奈医誌. (J. Nara Med. Ass.) 42, 62～66, 平3

TUMOR MARKERS IN BONE MARROW IN PATIENTS WITH PROSTATIC CANCER

AKIO IWAI, SEIICHIRO OZONO, YOZO TANAKA, JUNICHI NAGAYOSHI, AKIHIDE HIRAYAMA, TOSHIHIKO KUMON, MASANORI JOKO, NAOYA HIRATA, MOTOYOSHI YOSHIKAWA, SHOICHI TABATA, HIROTSUGU UEMURA, AKIRA MORIYA, YOSHITERU KANEKO, SHINJI OKAMOTO, YOSHIHIKO HIRAO and EIGORO OKAJIMA

Department of Urology, Nara Medical University

Received January 29, 1991

Summary: We compared prostatic specific acid phosphatase (PAP), prostatic specific antigen (PA) and γ-seminoprotein (γ-SM) levels between bone marrow and serum for the purpose of assessing of the usefulness of these tumor markers in early detection of bone metastasis in cases with prostatic cancer. Thirty-three patients were entered into this study. Of the patients, 20 had prostatic cancer including 11 with bone metastasis, and 13 patients had benign prostatic hypertrophy (BPH) served as controls. It seemed unlikely that bone marrow PAP, PA and γ-SM are more useful than their serum levels for detection of bone metastasis of prostatic cancer. Because correlation between bone marrow and serum levels of each marker was observed not only in cases with prostate cancer accompanied by bone metastasis but also in metastasis-free prostatic cancer and BPH cases, it seems likely that PAP, PA and γ-SM in bone marrow circulate from peripheral blood rather than from bone metastasis of prostatic cancer.

Index Terms

tumor markers, bone marrow, prostatic cancer

INTRODUCTION

Prostatic specific acid phosphatase (PAP), prostatic secific antigen (PA) and γ-seminoprotein (γ-SM) in bone marrow are used as markers of prostatic cancer as well as in serum. However, it is controversial whether or not these markers in bone marrow are useful in the early detection of bone metastasis of prostatic cancer. We recently analyzed prostatic tumor markers in bone marrow with several noteworthy findings.

MATERIALS AND METHODS

Thirty-three patients were entered into the study from 1986 to 1988 after informed consent was obtained at Nara Medical University or affiliated hospitals. The patients ranged in age from 53 to 86 years, with a mean age of 70.3 years. They included 20 cases with prostatic cancer which were histologically diagnosed. The remaining 13 cases were clinically suspected prostatic cancer; however, they were diagnosed as benign prostatic hypertrophy (BPH) histopathologically and served as controls in this study. All 20 cases of prostatic cancer examined were untreated fresh cases or relapsed cases. All cases with prostatic cancer underwent palpation, pelvic computerized tomography, transrectal prostatic ultrasonography, vesiculography,

lymphography, plain bone roentgenography and bone scintigraphy. Based on the results of these examinations, 3 cases were determined as Stage B2, 5 cases as Stage C, 1 case Stage D1 and 11 cases as Stage D2 according to the Rules for General Rule for Clinical and Pathological Studies on Prostatic Cancer established jointly by the Japanese Urological Association and the Japanese Pathological Society in 1985. All of the Stage D2 cases had bone metastases (Table 1).

Bone marrow fluid, about 10ml, was sampled via the anterior iliac crest using a Komiya's needle. PAP was determined with a PAP RIA Kit (Eiken Chemimal Co., Ltd., Tokyo). PA and γ-SM were detemined by enzyme immunoassay using a Markit FPA (Dainippon Pharmaceutical Co., Ltd., Osaka) and a γ-SM Kit Chugai (Chugai Pharmaceutical Co., Ltd., Tokyo), respectively.

At the same time, cytological examination was performed using Papanicolaou method. In addition, PAP, PA and γ-SM in serum, collected on the same day as bone marrow sampling, were determined.

RESULTS

A shown in Table 2, serum and bone marrow levels of PAP, PA and γ-SM were compared among the following three groups of paitents: (1) patients with BPH(BPH group), (2) patients with stage D2 prostatic cancer accompanied by bone metastasis (metastasis group), and (3) patients with stage B, C or D1 prostate cancer without bone metastasis (metastasis-free group).

