}\text{Tl}$ -SPECT) (3–9),  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography (FDG-PET) (10–12), gallium imaging (13), and MR proton spectroscopy (14, 15).

A 1994 study by O'Malley et al (7) and more recent work by Ruiz et al (3) have shown that  $^{201}\text{Tl}$ -SPECT is highly accurate in differentiating toxoplasmosis from lymphoma. The latter study yielded a sensitivity and specificity of 100% in depicting lymphoma in AIDS patients. Despite this reported high accuracy rate, however, false-negative and false-positive results

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have been encountered by other authors (6, 7, 16) and have been reported anecdotally by investigators at our institution as our experience with this technique has grown.

Our study was undertaken to examine the experience at our institution in interpreting  $^{201}\text{Tl}$ -SPECT studies in AIDS patients with focal CNS lesions. We identified and studied those cases with a false-positive or false-negative result in order to determine any potential pitfalls in interpretation that could lead to these discrepancies as well as to suggest methods for technique optimization.

## Methods

A list of all patients undergoing brain  $^{201}\text{Tl}$ -SPECT examinations from January 1993 through July 1995 was compiled from nuclear medicine dose administration records. A retrospective chart review was then performed, with immediate exclusion of all non-AIDS patients. Exclusion of patients in whom the clinical question was not that of focal CNS mass lesions left a total of 162 eligible subjects. Parameters examined included CT and MR imaging findings of lesion morphology, size, and location, as well as presence of necrosis or enhancement.  $^{201}\text{Tl}$ -SPECT findings, serum and CSF serologic/cytologic examinations, when available, use of steroids, lesion size on CT and MR studies as compared with that on SPECT scans, response to therapy, and presumptive or pathologic diagnosis were also recorded. CT examinations consisted of high-resolution plain study of the brain, with either an immediate routine contrast-enhanced scan or a 45-minute to 1-hour delayed double-dose contrast study (using approximately 78 g of iodinated intravenous contrast medium). Standard axial 5- and 10-mm cuts were obtained through the posterior fossa and supratentorial regions, respectively.

MR examinations were performed on a 1.0- or 1.5-T unit and consisted of T1-weighted coronal images (700/20/2–4 [TR/TE/excitations]), T2-weighted axial images (2400/20,80/1), and axial, coronal, and sagittal T1-weighted images (600/30/2) after intravenous administration of 0.1 mmol/kg gadopentetate dimeglumine. Section thickness was 5 mm.

For  $^{201}\text{Tl}$ -SPECT studies, 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 thallium-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 study was performed in a "step and shoot" mode using a circular orbit and  $\times 2.0$  magnification. Each head underwent 30 stops lasting 40 seconds per stop at 4° increments for each head. A  $64 \times 64$  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 a 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  $^{201}\text{Tl}$ -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 tissue on the planar studies and on the 1.1-cm transaxial sections showing 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. Tumor was considered when a focus of increased intracranial activity was greater than the activity of the contralateral scalp (ratio  $> 1.0$ ).

Diagnoses were arrived at by findings at pathologic examination or autopsy in four of 43 patients with lymphoma and in five of 119 patients with other diagnoses, and by clinical and laboratory findings as well as by radiologic follow-up in the remainder. Those cases in which the diagnosis by  $^{201}\text{Tl}$ -SPECT did not correspond with the known pathologic or clinically proved diagnosis were then singled out and their CT, MR, and  $^{201}\text{Tl}$ -SPECT studies reviewed, including blinded readings of the  $^{201}\text{Tl}$ -SPECT study alone and alongside the corresponding CT and MR studies.

## Results

A total of 162 eligible patients' charts were reviewed. Of these, 111 patients, none with lymphoma, had negative findings on brain  $^{201}\text{Tl}$ -SPECT scans and 51 patients had positive findings; 43 of these had primary CNS lymphoma, four as determined by pathologic studies or autopsy results and 39 by clinical, laboratory, or radiologic data. The other eight patients in the group consisted of seven with toxoplasmosis (one diagnosed pathologically) and one with streptococcal infection (diagnosed at autopsy). It was these eight false-positive studies that were chosen for review of all prior relevant imaging findings.

