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Scintigraphic changes in bone metastasis from prostate cancer after hormonal therapy—Comparison with tumor markers and bone X-ray

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Bone scintigraphy is often performed to assess the response to systemic therapy of bone metastasis from prostate cancer. We examined the changes in bone scintigraphic findings and the agreement with AlP, AcP, or other tumor markers measured in the follow-up of patients with known bone metastasis after hormonal therapy. Out of 32 patients, 22 (69%) showed improved scintigraphic findings on the first follow-up bone scintigraphy after hormonal therapy. However, 7 out of 22 patients who showed improvement on the first follow-up scintigraphy, deteriorated thereafter. Changes in the scintigraphic findings were closely correlated with those in the measured tumor markers except for patients with small bone metastasis. Though there were no significant differences in the agreement ratios of the 6 tumor markers evaluated, AlP might be a practical and acceptable indicator. Bone X-ray findings did not change at all in almost half of the cases though the scintigraphic findings showed improvement or deterioration.

Key words: bone scintigraphy, prostate cancer, bone metastasis, tumor marker

INTRODUCTION

PROSTATE CANCER is a well known malignant tumor which often metastasizes to the skeleton. If metastases are present, hormonal therapy and chemotherapy are indicated instead of radical surgery; bone survey is therefore very important in patients with newly diagnosed prostate cancer. Bone scintigraphy is more sensitive diagnostic method for detecting metastases than serum alkaline phosphatase (AlP) measurements, enzymatic assays for serum acid phosphatase (AcP), and radiographic skeletal surveys.[1] For this reason, bone scintigraphy should be performed at early as well as late stages of prostate cancer.[2] Bone scintigraphy can also be used to assess the response to systemic therapy of bone metastases from prostate cancer.[3] We evaluated the changes in bone scintigraphic findings and the agreement with measured tumor markers and bone X-ray findings in the follow-up of patients with known bone metastasis after hormonal therapy.

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MATERIALS AND METHODS

Patients with untreated prostate cancer with bone metastasis were included in this study. The total number of scintigrams reviewed was 147 studies in a total of 39 patients. Initial bone scintigraphy was conducted within a few weeks before castration. Several follow-up scintigrams were taken after castration and during estrogen administration. The length of time between castration and the first follow-up scintigraphy or between the first and the following scintigraphy varied; that is, the first follow-up scintigraphy was conducted 2 to 24 months (mean 7.9 ± 5.3) and the last scintigraphy was conducted 4 to 65 months (mean 28.8 ± 15.4) after the initial scintigraphy.

Anterior and posterior whole body bone scintigrams and additional spot images were taken with a Toshiba Gamma-camera GCA401-5 three to four hours after an injection of 740 MBq of Tc-99m methylenediphosphonate (MDP) or hydroxymethylenediphosphonate (HMDP). Scintigraphic findings were determined visually and classified into three categories: improved, unchanged, or deteriorated compared with the previous bone scintigraphy.

Values for the following tumor markers: alkaline phosphatase (AlP), acid phosphatase (AcP), prostatic acid phosphatase (PAcP), prostatic acid phosphatase

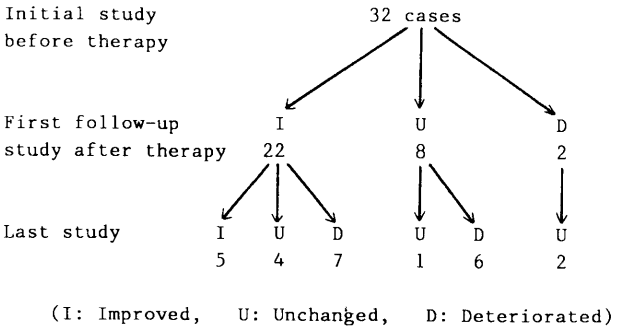

Fig. 1 Changes in scintigraphic findings after hormonal therapy. Out of 32 patients, 22 (69%) showed improvement on the first follow-up bone scintigraphy after therapy.

