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Tissue Polypeptide Antigen (TPA) and Prostatic Acid Phosphatase in Serum of Prostatic Cancer Patients

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Summary. Tissue polypeptide antigen (TPA) and prostatic acid phosphatase were both detected by radioimmunoassay in the sera of a male population (age > 45 years) consulting the clinic for urological problems or check-up on treatment. Increased concentrations of TPA were associated mostly with advanced stages of prostatic carcinomas, parallel to PAP. Some enhanced TPA concentrations were detected with haematuria and adenomas of the prostate.

Key words: Tissue polypeptide antigen (TPA), Prostatic acid phosphatase (PAP), Prostatic cancer.

Introduction

Researchers in the field of prostatic tumours have increasingly become aware of the limitations of even the immunological quantitation of prostatic acid phosphatase (PAP) in the detection of prostatic cancer. PAP concentrations in serum increased in such a way that a discrimination between a benign hyperplasia of the prostate (BHP) and cancerous growth becomes possible, usually only with the more advanced stages of prostatic carcinoma [1, 2]. Other marker proteins such as Creatine kinase BB (CK BB) [3, 4] or Prostate-specific antigen [5] offer no better detection rate for early stages of prostatic cancer and are no better aid in the discrimination between BHP and intracapsular tumours.

Recently, a commercial radioimmunoassay (RIA) test system has become available for the quantitation of the so-called "Tissue-polypeptide-antigen-B1" (TPA). TPA is a membrane-bound protein which is shed into the blood system by tumorous tissue of different origin. It is a protein with a molecular weight of approximately 43,000 daltons with no lipids, carbohydrates or prostetic groups attached to it [6, 7].

The purpose of the work reported on here was to test whether the actual combination of a tissue-unspecific marker (TPA) with a tissue-specific marker (PAP) gives more significant results in the detection of prostatic carcinoma than PAP itself. A group of patients was chosen in whom a disorder of the urogenital tract was suspected. In the serum of these patients TPA and PAP concentrations were quantitated and the results were statistically tested for their power to detect prostatic cancer relative to each other and in combination.

Materials and Methods

RIA Tests. The RIA test for TPA was provided by Sangtec-Medical, Stockholm/Sweden through Medipro, Teufen/Switzerland. The Prolifigen® test is a radioimmunoassay for the detection of the tumour-associated tissue polypeptide antigen. Clinical Assays (Travenol) test system for the radioimmunological determination of prostatic acid phosphatase (PAP) served as a reference method.

Serum samples were used for both determinations, TPA and PAP.

Patients. Male patients (age above 45 years) admitted to the clinic for treatment of some ailment of the urogenital tract or for a check-up on treatment were included in this study. As soon as the RIA data were available the code was broken and the patient's case-history was introduced in order to determine type and stage of the ailment – no prostatic lesion, benign hyperplasia of the prostate (BHP) or prostatic cancer of different stages, treated and untreated. Classification of the carcinomas were according to the TNM system [8].

Treatment of Data. Inverse distribution plots [9] were used to compare data in the groups prostatic cancer (treated and untreated) vs. benign conditions and to obtain information on the specificity and the sensitivity of the test(s) [10].

Results

Figure 1 shows the distribution of the results on TPA in an inverse distribution plot (IVF). TPA concentrations obtained from sera of prostatic cancer patients were consistently higher than from their benign counterparts. The 95 percentile given in this figure corresponds to 85 U/l TPA, which was calculated from the data presented on controls,

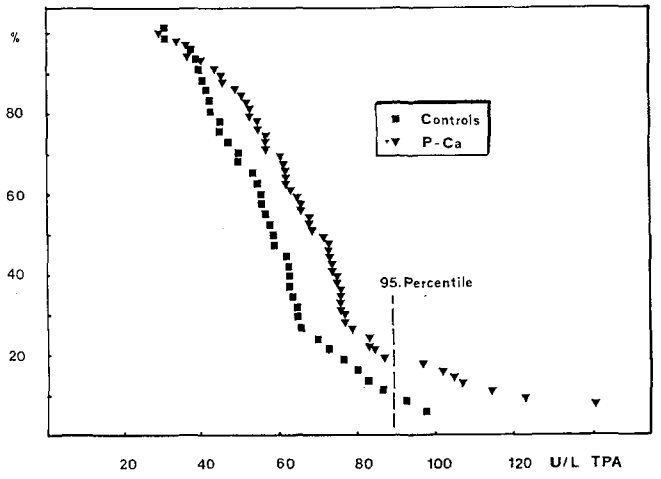

Fig. 1. Inverse distribution function of TPA concentrations in sera of controls (N = 38) and patients with prostatic carcinoma (N = 56)