All cases of lymphoma were detected by  $^{201}\text{Tl}$ -SPECT, yielding a sensitivity of 100% (there were no false-negative results). Because of the eight false-positive studies, specificity was 93% (at the time of the initial interpretation).

Review of the scans of the eight false-positive  $^{201}\text{Tl}$ -SPECT studies revealed that in virtually all cases, activity not significantly greater than that of the scalp was present on the  $^{201}\text{Tl}$ -SPECT scans in the areas of the lesions seen on CT or MR examinations. While the findings on these scans were initially interpreted as positive, our review, using a quantitative approach, proved that these results were in fact negative (when uptake greater than that of scalp activity was used as the criterion for a positive study). On two scans, areas of activity similar to but not greater than that of the scalp were noted to be in proximity to adjacent structures; namely, the skull base, which may also have caused confusion in interpretation (Figs 1–3).

## Discussion

The efficacy of thallium-201 in diagnosing cerebral neoplasms is well known. A large-scale study by Ancrì et al (4) revealed the superior sensitivity and contrast of thallium-201 over technetium-99m pertechnetate in the detection of cerebral neoplasms. Since that time, numerous studies have documented the utility of both planar and  $^{201}\text{Tl}$ -SPECT cerebral imaging in detecting neoplasms (3, 5–9, 13). The degree of radionuclide uptake by cerebral lesions has been shown to roughly correspond to the histologic grade of the neoplasm (5). In general, neither normal brain nor nonneoplastic disease accumulates significant amounts of the tracer. Thallium behaves biologically like potassium and is taken up intracellularly by three proposed mechanisms: 1) the  $\text{Na}^+ - \text{K}^+$  ATPase system, 2) an  $\text{Na}^+ - \text{K}^+ - \text{Cl}^-$  cotransport system, and 3) a



