Letters to the Editor

Accumulation of N-Isopropyl-p-[^{123}I]Iodoamphetamine and [^{99m}Tc]Hexamethyl-Propyleneamine Oxime in Metastatic Hepatocellular Carcinoma

TO THE EDITOR: Recently, technetium-99m-Sn-N-pyridoxyl-5-methyltryptophan ([^{99m}Tc]PMT) which is concentrated in hepatobiliary tract was also used in delineating some extrahepatic metastases of hepatomas (*1*). N-isopropyl-p-(iodine-123)iodoamphetamine ([^{123}I]IMP and [^{99m}Tc]hexamethylpropyleneamine oxime ([^{99m}Tc]HM-PAO), developed for cerebral perfusion imaging, distribute physiologically in the normal liver tissue. In the diagnostic exploration for metastatic lesions from HCC, we studied two cases with bone metastases from HCC using [^{123}I]IMP and [^{99m}Tc]HM-PAO. The bony metastases accumulated both tracers as well as the hepatobiliary agent.

Planar images were obtained at 120 min after the i.v. administration of 3 mCi [^{123}I]IMP or 10 mCi [^{99m}Tc]HM-PAO, using a conventional gamma camera. Single photon emission computed tomography (SPECTs) of brain, using a rotating gamma camera was performed at 30 min or 15 min, respectively for the two agents.

Hepatobiliary scintigraphy with 5 mCi [^{99m}Tc]PMT was performed at 30 and 120 min following i.v. injection and bone scintigraphy with 15 mCi [^{99m}Tc]hydroxymethylene diphosphonate (^{99m}Tc-HMDP) at 120 min. after the i.v. administration.

A 50-yr-old man was admitted to our hospital because of gradually increasing dysarthria, dysphagia, and neck pain. Two years before referral, he was diagnosed to have HCC and underwent a transcatheter arterial embolization. Thereafter, hoarseness, dysphagia, dysarthria, and left neck pain had developed and progressed. On a brain computed tomographic (CT) scan taken on admission, the left occipital bone was

