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Serum TPS, PSA, and PAP values in relapsing stage D2 adenocarcinoma of the prostate

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Abstract Serum tissue polypeptide-specific antigen (TPS), prostate-specific antigen (PSA), and prostatic acid phosphatase (PAP) concentrations were serially measured in 31 prostate cancer patients with bone metastases who had relapsed following hormonal therapy. Of these subjects 7 had well-differentiated cancer (G1), 13 patients were assessed to have moderately differentiated tumor (G2) while in 11 subjects poorly differentiated tumor (C13) was found. With increasing tumor grade (G1 to G3), a proportional increase in mean TPS value was found while the increase in respective PAP serotest values was not linear. Simultaneously measured mean PSA values showed a curved effect. Both PSA and PAP serotest concentrations depend on the respective hormone-dependent gene expressions that gradually decrease with tumor dedifferentiation. Therefore, in progressive hormonally treated stage D2 prostate cancer patients an androgen-independent TPS serotest seems to be a useful clinical addition for monitoring protocols. The combined use of TPS, PSA, and PAP seems to give a better reflection of tumor status. According to the bone scan data metastatic tumor mass in G3 carcinomas was virtually equal to cancer burden in G2 tumors. Hence, the marked elevation of TPS serotest values in G3 adenocarcinomas could not be attributed to greater tumor mass but was most likely due to an increase in proliferation rate. Some authors have recently proposed cytokeratins 8, 18, and 19 to be the origin of TPS serum findings. However, cytokeratin content has been proven to be lower in G3 tumors than in better-differentiated neoplasms. TPS serotest values in progressive G3 cancer patients strikingly higher than the TPS levels in G1 and G2 tumors, when correlated with the above data, seem to imply TPS is a cell proliferation marker rather than an indicator of tumor degradation.

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Various modes of androgen deprivation remain the mainstay of metastatic prostate cancer therapy. In monitoring protocols prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) are routinely used as tumor load serotests. The expressions of PSA and PAP are androgen-dependent events [1, 8, 12]. Therefore, mean serum PSA concentrations in hormonally treated and progressive subjects when plotted against the respective increase in cancer grade (benign prostatic hypertrophy, well, moderately, poorly differentiated adenocarcinoma, and small cell prostate cancer) yield a bell-shaped curve [16]. A similar result is obtained when in stage D2 patients the increasing number of scintigraphic hot spots is cross-correlated with the mean blood PSA concentrations [17]. In parallel, cancer dedifferentiation lowers tumor androgen sensitivity and thus also the number of respectively active cells [8, 11, 18]. In contrast, tissue polypeptide-specific antigen (TPS) concentrations reflecting the overall cell proliferation show a continuing increase in value along with the increase in cancer status and tumor load [14, 17, 19]. We have attempted to verify the close relationship between cancer load, differentiation grade, and the capacity to metastasize in prostatic adenocarcinoma [10] by cross-correlating TPS values, tumor load markers, and respective cancer grade in stage D2 cancer patients who relapsed during hormonal treatment.

Materials and methods

Blood samples for the assessment of serotests were taken at least 7 days after any prostatic manipulation and/or 35 days after transurethral resection of the prostate (TURP). In the majority of subjects blood was collected prior to any manipulation of the prostate.

Serum was separated and frozen in aliquots at −70 °C until measured. Circulating PSA and PAP concentrations were measured during monitoring as previously described [8, 12]. TPS serotest assessment was performed retrospectively [14, 17, 18] in 31 stage D2 prostate adenocarcinoma patients who had relapsed following androgen deprivation. After three patients were eliminated due to diabetes and kidney failure, chronic diseases which elevate serum TPS concentration, a total of 34 patients initially entered the study. Serotest marker values were measured prior to treatment and every 12–15 weeks during monitoring. In all subjects bone metastases were checked by serial bone scans at intervals of 6–12 months. Bone imaging was performed as previously reported [17, 18]. In patients who had relapsed TPS values were elevated compared with prior to therapy.

Patients were divided into three groups according to tumor differentiation grade: well-differentiated cancer, G1, 7 patients, 45 recordings; moderately differentiated cancer, G2, 13 patients, 34 recordings; and poorly differentiated tumor, G3, 11 patients, 31 recordings. In 12 subjects the Gleason score was determined on post-TURP tissue specimens. Pathohistological data were converted to tumor grades that were cytologically assessed in the majority of patients. In the control group, serum TPS, PSA, and PAP values from ten patients with benign prostatic hypertrophy were measured. The means ± SD are given in Table 1. Radioimmunodetective data were analyzed by means of Macintosh software and a *t*-test for paired samples.

