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Significance of Plasma Tissue Polypeptide Antigen Determination for Diagnosis and Follow-up of Urothelial Bladder Cancer

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Summary. Plasma concentrations of tissue polypeptide antigen (TPA) were determined in 104 patients with all stages and grades of urinary bladder cancer. Patients with evidence of bacterial or virus infections were excluded. In addition, follow-up controls after treatment were performed. At a rate of 5% false positive values, the diagnostic sensitivity for the tumour stage pTis/pT1 was 63% and for the stages pT2–4 it was 76%. Patients with proved lymph node or distant metastases showed elevated values in 100% of cases. A positive correlation was found between the 3 grades of malignancy and the TPA concentrations. Except for the tumour diagnosis, TPA is a valuable parameter for follow-up controls. Our results show a very good correlation of the plasma TPA concentration with tumour progression as well as with stabilisation and regression after treatment.

Key words: Bladder cancer, Tumour marker, Tissue polypeptide antigen (TPA), Diagnosis, Follow-up, Sensitivity, Specificity.

Introduction

Tissue polypeptide antigen (TPA) was first isolated 1957 from membranes of various human cancers [1] and has been successfully demonstrated in cancer cells by the peroxidase technique [2]. Plasma TPA concentrations were found to be elevated in many types of malignant disease [1, 4, 7] as well as in certain benign conditions [1, 5, 6]. There is little data in the literature regarding plasma TPA level in patients with urinary bladder cancer [1, 3, 6] and no definite conclusions on the diagnostic sensitivity of this tumor-associated antigen in different stages of disease. Our study was prospectively designed to provide better insight into this subject.

Material and Methods

For systematic evaluation of diagnostic sensitivity and specificity plasma was stored at −20 °C from:

1. 118 healthy controls (75 males and 46 females) without any evidence of infection or other disease.

2. 50 patients (38 males and 12 females) with benign bladder disease, such as infections, stones, urothelial lesions after TUR etc.

3. 104 patients (80 males and 24 females) with transitional cell carcinoma of the urinary bladder without any evidence of infectious disease. The different tumour stages were grouped according to the UICC as follows:

Stage	pTis/pT1	(n = 46)
	pT2–4	(n = 21)
	N1–4	(n = 15)
	M1	(n = 22)

The following distribution of tumour grades was obtained:

G1 (n = 28)
G2 (n = 39)
G3 (n = 37)

Plasma TPA analysis was performed as previously described [7]. The results were plotted in frequency distribution curves, the principle of which has also been published [7]. Basically, these curves were obtained by plotting the percentage of patients on the ordinate exhibiting TPA concentrations which exceede those values which are indicated on the abscissa.

Results

The frequency distribution curves obtained for both healthy males and females (Fig. 1) clearly indicated that there was no difference between the two groups. Setting the rate of false-positive results arbitrarily at 5%, the cut-off level was 37 U/l. Thus, there is no need to distinguish between males and females for diagnostic purposes. Therefore, taking the two sexes together, a clear distinction between healthy controls, patients with benign disease, and cancer patients could be made (Fig. 2). Using the rate of

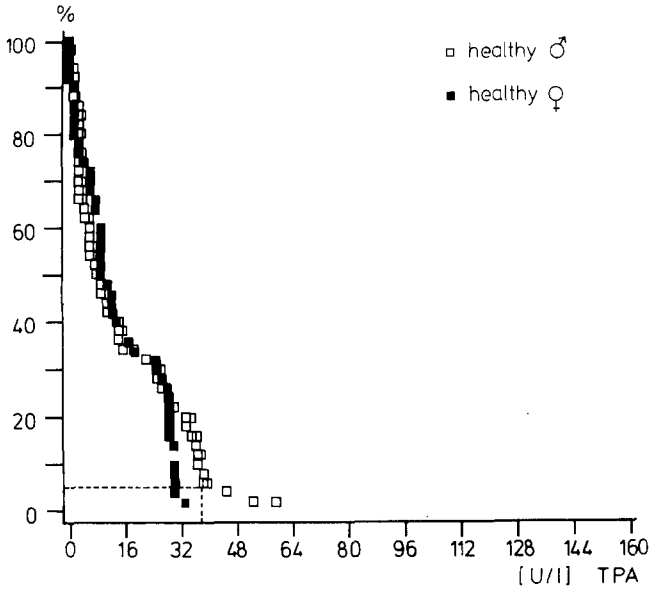


Fig. 1. Frequency distributions of TPA concentrations in plasma of healthy males and females