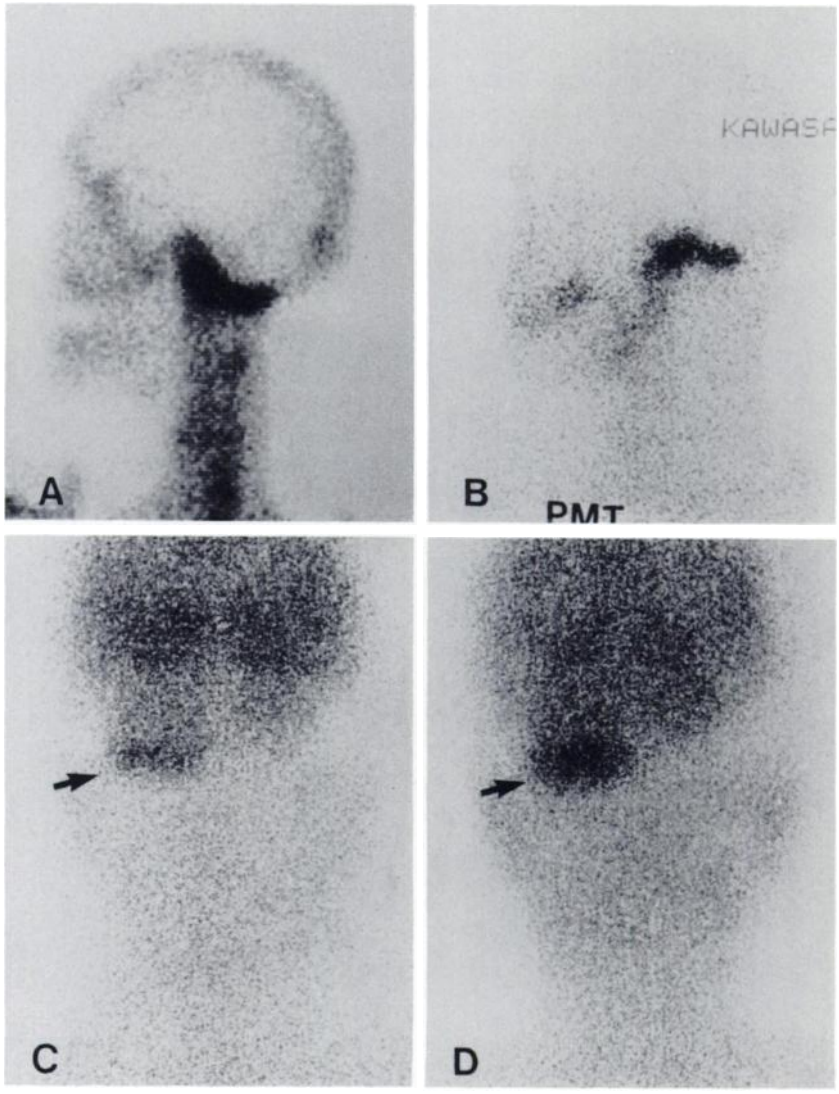

FIGURE 1
Bone scintigraphy (A) using [^{99m}Tc] HMDP and [^{99m}Tc]PMT scintigraphy (B) (left lateral view). In the skull base the increased concave accumulation in the former, and the increased convex accumulation in the latter were demonstrated. [^{123}I]IMP (C) and [^{99m}Tc]HM-PAO (D) scintigraphies (posterior view). Both radiopharmaceuticals demonstrate the slightly increased accumulation in the left skull base (arrow).

destroyed, and the tumor was protruded into intracranial space from the skull base, with a resultant obstruction of the hypoglossal canal and jugular foramen. The lesion in the skull base was histologically confirmed to be well-differentiated metastatic HCC at autopsy. His AFP level was 34 ng/ml.

On bone scintigraphy, an intense accumulation of radioactivity was observed in the left posterior skull base (Fig. 1A), the left ilium and the right ischium.

The hepatobiliary scintigraphy showed a convex shaped area of markedly increased accumulation of radioactivity, comparable to the concave shape seen on bone scintigraphy, in the left posterior skull base (Fig. 1B). Primary lesion in the liver showed slight increased uptake of the tracer.

Iodine-123 IMP scintigraphy and [^{99m}Tc]HM-PAO scintigraphy showed a significant accumulation in the left skull base (Fig. 1C, 1D) and the left ilium. No increased nor decreased accumulation of the tracers was seen in the primary lesion in the liver. Single photon emission computed tomography of the brain using [^{123}I]IMP and [^{99m}Tc]HM-PAO also showed an area of high radioactivity at the left posterior skull base.

A second case was encountered, a 62-yr-old man admitted to our hospital with complaints of lumbago and anterior chest pain. A chest x-ray film revealed a mass lesion in his left upper lung field, suspected to be metastatic lung tumor from HCC. Six months after admission, he died of the gastrointestinal bleeding and liver dysfunction. The findings at autopsy revealed metastatic lesions from well-differentiated HCC to the left first and second rib, the lower thoracic and lumbar vertebrae, and the left femur. The mass lesion in his left upper lung field was a direct invasion from the left first and second rib lesions. His AFP level was 27 ng/ml.

Bone scintigraphy showed areas of slight increased uptake of the radionuclide in the left first rib, bilateral eleventh rib, left scapula, eleventh thoracic vertebra, and the left femur.

Technetium-99m-PMT scintigraphy revealed markedly increased accumulation in the left upper lung field, the sternum, the lower thoracic vertebra and the left femur, and slightly increased uptake of the tracer in the primary lesion in the liver.

Iodine-123 IMP and [^{99m}Tc]HM-PAO scintigraphies showed increased accumulation of radioactivity in the same areas of the sternum, the lower thoracic vertebra and the left femur. It showed no increased nor decreased uptake of the tracers in the primary lesion in the liver. However, [^{123}I]IMP did not accumulate in the metastatic lesion of the left upper lung field, while [^{99m}Tc]HM-PAO did.

It has been reported that some cholecystoscintigraphic agents such as [^{99m}Tc]PIPIDA (*2*), [^{99m}Tc]HIDA (*3*), and [^{99m}Tc]PMT (*1*) concentrate in metastatic lesions from HCC. In our two cases, [^{99m}Tc]PMT was also accumulated in the metastatic bone lesions, suggestive of originating from HCC. As for the 50-yr-old man, although both [^{99m}Tc]HMDP and [^{99m}Tc]PMT were accumulated in metastatic lesions, the distribution of two tracers was different: the concave shape for [^{99m}Tc]HMDP scintigraphy and the convex distribution for [^{99m}Tc]PMT scintigraphy (Fig. 1A and 1B). This finding might reflect that [^{99m}Tc]HMDP was accumulated in the reactive bone formation around the metastatic tumor, while [^{99m}Tc]PMT was in the tumor itself which was protruding intracranially as the CT scan. At the present time, [^{123}I]IMP and [^{99m}Tc]HM-PAO are mainly and widely used for the evaluation of the brain blood flow in cerebrovascular disease, epilepsy, dementia, brain tumor and so on. Both [^{123}I]IMP and [^{99m}Tc]HM-PAO are reported not to concentrate in most tumor tissues (*4–6*). However, a low-grade astrocytoma (*7*) or metastatic brain tumor from a small cell carcinoma of the lung (*8*) have concentrated [^{123}I]IMP. The mechanism of the uptake by the tumors could be attributed to the regional hyperemia and the increased extraction efficiencies for the [^{123}I]IMP, and/or the specific bindings to the amine receptors in the tumor cells. Furthermore, [^{123}I]IMP was also reported to concentrate in malignant melanoma (*9,10*). The mechanism of [^{123}I]IMP accumulation was speculated as being due to the nonspecific binding of the radiocompound to the melanin molecules in melanoma cells (*11*). However, Liewendahl et al. reported that [^{123}I]IMP did concentrate in amelanotic melanoma as well as melanotic melanoma (*10*). Thus, the mechanism of [^{123}I]IMP accumulation in tumor appears to be multi-factorial. The mechanism of the accumulation of [^{99m}Tc]HM-PAO in the HCC is also not known, but it might be attributed to the facts that [^{99m}Tc]HM-PAO is accumulated in the liver and is excreted into the bile duct (*12*).