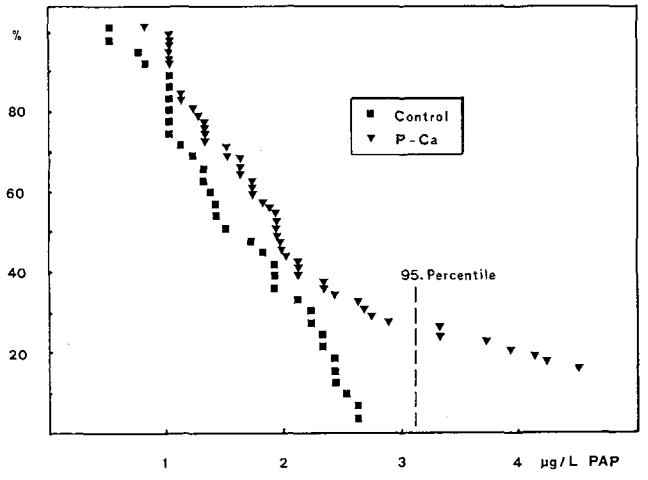

Fig. 2. Inverse distribution function of PAP – concentrations in the sera of the same patients as in Fig. 1

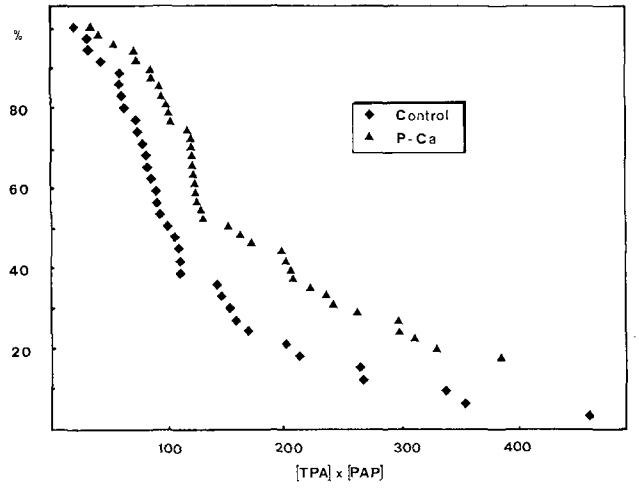

Fig. 3. Inverse distribution function of the combined concentrations of TPA and PAP in the same populations as in Figs. 1 and 2

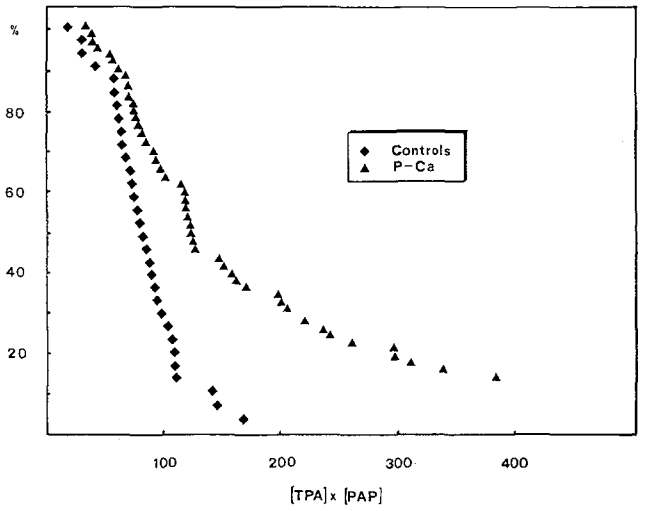

Fig. 4. Effect on the inverse distribution function by the ommission of a few (N = 4) of clearly false-positive results from patients with defined diseases of non-prostatic origin

and which is also given by the kits manufacturer. Approximately 20% of the carcinoma have higher values than the upper limit of 85 U/l TPA.

Figure 2 represents the data of the same patients for PAP. Setting the limit at 3.1 µg/l PAP as published earlier [1] no false-positives are detected, which is in contrast to TPA (Fig. 1).

Since TPA is not organ-specific we tried to introduce the more specific marker PAP in order to increase the organ specificity of TPA. By multiplying TPA concentrations with PAP concentrations and plotting the obtained data in an inverse distribution plot [9] we found the data arranged as indicated in Fig. 3. Interestingly, the same shape of distribution as found in TPA alone was developing. Omitting a few cases of haematuria (N = 2) and adenoma of the prostate (N = 2) drastically changed the distribution of values and caused an increase in specificity (Fig. 4). We were interested in the extent of the ratio of false-positives to true-positives (clinical specificity), and found (Fig. 5a) a slightly lower specificity for TPA than for PAP.

Figure 5b shows that on a level of 10% false-positives the specificity of TPA is slightly increased by multiplication of TPA concentrations with PAP concentrations (20% true-positives at the 10% level). Excluding (in retrospect) some obviously false-positive cases, the level is increased to approximately 40% which would correspond to the detection rate of prostatic cancer by PAP (RIA) measurement alone [1].

Figure 6 shows the scattergram of TPA and PAP concentrations with respect to stages T_0 through to T_4. As is easily recognized, there are no increased values for either PAP or TPA in the early stages of carcinoma. Only starting with the stage T_3 (break-through of carcinoma through the boundaries of the organ) did we observe a statistically significant increase in TPA values.