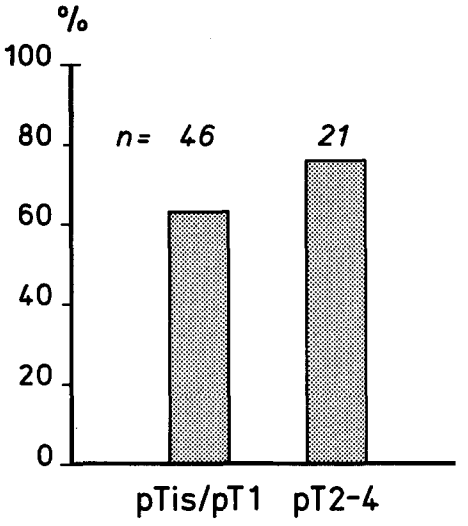


Fig. 3. Percentage of elevated plasma TPA concentrations in patients with superficial (*pTis/pT1*) and invasive (*pT2–4*) bladder cancer

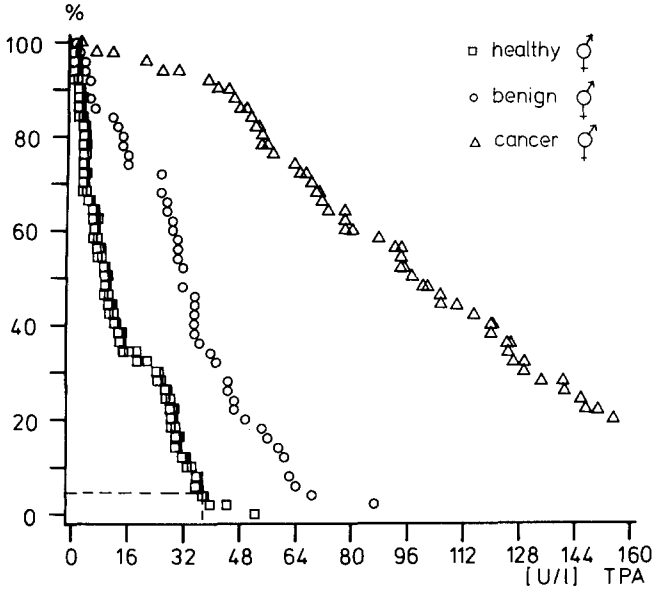


Fig. 2. Frequency distributions of TPA concentrations in plasma of healthy individuals, patients with benign bladder disease and patients with bladder cancer

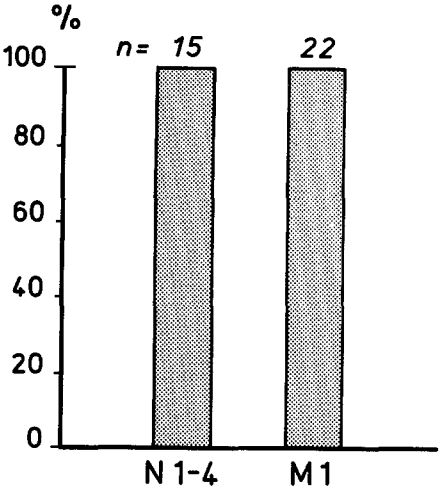


Fig. 4. Percentage of elevated plasma TPA concentrations in patients with lymph node (*N1–4*) or distand (*M1*) metastases

5% false-positives, the over-all diagnostic sensitivity was 90%. Using the percentage of elevated (>37 U/l) plasma TPA concentrations the primary tumour stages were grouped with regard to superficial (pTis/pT1) and invasive cancer (pT2–4) (Fig. 3). The diagnostic sensitivities in these groups were 63 and 76%, respectively. Applying the same principle in cases of metastatic disease irrespective of the primary tumour stage, the sensitivity was uniformly high (100%) in patients with biopsy proved lymph node as well as distant metastases (Fig. 4). As to the tumour grades a positive correlation existed between the degree of anaplasia and the percentage of elevated TPA concentrations (Fig. 5).

Since 1978, we have employed plasma TPA measurements for follow-up controls. The following 3 case reports prove the usefulness of this antigen in this respect.

Case 1: Patient S. W. with pT4 pN1 M0, grade III urothelial bladder cancer was operated by TUR and radical cystectomy (Op1). After complete wound healing 4 courses of polychemotherapy were applied. Five months postoperatively a pyonephrosis on the left side developed due to a local tumour recurrence. After nephrectomy