Furthermore, in both cases presented here, the histologic findings showed well-differentiated hepatocellular carcinoma cells in the metastatic lesions. As [^{123}I]IMP and [^{99m}Tc]HM-PAO accumulated physiologically in the normal liver tissue, the well-differentiated tumor cells such as our cases might have the ability to accumulate these two radiopharmaceuticals. On the other hand, no significant uptake in the primary lesions was recognized. The high concentration of the tracers in the adjacent normal liver tissue might contribute to this finding.

Although the precise mechanism of the accumulation of [^{123}I]IMP and [^{99m}Tc]HM-PAO into the HCC is not clear, both agents have a potential of being useful tools in detecting metastatic lesions from HCC.

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Bone Formation in Metastatic Transitional Cell Carcinoma: Detection with Technetium-99m Methylene Diphosphonate

TO THE EDITOR: The occurrence of heterotopic bone formation associated with metastases of breast and colorectal carcinoma (*1–4*) as well as transitional cell carcinoma (*5–8*) has been infrequently reported. To our knowledge, this is the first reported case of the scintigraphic demonstration by technetium-99m methylene diphosphonate ([^{99m}Tc]MDP) of a soft-tissue metastasis of transitional cell carcinoma undergoing heterotopic ossification.

A 68-yr-old man with recurrent transitional cell carcinoma was admitted for severe anemia secondary to urethral bleeding. He was initially diagnosed with grade III transitional cell carcinoma of the left ureter 15 mo earlier, and had a left ureteronephrectomy at that time. Six months later, gross hematuria recurred and cystoscopy revealed a grade III recurrence at the previous operative site and at the right ureteral orifice. After pelvic irradiation with 20 Gy, a radical cystoprostatectomy with ileal conduit was performed. Preoperative evaluation, including a [^{99m}Tc]MDP bone scan, chest radiograph and abdominal CT scan, disclosed no evidence of metastatic disease.

Nine months after radical cystoprostatectomy, the patient was readmitted for severe anemia and urethral hemorrhage. A repeat [^{99m}Tc] scintigram showed no evidence of osseous metastatic disease, but an abnormal area of activity was present in the left supraclavicular region (Fig. 1A). The left shoulder roentgenogram demonstrated amorphous calcification in a well-defined focus corresponding to the abnormality on the bone scintigram (Fig. 1B).

Urethral fulguration was performed to control bleeding from recurrent carcinoma and the left supraclavicular mass was biopsied concurrently. A 2.0 by 1.8 cm grossly calcified mass was resected from the left supraclavicular region. Microscopically, the mass consisted of a single enlarged lymph node almost totally replaced by broad, well-developed, anastomosing bony trabeculae. Interspersed within the trabeculae were nests of malignant cells cytologically identical to the previously resected transitional cell carcinoma (Fig. 1C).

The ability of transitional-cell epithelium to induce heterotopic bone formation, or osseous metaplasia of soft tissue, was first documented by Huggins in 1931 (*8*). He performed auto-transplantation of normal dog transitional cell epithelium to fascia and muscle of the anterior abdominal wall. Bone formation occurred and was intimately related to growing transitional cell epithelium. Induction of heterotopic bone formation by transitional epithelium in humans was subsequently demonstrated by Welcker in 1950 (*9*).

Although not clearly defined, the mechanism of heterotopic bone formation is most likely related to production of a humoral factor by transitional cell epithelium (*10*), and may be similar to the bone-inducing substance, probably a protein, which has been isolated from mice osteogenic sarcoma cells (*11*).

Three cases of osseous metaplasia in metastatic transitional cell carcinoma and its roentgenographic appearance have been reported previously (*5–7*). To our knowledge, this is the first case report of the scintigraphic detection of heterotopic bone formation in metastases of transitional cell carcinoma. While skeletal scintigraphy has demonstrable utility in the evaluation of bone metastases in transitional cell carcinoma (*12*), the appearance of extraosseous uptake may also therefore suggest metastatic disease to soft tissue.

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