Table 1 Comparison of bone scan findings with tumor markers

(Enzymatic method)

Bone scan findings	AlP			AcP			PAcP		
	I	U	D	I	U	D	I	U	D
I	15	5	0	15	1	1	11	3	1
U	6	25	2	7	16	0	9	10	3
D	0	9	13	0	12	9	1	6	13
Agreement	53/75 (70.7%)			40/61 (65.6%)			34/57 (59.6%)		

I: Improved, U: Unchanged, D: Deteriorated

Table 2 Comparison of bone scan findings with tumor markers

(Immunometric assay)

Bone scan findings	PAP-RIA			PA			γ-Sm		
	I	U	D	I	U	D	I	U	D
I	4	1	0	3	1	0	2	1	0
U	1	4	2	0	3	1	1	3	0
D	1	2	7	1	0	2	0	3	3
Agreement	15/22 (68.2%)			8/11 (72.7%)			8/13 (61.5%)		

I: Improved, U: Unchanged, D: Deteriorated

Table 3 Comparison of bone scan findings with bone X-ray

Bone scan findings	Bone X-ray findings		
	Improved	Unchanged	Deteriorated
Improved	3	7	1
Unchanged	0	1	0
Deteriorated	0	6	8
Agreement	12/26 (46.2%)		

radioimmunoassay (PAP-RIA), prostate antigen (PA) and gamma seminoprotein (γ-Sm), which were measured within four weeks before or after each bone scintigraphy, were compared with the scintigraphic findings. AlP, AcP, and PAcP were measured by an enzymatic method. PAP-RIA, PA, and γ-Sm were measured by an immunometric assay. Changes in the values were classified into three categories: improved (decreased to less than 2/3 of the previous value), deteriorated (increased to more than 1.5 times the previous value), or unchanged (fluctuation within these two limits).

Bone X-ray findings obtained within a few weeks of each bone scintigraphy were also compared.

RESULTS

Figure 1 shows changes in the scintigraphic findings after hormonal therapy. Out of 32 patients, 22 (69%) showed improved scintigraphic findings on the first follow-up bone scintigraphy conducted 3 to 19 months after castration and starting administration of estrogen. Eight patients (25%) showed no change during 3 to 24 months after the therapy, and 2 patients (6%) showed deterioration 2 to 6 months after the therapy. Out of 22 patients who showed improvement on the first follow-up scintigraphy, five patients improved further but 7 deteriorated thereafter. None of the patients who were unchanged or deteriorated on the first follow-up scintigraphy improved later on the last scintigraphy.

Comparison of the scintigraphic findings with the tumor markers is shown in Table 1 (enzymatic method) and Table 2 (immunometric assay). Though the number of cases measured by the immunometric assay was less than that of the cases measured by the enzymatic method, changes in the scintigraphic findings were closely correlated with those of the measured tumor markers. There were no cases which showed inversely related changes in the scintigram and AlP measurement. Agreement ratios, which are the ratios of the number of cases showing the same directional changes divided by the total number of cases, were fairly good from 59.6% at the lowest to 72.7% at the highest, though these differences are not significant.

Comparison of the scintigraphic findings with the bone X-ray findings is shown in Table 3. Agreement of the scintigraphic findings with changes in the bone X-ray findings was not very close. Bone X-ray findings did not change at all in almost half of the cases, though the scintigraphic findings showed improvement or deterioration.

Four informative cases will now be described. Figure 2 shows the bone scintigrams of a 72-year-old patient. The AlP 4440 U/l (normal; 83–227) and AcP 9.9 KAU (normal; 0–4.0) values were abnormally increased, though PAcP 0.4 KAU (normal; less than 0.8) and PAP-RIA 1.1 ng/ml (normal; less than 3.0) were normal when the initial bone scintigraphy was conducted. PA (normal; less than 2.0) and γ-Sm (normal; less than 4.0) were not measured in this patient. After castration and estrogen administration, scintigraphic findings continuously improved and both AlP and AcP also improved. PAcP showed a temporary increase, but was within the normal range. PAP-RIA also stayed within the normal range. This case shows that