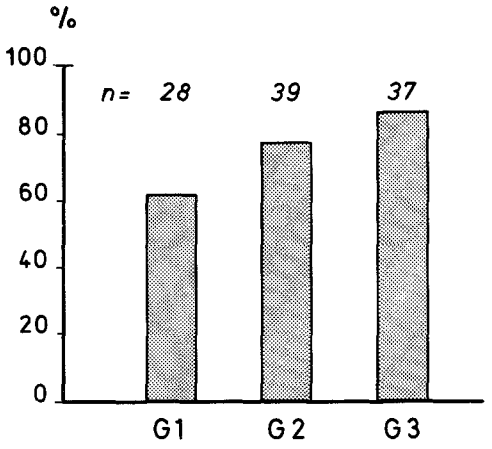
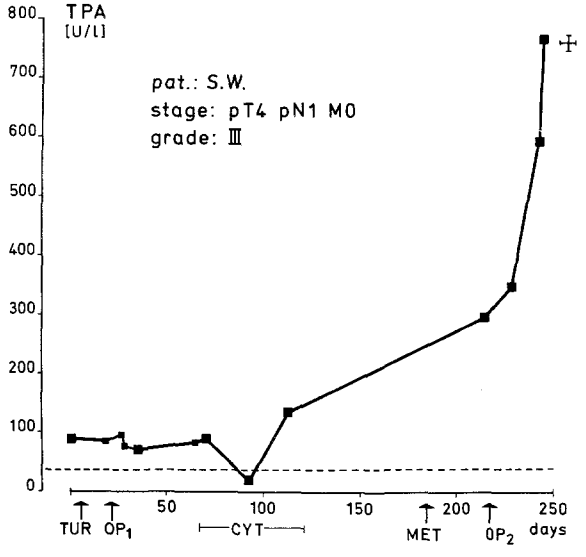


Fig. 5. Percentage of elevated plasma TPA concentrations in relation to the tumour grades 1–3



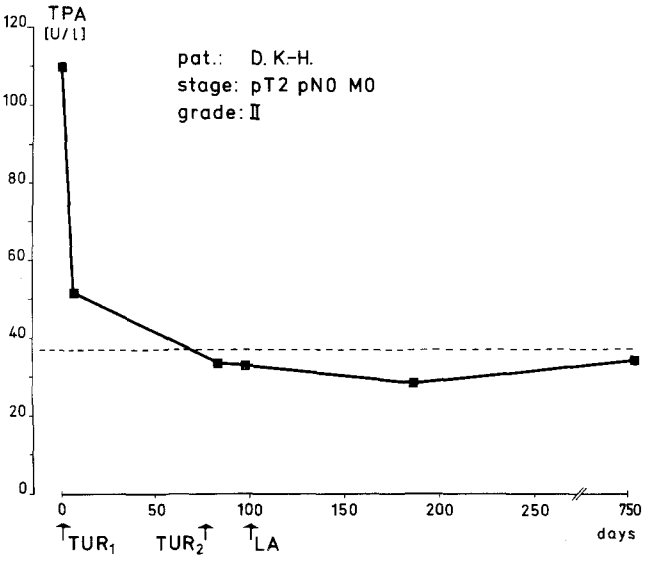


Fig. 7. Follow-up controls of plasma TPA in a patient (case 2) with pT2 pN0 M0 grade II bladder cancer. *TUR1/2*, first and second transurethral resection; *LA*, pelvic lymphadenectomy

◀ Fig. 6. Follow-up controls of plasma TPA in a patient (case 1) with pT4 pN1 M0 grade III bladder cancer. *TUR*, transurethral tumor resection; *OP1*, radical cystectomy; *CYT*, cytostatic polychemotherapy; *MET*, first radiologic evidence of metastasation; *OP2*, nephrectomy

(Op2) the patient's condition rapidly deteriorated and he died one month later (Fig. 6).

Case 2: Patient D. K.-H. with pT2 pN0 M0 grade II bladder cancer underwent two transurethral resections. Regional lymph node metastastases were excluded by pelvic lymph node dissection (LA). Serial plasma TPA controls up to $2^1/_2$ years were within the normal range without clinical evidence of tumour recurrence (Fig. 7).