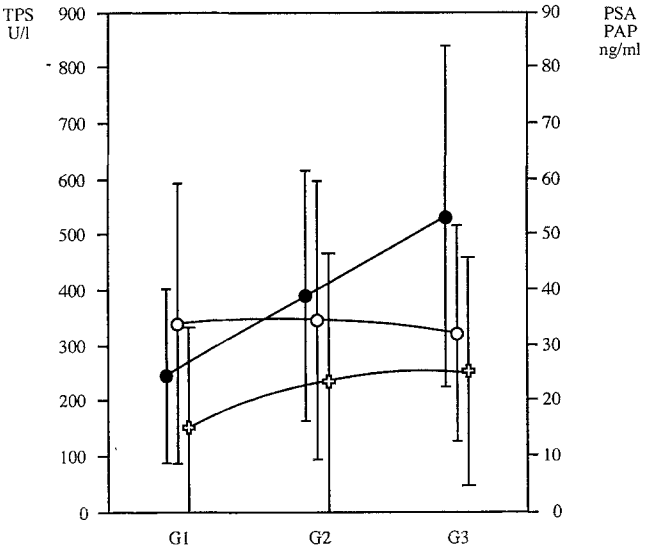

Fig. 1 Prostate adenocarcinoma grades (well (G1), moderately (G2), and poorly (G3) differentiated cancer) plotted against respective mean ± SD serum TPS (●), PSA (○) and PAP (✣) serotest values measured in 31 relapsing stage D2 patients following hormonal treatment

Results

Three progressive and hormonally treated stage D2 prostate cancer patients were eliminated from the study on the diagnosis of untreated diabetes (one subject) and severe kidney insufficiency (two patients). These diseases were found to interfere significantly with serum TPS concentrations [14, 17]. In all reported patients blood NSE concentrations (RIA, Pharmacia-Kabi, Uppsala) were measured [15] in order to eliminate subjects with contributing neuroendocrine (NE) structures within the adenocarcinoma. NE differentiation has been found to be quite frequent in prostate adenocarcinoma [7, 15] and has been reported to decrease serum TPS levels [18]. Prostate cancer differentiation was assessed by fine-needle aspiration biopsy while in an additional 12 subjects (12/31, 39%) post-TURP (transurethral resection of the prostate) pathological assessment according to the Gleason system was done. The data shown in Table 1 are based on serum samples taken when patients had relapsed under hormonal therapy.

Respective values were plotted against tumor differentiation grade (G1, G2, and G3) as presented in Fig. 1. Mean serum TPS values showed a nearly linear increase with increasing tumor grade while the corresponding mean PSA and PAP concentrations showed nonlinear relationships (hook effect, Fig. 1).

Patients with G1 and G2 cancer were treated with orchiectomy and Flucinom (flutamide) (four subjects), diethylstilbestrol (DES, eight subjects), cyproterone acetate (CPA, four subjects), and Estracyt (estramustine phosphate) (four patients). All patients with G3 tumor (11 subjects) were given Estracyt. Pharmacological agents were administered in routine daily doses (Flucinom 750 mg, CPA 200–300 mg, DES 1 mg, Estracyt 420–700 mg).

Table 1 Mean serum tissue polypeptide-specific antigen (TPS), prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) concentrations serially measured in stage D2 patients with relapsing hormonally treated prostate adenocarcinoma. Correlation with tumor grade. Ten control BPH patients. Normal serotest values are: TPS 0–80 U/l, PSA 0–10 ng/ml, PAP 0–2 ng/ml. The range of scintigraphic bone lesions was G1 cancer 3–10 hot spots, G2 and G3 disease 5–25 lesions. The approximate mean number of osseous lesions was 4.5, 14, and 12.5, respectively

Tumor grade	Patients	TPS (U/l)	PSA (ng/ml)	PAP (ng/ml)
Well differentiated	7	242.9 ± 157.1	33.4 ± 25.4	14.5 ± 18.2
Range		88–790	1.7–78.3	0.1–55.2
Moderately differentiated	13	386.5 ± 227.0	34.0 ± 25.1	22.8 ± 23.2
Range		110–1091	0.7–106.0	0.1–75.2
Poorly differentiated	11	530.0 ± 306.9	31.7 ± 19.6	24.7 ± 20.5
Range		137–1360	4.8–83.0	2.6–63.5
Benign prostatic hypertrophic	10	51 ± 39	8.4 ± 4.3	1.5 ± 0.4
Range		29–77	1.1–14.2	0.1–2.7

Discussion

According to our initial investigations [14], TPS serotest values remain normal in >95% of subjects with BPH [9] and in >90% of stage D0 prostate cancer patients. However, in stage D2 patients circulating TPS levels closely

reflect the status of the disease. Progressive patients, either untreated or those relapsing following hormonal therapy, show elevated serum TPS values. In parallel, healing processes are associated with a clear decline in TPS level.