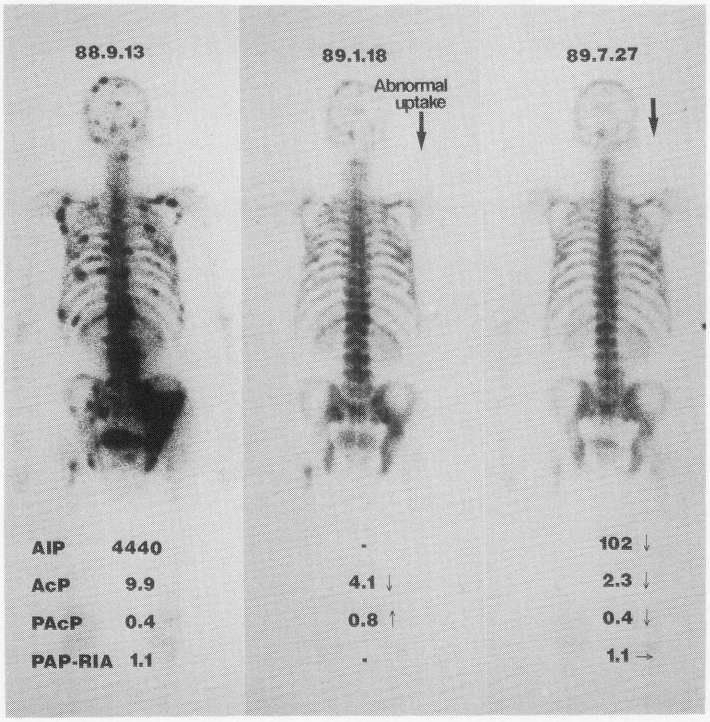

Fig. 2 A 72-year-old patient with good response to hormonal therapy. The values of AlP and AcP were in good agreement with the scintigraphic findings.

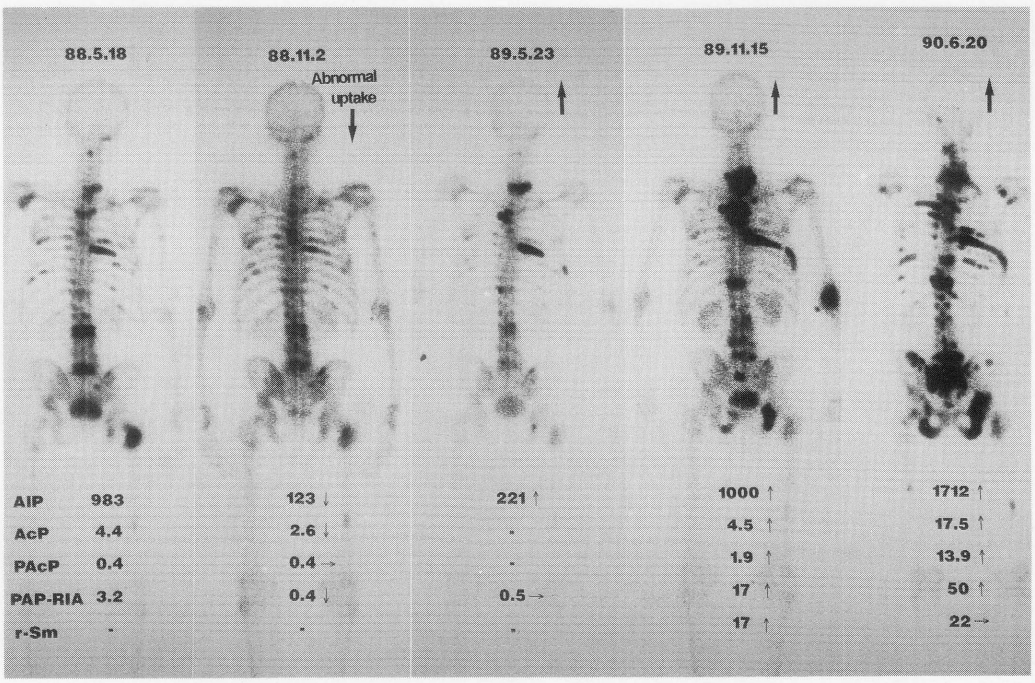

Fig. 3 A 73-year-old patient with temporary good response, but continuous deterioration afterward. Changes in the scintigraphic findings and tumor markers were in good agreement.

the AlP and AcP values were in good agreement with the scintigraphic findings. Bone X-ray was not consecutively performed in this patient. Figure 3 shows the bone scintigrams of a 73-year-old patient. The intensity of the abnormal uptake was temporarily decreased, especially in the spine and proximal right femor after castration and estrogen administration on November 2, 1988, but continuously increased thereafter from May 23, 1989 until the last scintigram. Changes in the tumor markers, especially AlP and AcP, were in good agreement with those in

