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Placenta-like Alkaline Phosphatase in Gynecological Cancers[1]

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SUMMARY

In 302 patients with tumors of the cervix, corpus uteri, and ovaries, assessment by clinical staging (tumors-nodules-metastasis system) (4) and histopathology has been related to the presence of serum heat-stable, placenta-like alkaline phosphatase (PLAP) activity.

Early stages of cervical tumors show the highest incidence of this isoenzyme. In advanced stages of this disease, a decrease in frequency was observed that might be interpreted as the result of gradual dedifferentiation of the tumor cells to a point where synthesis of PLAP became undetectable. The same observation was made in adenocarcinomas of the corpus uteri, *i.e.*, patients with advanced disease tended to have the lowest incidence of serum PLAP.

Only in cancers of the ovaries did we find a positive correlation between this enzyme marker and the extent of the disease. In more than one-third of the patients examined, PLAP levels were an index of the tumor burden.

INTRODUCTION

At present, classification and prognosis in female genital cancers are based mainly on morphological criteria, such as grading and staging. Our previous studies indicated that there was an increased incidence of PLAP[2] in the serum of female patients with breast and gynecological cancer (2), especially in those with active disease. These investigations were pursued in order to establish the following: (*a*) whether there is a correlation between serum levels of PLAP and the histology, grading, and staging of the tumors; and (*b*) in view of the difficulties in monitoring treatment and recurrence in this group of cancers, whether detection of the presence of specific biochemical markers would be of value to the clinician.

MATERIALS AND METHODS

We undertook to examine serum samples on a total of 302 patients with gynecological cancer who were admitted for assessment and treatment to the Princess Margaret Hospital (a large referral center in this area for patients with malignant disease). The clinical classification was based on the International Union Against Cancer proposals for grading and staging according to the tumors-nodules-metastasis (TNM) system (4). This was done by Dr. R. S. Bush.

Total alkaline phosphatase activity was determined according to a modification of the Autoanalyzer method (2) at 37° in an AMP buffer (pH 10.25) with 15 mM *p*-nitrophenylphosphate as substrate. Heat-stable alkaline phosphatase was measured by exposing the samples for 5 min at 65° followed by enzyme assay with 72 mM disodium phenylphosphate as substrate in a carbonate-bicarbonate buffer (pH 10.7). The results of the heat stability test are expressed in placental isoenzyme units (1). The heat-stable enzyme activity of 0.27 placental unit was established by us as the 95th percentile in the normal population. All serum samples were kept refrigerated and were processed within 5 days.

RESULTS

Our results are presented in 3 groups: tumors of the cervix, corpus uteri, and ovaries.

In patients with tumors of the cervix uteri (predominantly adenosquamous and squamous carcinoma), PLAP-positive sera were found both in patients with early and advanced disease. However, about 35% of patients in Stages Ia and Ib (Table 1) were positive, while in those with advanced disease the incidence of positivity decreased. There was no apparent correlation between the enzyme level and the tumor morphology (Chart 1). With the exception of conization, the patients had not been treated at the time of PLAP determination.

Patients with tumors of the corpus uteri showed increased levels of PLAP in 25% of the cases studied at Stage Ia of the disease; negative findings were noted in all patients with advanced disease including those with metastases (Chart 2). Adenocarcinomas appeared to be linked with higher total PLAP levels (Table 1).

In patients with tumors of the ovaries the highest overall incidence of PLAP-positive sera, over 35%, was observed in those with advanced or metastatic disease. This observation confirms our belief that PLAP might be of value in monitoring spread and recurrence in this group of tumors (Chart 3). All patients examined had undergone surgical treatment before the blood sample for PLAP determination was obtained.

DISCUSSION

Numerous investigators have shown that the presence of biochemical markers in cancer is associated with tumor burden as reflected in local invasion and distant spread of disease (5, 7), including gynecological cancer (6). There are

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[2] The abbreviations used are: PLAP, placenta-like alkaline phosphatase; CEA, carcinoembryonic antigen.

