

Immunoglobulins In Carcinoma Cervix

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Received for publication May 15 1971

Levels of IgG, IgA and IgM in 22 cases of patients suffering from carcinoma cervix, a part of whom were untreated patients and others who had received radiotherapy have been estimated by the modified Mancinis radial diffusion technique. In the untreated cases, the levels of IgG and IgA were raised. With radiotherapeutic treatment these levels reverted towards normal values. IgM was not significantly altered in either category of patients. Untreated carcinoma cervix patients showed the presence of cryoglobulins in their sera. These were characterized mainly as IgG-IgA complexes.

Introduction

There is highly suggestive evidence to indicate that tumours carry **nonsel** determinants that are immunogenic in the host in experimental animals (Klein 1966) and in human beings (Hellstrom et al 1968, Bubenik et al 1970). It has also been observed that expression of tumour specific antigenic determinants can be potentiated by treatment of malignant cells with neuraminidase both in animal (Sanford 1967, Currie and Baggshaw 1969) and in human patients (Vasudevan et al 1970).

The tumour antigens can induce the formation of humoral antibodies and/or evoke cell mediated immune responses. Evidence for the latter type of immunity has been reported earlier (Vasudevan et al 1970). This communication enquires into the quantitative levels of immuno-globulins in carcinoma cervix cases and changes in them following radiotherapeutic treatment.

Material and Methods

This study was confined to patients suffering from carcinoma cervix (Clinical Stages ii and iii). In the second category cases who had received radiotherapy 8 months to 1½ years earlier were taken.

Total proteins were estimated by the biuret methods. Albumin and globulins ratio was determined by sodium sulphate fractionation procedure (Varley 1967). Quantitative measurements of IgG, IgM and IgA were carried out by radial diffusion method of Mancini as modified by Fahey and Mckelvey (1965). Immunoglobulin standards were kindly provided by Dr. John Fahey and Dr. D. Rowe, WHO Ref. Laboratory (No. 67/97).

Cryoglobulins were prepared by keeping the serum samples at -10°C for one week and centrifuging the precipitates at $600\times g$ for 20 min in an International centri-

fuge at 4°C (Meltzer and Franklin 1966). The precipitate was resuspended in chilled iso-cosmotic saline (0.85% NaCl) and washed three times at 4°C. The pellet was then dissolved completely in 0.85% saline at 37°C.

Solubilized cryo-immunoglobulins were passed through diethyl-aminoethyl-cellulose column (20 cm × 2 cm) equilibrated with 5 mM phosphate buffer of pH 8. Two separate peaks were obtained. They were characterized by immuno-electrophoresis and Ouchterlony double diffusion in agar by reaction with mono-specific anti-globulin sera.

Results

Albumin and globulin levels in patients' sera: Table I gives the content of total proteins and albumin and globulin levels in sera of seven patients suffering from carcinoma cervix. The values in seven subjects that had received radiotherapy are also shown in Table I. The total serum proteins was found to be of the same order in the two categories of subjects. However, the relative proportion of albumin and globulins were different. The globulin levels were apparently high in active cases of carcinoma cervix.

Table I. Albumin and globulin levels in sera of patients

Patients suffering from carcinoma cervix				Patients cured of carcinoma cervix by radiotherapy			
Patient's RT No	Total protein g/100 ml	Albumin g/100 ml	Globulins g/100 ml	Patient's RT No	Total protein g/100 ml	Albumin g/100 ml	Globulins g/100 ml
70/1735	8.8	4.4	4.4	70/9	10.2	6.4	3.8
70/1514	9.2	4.2	5.0	69/75	9.2	5.9	3.3
70/1510	9.2	4.3	4.9	70/67	8.1	4.6	3.5
70/1663	8.5	4.2	4.3	70/1288	8.8	5.1	3.7
70/1560	8.2	3.8	4.4	70/102	7.5	4.1	3.4
70/1557	8.4	3.6	4.8	68/105	8.1	4.1	4.0
70/1561	8.2	4.6	3.6	69/1506	8.5	4.6	3.9
Mean	8.6	4.2	4.5		8.5	4.9	3.6

Table I gives the content of total proteins and the proportion of albumin and globulins in sera of seven patients studied. The values in seven subjects who had received radio therapy is also given. The total serum proteins were found to be of the same order in the two categories of subjects. However, the relative proportion of albumin and globulins were different. The globulins were apparently high in active cases of carcinoma cervix.

Levels of different classes of immunoglobulins : It was seen that the mean value of IgG in untreated cases was $2,445 \pm 616$ mg/100 ml ; IgM was 112 ± 159 , and IgA was $760 \pm$

538 (Table II). In patients who had completed radiotherapy, the values were reduced to 1159 ± 211 , 105 ± 40 and 243 ± 121 mg/100 ml respectively (Table III). The values for the normal Indian population have been reported to be 1145 ± 399 , 144 ± 60 and 273 ± 119 mg/100 ml respectively (Sehgal and Aikat 1970). The figures showed that there was a statistical increase in IgG and IgA levels in untreated cases, and these values came down to almost normal levels after radiotherapy. IgM values were not much altered from the normal in either group of patients (Graph).