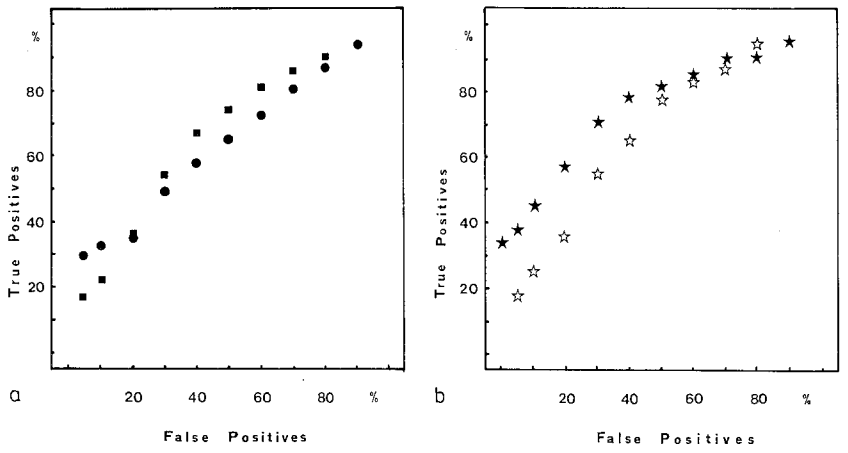

Fig. 5a, b. Specificity-sensitivity diagram obtained from Figs. 1 and 2 respectively. PAP (•) and TPA (■) (a). Specificity-sensitivity diagram from Figs. 3 and 4. (☆) all values included, (★) some (N = 4) values excluded (b)

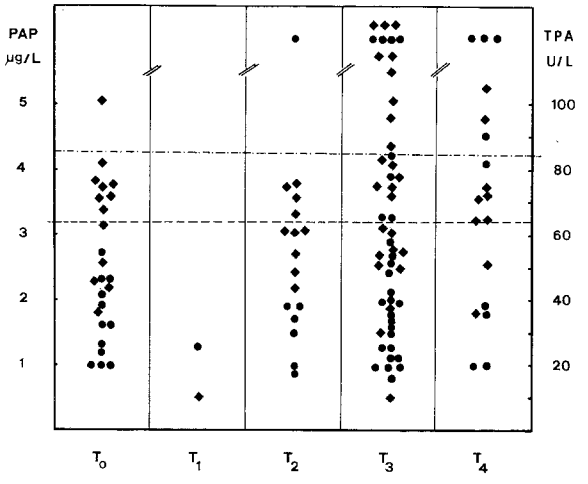

Fig. 6. Distribution of PAP concentrations (•) and TPA concentrations (♦) according to increasing stages of tumour growth. Cut-off for PAP at 3.1 µg/l and for TPA at 85 U/l

Discussion

From the literature it is to be learned that tissue polypeptide antigen (TPA) is a membrane bound protein [11], in contrast to acid phosphatase which is a secretory protein. The main activity is found in the Golgi apparatus [12]. Release of TPA from the tissue seems to occur during the phase of cell division and is released to the blood during rapid growth as occurs in carcinomas.

PAP is present during the normal function of the prostatic cell and is usually not released into the blood system. By simultaneous measurement of the blood concentrations of two substances with seemingly different properties we thought that it might be possible to increase the number of detected prostatic cancers on the grounds of varying growth properties of the carcinomas.

We set up the study as "search-test" by screening patients for serum TPA and PAP who were over 45 years old and therefore known to have a higher incidence of prostatic lesions than younger men. As it turned out, after the breaking of the code, most patients had received some type of treatment. However, considering that in surgically-treated prostatic carcinoma patients a complete removal of the tumorous tissue is not easily achieved we are confident that in combination with PAP measurement we can propose TPA as an alternative to PAP in search for advanced prostatic cancer. This is easily seen from Fig. 5, where PAP and TPA concentrations are plotted according to the stage of growth originally attributed to the prostatic tumour. A largely parallel scattering is observed.

Since the TPA serum concentrations in a normal population [13] and in patients with other lesions of the urogenital tract than prostatic carcinoma are rather high, a dissociation is only possible starting with T_3 stages.

From this study we cannot say conclusively that TPA is no marker for early detection of cancer of the prostate since we mostly looked at treated cases. But from the closely parallel behaviour of TPA concentrations to those of PAP we conclude that TPA has at least the same rather small potential as screening parameter as PAP [1].

An interesting finding are the two cases of makro- and microhaematuria of uncertain origin and with increased TPA concentrations. Of the two adenomas of the prostate with increased TPA one had pathological PAP values (3.7 µg/l), the other had a normal concentration of PAP.

In conclusion, having tested two proteins (TPA and PAP) as potential tumour markers and screening the literature for others, we have observed that these tests are only of value when the boundaries of the gland are broken through. The intracapsular tumours very rarely yield concentrations of "tumour marker" concentrations that are distinct from those found with BHP. The concept of the "polarized" cell, where certain proteins such as PAP are secreted only at one side, must, therefore, strongly be recommended as a route for further research. This means that not only serum tests but also urine tests must be developed to find the early stages of prostatic carcinoma.

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