Annals of Nuclear Medicine Vol. 19, No. 1, 35–40, 2005

Extraosseous accumulation of ^{99m}Tc-HMDP to radiation nephropathy, mimicking recurrent neuroblastoma

Koichiro ABE,* Masayuki SASAKI,** Yasuo KUWABARA,* Hirofumi KOGA,* Shingo BABA,*
Koichiro KANEKO,* Kazutaka HAYASHI,* Yoshiyuki SHIOYAMA,*
Tatsuro TAJIRI,*** Sachiyo SUITA*** and Hiroshi HONDA*

*Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University
**Department of Health Sciences, School of Medicine, Kyushu University
***Department of Pediatric Surgery, Kyushu University

Objective: The aim of this study is to clarify the period of extraosseous accumulation of ^{99m}Tc-hydroxymethylenediphosphonate (HMDP) to radiation nephropathy mimicking recurrent or remnant neuroblastoma in the pararenal region. ***Methods:*** We reviewed five neuroblastoma and one ganglioneuroblastoma patients (2 boys and 4 girls aged 1–9 years) who underwent ^{99m}Tc-HMDP bone scintigraphies periodically before and after radiation therapy. ***Results:*** Increased renal uptake coincident with the radiation port appeared in 5 of 6 patients from 0 to 3 months (mean 1.7 months), and persisted up to 7 months after the completion of radiotherapy. Renal uptake of ^{99m}Tc-HMDP was gradually decreased, and eventually became accumulation defects in 5 of 6 patients from 6 to 17 months (mean 8.9 months) after radiotherapy. ***Conclusion:*** When extraosseous accumulation is found after radiation therapy in neuroblastoma patients, radiation nephropathy would be a candidate in the differential diagnosis besides recurrent or remnant tumor.

Key words: radiation nephropathy, ^{99m}Tc-HMDP bone scan, extraosseous accumulation, neuroblastoma

INTRODUCTION

NEUROBLASTOMA are malignant tumors derived from either adrenal gland or sympathetic nervous system, and are one of the most common extracranial solid tumors found in infants and children. Despite the availability of many therapeutic regimens, the prognosis of high-risk neuroblastoma patients is still poor. Bone is one of the most common sites of distant metastasis, even in patients who are at an earlier stage of the disease,[1] and systemic evaluation, including bone scintigraphy, is essential in order to plan treatment and predict the prognosis.

Extraosseous uptake by malignant tumors, benign tumors, cerebral infarction or myocardial infarction is well known in ^{99m}Tc phosphate compounds bone scintigraphy.[2–5] Like other neural crest-derived tumors, the extraosseous accumulations of ^{99m}Tc phosphate compounds into the original tumors are often observed in staging or follow-up studies of neuroblastoma patients.[6–8] Garty et al. analyzed 14 neuroblastoma patients, and reported that 71% of original tumors and 100% of osseous or extraosseous metastases were detected by ^{99m}Tc-methylenediphosphonate (MDP) studies.[6] The extraosseous accumulation of ^{99m}Tc phosphate compounds in the tumor might be accompanied by calcium deposition, which is often seen in the neuroblastoma, though the exact mechanism of extraosseous accumulation of ^{99m}Tc phosphate compounds is still unknown.

The kidney is one of the most highly radiosensitive organs, and radiation-induced nephropathy was initially reported in the 1920's.[9] It is characterized by progressive and chronic glomerular alterations and tubular and microvascular damage.[10–12] Since, in neuroblastoma patients, the radiation port is close to the kidney, and sometimes extends over it, radiation nephropathy could occur during or after radiotherapy. Several case reports

Received July 23, 2004, revision accepted October 18, 2004.
For reprint contact: Koichiro Abe, M.D., Department of Clinical Radiology, Kyushu University, 3–1–1 Maidashi, Higashi-ku, Fukuoka 812–8582, JAPAN.
E-mail: k-abe@radiol.med.kyushu-u.ac.jp

Table 1 Patients and radiotherapies

case	age (y)	sex	histology	stage	origin	radiation dose (Gy)	radiation port
1	1.8	M	Neuroblastoma	IVA	rt. adrenal	30.4	rt. kidney ~ paraspine
2	1.8	F	Neuroblastoma	IVB	lt. adrenal	30.0	lt. adrenal ~ paraspine
3	2.3	F	Ganglioneuroblastoma	IVA	lt. adrenal	30.0	lt. kidney ~ paraspine
4	3.6	F	Neuroblastoma	IVA	rt. adrenal	30.0	rt. adrenal ~ paraspine
5	4.8	M	Neuroblastoma	IVB	lt. adrenal	30.0	lt. kidney ~ paraspine
6	9.3	F	Neuroblastoma	IVA	lt. adrenal	30.0	lt. kidney ~ paraspine