Table II. Immunoglobulin levels in untreated carcinoma cervix patients

Patient's RT No	IgG	IgM	IgA
69/1333	2000	180	1800
69/1335	3000	72	800
69/1336	2000	72	560
69/1327	2000	140	560
69/1360	2000	100	4000
69/1367	2000	140	800
69/1394	2300	300	700
69/1395	2000	75	300
69/1399	3000	75	250
69/1475	2300	75	250
70/1557	2000	100	1800
70/1737	3000	140	1200
70/1735	2000	75	560
70/1561	2000	100	800
70/1560	3000	100	800
70/1663	1500	100	1800
70/1510	2000	140	400
70/1514	3600	100	240
70/1512	2000	75	240
70/1507	3000	120	180
70/1669	3000	140	800
70/1722	3500	75	400
70/1765	2000	100	1800
70/1734	3500	72	800
Mean	2445.8	112	760
S.D.	615.7	50.2	537.7
P	0.01	NS	0.1

Normal values : IgG = 1145 ± 339 ; IgM = 144 ± 60 and IgA = 273 ± 119

Cryoimmunoglobulins : It was seen that out of 22 cases studied, 80% cases of carcinoma cervix contained cryoglobulins, while in the group of patients who had completed radiotherapy only 10% contained cryoglobulins. Out of 7 cases of active cancer studied in a more detailed manner, 5 samples of cryoimmunoglobulins were found to be complexes of IgG-IgA, the remaining two had IgG-IgM complexes in cryoglobulins. The quantitative estimations of the different types of immunoglobulins present in cryoglobulins of sera were done. The results are given in Table IV.

Table III. Immunoglobulin levels in carcinoma cervix patients who completed the radiotherapy

Patient's RT No.	IgG	IgM	IgA
69/69	1250	72	400
70/24	1000	100	240
68/105	1000	175	240
70/9	1500	100	80
64/1683	1500	175	240
66/359	1000	110	400
69/75	1000	63	180
70/138	1250	110	400
69/75	1000	75	135
70/1	1000	75	120
Mean	1150	105	243
S.D.	210.8	40.2	120.8
P	NS	NS	NS

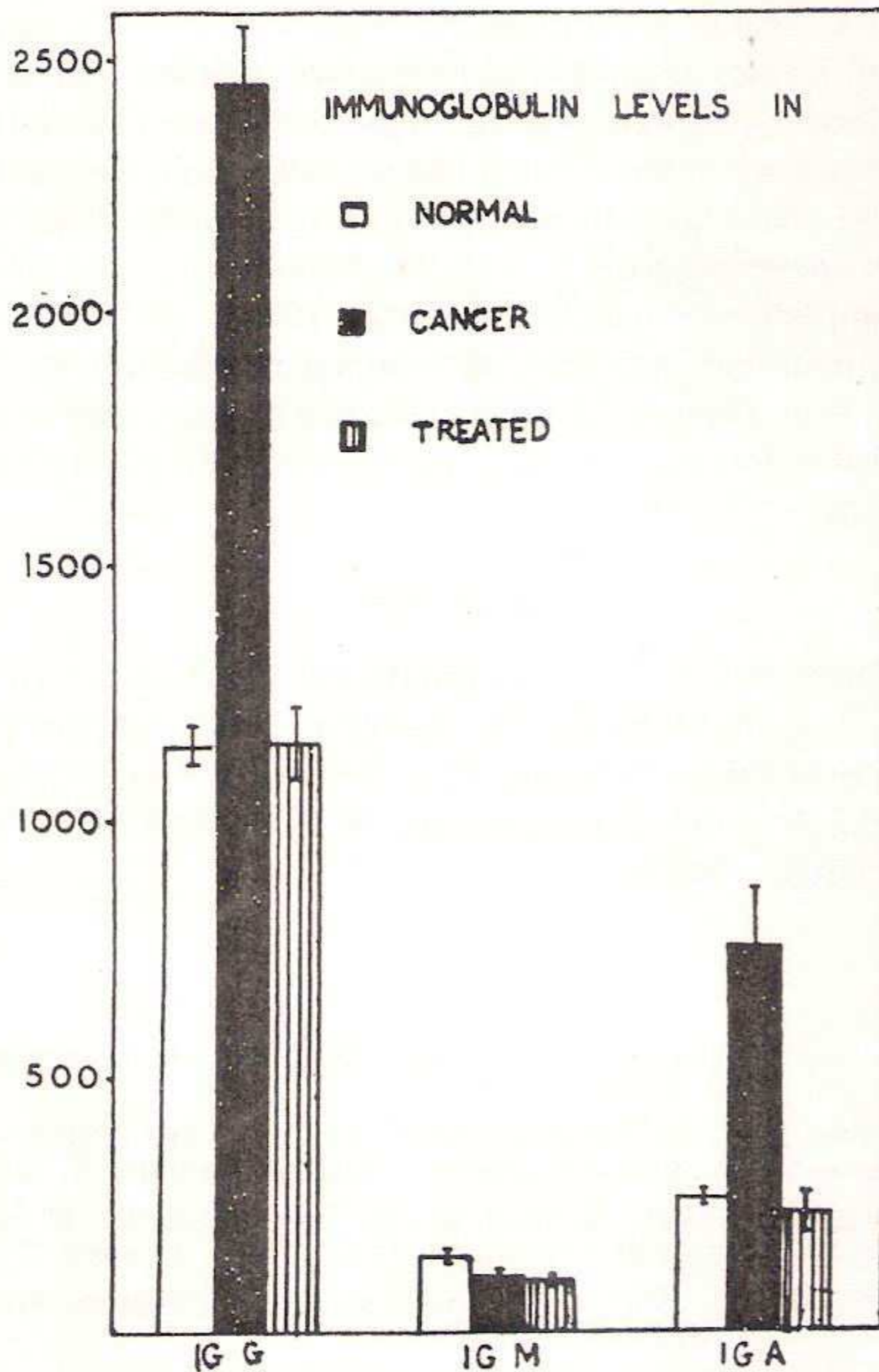
Table IV. Cryoimmunoglobulin levels in sera of carcinoma cervix cases

