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Prostate-specific antigen as a marker of adenocarcinoma of prostate

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Summary. Prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) serum levels were measured in 117 patients with prostatic adenocarcinoma, in 9 patients with prostatic hyperplasia and in 14 patients with other malignancies to compare the clinical usefulness of the PSA and PAP levels. PSA was elevated (PSA^+) in 14 of 18 untreated patients (78%) with prostatic cancer. PAP was elevated (PAP^+) only in 3 of these untreated cases (17%). Also in previously treated patients PSA was more often positive than PAP. PSA was positive in 40 of the 99 treated patients (40%), PAP was elevated only in 21 cases (21%). There was a significantly ($P<0.001$) higher tendency towards elevated PSA in the prostatic cancer patients: 32 (27%) patients with PSA^+ and PAP^- compared with only 2 cases (2%) with PAP^+ and PSA^-. The PSA^+/PAP^- patients were analyzed further. In seven of them the PSA level also returned to its normal level after orchiectomy or/and radiotherapy. In two patients the PSA levels indicated tumor progression earlier than PAP, their PAP levels did not rise until bone metastasizing was evident. There were also progressive disease in some patients evidenced only by increased PSA levels. In addition to cancer patients the PSA level was increased in three (30%) of the prostatic hyperplasia patients. It was also elevated in three patients with other malignancies. However, these three patients also had prostatic hyperplasia and the increase in the PSA level is considered more likely to be due to that. According to these findings it is suggested that PSA is more sensitive than PAP in local and advanced prostatic cancer and may be more useful in monitoring responses and recurrence after therapy.

Key words: Prostate-specific antigen – Prostatic acid phosphatase – Prostatic cancer

Introduction

Prostatic cancer is the second most common cancer of western world men. The treatment of prostatic cancer is a controverisal issue. Prostatectomy, radiotherapy and hormonal treatments have been used. The disease can vary from a very slowly growing to a rapidly progressive metastatic disease. Most patients (70–80%) respond to hormonal manipulation usually administered as pain relief in patients with bone metastases [1, 4, 8, 9, 14]. However, metastatic disease is almost never curable [2, 7]. There have been no easy or effective ways to detect the cancer at an early stage or to follow the effect of the treatment especially on patients with metastatic disease and to detect at an earlier stage the patients whose disease is going to progress.

Prostatic acid phosphatase (PAP) has been the most commonly used serum marker in monitoring prostate cancer patients. Another tumor marker, prostate-specific antigen (PSA) was introduced seven years ago. Even PAP immunoassay methods have been more specific than conventional enzymatic techniques in the measuring of prostatic acid phosphatase, the PAP serum level has not clearly correlated to the tumor volume. PSA has been shown to be more specific in the case of advanced cancer and also more sensitive in detecting prostatic cancer [5, 10, 12, 13, 15]. However, neither PSA nor PAP can be used in screening prostatic cancer [3]. PSA has been shown to be elevated in 50 to 80% of patients with prostatic hyperplasia [13].

In order to evaluate the usefulness of these two markers in clinical practice, the serum level of both PSA and PAP were analyzed and correlated to the current clinical status of prostatic cancer patients.

Materials and methods

Prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) were measured in all patients sent for routine clinical

Table 1. Tumor status of untreated prostatic cancer patients in subgroups of the four combinations according to positive ($PSA^+ > 4$ µg/l, $PAP^+ > 3$ µg/l) and negative ($PSA^- < 4$ µg/l, $PAP^- < 3$ µg/l) markers

Primary tumor classification	Number of patients			
	PSA^+ PAP^+	PSA^+ PAP^-	PSA^- PAP^+	PSA^- PAP^-
T0–T2[a]	0	8	0	3
T3–T4[a]	2	2	0	1
N^+ or M^+	1	1	0	0
Total	3	11	0	4 (18)

[a] No-NxMo, most of the patients had Nx tumor status

Table 2. Tumor status and treatments of treated prostatic cancer patients in subgroups of the four combinations according to positive ($PSA^+ > 4$ µg, $PAP^+ > 3$ µg) and negative ($PSA^- < 4$ µg/l, $PAP^- < 3$ µg/l) markers

Primary tumor classification	Number of patients			
	PSA^+ PAP^+	PSA^+ PAP^-	PSA^- PAP^+	PSA^- PAP^-
T0–T2[a]	2	5	0	34
T3–T4[a]	10	10	1	16
N^+ or M^+	7	6	1	7
Total	19	21	2	57 (99)
At the time of marker measurements:				
Local disease[b]	5	12	1	47 (5[b])
Distant metastases	14	9	1	5
Treatments:				
Prostatectomy	0	0	0	5
Radiotherapy	1	4	0	10
Castration	16	17	2	35
Radiotherapy + castra	2	0	0	7

[a] No-NxMo, most patients had Nx pre-treatment tumor stage
[b] patients treated with prostatectomy

laboratory serum PAP control from the Urological and Radiotherapy Units of the Turku University Central Hospital during the period December 1986 to April 1987. Serum samples of 140 patients altogether were analyzed. The patient histories were studied retrospectively. All treatments were recorded.

