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Serum immunoglobulins in patients with carcinoma of the oral cavity, uterine cervix and breast

T. Vijayakumar, Ravindran Ankathil, P. Remani, V. K. Sasidharan, K. K. Vijayan, and D. M. Vasudevan

Regional Cancer Centre, Trivandrum, India – 695 011

Summary. Serum immunoglobulin levels (IgG, IgA, IgM, IgD and IgE) were estimated in 196 patients with carcinoma of the oral cavity, 172 patients with cervical cancer and 166 patients with breast cancer. The values were compared with those of 50 patients with benign lesions of the breast and cervix and 100 healthy adult controls. Only the serum IgE levels were found to be elevated in the benign group. Serum IgA, IgD and IgE levels were found to be elevated in all the three types of cancers and the levels were found to increase with clinical stage. In carcinoma of uterine cervix IgG levels were also found to be elevated. Immunoglobulins A and D returned to normal after clinical cure whereas IgE remained slightly elevated. IgD and IgE remained high in patients who had residual cancer.

Introduction

Of 3500 new cancer cases registered per year at the Regional Cancer Centre, Trivandrum, 27% are affected with oral cancer, 14% with cervical cancer and 7% with breast cancer [15]. Thus these are the three most common cancers seen in this region.

Cell mediated immune responses are the major defence mechanisms against tumour cells both in animals and in human [5]. This was shown to be true in oral cancer [12], and in many other types of cancers [13]. Even though the presence of cytotoxic antibodies has been described, the humoral immune system has generally been described as interfering or blocking in nature [6, 8]. However, the cell mediated and humoral responses are interdependent on each other [2].

Pathological processes in tissues and organs usually produce tissue damage with a concomitant release of proteins into the circulation. The immunoglobulins play an important role in the inactivation and neutralization of these antigens. Hence the immunoglobulins continue to be the subject of intensive investigative interest. Serum immunoglubin levels are used as parameters to assess the status of humoral immunity in cancer patients, but reports are contradictory. Serum IgA and IgE have been reported to be increased in squamous cell carcinoma of oral cavity [4, 19], but others have reported a rise in IgA and IgM [9]. Similarly, contradictory results have been reported regarding immunoglobulin levels in carcinoma of the cervix [1, 22], and in breast cancer [14, 16, 21, 25].

Most of these studies included only a few patients and no attempts were made to correlate the clinical stage with the serum immunoglobulin levels. Hence the present study was undertaken to discover any alterations in serum immunoglobulin levels in carcinoma of the oral cavity, breast and cervix and whether this was of any prognostic significance.

Offprint requests to: T. Vijayakumar, Senior Research Officer, Regional Cancer Centre, Medical College, Trivandrum, India – 695 011

Materials and methods

The study was conducted on 196 patients with carcinoma of the oral cavity, 172 patients with cancer of the uterine cervix and 166 patients with carcinoma of the breast. None of the patients received any treatment prior to the study. Also included in the study were 32 women with mild to moderate dysplasia of the uterine cervix and 18 women with mammary dysplasia. Some 60 healthy males and 40 healthy females from the Medical college campus served as controls. The controls were in the age group 25 to 50 years and the patients between 30 and 60 years. The age and sex distribution of the subjects are given in Table 1. All the subjects were screened to exclude any previous history of asthma or allergy and subjects with parasitic infections and eosinophilia were also excluded. A total of 67 patients who were clinically cured after surgery and/or radiotherapy and 23 patients who had residual lesions were available for follow-up studies 6 months after therapy. None of the subjects had any liver involvement as revealed by clinical, biochemical and biophysical investigations. Venous blood (5 ml) was collected from all subjects, the serum separated, divided into aliquots and stored below −20 °C. All estimations were done in duplicate and the mean values taken. The IgG, IgA, IgD and IgM were estimated using single radial immunodiffusion plates and IgE was estimated by Enzyme Linked Immunosorbent Assay (ELISA) [7, 26] (Test kits, Standards and reference sera were supplied by Kallestad Laboratories Inc. USA). Statistical analysis of the results was performed using Student's *t*-test. In all cases the values of cancer patients were compared with those of the normal control subjects.