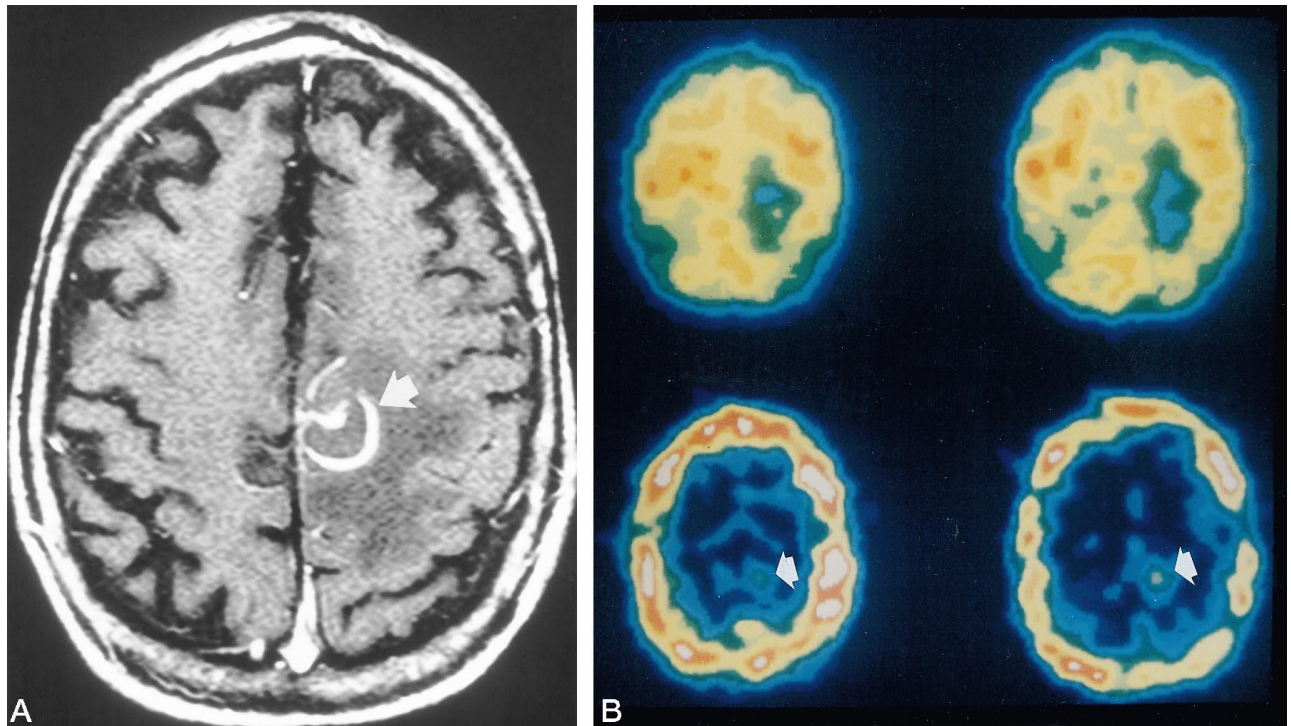


FIG 1. Mild thallium uptake by toxoplasmosis.

A, Postcontrast axial T1-weighted (600/30/2) MR image of the brain shows a ring-enhancing lesion with surrounding edema in the left parasagittal frontal lobe (*arrow*).

B, Axial brain <sup>201</sup>Tl-SPECT scans show an area of mild (less than that of the scalp) thallium uptake (*arrows*), corresponding to the lesion seen on the MR image. The upper two images represent corresponding HMPAO perfusion images.

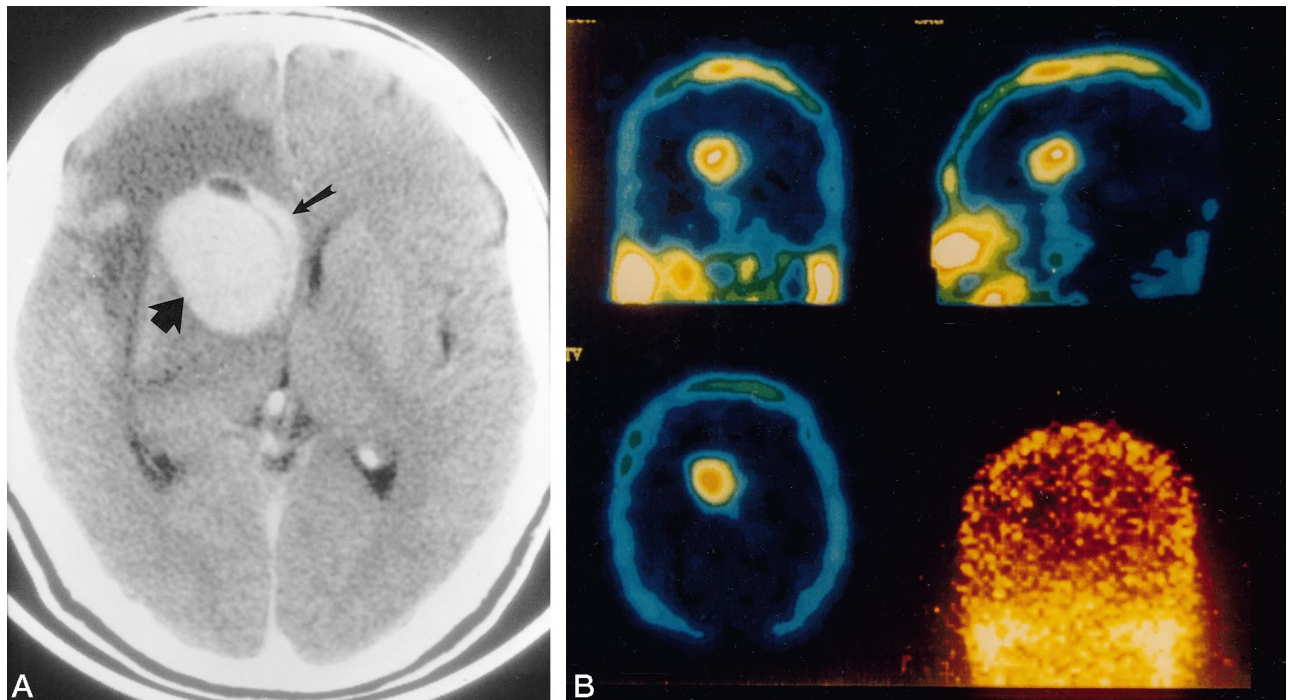


FIG 2. Lymphoma with marked thallium uptake.