There were 117 patients with prostatic adenocarcinoma. The staging of the tumors was carried out according to the TNM classification [6]. There were 18 untreated patients as shown in Table 1. The pre-treatment classification and the treatments as well as the staging (local disease or distant metastases) of the disease at the time of the marker measurements of 99 treated patients are presented in Table 2. Additional serum samples were analyzed from prostatic cancer patients with positive PSA and negative PAP levels.

In addition to prostatic cancer patients there were nine patients with an original diagnosis of benign prostatic hyperplasia. The estimated weight of prostate was from 10 to 20 grams in 4 patients, between 20 and 50 grams in one patient. Very large prostates (over 50 grams) were recorded in the case of 2 patients. The prostatic weight was unknown in one patient, TURP was performed before the serum marker analysis and the patient had chronic prostatitis. TURP was performed on five patients the same day the serum sample was taken.

Among 14 other malignancies there were three patients with renal cell cancer. All these cancers were local and were removed. The first one was operated five years ago, the second one a year ago and the last one in the same year that the serum marker analysis was made. The two latter patients had prostatic hyperplasia, (estimated weights of prostates 20 and 50 grams). There was one patient who had a clark III melanoma excised who also had prostatic hyperplasia (30 grams). One patient had a T1N0 laryngeal cancer treated by radiotherapy, his prostate was recorded to be enlarged. There were three lymphoma patients whose disease was in remission. Two of them had large prostates, both 50 grams and the third one had a small nodule in his prostate (his disease has been seven years in remission after nitrogen-mustard – vincristine/vinblastine-procarbazine – prednisone chemotherapy). One patient had gastric cancer and he died later with no records about prostate. One patient had colonic cancer which was operated and irradiated postoperatively. The tumor was adherent to the bladder. He is in remission at present and his prostate has been normal. One patient is in remission after rectal cancer operation and irradiation. The prostate was inside the treatment field. Another patient was operated two years ago for rectal cancer and he had a local perineal recurrence which was irradiated. At the time of the marker analysis he had pulmonary and inguinal metastases. Also TUPR was performed him two years ago for prostatic hyperplasia. A cystoprostatectomy operation was performed on one patient five years ago for bladder cancer. One patient had lung cancer with bone and suprarenal gland metastases without any records about this prostate.

PSA and PAP were measured with RIA kits, PSA with a tandem-R PSA bit (Hybritech, USA) and with a PAP-kit (Farmos Diagnostica, Finland). The normal values were: $PSA < 4$ µg/l and $PAP < 3$ µg/l.

McNemar's test and Chi-square test were used in the statistical analyses [11]. Statistical significance is indicated by $P \leq 0.05$.

Results

Prostatic adenocarcinoma

Most of the patients had a localized disease (94/177, 80%) at the time of the diagnosis. Dissemination was observed at the time of diagnosis in 23 (20%) patients and was seen later at the time of the serum marker analysis, in 31 patients (27%) (Tables 1 and 2).

Untreated patients

Both tumor markers were positive only in 3 patients of the eighteen untreated patients (17%). Two of them had a localized T3–4 disease and one metastatic disease at the time of tumor marker measurements. In addition, only PSA was elevated (PSA^+) in 11 patients

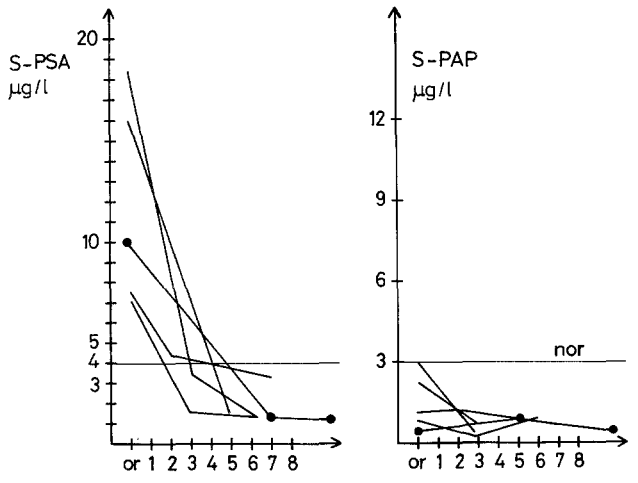

Fig. 1. The elevated PSA level declined to normal after orchiectomy (straight lines) and palliative radiotherapy of prostate (●—●). PAP was normal (nor) in all these patients during the whole follow-up time

(61%). Nine of them had a local disease and two disseminated disease. None had elevated PAP values (PAP^+) with negative PSA values (PSA^-). Both markers were negative in four patients who had a local disease (Table 1). Thus PSA was positive in 78% and PAP only in 17% of the untreated prostatic cancer patients.

