Urol Res (1984) 12:239–241

Urological Research

Importance of Serum Amyloid A (SAA) Level in Monitoring Disease Activity and Response to Therapy in Patients with Prostate Cancer

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Accepted: July 11, 1984

Summary. Serum amyloid A (SAA) and acid phosphatase (AcP) levels were determined in serial serum samples of 35 patients in different stages of dissemination and correlated with activity of carcinoma of the prostate. Up to 500-fold increases in SAA level were detected during active periods of cancer with a decrease towards the normal range in remission, in comparison with a 10-fold increase of AcP. The correlation between these two parameters was highly significant ($P < 0.001$), but while SAA shows 100% sensitivity during the active stage, AcP shows only 85% sensitivity. It is suggested that although SAA is not a specific marker for any particular illness, due to its characteristic pattern of change in malignant diseases and its high sensitivity, it represents a useful biochemical parameter for the assessment of the activity of the disease to monitor response to therapy during follow-up.

Key words: Prostate cancer, Serum amyloid A (SAA), Acid phosphatase (AcP).

Introduction

The follow-up of the progress and regression of patients with stage D carcinoma of the prostate is carried out by markers such as acid phosphatase, urinary hydroxyproline and/or LDH isoenzymes [7, 9]. So far, none of these markers have provided an accurate correlation with clinical presentation.

Serum amyloid A (SAA) is a normal serum protein which associates with high density lipoproteins [3, 17]. Being an acute phase reactant, its level increases markedly in many bacterial and viral infections, myocardial infarct and a variety of immunological stimuli, but returns to normal after a few days [17, 19, 20, 22]. SAA seems to be the circulating precursor of the main fibrillar protein of secondary amyloidosis [14] and it has been identified in various morphological forms [2]. The liver is known to be the primary site of synthesis of the proteins of the acute phase reaction with SAA and C-reactive protein giving the most dramatic response to stimulus [5, 13]. Other putative sites of SAA synthesis are connective tissue [15], spleen [1], and neutrophils [18]. It has been suggested that SAA may be involved in immunoregulation [4].

Our study was designed to determine whether SAA values would serve to monitor the dissemination of prostate cancer, and to detect disease activity or remission. SAA values were compared with acid phosphatase levels in the follow-up of patients, most of whom had reached the stage of osseous metastasis.

Materials and Methods

Serial serum samples for SAA and acid phosphatase levels were obtained from 35 patients with carcinoma of the prostate. Nineteen of them were classified as stage D (bone metastasis) which was confirmed by radioisotropic studies. Four cases were considered to be in stage A_2 (multiple carcinoma foci in postprostatectomy specimen), seven were in stage B_1 (nodule less than 1.0 cm confined to the prostate), four patients were classified as stage B_2 (nodular carcinoma still confined to the prostate) and one with stage C (extracapsular extension). At the time of initial evaluation of their clinical status, 12 patients were considered to be in remission, based on lack of subjective symptoms, normal IVP, negative bone scans and normal serum acid phosphatase levels. Twenty-three patients were clinically active with urinary retention, voiding problems and/or bone pain as the main symptoms. The average age of this group was 72 years. The SAA levels were compared to that of 30 healthy adults of similar age group. All carcinoma patients were free of infection, fever or any other acute diseases at the time of testing.

SAA levels were determined by radioimmunoassay using purified amyloid A from human amyloidogenic spleen of a Familial Mediterranean Fever patient, and rabbit antibody against human amyloid A. Iodination of amyloid A was performed by the chloramine T method [12]. The assay was carried out as described in [22]. SAA levels are expressed in μg/ml AA equivalent.

Acid phosphatase was measured by the Gutman and Gutman method [10] and levels are expressed in Bess-Lowry units.

