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Transient Cranial Neuropathy in Prostatic Cancer with Bone Metastases after Rhenium-186-HEDP Treatment

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Rhenium-186 (tin) hydroxyethylidene diphosphonate (^{186}Re-HEDP), a bone-seeking radiopharmaceutical, has been successfully used in the treatment of patients with painful bone metastases. Toxicity is usually limited to reversible thrombocytopenia. An infrequent but clinically significant side effect is the occurrence of transient cranial neuropathy. We report on two prostatic cancer patients with metastatic bone cancer. Both patients developed transient cranial neuropathy shortly after treatment with ^{186}Re-HEDP. Transient neuropathy of cranial nerves needs to be distinguished from neurological abnormalities caused by disease progression.

Key Words: rhenium-186-HEDP; bone metastases; cranial neuropathy

J Nucl Med 1996; 37:465–467

Up to 80% of patients with prostate cancer develop painful bone metastases, including metastases to vertebral bodies (*1*). The majority of these patients will require single or multiple courses of external beam radiotherapy to palliate the pain and/or treat or prevent epidural compression caused by local tumor progression. Alternatively, bone-seeking radiopharmaceuticals have recently been used successfully in the treatment of painful bone metastases (*2–4*). Rhenium-186 (tin) hydroxyethylidene diphosphonate (^{186}Re-HEDP) is one of the radiopharmaceuticals currently under investigation for this indication. Pain relief has been reported in up to 80% of the patients (*5–7*) and toxicity is limited to transient bone marrow suppression, typically presenting as thrombocytopenia (*8*). Metastases to the base of the skull are the most common causes of cranial neuropathy in patients with systemic malignancies, especially in those patients suffering from prostate and breast cancer (*9,10*). To date, at our institution, 154 treatments of ^{186}Re-HEDP were given to patients with metastatic bone pain originating from prostatic cancer.

This report describes two patients with metastatic prostate cancer who developed transient cranial neuropathy shortly after a therapeutic dose of ^{186}Re-HEDP. The low frequency of these adverse events and the transient character are important in distinguishing from much more frequently occurring neurological dysfunction caused by progressive growth of the metastatic tumor.

CASE REPORT

Patient 1

A 64-yr-old man was referred to our department because of increasing bone pain due to hormone-resistant metastatic prostate cancer. Six months after the presentation of the primary tumor, bone metastases were detected and systemic therapy with luteinizing hormone releasing hormone (LHRH) analogues was started. Later on, cyproterone acetate was added. Stabilization of the disease lasted about 1 yr. He then received a therapeutic dose of 1295 MBq ^{186}Re-HEDP. The day after ^{186}Re-HEDP administration the patient noted increasing difficulty in swallowing solid foods and liquids. This was reported by the patient at the first follow-up visit after 1 wk. At that time, he already noted some improvement of these complaints. On neurological examination, paresis of the right pharyngeal musculature and a deviation of tongue motility towards the right side was diagnosed, indicating dysfunction of the

Received Jan. 18, 1995; revision accepted Jun. 29, 1995.
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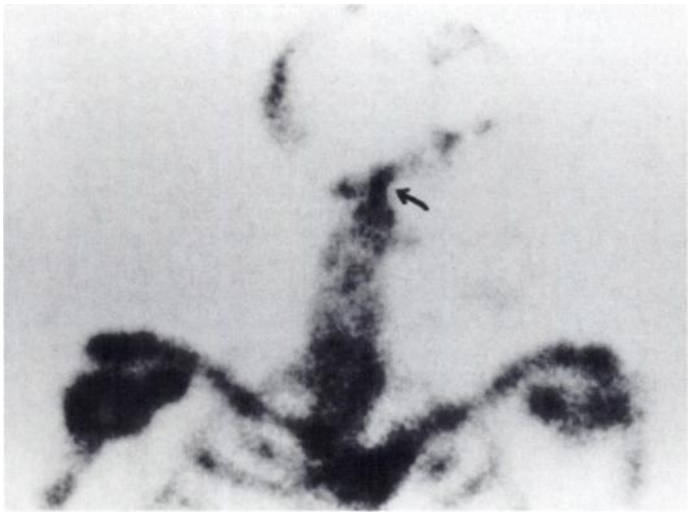

FIGURE 1. Scintigraphic evidence of bone metastasis at the skull base in Patient 1 (arrow).

right glossopharyngeal and hypoglossal nerves. Bone scintigraphy (Fig. 1) showed involvement of the bone of the base of the skull and MRI (Fig. 2) revealed a lesion in the region of the clivus encompassing the jugular foramen and hypoglossal canal on the right. There was also a suggestion of thickening of the periosteum of the base of the skull, adjacent to the ventral part of the brainstem. During the second week after the onset of complaints, spontaneous regression of the paresis continued and the intake of food was less hampered. Neurological examination at that time no longer demonstrated paresis of the pharyngeal musculature and tongue motility was improved considerably.