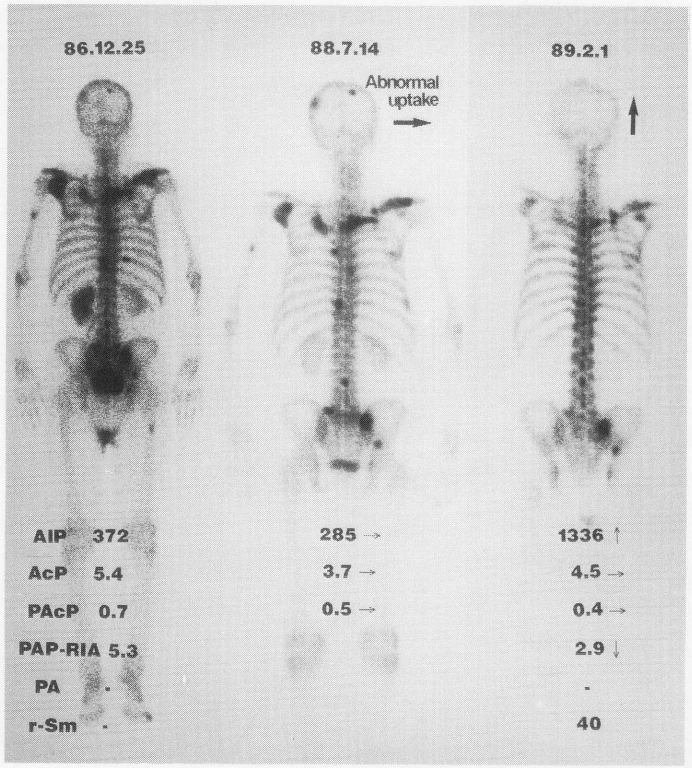

Fig. 4 A 68-year-old patient with severe deterioration at the last. The last scintigraphy showed almost an super bone scan. High levels of AlP and γ-Sm were in good agreement with the scintigraphic findings.

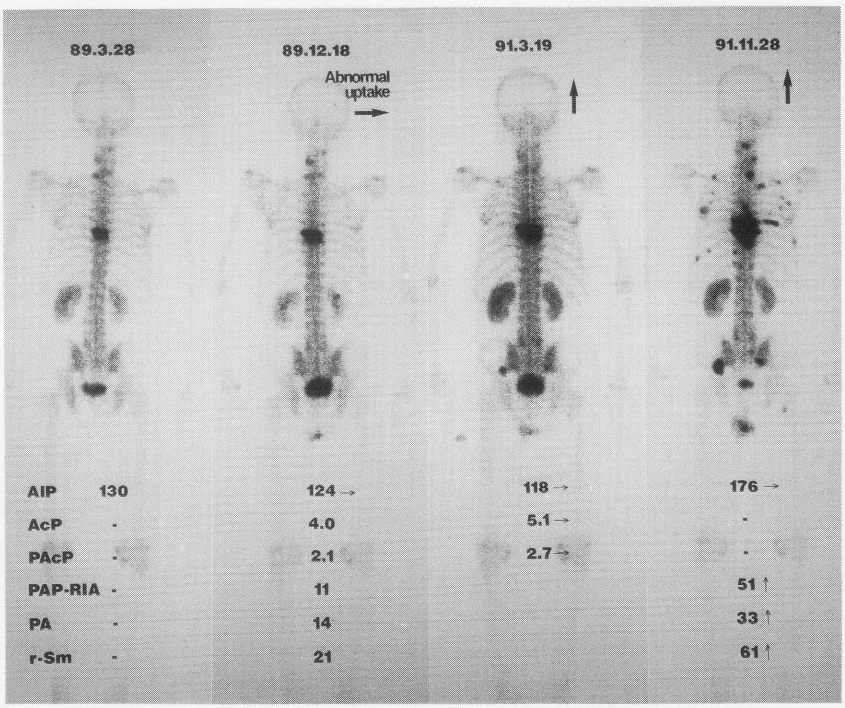

Fig. 5 A 66-year-old patient with an exceptionally poor response of AlP. Scintigraphic findings showed deterioration, though AlP did not change at all.