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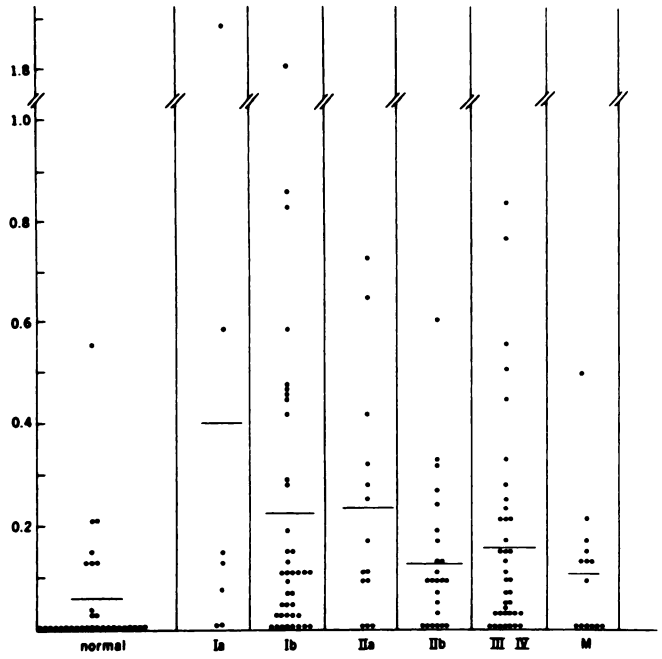

Chart 1. Levels of PLAP in sera from patients with tumors of the cervix, expressed in placental isoenzyme units (*ordinate*), grouped according to the tumor-nodules-metastasis system. *Horizontal lines*, mean of placental isoenzyme unit values in each group.

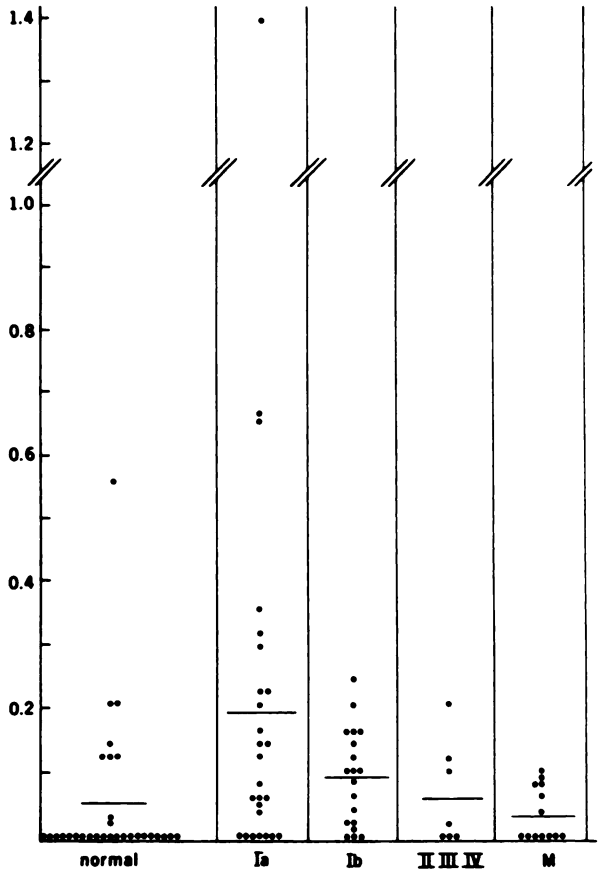

Chart 2. Levels of PLAP in sera from patients with tumors of the corpus uteri, expressed in placental isoenzyme units (*ordinate*), grouped according to the tumor-nodules-metastasis system.

Table 1

Elevated PLAP levels expressed in percent of total number of patients according to tumor localization and staging

A. Tumors of the cervix

	Histology			
	Adenosquamous and squamous carcinoma		Adenocarcinoma and papillary serous adenocarcinoma	
Stage	*n*	% > 0.27 PIU[a]	*n*	% > 0.27 PIU
Ia	7	35		
Ib	39	35	8	25
IIa	14	28		
IIb	24	12		
III + IV	39	16		
M	17	12		

B. Tumors of the corpus uteri

	Histology			
	Adenosquamous and squamous carcinoma		Adenocarcinoma and papillary serous adenocarcinoma	
Stage	*n*	% > 0.27 PIU	*n*	% > 0.27 PIU
Ia	3	0	27	25
Ib	3	0	19	0
II-IV	3	0	7	0
M	2	0	13	0