The patients group with PSA^+/PAP^- ($N = 11$) was further evaluated and we were able to get more serum samples ten of them. In seven of them the PSA value declined to its normal value; in four, after orchiectomy and in three, after radiotherapy. In one patient the PSA value declined after radiotherapy, but remained slightly elevated (Fig. 1). In two patients, who received no treatment, the PSA value remained positive.

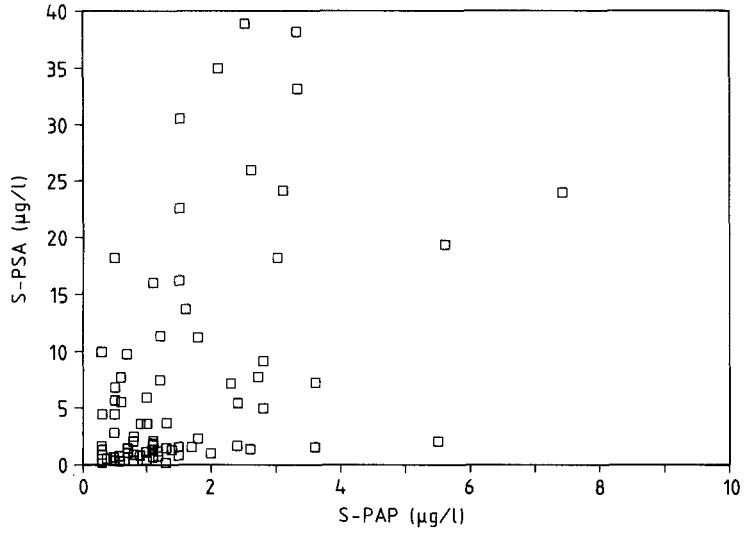

Fig. 2. Relation of the serum PSA levels and the PAP levels at the PSA value < 40 µg/l and PAP value < 10 µg/l

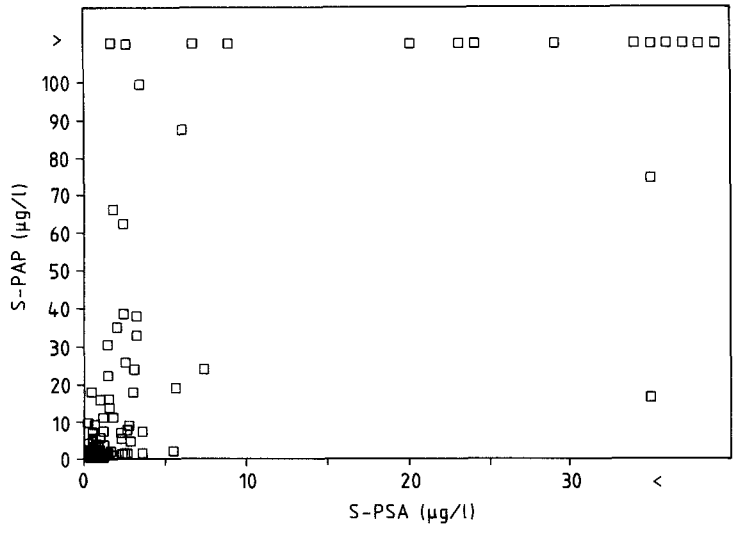

Fig. 3. Relation of the serum PSA and PAP levels of all patients with prostatic adenocarcinoma (when the patients with PSA > 100 µg/l and PAP > 30 are excluded: $y = 6.89x - 0.83$, $r = 0.53$)

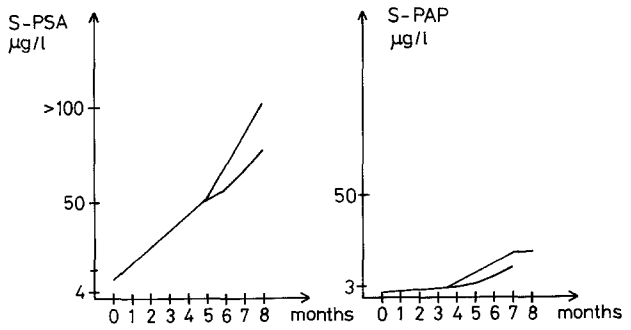

Fig. 4. The PSA level increased earlier and more than PAP in these two patients when metastasizing during the follow-up time

Table 3. Patients with positive PSA (>4 µg/l) serum levels

Diagnosis	Number of PSA^+ patients/ total number	per cent
Prostatic hyperplasia	3/9	30%
Other malignancies	3/14	22%[a]
Prostatic cancer	54/117	46%

[a] These patient had prostatic hyperplasia in addition to their malignant disease

Treated patients

Most of the patients were treated (99/117, 85%) before the serum marker analysis. Both tumor markers were positive in 19 treated patients (19%). Fourteen of them had metastatic disease and in addition local disease progression occurred in two of them at the time of the marker measurements. PSA^+/PAP^- occured in 21 patients (21%) out of whom 11 had local and eight a metastatic disease. There were only two patients with elevated PAP (2%) and negative PSA; one with a local disease and one with metastases. 58% of the treated patients had negative serum tumor marker levels. There were less distant metastases in this group (5 out of 57, 9%; Table 2). Thus PSA was positive in 40% of these treated patients and PAP only in 21%.