Patient 2

This 64-yr-old man underwent prostatectomy for an obstructive prostate. Bone metastases were also detected at diagnosis. The patient was subsequently treated with an LHRH analog. One year later, pain in the lumbosacral spine occurred and because of the presence of multiple bone lesions the patient was referred for palliative treatment with ^{186}Re-HEDP. Bone scintigraphy revealed multiple bone metastases and diffuse involvement of the mandibula (Fig. 3). He received a dose of 1850 MBq ^{186}Re-HEDP intravenously. After an uneventful administration and no objective or subjective abnormalities during the first 24 hr, the patient experienced numbness on his lower lip, indicating mandibular nerve dysfunction. This occurred during the second week after ^{186}Re-HEDP treatment and was reported by the patient at his second outpatient visit, i.e., 5 days after the start of his complaints. Because there was strong clinical evidence that these complaints were not progressive, we did not initiate specific treatment such as corticosteroid therapy. The dysfunction improved over the following weeks and had resolved completely 4 wk after treatment.

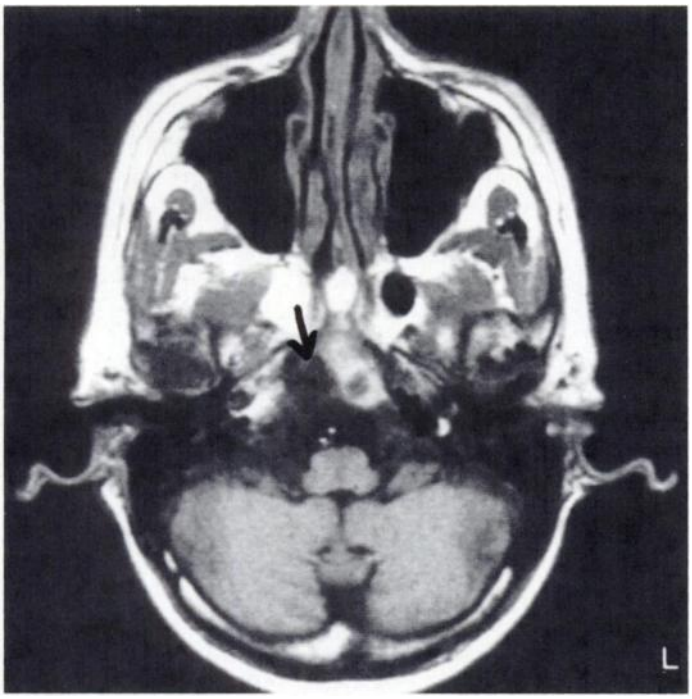

FIGURE 2. MRI scan of Patient 1 shows bone involvement of the skull base at the right side just posterior to the sphenoid sinus (arrow).

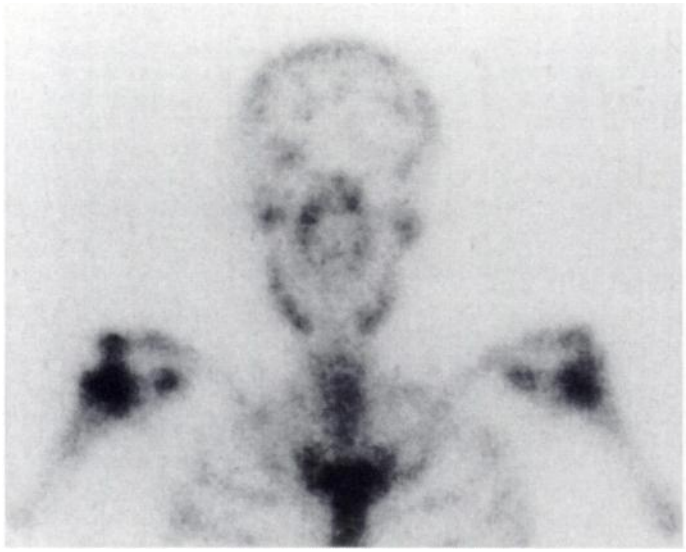

FIGURE 3. Bone scintigram reveals metastatic involvement of the mandibula in Patient 2.

DISCUSSION

Transient cranial neuropathy was found in two patients with painful bone metastases shortly after treatment with ^{186}Re-HEDP. Diagnostic bone scintigrams of these patients showed metastatic involvement at the site of the foramina corresponding with the dysfunctional cranial nerves. Additionally, an MRI scan of the head in one patient clearly demonstrated a metastatic lesion in the region of the foramina, where the nerves in this patient exit the skull. The presence of metastatic bone involvement in the region of cranial foramina and the temporary nature of the corresponding neurological deficits suggest that transient edema in response to local radiation may have been responsible. Another explanation might be direct radiation injury (*11*) of these cranial nerves surrounded by metastatic bone tissue.