C. Tumors of the ovary

	Histology			
	Adenocarcinoma		Cystadenocarcinoma and papillary serous cystadenocarcinoma	
Stage	*n*	% > 0.27 PIU	*n*	% > 0.27 PIU
1	2	0	5	0
2	1	0	5	0
3	1	0	4	25
4	12	8	19	25
M	8	37	6	33

[a] PIU, placental isoenzyme units.

conflicting data, however, on the relationship of tumor differentiation and the appearance of such markers (3). Most of the reports in this field are based on results obtained in studies with CEA. In a previous investigation (2), using PLAP as a marker, we observed that there was a highly positive correlation between active disease in patients with breast cancer and the presence of this particular marker.

Our present results with respect to carcinoma of the cervix and corpus uteri appear to be in conflict with the foregoing general observations regarding tumor burden and appearance in the serum of the chosen marker. In both of these groups of tumors, the frequency of PLAP positivity was high in early stages and decreased with advanced disease. The reason for these observations is not clear. It has been noted that CEA production is associated with ad-

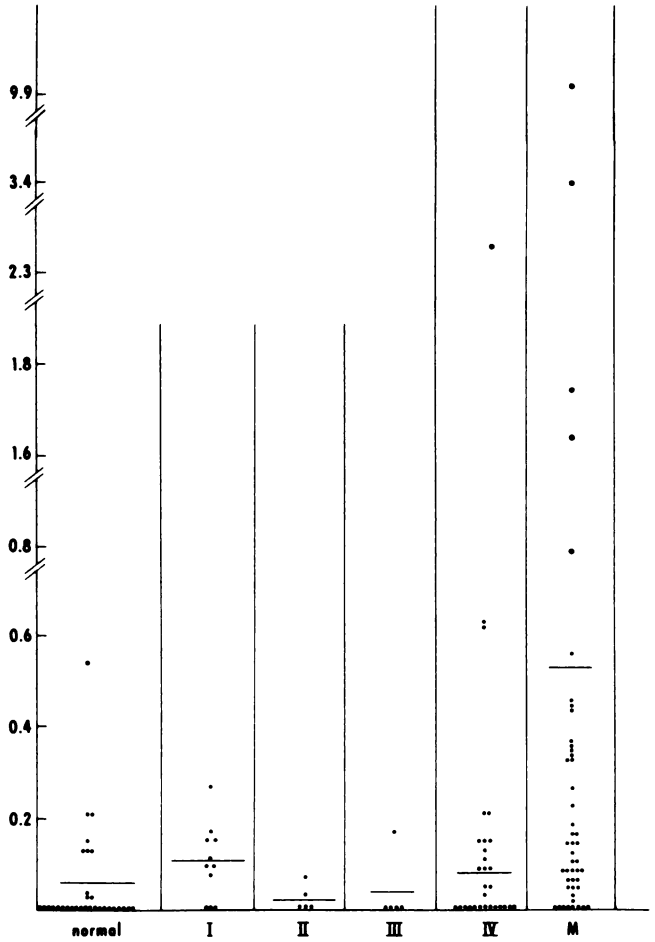

Chart 3. Levels of PLAP in sera from patient with tumors of the ovaries, expressed in placental isoenzyme units (*ordinate*), grouped according to the tumor-nodules-metastasis system.

vanced-stage disease in these 2 groups (3), in contradistinction to our observation with PLAP, which leads us to conclude that the cells of origin of these 2 markers may be completely different. Alternatively, the same cell type may produce an array of markers but different ones may make their appearance depending on the degree of dedifferentiation of the particular clone of cells. A useful corollary to these findings is the fact that, by utilizing several markers, the dynamics of the disease process can be monitored more effectively.

With the exception of the patients suffering from tumors of the corpus uteri, there was no apparent correlation between serum PLAP levels and histomorphology in any of the gynecological cancers studied (Table 1).

Serum PLAP levels appeared to reflect tumor burden most significantly in patients with ovarian cancer. This observation coincides with the results of van Nagell (6) using CEA as a marker. At the present time, we are attempting to ascertain whether these markers supplement each other in monitoring this disease. The use of a battery of markers to recognize persistence or recurrence of ovarian tumors is of utmost importance in view of the diagnostic difficulties and poor survival rate in those unfortunate enough to be afflicted with this disease.

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