Significant differences in serum and bone marrow PAP were observed between the metastasis and BPH groups, and between the metastasis and metastasis-free groups. Serum and bone marrow PA significantly differed between the BPH and metastasis groups. In analysis of the significance of inter-group difference of γ-SM, the only significant difference was that of serum γ-SM observed between the BPH and metastasis groups. When serum levels

Table 1. Patient characteristics

Total No.Pts.		33	
Age	53-86 y. o. (Mean 70.3)		
Pathology	B. P. H.	13	
	Prostatic cencer	20	
	Stage	B	3
		C	5
		D1	1
		D2	11
	Grade*	Wel	2
		Mod	6
		Por	12

*Wel: Well-differentiated adenocarcinoma
Mod: Moderately differentiated adenocarcinoma
Por: Poorly differentiated adenocarcinoma

Table 2. Serum and bone marrow PAP, PA and γ-SM levels

	BPH	Prostatic cancer	
		With Metastasis	Without Metastasis
Total No. pts.	13	11	9
PAP			
serum	2.3±1.6[a)]	14.8±12.1[a)b)]	5.3±8.1[b)]
bone marrow	4.3±5.0[c)]	20.2±24.2[c)d)]	5.0±5.6[d)]
PA			
serum	3.3±2.6[e)]	36.7±38.9[e)]	13.6±18.1
bone marrow	2.6±2.3[f)]	31.2±32.3[f)]	11.1±15.2
γ-SM			
serum	3.6±2.5[g)]	10.5±6.5[g)]	7.4±7.1
bone marrow	6.6±12.9	12.0±9.3	9.8±9.8

P values were obtained by the Student's T test.
a) :$p<0.01$
b),c),d),e),f),g) : $p<0.05$

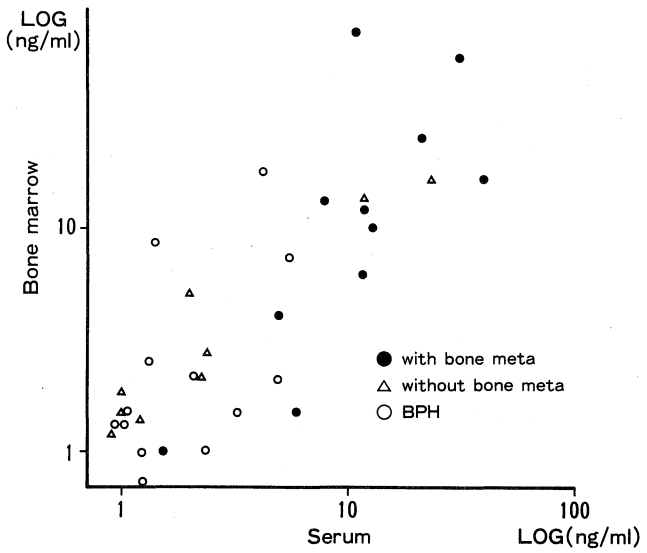

Fig. 1. Correlation between bone marrow and serum levels of PAP.
Y=0.923X+3.03, R=0.770 ($p<0.01$) with bone meta
R=0.953 ($p<0.01$) without bone meta
R=0.794 ($p<0.01$) BPH

of PAP, PA and γ-SM were compared with bone marrow levels of the same markers in each group, no group showed any significant difference between the serum and bone marrow level of any marker.

When correlation between serum and bone marrow levels of PAP was explored, a significant positive correlation was found ($p<0.01$; Fig. 1). Significant positive correlation was also found between serum and bone marrow levels of PA and γ-SM ($p<0.01$; Fig. 2 and 3).

In cytological examination of bone marrow, only one case of stage D2 prostatic cancer was judged too be abnormal.

DISCUSSION

In 1970, Chua *et al.*[1] first reported that acid phosphatase in bone marrow was useful in the early detection of bone metastasis of prostatic cancer. Since then, numerous reports indicating

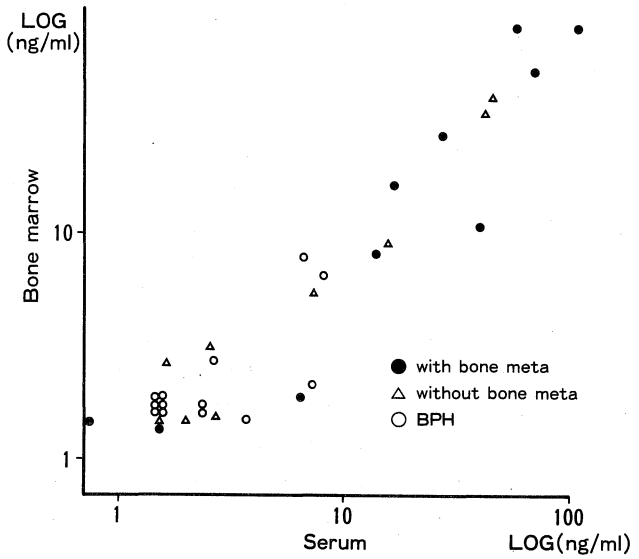

Fig. 2. Correlation between bone marrow and serum levels of PA.
Y=0.776X+1.035, R=0.916 ($p<0.01$) with bone meta
R=0.967 ($p<0.01$) without bone meta
R=0.789 ($p<0.01$) BPH