Table 2 Time course of the renal uptake of ^{99m}Tc-HMDP

case	months after radiotherapy														
	before	0	1	2	3	4	5	6	7	8	9	10	11	12	17
1	±	+++				+++		+							
2	±	±			++	+++		+						±	−
3	+		+++		+			−							
4	±		±	±	++	++	+		+	−					
5	++		+			+		−							
6	++	+	+++			±		±		−					

The levels of renal uptakes of ^{99m}Tc-HMDP are noted according to the criteria described in Patients and Methods.

have demonstrated a high uptake of ^{99m}Tc phosphate compounds in nephritis or nephropathy occurring during radiation therapy.[10,13–17] High renal uptake due to radiation nephropathy might mimic recurrent or remnant tumors, and should be differentiated from them. Up to the present, there have been no studies analyzing the time course of renal uptake by radiation nephropathy besides case reports.

In this report, we present five neuroblastoma and one ganglioneuroblastoma patients who presented with the extraosseous accumulation of ^{99m}Tc-hydroxymethylenediphosphonate (HMDP) due to radiation nephropathy after radiotherapy to the abdomen. The time and duration of renal accumulation after radiotherapy were analyzed on serial ^{99m}Tc-HMDP bone scintigraphy.

MATERIALS AND METHODS

Patients

Six patients (2 boys, 4 girls) aged 1–9 years (mean ± SD = 3.8 ± 3.0 years) were included in this study (Table 1). Five of the children had neuroblastoma and one girl had ganglioneuroblastoma in the unilateral adrenal gland, which was confirmed histopathologically. Four were Stage IVA and 2 were Stage IVB. A total 30–30.4 Gy of irradiation fractionated over 20 days was given using a 6 MV linear accelerator, which covered the tumor and ipsilateral paravertebral region. The radiation port of all patients included the medial and/or upper margin of the ipsilateral kidney, and medial margin of the contralateral kidney in some patients.

Imaging and analysis

^{99m}Tc-HMDP bone scintigraphies were performed periodically before and after radiation therapy. Doses of 74–296 MBq of ^{99m}Tc-HMDP were administrated intravenously. Four hours after injection, anterior and posterior whole body images were obtained using gamma cameras (GCA-901A/WB; Toshiba, Tokyo, Japan, E.CAM; Siemens, IL, USA).

The level of renal uptake of ^{99m}Tc-HMDP was visually assessed and graded by three nuclear medicine physicians as follows:

(−): defect
(±): accumulation lower than ribs (normal)
(+): accumulation equal to ribs

(++): accumulation higher than ribs, but lower than lumbar spine

(+++): accumulation equal to or higher than lumbar spine

For case 2, a renoscintigraphy was performed. After a bolus injection of 111 MBq ^{99m}Tc-mercapto-acethyl-triglycine (MAG_3), renal images were acquired with a gamma camera (GCA-901A/WB; Toshiba, Tokyo, Japan) at 1, 5, 10 and 20 min.

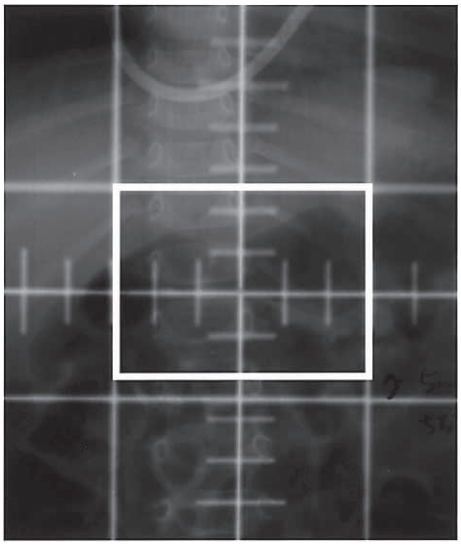

Fig. 1 Radiation portal in Case 2. Radiation portal is outlined by a rectangle. Radiation therapy of 30 Gy fractionated over 20 days was given through a 4.5- by 6.0-cm field with a 6 MV linear accelerator.