* The work was supported by a grant from the Israel Academy of Science-Basic Research

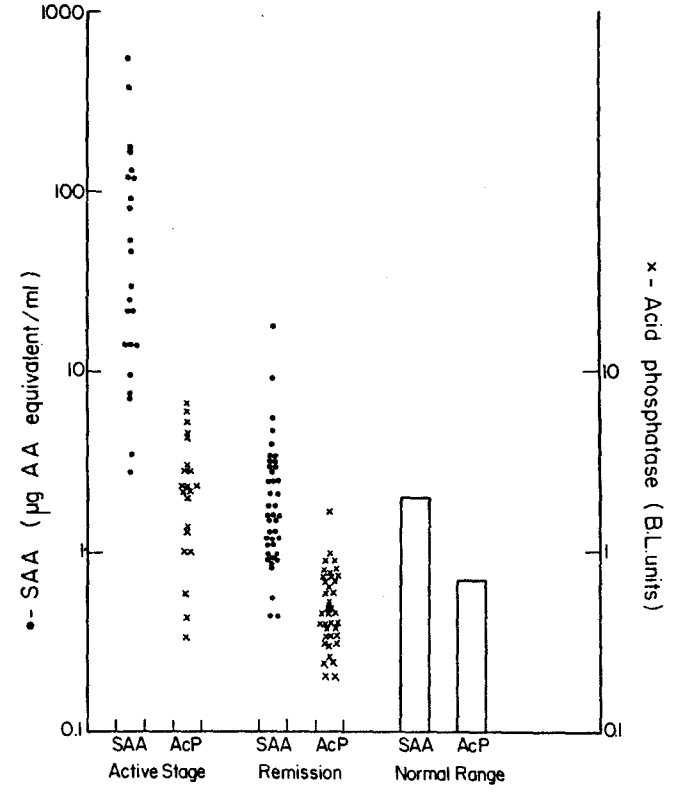
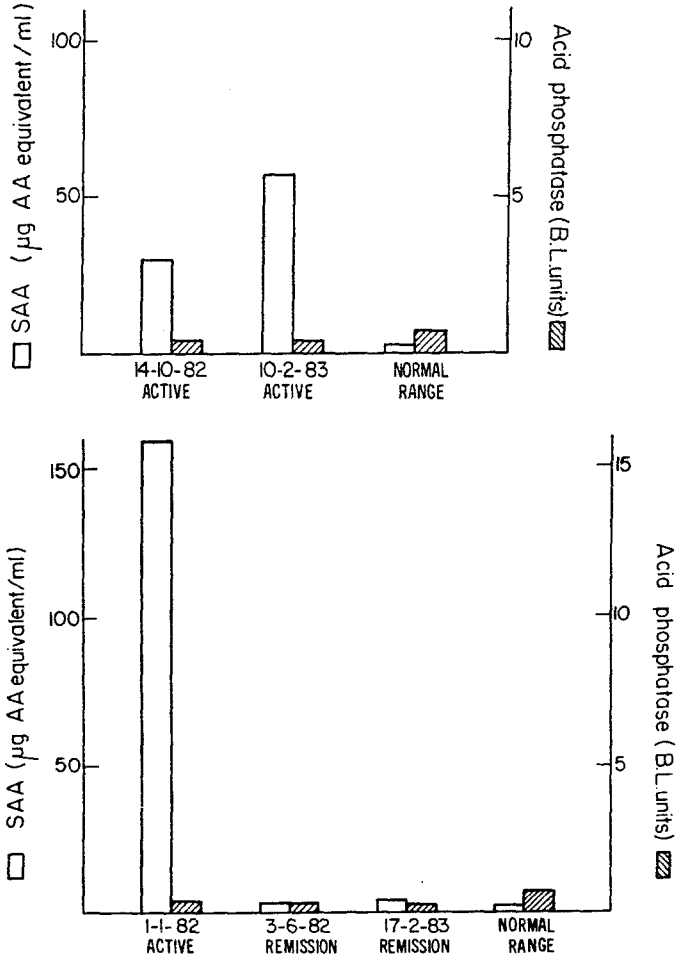


Fig. 1. Serum amyloid A and acid phosphatase levels in patients with carcinoma of the prostate



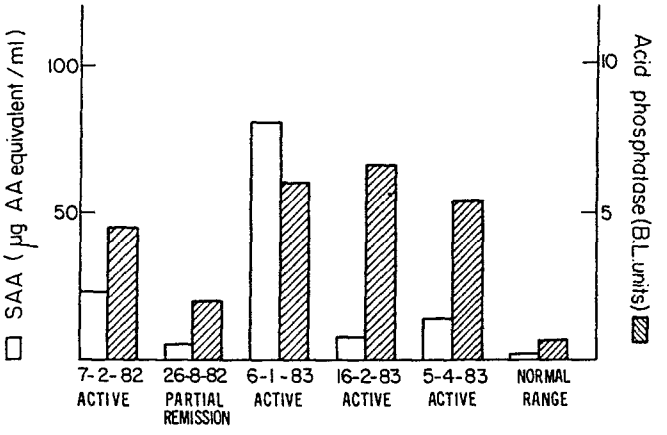


Fig. 3. Serum amyloid A and acid phosphatase level during a 9-months follow-up in a patient with very poor prognosis

