

Variations in the level of a pregnancy-associated α -macroglobulin in patients with cancer

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SYNOPSIS The concentration of a pregnancy-associated α -macroglobulin (PAM) was determined in the blood of patients with various cancers. PAM was detectable in subjects with all types of malignant disease studied, and the level of the serum protein correlated well with the course of the disease: the concentration increased before clinical recognition of metastases and decreased significantly on successful treatment. Periodic PAM determinations may allow detection of tumour recurrence while it is still at a treatable stage and could aid in the evaluation of therapy.

Attempts to correlate cancer diagnosis and prognosis with simple quantitative procedures have so far met with mixed success. Although techniques for measuring the cell-mediated immune response, employing tumour-associated antigens (Herberman, 1973) and phytohaemagglutinin (Chretien *et al*, 1973), have been mentioned in this context, perhaps the best studied procedures are the blood-levels of the embryonic antigens, α -fetoprotein (Abelev, 1968; Ruoslahti and Seppälä, 1972) and carcinoembryonic antigen (Gold and Freedman, 1965; Dhar *et al*, 1972; Laurence and Neville, 1972; Costanza *et al*, 1974; Barrelet and Mach, 1975). Pregnancy-associated α -macroglobulin (PAM) has not as yet been identified in the fetus, but increased serum concentrations have been shown in patients with malignant disease (Stimson, 1974).

PAM is a high-molecular-weight glycoprotein (Stimson and Eubank-Scott, 1972; Von Schoultz and Stigbrand, 1973), the level of which rises substantially throughout pregnancy and decreases to a comparatively insignificant value within six weeks post partum (Stimson, 1974; von Schoultz, 1974; Stimson, 1975a). Peripheral-blood leucocytes appear to be capable of synthesizing the α -globulin (Stimson and Blackstock, 1975), and oestrogen can stimulate its production *in vitro* and *in vivo* (Horne *et al*, 1973; Berne, 1973; Beckman *et al*, 1973; Stimson, 1974; Than *et al*, 1974). However, PAM is not a steroid-transport protein (Stimson, 1973; von Schoultz *et al*, 1973a) and it has been suggested that it may function as an immunosuppressive factor

in vivo (Stimson, 1972; von Schoultz *et al*, 1973b; Stimson, 1975b).

In this investigation the PAM concentrations of patients with cancer were studied in order to ascertain whether changes in the level of the serum protein correlate with the course of the disease and actually show a 'lead-time' over clinical diagnosis (Stimson, 1975c). It was not envisaged that PAM concentrations could diagnose preclinical disease since values for cancer patients often fall within the ranges of subjects with other physiological conditions.

Materials and Methods

Blood samples were obtained from patients who had been diagnosed for malignant disease and the serum was separated and kept frozen at -20°C until tested. Single samples were taken from a large number of subjects with a variety of cancers and blood was also obtained from a smaller group, as often as possible before, during, and after treatment.

PAM concentrations were determined in triplicate using an enzyme-immunoassay procedure, as previously described (Stimson and Sinclair, 1974), or quantitative immunoelectrophoresis (Laurell, 1966) at the higher levels. The sensitivity limit of the immunoassay is approximately 200 ng PAM/ml.

Results

The PAM concentrations in patients with various cancers are given in the table. The distribution curves of PAM were found to be asymmetrical and therefore

Type of Cancer	No. of Patients	PAM Concentration ¹	
		(μ g/ml)	Range
Breast	262	72	8-1540
Cervix	12	58	31-183
Vulva	4	34	17-65
Ovary	21	63	10-132
Stomach	24	81	0-984
Colon	26	59	8-200
Rectum	23	57	15-205
Bladder	31	55	6-1102
Testis	19	58	14-172
Pancreas	4	93	62-322
Kidney	5	38	21-72
Prostate	18	46	1-134
Lung	35	62	0-280
Malignant melanoma	11	48	21-418
Osteosarcoma	2	212	144-280
Lymphosarcoma	4	60	42-141
Fibrosarcoma	3	26	8-31
Histiocytic lymphoma	2	52	12-92
Mixed lymphoma	2	102	41-163
Hodgkin's disease	11	68	29-572
Acute lymphatic leukaemia	3	105	85-142