A direct nearly linear relationship between serum TPS concentrations and extent of metastatic disease has been reported in progressive stage D2 subjects with hormonally treated prostatic adenocarcinoma [18]. This result correlates well with the proposed linearity between serum TPS values and the number of dividing cells [2]. Blood PSA and PAP levels did not follow such a degree of linearity [11], presumably due to their androgen-dependent production [1, 12].

Three years ago, Leo et al. concluded from studies on hormone therapy [8] that "Serum PSA levels in prostate cancer patients treated hormonally may have a significantly different meaning than the same serum PSA levels in patients who have not had hormonal therapy. In addition, findings provide further evidence for a direct effect of androgen ablation on serum PSA expression, independent of the response due to cellular death." According to this report, this effect holds true for both responders and nonresponders to androgen withdrawal. Loss of PSA and PAP expression during tumor dedifferentiation has been reported on the basis of immunopathological analysis [3, 4, 11] biochemical studies [6], clinical studies [7], and review articles [12]. A gradual loss of PSA and PAP expression with prostate cancer dedifferentiation was found in metastatic and relapsing cancer patients during hormonal therapy [6, 7, 11]. Although many reports indicated that PSA in serum is related to tumor grade [12], it clearly depends on both tumor stage and degree of cancer dedifferentiation. Among poorly differentiated carcinomas Gleason score 9–10 tumors express only minor quantities of PSA [3, 4, 11]. It may also be mentioned that androgen-related PSA expression [1, 8] is an even less reliable marker for monitoring hormonally treated, advanced and highly dedifferentiated prostatic carcinoma.

We measured serum TPS, PSA, and PAP concentrations in patients with progressive metastatic adenocarcinoma during androgen deprivation (Table 1). These serotest values were cross-correlated with tumor differentiation in order (1) to determine the sensitivities of these markers in various differentiation grades during tumor progression and (2) to accumulate clinical data that may be of help in defining TPS as the marker of either cell proliferation [2] or degradation [13].

The plot of the increasing tumor grade (from G1 to G3) against respectively mean serum TPS values yielded practically a straight line. This outcome suggests a progressive increase in the number of cell divisions with the loss of cancer differentiation since tumor burdens were similar in G2 and G3 tumors (Table 1). The respective plot of PSA concentrations gave a curve-like relationship (Fig. 1) that closely resembled the previously published bell-shaped curve [16]. Simultaneously assessed mean PAP values yielded a constant increase from G1 to G3 cancer with a significant deviation from linearity (Fig. 1). These results are in line with the observed gradual loss of tumor ability to produce PSA during dedifferentiation that finally disappears prior to the disappearance of PAP gene expression [11]. This fact is in accordance with the clinically observed reversal in numerical values of PSA and PAP serotests (PSA/PAP <1) in some G3 prostate cancer patients with poor prognosis (unpublished data). Although the tumor marker data overlap significantly (Fig. 1), general trends in the changes in TPS, PSA, and PAP serotest values with grade are apparent.

Some still unpublished observations suggest that TPS may be the marker of cell destruction [13] originating from cytokeratins 8, 18, and 19. There is a large body of evidence suggesting a steady decrease in cytokeratin content with the loss of prostate cancer differentiation [5]. If this holds true, it is difficult to explain the rise in serum TPS levels in progressive G3 tumor subjects relative to G1 and G2 cancer patients as the result of cell degradation (Table 1). Accordingly, the results reported herein seem to justify the theory of TPS as a tumor proliferation marker.

The assessment of the TPS marker appears to be of importance in hormonally treated progressive prostatic adenocarcinomas. In these high-grade tumors serum PSA (and PAP) values may not always properly delineate the status of the disease [3, 4, 7, 8, 16]. PSA expression, according to Oesterling [8], is under androgen regulation and may be independent of the response obtained by androgen withdrawal. Androgen-independent serum TPS levels that reflect cell proliferation rate seem to follow more closely the increase in tumor grade and thus also aggressiveness. In conclusion, we encourage urologists to add the assessment of serum TPS values to their regular armamentarium used in monitoring relapsing patients with advanced and disseminated prostatic adenocarcinoma.

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