A SEQUENTIAL STUDY OF SERUM IMMUNOGLOBULINS AND CIRCULATING IMMUNE COMPLEXES IN OVARIAN NEOPLASMS

by

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SUMMARY

A sequential study of serum immunoglobulins and circulating immune complexes has been done in 10 benign and 15 malignant ovarian tumours. In benign tumours serum immunoglobulins showed a significant increase of IgG and IgM but IgA was not altered. Postoperatively on 10th day, IgM and IgA significantly increased. On 30th postoperative day, all the three immunoglobulins decreased significantly from 10th day level. In malignant tumours, preoperative level of IgM, A and G showed a significant increase. On 10th postoperative day, IgM further increased but IgA and IgG decreased. On 30th postoperative day, IgM and IgG increased significantly from 10th day level. IgA remained stationary. On 90th postoperative day, all the three immunoglobulins showed a decreasing trend. Similarly, circulating immune complexes, showed an insignificant increase in benign tumours but significant higher levels were seen in cancer patients. Postoperatively on 30th day, their levels came down to normal in benign group but decreased significantly after surgery and/or chemotherapy in cancer group. In the latter group levels returned to normal on 90th day. The level was found to increase with recurrence.

Material and Methods

Sequential study of serum immunoglobulins and immune complexes has been done in 15 patients with histologically proved ovarian carcinoma and 10 cases with benign ovarian tumours. The sera sample were studied before and on 10th, 30th and 90th day of the therapeutic schedule. For the control study, sera from healthy women of the same age range as the patients were studied.

Immunoglobulins were estimated by radial immunodiffusion technique (Fahey and McKelvey, 1965). Immune complexes were detected by polyethylene glycol—

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6000 precipitation method (Riha *et al*, 1979). All the values were statistically evaluated using students 't' test.

Results and Discussion

Serum immunoglobulins:

In healthy control subjects, mean values for serum IgM, IgA and IgG were found to be 121.1 ± 21.13 mg, 218.0 ± 20.16 mg and 1141.0 ± 110.41 mg per cent respectively.

Benign ovarian tumours showed a significant increase of IgM and IgG pre-operatively. The IgA was not altered. Post-operatively on 10th day, all the three immunoglobulins showed an increasing trend in relation to pre-operative values, though the rise in IgG was statistically not significant. On 30th post-operative day, all the three immunoglobulins were found to be significantly decreased in relation to 10th post-operative day (Fig. 1).

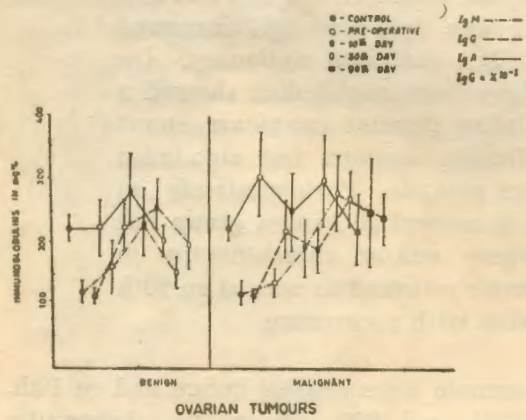

Fig. 1
Sequential serum immunoglobulins in ovarian tumours.

In malignant ovarian tumours, serum IgM, IgA and IgG showed a significant increase when compared to the control group. On 10th post-operative day, IgM level showed a further significant increase from pre-operative level, but IgA and IgG showed a significant decrease. On 30th post-operative day, IgM and IgG increased significantly compared to 10th day. The rise in IgA was not significant. Post-operatively on 90th day, all the three immunoglobulins showed an insignificant decrease from 30th day (Fig. 1).

Anderson (1966) observed that the serum levels of IgG was dependent upon the intensity of antigenic stimulation and on the functional capacity of the antibody producing mechanisms. Vasudevan *et al* (1971) suggested that high levels of IgG could be due to an enhancement of immunoglobulin synthesis induced by solid tumours. The increased levels returned to normal after tumour ablation by radiotherapy. It suggested a direct correlation beween the tumour mass and IgG. The findings in this study are in accord with those of Anderson (1966) and Vasudevan *et al* (1971). The increase in IgG could be due to intensive stimulation by tumour antigens. This is further supported by the fact that IgG level decreased significantly post-operatively. In contrast to these observations, Tee and Watkins (1967) observed that IgG catabolised at a faster rate in cancer patients than in healthy individuals, thereby reducing IgG levels in cancer patients.

Post-operatively on the 10th and 30th day, the rise of IgM could be due to non-specific effect of surgery as similar findings were found both in benign and malignant tumours. This is corroborated by the observations of Hughes and Whitehead (1976), who also observed raised IgM levels post-operatively both in cancer and benign tumour patients. Post-operatively on 90th day, fall of all the three immunoglobulins may be due to gradual decrease in the tumour antigen.

Laurova *et al* (1979) observed no signi-

ficant change in serum immunoglobulin levels in patients with stage I ovarian cancer during a follow-up study of 4 years at 3 months interval. However, patients in stage III, who were subjected to partial tumour resection and/or cytostatic therapy and had no tumour progression during the follow-up, showed reduced IgG levels in the samples taken at 12 months after surgery. In the present study follow up was done only upto 3 months. On the other hand, Laghi *et al* (1979) did not observe any abnormal immunoglobulin level in ovarian cancer patients. Kudeda and Kouril (1980) measured immuunoglobulins in 20 women with ovarian cancer who were subjected to surgery and chemotherapy. They reported that the raised serum immunoglobulin levels subsided before the patients expired. Similarly in 4 out of 6 patients who had raised immunoglobulin levels and who died during the period of study, a fall in the levels of all the three immunoglobulins was found in the serum samples taken before their death. In the remaining 2 patients, the results were inconclusive (Table I).

