Extracranial Metastatic Glioblastoma: Appearance on Thallium-201-Chloride/ Technetium-99m-HMPAO SPECT Images

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Sequential thallium-201-chloride and technetium-99m-hexamethylpropyleneamine oxime single-photon emission computed tomography (SPECT) images were obtained in a patient with extracranial metastatic glioblastoma multiforme. Thallium-201 uptake was high (three times the scalp background) in all pathologically confirmed extracranial metastases and moderate (1.6 times scalp background) intracranially, where most biopsy specimens showed gliosis with scattered atypical astrocytes. Technetium-99m-HMPAO uptake was decreased intracranially in the right frontal and parietal lobes which had been irradiated. It was also decreased in one well-encapsulated scalp lesion and high in another scalp mass with less defined borders. Possible mechanisms of tumor uptake of these agents are reviewed.

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After surgery and radiotherapy, identification of residual or recurrent intracranial glioblastoma is a diagnostic challenge since computerized tomography (CT) and magnetic resonance imaging (MRI) are unable to distinguish post-treatment changes (edema, gliosis, and necrosis) from active tumor (*1*). Furthermore, histopathologic findings at this stage may have little prognostic value since the metabolic function of tumor cells may be significantly suppressed after iodine-125 implants (*2*). Positron emission tomography (PET) has been shown to be effective in making this distinction (*3,4*), but it is expensive and not widely available.

Recently, thallium-201 (^{201}Tl) chloride uptake has been used in the quantitative estimation of residual astrocytomas after radiation therapy (*5*). Thallium-201-chloride uptake has also been shown to correlate with the malignancy grade of primary brain tumors, before and after irradiation (*6*). In addition, preliminary studies in our laboratory have shown that the combined use of ^{201}Tl and perfusion imaging with technetium-99m-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) enhances the ability to distinguish glioma from radiation necrosis, particularly in cases of moderate ^{201}Tl uptake, where decreased ^{99m}Tc-HMPAO uptake suggests radiation necrosis (*7*).

We used sequential ^{201}Tl and ^{99m}Tc-HMPAO SPECT to study extracranial uptake of these tracers in a patient with scalp metastases after surgical removal of a right hemisphere glioblastoma multiforme and radiation therapy.

CASE REPORT

A 26-yr-old white female underwent a right temporal craniotomy and subtotal resection for a posterior right temporal glioblastoma. External beam radiation therapy was followed by stereotactic implantation of high activity iodine-125 seeds.

After the initial treatment, three scalp lesions and one cervical lymph node were confirmed to be metastatic glioblastoma. The patient underwent electron beam therapy to the scalp and chemotherapy for 6 mo.

Approximately 16 mo after the primary tumor resection, additional lesions over the right temporal and parietal areas of the scalp were identified. A CT scan obtained at this time showed contrast enhancement intracranially, which was felt to be due to recurrent tumor or radiation necrosis.

SPECT images were performed after obtaining the patient's informed consent. Cobalt-57 markers (5 μCi) were placed over three scalp positions to assist in positioning and to assess patient motion during acquisition. After the i.v. injection of 3 mCi of ^{201}Tl-chloride, the patient was positioned in the ASPECT brain imaging system (*8*). Data were acquired in 120 projections with a 360-degree rotation of the collimators (74–80 keV photopeak). After acquisition was completed, and without moving the patient, ^{99m}Tc-HMPAO (15–20 mCi) was injected intravenously and a second SPECT image was acquired (140 ± 14 and 119 ± 7 keV photopeaks). After acquisition, the collimator and crystal corrections were performed. The projections were prefiltered (Butterworth filter) and the

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reconstructed slices were attenuation corrected and displayed on a 128 × 128 matrix (1.67 mm^2 pixel size) as a set of 64 transaxial slices (1.76 mm slice thickness).