A, Contrast-enhanced CT scan of the brain shows a large enhancing lesion in the right basal ganglia (*small arrow*) with adjacent subependymal enhancement (*large arrow*) and vasogenic edema.

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

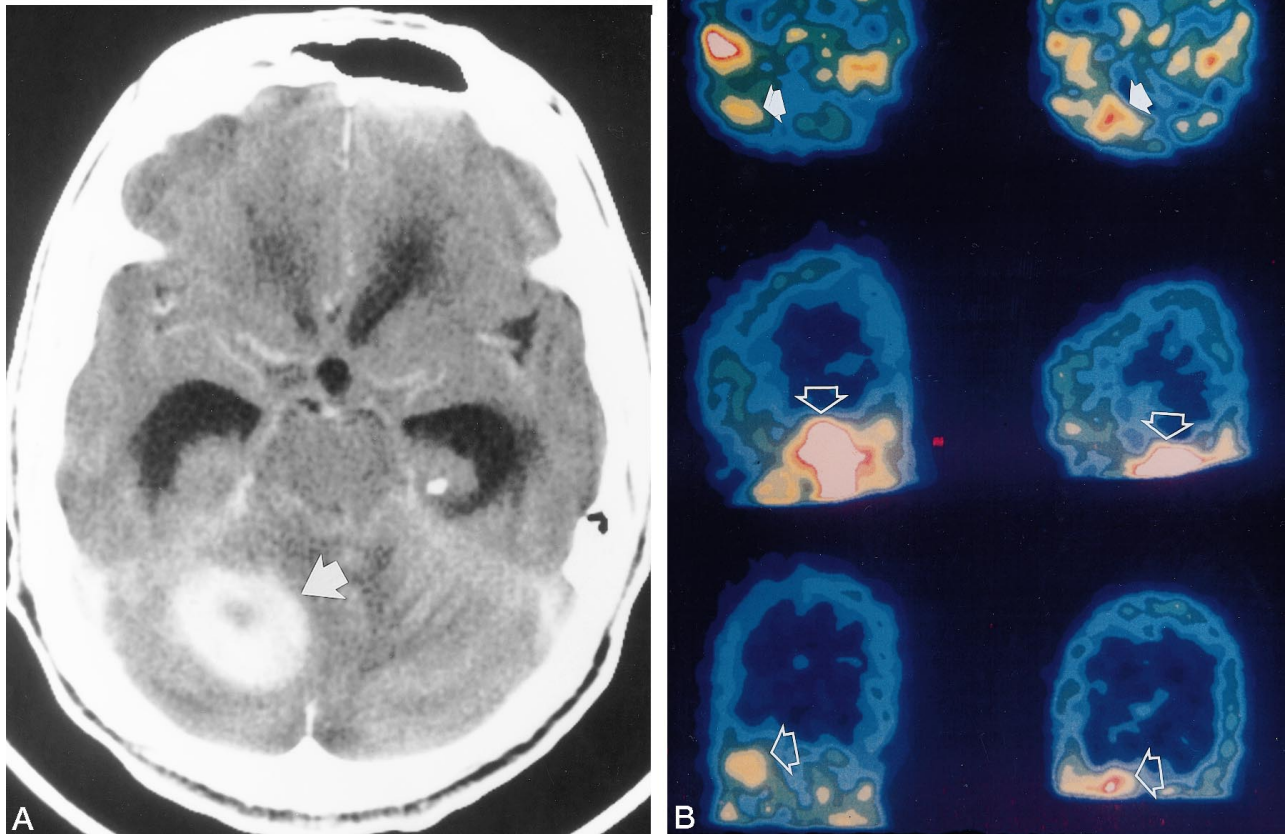


FIG 3. Right skull base intense thallium uptake simulating uptake in right posterior fossa toxoplasma lesion.