Table Concentration of PAM in the serum of patients with various types of malignant disease

¹Concentration expressed as median values

the average concentrations are expressed as median values. Five hundred and twenty-two subjects (371 women, age range 28-84 years; 151 men, age range 24-74 years) with 21 types of malignant disease were examined for PAM and in only two cases, men aged 34 and 41 with cancers of the lung and stomach respectively, could the α -globulin not be detected by the immunoassay. The range of values obtained for each cancer was extremely

large and it was therefore impossible to correlate PAM levels with the type of disease. However, when patients with metastatic disease were compared with those with localized tumour (fig 1) it was found that the subjects with metastases tended to have higher levels of PAM.

The percentage changes in PAM concentration in six women (age range 44-63 years), all of whom had been diagnosed as having localized carcinoma of the breast, are shown in figure 2. All the patients initially underwent mastectomy and then received radiation therapy at the time and for the durations indicated. In the three women who developed meta-

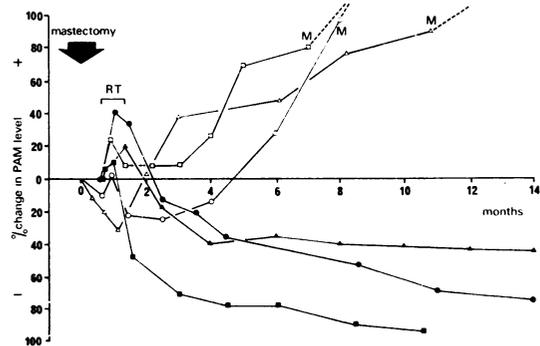


Fig 2 Percentage changes in serum PAM levels in six women receiving treatment for breast cancer: M = metastatic disease diagnosed at this time; RT = radiotherapy.

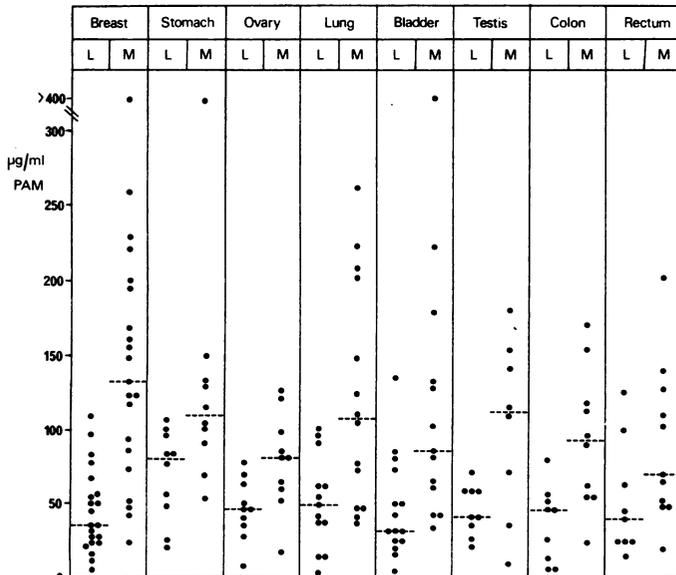


Fig 1 Comparison of the serum PAM concentration in patients with localized (L) and metastatic (M) cancer. Broken lines = median values. Statistical comparison, of the localized and metastatic cancer values, was performed using the Mann-Whitney U test. All were different at the 5% level of significance.

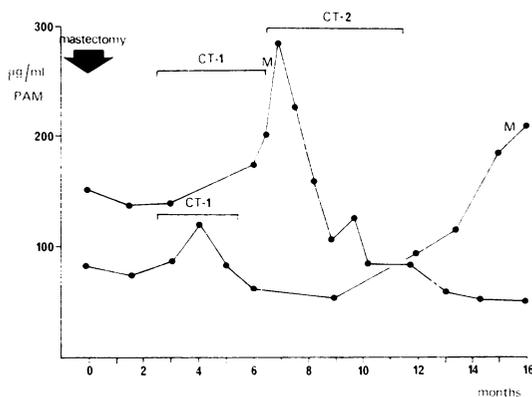


Fig 3 Changes in serum PAM levels in two women receiving treatment for breast cancer: M = metastatic disease diagnosed at this time; CT-1/2 = different types of chemotherapy.

stases, the level of PAM had risen substantially some time before clinical diagnosis was made; whereas in the subjects who were reported to have responded well to treatment and whose condition was good at the time of completion of the trial (all were clinically devoid of tumour at the time the last blood sample was taken) the PAM concentration dropped significantly, after which little further change in level was observed.