Circulating immune complexes (CICs):

Various techniques have been used for identfication of immune complexes in cancer patients, but none of the available techniques seem to be ideal for detection of ICs in all malignancies. Most of the workers (Poulton *et al*, 1978 and Clayton *et al*, 1982) have observed that PEG assay was a better method for detection of ICs in sera of ovarian cancer patients. This method is easy to carry out and sensitive. Therefore, in the present study this technique has been adopted.

Mean value of circulating immune complexes in the control subject was 315.6 ± 45.2. It is higher in comparison to the values reported by other workers. Rayner *et al* (1981) found that patients who were hospitalized for elective surgery had mean immune complex level of 198 ± 11.5. The raised value of ICs in the control subjects in this study could be explained on the basis of concurrent subclinical infections in this country. Patients with benign ovarian tumours showed a slightly raised value of serum ICs which was statistically not significant. However, Clayton *et al* (1982) found significantly raised level of ICs in patients with benign ovarian tumour as compared to that of the normal controls.

In patients with malignant ovarian tumours, the pre-operative level of ICs was significantly higher than that of the normal control subjects or those with benign lesions (Table II). All these patients underwent surgery and/or chemotherapy. On the 10th post-operative day, the level of CICs was found to be significantly decreased in 12 out of 15 cases. Two cases (case 11 and 13) expired. In 1 case (case 14) there was no significant change from pre-operative level (Table I).

At one month, in 5 out of remaining 13 cases there was further reduction in the CICs. Four patients expired early (Table II). In 2 cases (case 5 and 12) the levels of CICs were increased. Case 5 was found to have upper respiratory tract infection, whereas case 12 had recurrence of the tumour. Two cases were not available for further study. At 3 months follow-up, and 4 out of 9 surviving cases were available. All the cases showed further decrease in the CICs including case 5. This patient had treated for upper respiratory tract infection and was cured of this ailment prior to 3 months follow up.

In the present study, the level of CICs

TABLE I

Sequential Serum Immunoglobulins in Patients With Malignant Ovarian Neoplasms (in mg%) Who Expired During Study

	Age in years	Serum immunoglobulins in mg per cent						
		Postoperative			Postoperative			
					10th day		30th day	
		IgM	IgA	IgG	IgM	IgA	IgG	IgM IgA IgG
Controls (20)		121.1 ±21.13	218.0 ±20.16	1141.0 110.41				
Oyarian neoplasms								
Mucinous adenocarcinoma	65	153.5	338.0	2750.0	195.8	279.4	2157.6	Expired
Mucinous adenocarcinoma	42	177.2	326.5	2476.2	226.8	247.8	1798.0	Expired
Mucinous adenocarcinoma	60	153.5	279.4	1656.0	Expired			—
Papillary adenocarcinoma	65	111.3	335.9	2642.0	145.8	244.7	1642.6	Expired
Mixed germ cell tumour	25	109.1	225.1	1798.0	Expired			—
Metastatic choriocarcinoma	30	125.0	293.0	2558.6	226.8	247.8	2157.6	Expired

Figure in parenthesis indicate number of cases studied.

TABLE II

Immune Complexes in Ovarian Tumour (*OD* x 10^3)

Category	No. of cases	Preoperative	Postoperative 10th day	Postoperative 30th day	Postoperative 90th lay
Healthy controls	8	315.6 ±45.2			
Benign tumours	10	382.5 ±90.2	343.0 ±70.13	327.5 ±72.96	NA
't'		1.8035	1.035	0.459	
'p'		NS	NS	NS	
Malignant tumours	15				
Granulosa cell tumour	4	895	655	525	370
		600	500	460	NA
		675	550	450	410
		590	410	300	NA
Papillary cyst-Adenocarcinoma	3	980	820	Expired	—
		1070	700	NA	NA
		970	630	NA	NA
Mucinous adeno-carcinoma	3	1070	620	Expired	—
		865	750	Expired	—
		750	Expired	—	—
Immature teratoma	1	1190	850	1030	840
Mixed germ cell tumour	1	840	Expired	—	—
Metastatic chorio-carcinoma	1	1190	1200	Expired	—
Metastatic Krukenberg tumour	1	660	590	400	NA

NS = Not significant. NA = Not available.

correlated well with clinical response to surgery and/or chemotherapy. In all the patients after tumuor ablation IC level showed a significant decrease util there was recurrence which was associated with an increased level as observed in case 12. Populton *et al* (1978) and Clayton *et al* (1982) also demonstrated significantly higher levels of immune complexes in the sera of patients with ovarian cancer. These patients had surgrey and/or chemotherapy. During remission, the level of immune complexes was found to be similar to the control group until recurrence occurred. Clayton *et al* (1982) further observed that upper respiratory tract infection might cause elevation of CICs. In conrast to the above findings, some workers (Teshima *et al* 1977; Price *et al* 1980 and Clarke *et al* 1982) found no difference in ICs level in control, pre-operative or post-operative sera of patients with ovarian cancer.

The observations of the present study suggest that immune complexes are composed of antitumour antibody and tumour derived antigens, since highest values were from patients with a large tumour load. Furthermore, levels fell in patients who obtained remission from

disease either by surgery and/or chemotherpay, in whom there was little or no residual tumour to create the quantity of circulating tumour antigens necessary to maintain an elevated level of ICs. Therefore, the study of immune complexes may be used to know the extent of tumour load, the efficacy of therapeutic protocol and to detect recurrences.

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