A, Contrast-enhanced CT scan of the brain shows a thick ring-enhancing lesion of the right cerebellum (*arrow*) with surrounding vasogenic edema.

B, Axial, sagittal, and coronal brain  $^{201}\text{Tl}$ -SPECT scans show an area of uptake in the region of the right posterior fossa, which on axial images appears to correspond to the lesion seen on CT scans (*closed arrows*). This is better seen on coronal and sagittal scans as simply representing activity in a portion of the skull base (*open arrows*).

$\text{Ca}^{2+}$ -dependent ion channel (17). Its uptake is also influenced by blood flow, cell viability, and membrane permeability. Many of these processes are accentuated in actively growing and dividing cells, such as in neoplasms. While blood-brain barrier breakdown as a contributing cause of thallium accumulation has been theorized, the noticeable absence of thallium uptake in nonneoplastic lesions with increased blood-brain barrier breakdown, such as radiation necrosis or resolving hematomas, makes this less plausible.

Cases of high-grade thallium uptake in nonneoplastic processes have been known to occur; notably in two reported cases: one of cerebral candidiasis (18) and one of a bacterial brain abscess (17). Postulated mechanisms for the abnormal thallium accumulation in these instances are related to the nature of the inflammatory infiltrate surrounding the infectious process, with intense reactive gliosis and endothelial proliferation simulating the biochemical milieu of a neoplastic process. Another potential cause of false-positive findings is the qualitative visual interpretation of borderline uptake as neoplasia, particularly in

ruling out lymphoma in patients with AIDS, as this is typically a high-grade lesion.

Several quantitative methods for evaluating a suspected lesion have been discussed in the literature, such as that proposed by Kim et al (5), in which a thallium-201 index ratio is calculated on the basis of the ratio of counts within a lesion as compared with the counts in the contralateral, presumably normal, side. The scalp and cardiac blood pools have also been proposed as regions for comparison (3, 5). The usefulness of such a ratio in differentiating lymphoma from nonneoplastic processes in AIDS patients was shown in a study by O'Malley et al in 1994 (7), in which there was a marked disparity between the ratios of neoplastic and nonneoplastic lesions in AIDS patients, with the ratio of the study's one false-positive result (calculated retrospectively) falling well within the nonneoplastic range. Similarly, in the case of the eight false-positive results that we discovered at our institution, the lesions described when reviewed retrospectively displayed weak uptake only (as well as appearing smaller in size than the lesion seen on CT



or MR examinations), and such a quantitative analysis may have prevented confusion in these cases.

Reported false-negative findings on  $^{201}\text{Tl}$ -SPECT scans of neoplasm, particularly of CNS lymphoma in AIDS patients, are rare. They are thought to result from marked tumor necrosis, with one case reported recently by Berry et al (6). Another recent report by Fisher et al (16) describes two large lesions (in one patient) of CNS lymphoma not detected by  $^{201}\text{Tl}$ -SPECT. While the authors stated that the cause of this lack of uptake was unclear, the tumors were noted histologically to contain extensive areas of necrosis.

Lesion size below the limit of lesion resolution by the gamma camera (about 6 to 8 mm) is another reported cause of missed lesions. Borderline uptake interpreted as being below the threshold for tumor activity could also potentially pose a problem, as could detection of ependymal or gyral tumor involvement.

### Conclusion

$^{201}\text{Tl}$ -SPECT of the brain is an effective means of examining AIDS patients with cerebral mass lesions, because it has a high sensitivity for neoplastic processes, the detection of which has a profound impact on clinical decision making. Specificity can be improved by consistently performing and reporting a quantitative analysis of all suspected lesions. In our series of 162 patients with mass lesions who had brain  $^{201}\text{Tl}$ -SPECT examinations, all 43 cases of lymphoma were correctly diagnosed. Lymphoma could be ruled out in the remainder by performing a quantitative analysis of the  $^{201}\text{Tl}$ -SPECT scans, in which lesions with activity not greater than that of scalp were excluded (100% sensitivity and specificity).

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