Figure 3 indicates the changes in PAM values occurring in two women (aged 32 and 34 years) being treated for breast cancer. Surgery was initially performed on both patients followed by chemotherapy. One of these women did not respond to the first type of chemotherapeutic agent employed, and metastatic disease of the lymph nodes was diagnosed at the time indicated (approximately 6½ months). However, the administration of another form of chemotherapy proved beneficial (no cancer was evident at the time of the last sample) and it can be seen that the PAM level fell substantially with this second treatment. The other patient was reported to have developed metastases 15 months after the start of treatment but increased PAM concentrations were evident several months earlier.

The variations in PAM level found in subjects being treated for carcinoma of the breast were also seen in patients with other cancers. The PAM concentration profiles of a man aged 53 with malignant melanoma and a woman aged 47 with cancer of the cervix (stage 1) are presented in figure 4. The latter had had no clinically detectable recurrence of cancer up to the time the last blood sample was taken and, as before in such cases, the PAM level dropped from its initial value and then tended to level out. The melanoma case, however, did not

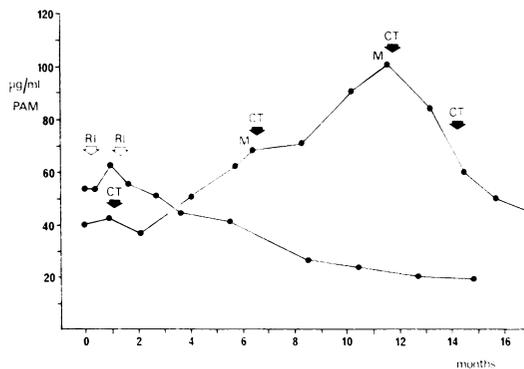


Fig 4 Changes in serum PAM levels in two patients receiving treatment for cancer. A = malignant melanoma; B = carcinoma of the cervix, stage 1; M = metastatic disease diagnosed at this time; RI = radium insert; CT = chemotherapy.

at first respond to treatment and metastases developed. A total of four pulses of chemotherapy were given to this patient before the cancer was finally brought under control at approximately 16 months. The concentration of PAM in this subject increased until the therapy proved effective when a sharp decline was recorded. The changes in level always showed a 'lead-time' over the clinical diagnosis of the patient's condition.

Discussion

Although the presence of PAM in the blood is commonly associated with pregnancy it was found possible to identify the serum protein in patients with various types of cancer. The concentration of PAM tended to be higher in patients who had been diagnosed for metastatic disease compared with those with localized tumour, and therefore subjects were studied during and after treatment to ascertain whether PAM concentrations could assist in the diagnosis of a patient's condition.

There was good correlation between the levels of PAM and the results of therapy in the cancer patients examined serially. In adequately treated patients the PAM level fell below the pre-treatment value and remained constant at that concentration following surgery, radiotherapy, or chemotherapy. However, in the subjects who later developed metastases, the α -globulin's concentration was found to have increased before this development was diagnosed clinically. Serial determination of PAM may therefore be useful in following the course of the disease.

Cases in which PAM levels either continue to rise or do not decrease following treatment may signal the need for re-examination and re-evaluation of the

patient, or the need to introduce a different mode of therapy. This point is clearly demonstrated in the woman with breast cancer who required two forms of chemotherapy before an improvement was attained and in the man with malignant melanoma who needed several pulses of chemotherapy before some measure of control was effected. The changes in PAM level therefore may afford a point of attack for the treatment of recurrent cancer.

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