RESULTS

Time course of the renal uptake of ^{99m}Tc-HMDP for all 6 children is summarized in Table 2. Increasing accumulation of ^{99m}Tc-HMDP in the kidney appeared 0 to 3 months after the completion of radiotherapy, except for in case 5. After radiation therapy, the mean duration to the appearance of renal uptake was 1.7 months. In case 5, the accumulation of ^{99m}Tc-HMDP in the bilateral kidneys was high even before the beginning of irradiation, because of the chemotherapy this patient had already received. The increased renal uptake was gradually resolved, and an accumulation defect was found 6 to 17 months (mean 8.9 months) after the completion of radiotherapy, except in case 1. It was unknown when renal uptake disappeared in case 1, because his parents withdrew him from the follow-up study midway through it. Considering this issue from another point-of-view, increased renal uptake was seen 0 to 7 months after the completion of radiation therapy.

Case 2 was a 1.8-year-old girl who presented with delayed development, and had been running a fever periodically since the age of 1.2 years. She was found to have a left adrenal neuroblastoma which had invaded the left kidney and renal vein. She underwent a total of 5 courses of chemotherapy, and a course of radiation therapy to the left adrenal and paravertebral region from Th11 to L2 (Fig. 1). Radiation therapy of 30 Gy was fractionated over 20 days, and was given through a 4.5- by 6.0-cm field with a 6 MV linear accelerator. ^{99m}Tc-HMDP bone scintigraphy was performed 2 months before irradiation, and demonstrated normal renal uptake (Fig. 2A, *upper panel*). ^{99m}Tc-HMDP bone scintigraphy performed 4 months after the completion of radiotherapy revealed

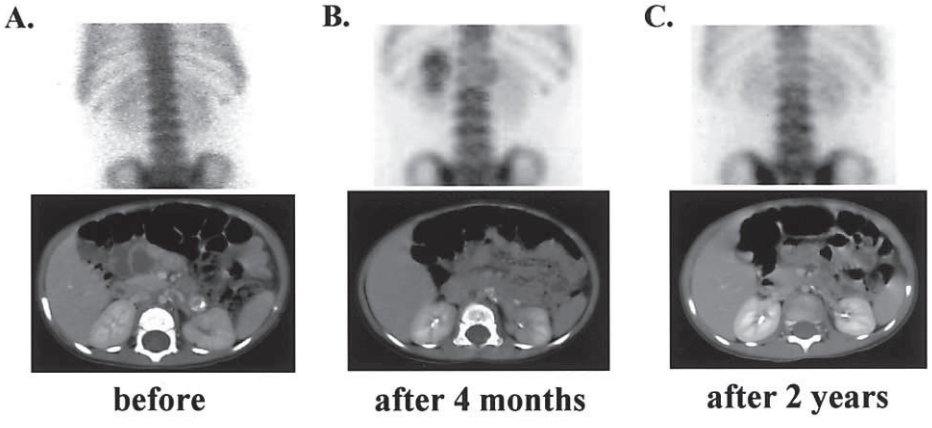

Fig. 2 Sequential ^{99m}Tc-HMDP bone scintigraphies and CT scans in Case 2. (A) Bone scintigraphy and CT scan performed 2 months before radiotherapy demonstrate no abnormalities in the kidney. (B) Four months after irradiation, increased accumulation of ^{99m}Tc-HMDP and delayed enhancement of the CT scan were observed in the upper portion of the left kidney. (C) Two years after irradiation, bone scintigraphy showed accumulation defect at the upper pole of the left kidney. CT scan showed atrophy of the medial part of the left kidney.

increased accumulation at the upper portion of the left kidney, which was included in the radiation port (Fig. 2B, *upper panel*). Computed tomography (CT) performed simultaneously demonstrated no recurrent tumor, but delayed enhancement of the parenchyma at the upper portion of the left kidney (Fig. 2B, *lower panel*). The renal uptake of ^{99m}Tc-HMDP was shown to have gradually decreased in follow-up bone scintigraphy, and eventually disappeared 2 years after the completion of radiotherapy (Fig. 2C, *upper panel*, and Fig. 3). The CT scan, which was also conducted 2 years after the completion of radiotherapy, showed that the medial part of the left kidney had atrophied (Fig. 2C, *lower panel*). ^{99m}Tc-MAG_3 renoscintigraphy was also performed 4 months after radiation therapy (Fig. 4). An accumulation defect at the upper portion of the left kidney was shown 1 min after the administration of ^{99m}Tc-MAG_3. After 5 min, the accumulation of ^{99m}Tc-MAG_3 in this portion was gradually increased, and the excretion of urine delayed.