Matched transaxial slices were visually assessed for areas of abnormally increased or decreased uptake and regions of interest were drawn around areas of maximal ^{201}Tl activity and normal scalp (Fig. 1). Thallium-201 uptake was judged to be high, moderate, or low relative to scalp according to a maximal ^{201}Tl lesion/scalp activity ratio (low = <1.0; moderate = 1.0 to 2.0; high = >2.0). Normal brain corresponded to low ^{201}Tl uptake. Local perfusion was judged to be increased, similar, or decreased relative to a corresponding region of the contralateral hemisphere.

As depicted in Figure 1C, a moderate intensity (1.6 times the scalp activity) ring-shaped region of ^{201}Tl uptake corresponded to the right hemisphere area of edema and necrosis on MRI. Perfusion, as assessed by ^{99m}Tc-HMPAO, was significantly decreased in this area. There was intense focal ^{201}Tl uptake over the right frontal scalp (3.4 times the scalp activity) and over the right temporal scalp (2.9 times the scalp activity) (Fig. 1A-B). Technetium-99m-HMPAO uptake was increased over the anterior lesion only. On the basis of our previous experience, it was concluded that there was a low probability of significant intracranial tumor recurrence but, with two foci of abnormal ^{201}Tl uptake in the scalp suggesting metastatic recurrence.

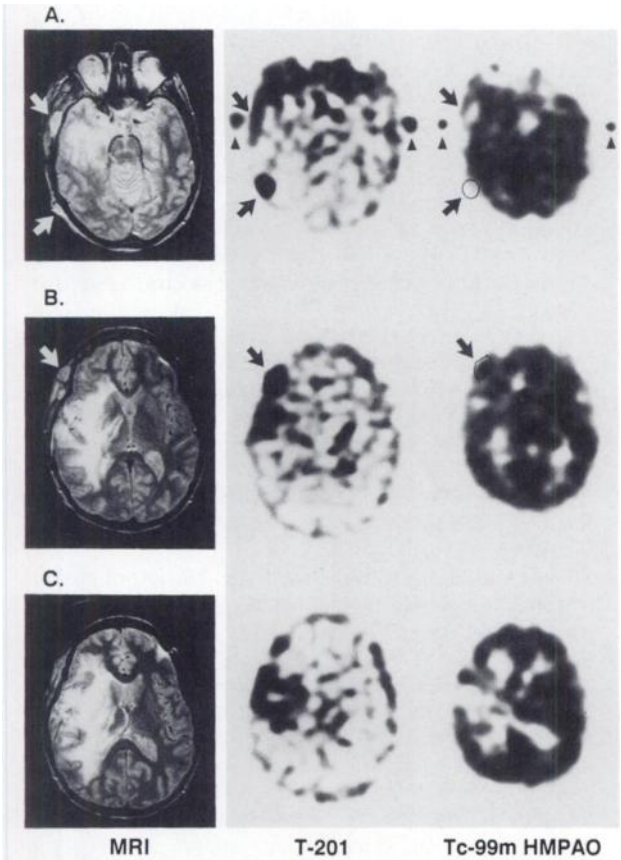

FIGURE 1
Matching MRI (TR 3000 ms, TE 30 ms), ^{201}Tl-chloride, and ^{99m}Tc-HMPAO images at different levels of the brain. (A-B) MRI images show increased signal in the right temporal lobe and, peripherally, focal areas of signal isointense to the brain in the scalp overlying the right frontal and temporal regions (white arrows). There is increased ^{201}Tl uptake in both scalp lesions (black arrows), and ^{99m}Tc-HMPAO uptake in the frontal, but not in the parietal scalp lesion (black arrow/circle). Cobalt-57 markers are identified (black arrowheads). (C) MRI image shows large area of abnormally increased T2-signal intracranially in the right hemisphere. There is localized ^{201}Tl uptake with associated decreased perfusion.