Results

Serum amyloid A and acid phosphatase levels in active carcinoma state, in comparison with levels in remission and in controls are shown in Fig. 1. All 23 patients with active carcinoma have SAA levels above the normal range (100% sensitivity) while only 18 out of 21 have high AcP levels (85% sensitivity). After therapy, when patients went into remission, the level of both SAA and AcP decreased towards the normal range. Mean SAA level was 95.4 ± 131.4 μg AA equivalent/ml in the active state and 3.2 ± 4.2 μg AA equivalent/ml in remission, while mean AcP level was 2.7 ± 1.75 BL units in the active state and 0.54 ± 0.26 BL units in remission. Highly significant correlation was detected between these two parameters, $r = 0.4, P < 0.001$.

In Figs. 2A and 2B, the behaviour of the two patients in stages C and D respectively, during an up to 14 months follow-up, including treatments, is described. In both cases, SAA level was high during the active period while AcP was not sensitive.

Serum levels of the same two parameters were high in a patient with a very poor prognosis, shown in Fig. 3. Here, the rise in AcP, which originates in the affected tissue is more striking than the rise in SAA level, suggesting only a mild acute response, i.e. inability of the entire body to overcome the malignant disease in its final stages.

Discussion

The sensitivity and specificity of markers such as acid phosphatase, urinary hydroxyproline, creatine kinase (CK-BB) and LDH isoenzymes and their role in monitoring patients with carcinoma of the prostate have been published previously [7–9].

Most of these markers lack the sensitivity necessary for the early detection of dissemination of the disease and the

◀**Fig. 2A, B.** Serum amyloid A and acid phosphatase levels in two patients in different stages of cancer dissemination, during a 4–14 months follow-up and treatment. **A**, stage C; **B**, stage D

ability to assess the response to the various treatment modalities. The present dilemma resides in recognition of the biological behaviour of the tumour within each individual. Often, we are confronted with new markers which may possibly play a role in the diagnosis or prognostic value in prostatic carcinoma. Despite this, bone survey, acid and alkaline phosphatase determinations are still the best methods for detecting and following distant metastasis. However, serum acid phosphatase determination is inconsistent in evaluating osseous metastasis and objective response [9, 11]. Normal acid phosphatase levels may be seen in more than 20% of the patients with osseous metastasis. Although radioimmunoassay for the analysis of the prostatic acid phosphatase seems to be superior to enzymatic procedures, marked discrepancies exist in the overall clinical results reported and in the interpretations made by the investigators [6]. The confusion which is caused to the physician by the different techniques, poorly conducted clinical trials, and lack of specificity of various markers lead the investigators to search for new standardised methods [16]. In view of these limitations and the need for a sensitive biochemical marker in cases of carcinoma of the prostate led us to look at SAA levels as early index of remission and/or relapse during the course of the disease.

To date, our results are promising. Determination of SAA levels in these patients seems to be valuable in monitoring disease activity and response to therapy. The mechanism by which various stimuli induce synthesis if SAA has been subject to active investigations [23]. SAA was found to be synthesised in vitro, by isolated hepatocytes cultured in the presence of a monokine (termed SAA inducer), derived from lipopolysaccharide stimulated macrophages [21]. Even though SAA is a non-specific acute phase reactant, it displays a specific pattern of changes in malignant diseases, and its level remains high during all active periods, in comparison to its rapid decrease after acute inflammation [19]. SAA seems to be a more highly sensitive marker in evaluating the dissemination of carcinoma of the prostate, than the acid phosphatase determinations, which, even in the presence of stage D disease, may be in the normal range. The problem of SAA non-specificity could be easily overcome by measuring its levels at several day intervals; if the rise is not caused by malignant disease, it should fall to a normal level within a few days.

Since various species of SAA have already been identified [2], determination of SAA level may have more specific diagnostic value if it should be found that different SAA's are produced in response to different inducers.

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