A similar mechanism is thought to be responsible for the deterioration of neurological function seen in patients who are treated with external beam radiotherapy for spinal cord compression due to bone metastases. These complications are frequently treated with high doses of corticosteroids (*12,13*). Because the neurological dysfunction in the first patient was already improving at his first outpatient visit and the stable situation in the second patient, we decided not to initiate this therapy, but rather, chose to await the natural course. Although transient cranial neuropathy is a rather uncommon event after treatment with bone-seeking radiopharmaceuticals, physicians should be aware of this complication when treating patients with ^{186}Re-HEDP. Furthermore, this condition must be differentiated from neurological dysfunction as a result of progressive disease. In

that case external beam radiotherapy combined with high dose corticosteroid treatment is indicated (*14*).

ACKNOWLEDGMENTS

The authors thank Jan de Groot and Ludo Peters for audiovisual assistance and Ruth van der Wijngaart for administrative assistance with these studies.

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Reversible Cerebral Perfusion Abnormalities Associated with Cyclosporine Therapy in Orthotopic Liver Transplantation

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A 60-yr-old woman experienced several episodes of generalized seizures following 2 wk of immunosuppressive therapy with cyclosporine for orthotopic liver transplantation. CT showed low density in the white matter of the parieto-occipital lobes. A ^{99m}Tc-HMPAO brain SPECT showed diminished perfusion in the parieto-occipital cortex bilaterally. Although the cyclosporine was discontinued, the patient's neurologic status initially worsened and then improved over the next several days. Repeat perfusion brain SPECT showed resolution of most of the perfusion abnormalities, while repeat CT showed persistent white matter changes in the parieto-occipital lobes. We report the presence of reversible cortical perfusion abnormalities in conjunction with cyclosporine therapy. The findings suggest that perfusion brain SPECT may be a sensitive monitor of cyclosporine-induced neurotoxicity.

Key Words: cyclosporine; liver transplantation; seizures; brain SPECT

J Nucl Med 1996; 37:467–469

Orthotopic liver transplantation is associated with neurologic complications in 19%–47% of the cases (*1–4*). The clinical presentations include alterations of consciousness, seizures, myoclonus, tremor, headache, quadriplegia, cerebellar dysfunction and polyneuropathy (*4*). Cyclosporine has been used in humans for immunosuppression after transplantation and has reduced the rate of allograft rejection substantially. Cyclosporine, however, is implicated as a major cause of drug-induced neurotoxicity (*5*). Blood levels of cyclosporine do not correlate clearly with neurologic toxicity. CT and MRI may show a characteristic abnormality in the brain. These changes, however, are not invariably present nor does their resolution parallel clinical improvement (*6*). Cerebral blood flow scintigraphy using ^{99m}Tc-HMPAO and SPECT imaging is a readily available and accurate technique for detection of perfusion abnormalities in patients with cerebrovascular and neurological abnormalities. We present the findings of brain perfusion studies in a case of transient cyclosporine-induced neurotoxicity that showed good temporal correlation with the clinical course of the disease.

Received Feb. 2, 1995; revision accepted Jun. 17, 1995.

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CASE REPORT

A 60-yr-old woman with cirrhosis, secondary to chronic hepatitis, underwent an uncomplicated liver transplantation. Six weeks after discharge, she was readmitted with signs of rejection and treated with intravenous and oral cyclosporine. Her trough cyclosporine blood levels were monitored daily, using the fluorescent polarization immunoassay with monoclonal antibodies. She subsequently received a second liver transplantation. Five days after surgery the patient experienced a grand mal seizure which was controlled with intravenous diazepam and phenytoin. At that time, the cyclosporine trough level was 378 ng/ml (normal value <350 ng/ml). Her serum magnesium level was 1.1 mg/dl (normal 1.5–2.5 mg/dl) and her cholesterol level was 121 mg/dl. A normal serum ammonia level of 31 mcg/dl (normal 15–50 mcg/dl) and a normally functioning liver after transplantation excluded the possibility of hepatic encephalopathy. Noncontrast head CT performed on the same day showed low density in the white matter of parieto-occipital regions bilaterally (Fig. 1A).

Brain perfusion SPECT imaging was performed using a dual-head gamma camera equipped with a low-energy, high-resolution collimator. Imaging began 30 min after intravenous injection of 740 MBq ^{99m}Tc-HMPAO. Ninety-six frames of 30 sec were acquired. The images were prefiltered using a Butterworth filter