The patient's scalp lesions were excised and multiple intracranial biopsies of the tumor were taken. Pathologic evaluation showed that the anterior scalp lesion was gelatinous and not well circumscribed, while the posterior lesion was firm and well-encapsulated within the temporalis muscle. Both lesions were described as malignant glioblastoma, histologically similar to the primary tumor. Intracranial biopsy specimens revealed necrotic tissue with gliosis and scattered infiltrating anaplastic cells, but no major tumor focus.

Forty-three days later, approximately 17 mo after initial diagnosis and surgery, the patient returned with a new, rapidly enlarging extracranial lesion in the right temporal lobe. There was an increase in size and contrast enhancement intracranially, in the right frontoparietal area. In addition, extracranial masses in the right subgaleal region and infratemporal fossa were present.

A repeat ^{201}Tl and ^{99m}Tc-HMPAO SPECT study showed intense and extensive ^{201}Tl uptake in the right infratemporal fossa, with ^{99m}Tc-HMPAO uptake at its superior and inferior borders. Intracranially, ^{201}Tl uptake was unchanged and ^{99m}Tc-HMPAO uptake was decreased in the right frontal, temporal and parietal regions, suggesting recurrent scalp metastases but without significant intracranial recurrence.

Extensive resection of the extracranial masses was performed and these were shown to be metastatic glioblastoma. Intracranial biopsies were again negative for recurrent tumor.

DISCUSSION

Thallium-201-chloride is a potassium analog but with significantly greater affinity for the Na^+-K^+ ATPase pump (*9*) and a slower washout from cells than potassium (*10*). It does not cross the intact blood-brain barrier (BBB) in significant amounts. In glioblastomas, however, disruption of this protective barrier and neovascularity favor ^{201}Tl-chloride uptake (*11,12*). In this case, ^{201}Tl uptake was intense in scalp metastases of glioblastoma. Without a BBB to prevent detectable transcapillary transport of ionic ^{201}Tl, scalp tumor uptake of this radiotracer may be dependent only on cell membrane Na^+-K^+ ATPase function and on diffusion (*13–15*), but the weighted contribution of these factors to the net ^{201}Tl uptake is unknown.

Technetium-99m-HMPAO, a neutral lipophilic compound, crosses the intact BBB and distributes proportionally to regional blood flow in human subjects (*16,17*). Recent studies, comparing ^{99m}Tc-HMPAO with well-established regional cerebral blood flow measurement techniques have demonstrated a flow-dependent uptake and retention of this tracer in primary brain tumors (*18*), but its tumor cell kinetics is unknown. In addition, the effects of radiotherapy on both ^{201}Tl and

^{99m}Tc-HMPAO uptake mechanisms have not been studied and remain to be determined.

Both scalp metastatic foci were avid for ^{201}Tl in keeping with prior reports of marked ^{201}Tl uptake in glioblastoma. However, ^{99m}Tc-HMPAO activity was increased only in the anterior scalp lesion (Fig. 1). These lesions differed macroscopically, as a well-defined capsule surrounded the posterior metastasis with decreased ^{99m}Tc-HMPAO uptake, while the anterior lesion had no such capsule. Technetium-99m-HMPAO uptake in metastatic lesions may be related to neovascularity with a facilitated transport across abnormal vessel walls and cell membranes (*11–13*). Although blood flow and metabolism vary over a wider range of values in tumor tissue than in normal brain (*19–22*), this fact alone does not explain the difference in ^{99m}Tc-HMPAO uptake by the histologically similar scalp lesions with similar ^{201}Tl uptake. Variability in the proliferative potential of histopathologically similar gliomas has recently been demonstrated by labelling of tumor cells undergoing DNA synthesis (*23*). If ^{99m}Tc-HMPAO uptake is related to tumor cell proliferative potential, histopathologically similar tumors with different proliferative capabilities would explain the observed difference in uptake intensities. After resection of two metastatic scalp lesions, only the anterior one recurred suggesting greater aggressiveness.

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