Case 4 was a 3.6-year-old girl who presented at the age of 3 years with fever and diarrhea. She was found to have a right adrenal neuroblastoma with cranial bone metastasis, and underwent 5 courses of chemotherapy. Radiation therapy consisted of a total of 30 Gy fractionated over 20 days. The radiation was given to the right adrenal region, including the thoracolumbar spine from the 11th thoracic vertebra down to the 2nd lumbar vertebra, and the upper portion of the right kidney. ^{99m}Tc-HMDP bone scintigraphy performed 4 months after irradiation showed increased accumulation in almost two-thirds of the upper portion of the right kidney (Fig. 5B). The accumulation gradually decreased, in the same manner as in case 2, and finally disappeared 8 months after the completion of radiotherapy (Fig. 5C).

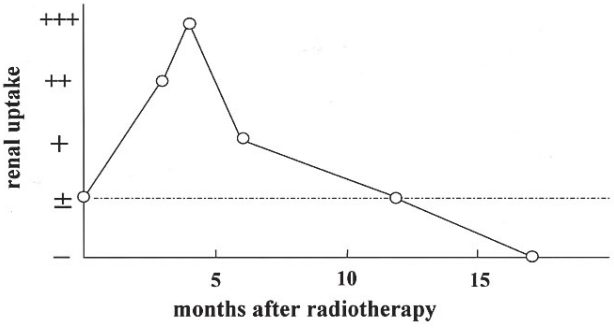

Fig. 3 Time course of ^{99m}Tc-HMDP uptake in the irradiated part of the left kidney. The renal uptakes were evaluated as (−) ~ (+++), as described in Materials and Methods, and plotted sequentially.

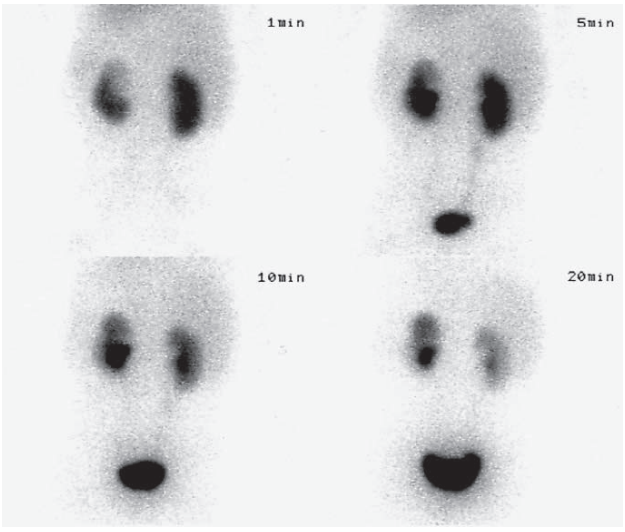

Fig. 4 ^{99m}Tc-MAG_3 renoscintigraphy in Case 2 performed 4 months after the completion of radiotherapy. An accumulation defect at the upper pole of the left kidney was shown 1 min after the administration of ^{99m}Tc-MAG_3. After 5 min, the accumulation of ^{99m}Tc-MAG_3 in this portion was gradually increased. In addition, the excretion of urine was delayed.

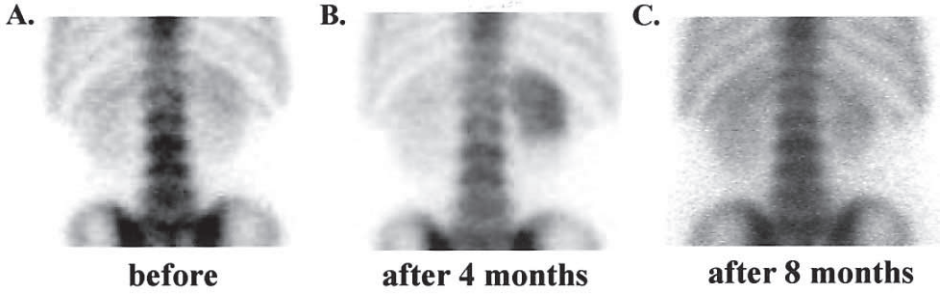

Fig. 5 Sequential ^{99m}Tc-HMDP bone scintigraphies in Case 4. (A) Bone scintigraphy performed 10 days before radiotherapy demonstrated no abnormalities in the kidney. (B) The increased accumulation of ^{99m}Tc-HMDP was observed at the upper two-thirds of the right kidney four months after irradiation. (C) Eight months after irradiation, bone scintigraphy showed an accumulation defect at the upper part of the right kidney.