The tendency towards positivity in PSA compared with PAP in prostatic adenocarcinoma was significant ($P<0.001$) in McNamer's statistical analysis. The same tendency is seen in Figs. 3–4 where the serum values of all patients are included.

Most of the patients were castrated (70/117, 60%), 68 orchiectomized and 2 medically castrated. In addition, 29 patients had received local treatments. Most of the patients in the group with both markers positive had metastatic disease (14/19, 74%), while most of the patients in the group with both markers negative had local disease or had undergone prostatectomy (52/57, 91%) at the time of the marker analysis.

The group of patients with a positive serum PSA level and a negative PAP level ($N = 21$) were further evaluated with a help of new serum samples. There were 12 patients with two or more serum analyses available. In eight patients the PSA value remained positive and the PAP level negative; five had metastatic disease, two were treated with radiotherapy and one with orchiectomy. In four patients the PAP levels also increased above normal during the follow-up period. Two of them had progressive disease in bone (Fig. 4), one had local disease without any treatment, one had been taking Estradurin® at the time of the first measurement for local disease.

Prostatic hyperplasia and nonprostatic cancer

The PSA level was higher than normal in three of the nine patients (30%) with prostatic hyperplasia. Transurethral prostatic resection was performed on two of them the same day the measurements were taken. The prostatic weights in operation were 28 and 59 grams. TURP was also performed on the third patient for hyperplasia later on. In three of the fourteen other malignancies (two renal cell cancers and one laryngeal cancer) the PSA value was elevated. However, these three patients had prostatic hyperplasia (Table 3).

Discussion

In this study the tumor markers were positive in 48% of the patients with prostatic cancer. There was a more significant tendency towards increased PSA rather than PAP levels in these cancer patients. 32 out of 117 patients had an elevated serum PSA level with a normal PAP level, while only two were in the reverse situation. Both tumor markers were negative in half of the patients. This may be due to the fact that most of these patients had received some kind of therapy for their disease. However, the values were negative in seven patients with dissemination to a wider area than the prostate. These results are in agreement with the study of Stamey et al. [12] in which prostatectomy and postoperative radiotherapy was shown to decrease PSA to an undetectable level. Orchiectomy was also shown to decrease PSA to an undetectable level in this study. Only in the patient group with a positive PSA were there significantly more untreated patients as compared with other groups. These results suggest that the negativity of the markers in half of the patients was due to treatment as also shown in other studies [12].

In the treated patient group with an increased PSA level and a normal PAP level there were both patients with no evidence of clinical progression yet, and patients with tumor progression. Five patients even showed progression in their metastatic disease without any increase of PAP in serial measurements. In an additional two patients, the PAP level increased later, at the time when clinical dissemination was shown. Thus these findings suggest that PSA is more sensitive in detecting tumor progression.

The diagnostic specificity of both markers has been shown to be too low to be used in the early detection of prostatic cancer [13]. Also the false positive marker levels can be seen in this study as in the other studies [12, 13], namely in the case of patients with prostatic hyperplasia. The elevated PSA levels in the two patients with renal cell cancer are considered more likely due to prostatic hyperplasia, than to adenocarcinoma of the kidney. On the other hand, PSA was positive more often (78%) than PAP (17%) in untreated, mostly local disease in this study, suggesting that PSA might also be a more effective tool in an early diagnosis of prostatic cancer. Another point in the usefulness of PSA as a tumor marker is the upper limit of the normal PSA value. In this study there were eleven prostatic cancer patients with a PSA value between four and ten. Five of them had bone metastases and three had local untreated tumors. One had Estradurin treatment and one had orchiectomy five years ago, another one had local disease and the last one of these eleven patients was orchiectomized two months before the marker analysis. Thus at least half of them had an advanced disease. On the other hand, all three hyperplasia patients and the two renal cell cancer patients with positive PSA had a PSA value higher than 10 μg/l. These findings suggest that there is no need to change the limit of 4 μg/l used in the present study.

According to the present study and to the literature, it is suggested that PSA is more sensitive than PAP in the monitoring of the treatment results and may also be used in the follow-up of prostatic cancer patients.

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