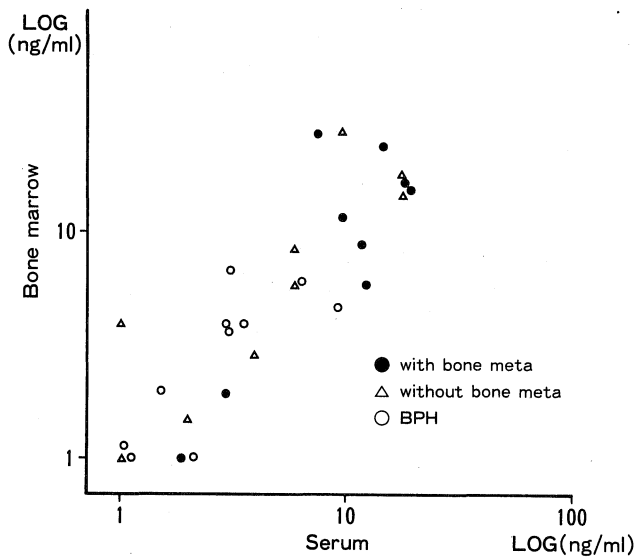

Fig. 3. Correlation between bone marrow and serum levels of γ-SM.
Y=1.039X+2.23, R=0.879 ($p<0.01$) with bone meta
R=0.861 ($p<0.01$) without bone meta
R=0.905 ($p<0.01$) BPH

the usefulness of bone marrow acid phosphatase or prostatic specific acid phosphatase have been published[2,3]. However, with the recent use of radioimmunoassay, which is more specific to prostatic cancer for determination of bone marrow PAP level, reports have increasingly indicated the uselessness of bone marrow PAP dermination for early detection of bone metastasis of prostatic cancer[4~6]. Bone marrow PA has been reported by Morote *et al.*[6] to be of no aid in early detection of bone metastasis of prostatic cancer. Regarding determination of bone marrow γ-SM, no report has been published.

In the present study, we compared PAP, PA and γ-SM levels between bone marrow and serum in the present study for the purpose of assessing the usefulness of these tumor markers in the early detection of bone metastasis. Bone marrow PAP significantly differed between metastasis and metastasis-free groups. Serum PAP also significantly differed between these two groups. On the other hand, no significant inter-group difference was observed for bone marrow PA or γ-SM. When differences between serum and bone marrow levels were examined for each of PAP, PA and γ-SM in each group, no significant difference was observed. These results indicate that the bone marrow level of PAP. PA or γ-SM is not more useful than the serum level of these markers for detection of bone metastasis of prostatic cancer.

To study the origin of these markers in bone marrow, we compared bone marrow and serum of each marker. The bone marrow level of each marker significantly correlated with the serum level of the corresponding marker not only in the metastasis group but also in the metastasis-free and BPH groups. It is particularly noteworthy that patients with BPH showing elevated bone marrow levels of these markers, false positive cases in the diagnosis of prostatic cancer, also indicated elevation of serum levels of the same markers. That is, bone marrow levels of these markers reflected serum levels of the same markers in these cases of BPH. These results suggest that PAP, PA and γ-SM in bone marrow circulate from peripheral blood rather than from bone metastases of prostatic cancer.

(Read at the 38th Annual Meeting of the Central Section of the Japanese Urological Association.)

REFERENCES

1) **Chua, D. T., Veenema, R. J., Muggia, F.** and **Graff, A.**: Acid phosphatase levels in bone marrow: Value in detecting early bone metastasis from carcinoma of the prostate. J. Urol. **103**: 462-466, 1970.

2) **Gursel, E. O., Rezvan, M., Sy, F. A.** and **Veenema, R. J.**: Comparative evaluation of bone marrow acid phosphatase and bone scanning staging of prostatic cancer. J. Urol. **111**: 53-57, 1974.

3) **Usui, T.**: Studies on carcinoma of the prostate. II. Investigation on acid phosphatase activity in the bone marrow blood. Acta Urol. Jap. **24**: 281-293, 1978. (in Japanese)

4) **Schellhammer, P. F., Warden, S. S., Wright, G. L.** and **Sieg, S. M.**: Bone marrow acid phosphatase by counterimmune electrophoresis: pre-treatment and post-treatment correlations. J. Urol. **127**: 66-68, 1982.

5) **Vihko, P., Kontturi, M., Lukkarinen, O.** and **Vihko, R.**: Radioimmunoassayable prostate-specific acid phosphatase in peripheral and bone marrow sera compared in diagnosis of prostatic cancer patients. J. Urol. **128**: 739-741, 1982.

6) **Morote, J., Ruibal, A., Pascual, C., Palou, J.** and **de Torres, J. A.**: Bone marrow prostatic specific antigen and prostatic acid phosphatase levels: Are they helpful in staging prostatic cancer. J. Urol. **137**: 891-893, 1987.