DISCUSSION

We studied 6 children with neuroblastoma or ganglioneuroblastoma in the adrenal gland who were given radiation therapy at the renal portion. Increasing renal uptakes of ^{99m}Tc-HMDP due to radiation nephropathy were observed, and these findings were needed for differentiation from recurrent or remnant tumors.

In this study, high renal uptake appeared 0 to 3 months (mean 1.7 months) after the completion of radiotherapy. There have been several case reports demonstrating that an increasing accumulation of ^{99m}Tc phosphate compounds in the kidneys was found 3 to 9 months after radiation therapy was completed.[13–17] Wymer et al. reported that the radiation-induced high renal uptake of ^{99m}Tc phosphate compounds occurred 3 months after treatment.[13] Palestro reported 2 cases in which it appeared 9 months after radiotherapy.[14] Although the time when renal uptake appears depends on the time when bone scintigraphy is performed, radiation nephropathy could be detected 0 to 9 months after the completion of radiotherapy.

Cassady summarized radiation nephropathy as having an "acute" and "chronic" phase. Acute radiation nephropathy was observed 6 to 12 months after irradiation, and chronic radiation nephropathy appeared 18 months to years after irradiation.[18] White demonstrated that injury to the vascular endothelium was an early response to radiation nephropathy. The arterioles and capillaries might become occluded, and the glomeruli edematous and ischemic.[19] Dewit et al. indicated that tubular epithelium could be the most important target cells for radiation nephropathy.[11] It is not surprising that the latency was relatively long, as long as 9 months, because tubular cells have a long cell-turnover time. An accumulation defect on ^{99m}Tc-MAG_3 renoscintigraphy and poor enhancement on the CT scan at the irradiated part of the kidney might reflect damage to the vasculature. In addition, the delayed excretion observed on ^{99m}Tc-MAG_3 renoscintigraphy might be due to injury to the tubular cells. We speculated that the delayed excretion of the ^{99m}Tc phosphate compounds could be the cause of the increased renal uptake which was observed on ^{99m}Tc-HMDP bone scintigraphy. Another possibility is that the ^{99m}Tc phosphate compounds might simply accumulate into the tissue necrosis, including the arterioles, capillaries, glomeruli or tubules.

Increased renal uptake was gradually reduced, and eventually became an accumulation defect 6 to 17 months after the completion of radiotherapy. White characterized late radiation nephropathy as an arterial sclerosis, glomerular hyalinization, cessation of glomerular filtration, and interstitial fibrosis.[19] These alterations were reflected by the renal atrophy shown on the CT scan taken 2 years after irradiation in case 2 (Fig. 2C, *lower panel*). These alterations might have also affected the accumulation defect found on the ^{99m}Tc-HMDP bone scintigraphy at the delayed time.

It is difficult to determine at what threshold an irradiation dose will induce nephropathy. Cassady analyzed six previous papers on the subject, and concluded that a dose of over 25.0–30.0 Gy to the total renal mass with conventional fractionation is likely to evoke radiation nephropathy.[18] However, in these studies, the patients were followed for long periods of time, ranging from 8–19 years. In addition, the authors defined nephropathy as a clinical symptom, like hypertension, or as a renal function such as creatinine clearance. Wistow et al. reported that they observed the normal uptake of ^{99m}Tc phosphate compounds into the kidney, which received 16.5 Gy irradiation.[17] Avioli et al. reported that the glomerular filtration rate and plasma flow were temporally reduced after 4 Gy irradiation.[20] Some microscopic changes in the tubular or glomerular cells might occur after such a minimal dose of irradiation, and such changes could be reversible. However, a bone scan with ^{99m}Tc phosphate compounds seems to be able to detect these alterations, at least after around 20 Gy irradiation.

In this study, we examined radiation nephropathy only in pediatric patients. Previous reports included 3 adult cases and a young adult case.[13,14,16] This suggests that the increased uptake of ^{99m}Tc phosphate compounds is not a phenomenon specific only to children. Further examinations are needed to clarify whether or not this phenomenon is age-dependent.

CONCLUSION

In this report, increasing renal uptake of ^{99m}Tc-HMDP, which mimics recurrent or remnant neuroblastoma, was observed during the 0 to 7 month period after the completion of radiation therapy. It was revealed that the increased renal uptake was gradually resolved, and eventually became an accumulation defect 6 to 17 months after the completion of radiotherapy. It is useful, in order to reach a correct diagnosis, to obtain the patient's history of radiation therapy, and the extent of coverage of the area by the radiation port.