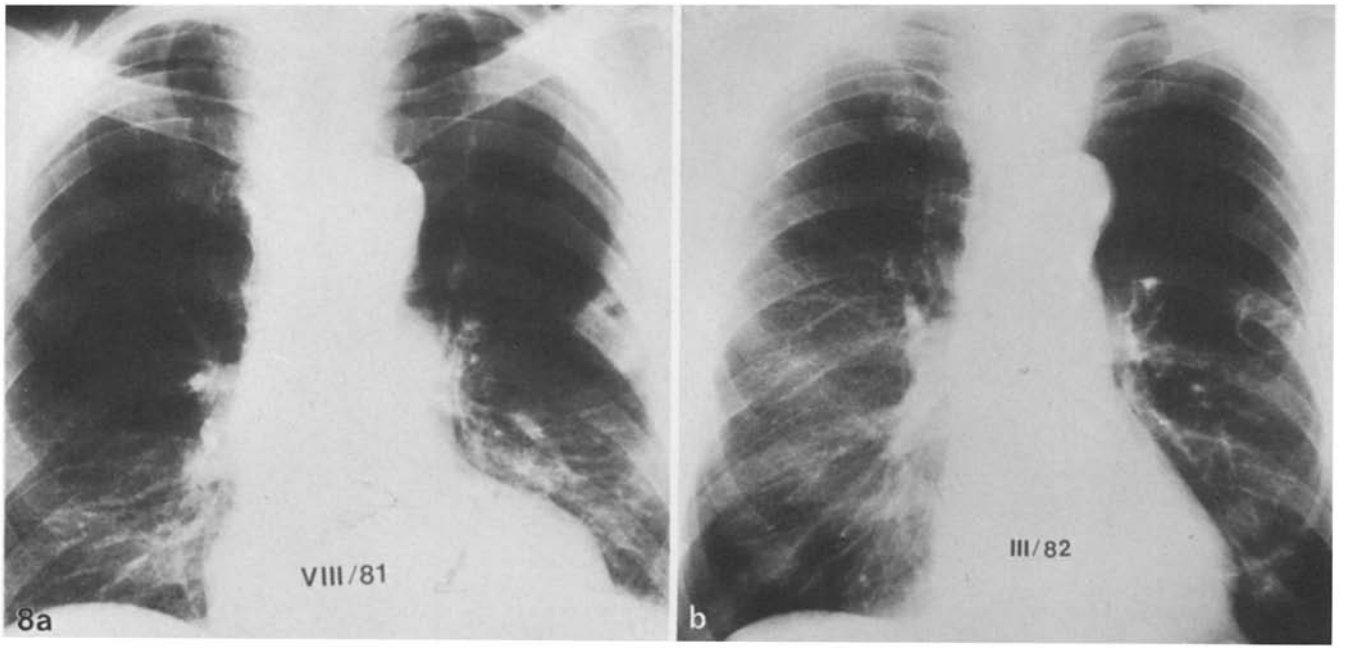


Fig. 8a, b. Solitary lung metastasis a before (left side) and b after (right side) polychemotherapy (case 3)

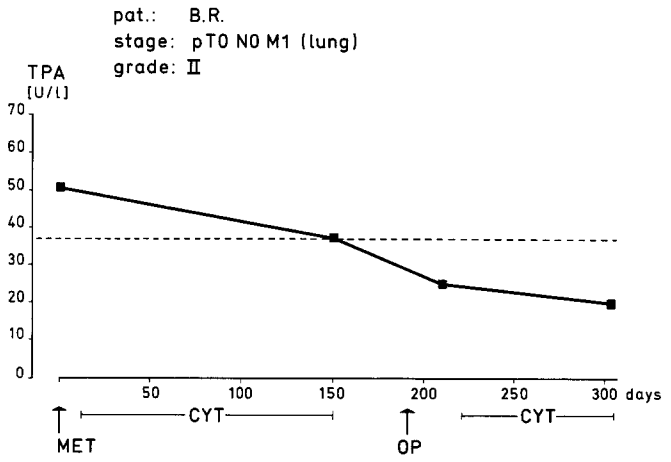


Fig. 9. Follow-up controls of plasma TPA in a patient (case 3) with solitary lung metastasis after radical cystectomy. *MET*, first radiologic evidence of metastasation; *CYT*, cytostatic polychemotherapy; *OP*, wedge resection of the lung

Case 3: Patient B. P. with a solitary lung metastasis after radical cystectomy was submitted to primary polychemotherapy (CYT) after which the lung lesion completely disappeared (Fig. 8a and b). After wedge resection of the lung which histologically contained a small area of residual tumour another polychemotherapy treatment was started. The clinical course of disease was accurately reflected by the plasma TPA concentrations (Fig. 9).

Discussion

To our knowledge, plasma TPA concentrations are documented in only 71 patients with urinary bladder cancer [1, 3, 6]. In these studies the diagnostic sensitivity in all types of bladder cancer ranges from 42% [3] to 75% [1, 6]. However, the rates of false-positive values are quite different so that the results cannot be compared as to the diagnostic sensitivity.

Our systematic evaluation of the different control and patient groups with regard to an arbitrarily set rate of false-positive values led to the conclusion that plasma TPA determination is an extremely helpful parameter for the diagnosis of bladder cancer. Kumar et al. [3] found this antigen even suitbale for identifying a group of workers who were at risk having been exposed to bladder carcinogens.

The high diagnostic sensitivity of plasma TPA makes it logical to use this antigen for follow-up control. The 3 case reports presented prove that plasma TPA concentrations correlate closely with the clinical course of the disease. In progressive cancer, this antigen concentration is elevated before the first clinical or radiological evidence of metastases appears, as demonstrated in case 1 as well as in many other clinical situations.

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