Patient's RT No.	IgG	IgM	IgA
	mg%		
70/1557	500	Nil	108
70/1737	200	Nil	30
70/1734	300	Nil	90
70/1561	500	Nil	250
70/1560	60	Nil	25
70/1669	150	13	30
70/1510	220	25	40

Discussion

IgG and IgA were found to be significantly raised in tumour bearing patients. The levels of these immunoglobulins were almost within normal range in patients after completion of radiotherapy. IgM levels were not significantly changed (*vide* Graph). Almost similar findings were reported in primary carcinoma of liver (Chew *et al* 1970) and in Kaposi's sarcoma (Master *et al* 1970). An increase in the IgA level has been reported in cancer of epithelial surfaces (Waldman *et al* 1970). Local production of IgA by plasma cells in mucosa of gastro-intestinal tract; respiratory tract and genitourinary tract has been shown (Tomasi *et al* 1965). In our studies the high levels of IgG and IgA in carcinoma cervix could be due to an enhancement of immunoglobulin synthesis induced by the solid tumour. It is also possible that IgA or some other immunoglobulin may, in fact, be acting also as an enhancing antibody.

Graph



The term **cryoglobulins** has been used to denote those proteins that have the property of precipitating from cooled serum. Cryoglobulins have been found in cases of multiple myeloma, leukaemia and lymphosarcoma (Farmer et al 1960), bronchogenic carcinoma (Meltzer and Franklin 1966), systemic lupus erythematosus and polyarteritis nodosa (Hanauer and Christian 1967), rheumatoid arthritis (Meltzer and Franklin, 1966). Sjogren's syndrome (Denko and Bergenstal 1960), syphilis (Lassus 1969) and lepromatous leprosy (Wager 1969). Usually, cryoglobulins consist of complexes of IgG-IgA or IgG-IgM or IgG-IgA-IgM. These complexes have been reported to show rheumatoid factor activity (Meltzer et al 1966, Wager 1969). Rheumatoid factor activity had been demonstrated in serum of cancer patients (Thunold et al 1970). It is believed that a second antibody is raised to the complexes formed by the initial stage antibody with excess of antigens.

In the present series of studies 80% of cases of carcinoma cervix were seen to have cryoglobulins in their sera, but they were found only in 10% of the samples obtained from patients who completed radiotherapy. In systemic lupus erythematosus also (Hanauer and Christian 1967). Cryoglobulins were shown to disappear after clinical improvement. Out of 7 cases investigated in a more detailed manner in this study, 5 were IgG-IgA complexes and 2 were IgG-IgA-IgM complexes (Table III). According to Wager (1969) cryoimmunoglobulin-G could be an auto-antibody causing some damage to tissues. Its action could be counteracted by an IgA antibody against this harmful IgG. Further studies are in progress to test this hypothesis. It is known that cryoglobulins have anticomplementary activity (Wager 1969). If this is so, these cryoglobulins may cause functional inactivity of complement, leading to enhancement of tumour by antibodies, even though they are cytotoxic in the presence of complement. It is possible that several of these factors act concomitantly to produce a tumour and to affect its rate of growth.

Acknowledgment

This work was supported by research grants of the Indian Council of Medical Research and World Health Organization, Geneva. We are thankful to Dr. K. Ramachandran for statistical analysis and Drs. John L. Fahey, National Institute of Health, Bethesda, (U.S.A.) and David Rowe, W.H.O. Reference Center for the Immunoglobulin standards.

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