REFERENCES

1. Berthold F, Hero B, Breu H, Christiansen H, Erttmann R, Gnekow A, et al. The recurrence pattern of stage I, II and III neuroblastoma experience with 77 relapsing patients. *Ann Oncol* 1996; 7: 183–187.
2. Suzuki A, Togawa T, Kuyama J, Nakahara T, Iuchi T, Oga M, et al. Extraosseous accumulation of bone scanning agents in malignant brain tumors: Comparison to semiquantitative evaluation with ^{99m}Tc SPECT/^{201}Tl SPECT and histological findings. *Ann Nucl Med* 2003; 17: 387–392.
3. Rengachary SS, Batnitzky S, Arjunan K. Diagnosis of intracranial meningioma with radionuclide bone scan. *Surg Neurol* 1980; 14: 337–341.

4. Grames GM, Jansen C, Carlsen EN, Davidson TR. The abnormal bone scan in intracranial lesions. *Radiology* 1975; 115: 129–134.
5. Buja LM, Tofe AJ, Kulkarni PV, Mukherjee A, Parke RW, Franci MD, et al. Sites and mechanisms of localization of technetium-99m phosphorus radiopharmaceuticals in acute myocardial infarcts and other tissues. *J Clin Invest* 1977; 60: 724–740.
6. Garty I, Friedman A, Sandler MP, Kedar A. Neuroblastoma: imaging evaluation by sequential Tc-99m MDP, I-131 MIBG, and Ga-67 citrate studies. *Clin Nucl Med* 1989; 14: 515–522.
7. Podrasky AE, Stark DD, Hattner RS, Gooding CA, Moss AA. Radionuclide bone scanning in neuroblastoma: skeletal metastases and primary tumor localization of ^{99m}Tc-MDP. *AJR* 1983; 141: 469–472.
8. Kinuya S, Taki J, Fujioka M, Michigishi T, Tonami N. Metastatic calcification: Accumulation of a bone tracer during dynamic data acquisition. *Ann Nucl Med* 1996; 10: 433–435.
9. O'Hare JP, Altnow H, Christian TD. Chronic nephritis produced by x-ray. *Boston Med Surg J* 1926; 194: 43–45.
10. Schulman N, Johnson PM. Scintillation imaging in generalized and localized radiation nephritis. *Radiology* 1973; 109: 639–642.
11. Dewit L, Anninga JK, Hoefnagel CA, Nooijen WJ. Radiation injury in the human kidney: A prospective analysis using specific scintigraphic and biochemical endpoints. *Int J Radiat Oncol Biol Phys* 1990; 19: 977–983.
12. Madrazo A, Suzuki Y, Churg J. Radiation nephritis: Acute changes following high dose of radiation. *Am J Pathol* 1969; 54: 507–527.
13. Wymer DC, Kies MS. Adrenal simulation by renal uptake of ^{99m}Tc diphosphonate after radiotherapy. *AJR* 1980; 134: 1256–1258.
14. Palestro C, Fineman D, Goldsmith SJ. Acute radiation nephritis. Its evolution on sequential bone imaging. *Clin Nucl Med* 1988; 13: 789–791.
15. Sty JR, Casper J, Babbitt DP. Extraosseous uptake of ^{99m}Technetium methylene diphosphonate: neuroblastoma or radiation therapy. *Pediatr Radiol* 1980; 9: 53–54.
16. Flanagan FL, Dehdashti F. Case report: Acute segmental radiation nephritis on bone scintigraphy. *Br J Radiol* 1996; 69: 1175–1177.
17. Wistow BW, McAfee JG, Sagerman RH, Thomas FD, Grossman ZD. Renal uptake of Tc-99m methylene diphosphonate after radiation therapy. *J Nucl Med* 1979; 20: 32–34.
18. Cassady JR. Clinical radiation nephropathy. *Int J Radiat Oncol Biol Phys* 1995; 31: 1249–1256.
19. White DC. The histopathologic basis for functional decrements in late radiation injury in diverse organs. *Cancer* 1976; 37: 1126–1143.
20. Avioli LV, Lazor MZ, Cotlove E, Brace KC, Andrews JR. Early effects of radiation on renal function in man. *Am J Med* 1963; 34: 329–337.