the scintigraphic findings. In this case changes in the scintigraphic findings and tumor markers were also in good agreement after therapy. Sclerotic changes in the second lumber spine on bone X-ray improved, though those for the eleventh thoracic spine did not change at all. Figure 4 shows the sequential bone scintigrams of a 68-

year-old patient. On the first follow-up bone scintigram on July 14, 1988, scintigraphic findings were essentially unchanged and the tumor markers were also unchanged, but the scintigram on February 1, 1989 showed a diffusely increased uptake to the thoracic spine and ribs. It was almost like a super bone scan because of the absence of renal uptake. High levels of AlP and γ-Sm were consistent with the scintigraphic findings, though AcP, PAcP, and PAP-RIA did not respond at all. Sclerotic change in the right clavicle on chest X-ray were unchanged. Figure 5 shows the bone scintigrams of a 66-year-old patient. The intensity and number of abnormal uptakes were increased on March 19, 1991 and had increased on November 28, 1991. PAP-RIA, PA, and γ-Sm values reflected the scintigraphic findings well, though AlP did not change at all. This is an exceptional case which showed poor response of AlP compared with the other tumor markers. Sclerotic change in thoracic spine on bone X-ray did not vary at all.

DISCUSSION

Bone scintigraphy is widely used for the detection of bone metastasis from prostate cancer,[1] but little attention has been directed to the use of a serial study in the follow-up of bone metastasis after hormonal treatment or chemotherapy.[4–6] Bone metastasis from prostate cancer is known to effectively respond to hormonal therapy. Changes in serial bone scintigrams are closely correlated to response to therapy.[1,4] In our series, as many as 69% of the patients showed improvement in their scintigraphic findings and an additional 25% did not show any change in their scintigraphic findings. These patients had experienced partial relief or complete relief of symptoms soon after treatment. In spite of a good response to their initial treatment, most of the patients had relapsed thereafter and their following subsequent scintigraphy results deteriorated.

There are some reports concerning the relationship between bone scintigraphic findings and the values for tumor markers, such as AlP, AcP, PAP-RIA, and PSA, in patients with bone metastasis from prostate cancer.[7–10] Some concluded that because these tumor markers are closely correlated with the bone scintigraphic findings, routine bone scintigraphy may not be warranted if these tumor markers are normal. However, some cases in our series showed apparent abnormal uptake, despite normal tumor markers in the initial bone scintigraphy. Furthermore, there was a case whose relapse was apparent in bone scintigraphy though his AlP level remained unchanged. The reason might be that metastatic lesions are too few or small to show an increase in the tumor markers. If the lesions are many or large enough, tumor markers might indicate abnormality.

Evaluation of the sensitivity and specificity of tumor markers was not our purpose in this study, but close agreement with scintigraphic abnormality was observed in all tumor markers. Although some new markers have been developed, AlP might be a fairly practical and acceptable indicator to use in detecting the relapse of bone metastasis from prostate cancer.[11] Bone X-ray findings correlated with bone scintigraphic findings less closely than did the tumor markers, because bone X-ray findings cannot well reflect metabolic bone changes compared with bone scintigraphic findings.

There was a case which showed a so-called super bone scan. It is sometimes misjudged as normal in bone scintigraphy, but increased tumor marker levels may be helpful in such a case. The so-called flare effect has been reported in patients with prostate cancer after hormonal therapy.[12,13] We did not see any flare effect in this study, probably because the first follow-up scintigraphy was usually conducted 6 months after the initiation of treatment. The flare effect is most often observed around 3 months after the initiation of treatment.[12]

Because this is a retrospective study, the length of time between castration and the first follow-up scintigraphy and between the first and the following scintigraphy varied. It might be more ideal to perform bone scintigraphy and to evaluate tumor markers consecutively; for example, 1 month and 3 months after initiation of the treatment. A prospective study with a well-scheduled protocol might be required.

In conclusion, the scintigraphic findings were greatly improved after hormonal therapy in patients with bone metastasis from prostate cancer. These scintigraphic changes were closely correlated with the changes in the measured tumor markers.

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