Table 1. Age and sex distribution of subjects

	Control		Benign uterine lesions	Benign breast lesions	Oral cancer		Cervical cancer	Breast cancer
	Males	Females			Males	Females		
No. of subjects	60	40	32	18	123	73	172	166
Age in years (mean ± SD)	35.4 ± 6.4	36.8 ± 7.5	40.7 ± 8.6	43.5 ± 6.9	47.4 ± 11.2	49.6 ± 9.3	44.2 ± 10.9	46.8 ± 12.1

Table 2. Serum immunoglobulin values in patients and in control groups

Subjects	IgG mg%	IgA mg%	IgM mg%	IgD mg%	IgE μg%
Normal controls ($n = 100$)	1521.4 ± 372.70	206.5 ± 31.17	127.2 ± 37.39	4.06 ± 3.91	9.35 ± 8.42
Benign lesions of breast ($n = 18$)	1408.1 ± 307.53	208.4 ± 35.43	130.3 ± 39.17	4.25 ± 3.87	* 13.67 ± 11.82
Benign lesions of cervix ($n = 32$)	1574.6 ± 345.62	237.6 ± 41.80	124.5 ± 41.43	3.98 ± 2.96	* 15.42 ± 10.65
Oral cancer ($n = 196$)	1489.7 ± 411.26	* * 307.8 ± 56.37	119.9 ± 44.08	* 6.21 ± 4.92	* * 45.86 ± 27.96
Cancer of uterine cervix ($n = 172$)	* 1687.8 ± 381.62	* * 339.41 ± 58.26	133.8 ± 50.54	* * 8.45 ± 6.07	* * 87.24 ± 49.17
Breast cancer ($n = 166$)	1465.6 ± 421.36	* * 284.3 ± 61.23	124.6 ± 53.27	* * 7.94 ± 5.82	* * 65.38 ± 31.36

All values are mean ± SD, *n* stads for number of patients
* = $P < 0.01$
* * = $P < 0.001$
Comparisons were done with values of normal controls

Table 3. Changes in immunoglobulin levels in cancer patients in different clinical stages

	No. of patients	Stage	Immunoglobulin levels				
			IgG mg%	IgA mg%	IgM mg%	IgD mg%	IgE μg%
Carcinoma of oral cavity	26	I	1471.3 ± 366.45	224.0 ± 56.45	131.3 ± 27.24	4.65 ± 3.09	* * 29.78 ± 19.64
	82	II	1478.7 ± 405.36	239.7 ± 59.12	125.4 ± 30.18	5.02 ± 4.75	* * 34.26 ± 24.15
	51	III	1497.8 ± 414.27	* * 297.4 ± 61.91	139.9 ± 41.53	* 6.87 ± 4.89	* * 49.16 ± 29.76
	37	IV	1431.8 ± 385.58	* * 335.9 ± 68.42	120.7 ± 29.54	* * 7.95 ± 6.05	* * 53.41 ± 32.46
Carcinoma of uterine cervix	12	I	1594.4 ± 305.17	* 228.3 ± 43.83	124.1 ± 31.64	5.36 ± 4.13	* * 57.51 ± 27.18
	76	II	1641.4 ± 371.22	* * 257.2 ± 40.75	129.8 ± 39.13	* 7.08 ± 4.96	* * 69.61 ± 30.55
	64	III	* 1694.3 ± 439.74	* * 331.8 ± 69.96	138.1 ± 43.76	* * 7.86 ± 5.65	* * 88.17 ± 39.96
	20	IV	* * 1721.2 ± 468.87	* * 359.12 ± 62.25	136.5 ± 41.82	* * 8.95 ± 8.14	* * 99.75 ± 48.83
Carcinoma of breast	8	I	1453.5 ± 548.27	* 219.2 ± 51.85	127.8 ± 54.12	4.41 ± 5.12	* * 31.14 ± 23.46
	61	II	1461.6 ± 391.18	* * 249.7 ± 60.36	119.7 ± 37.43	* 5.98 ± 4.80	* * 43.61 ± 29.33
	57	III	1473.4 ± 308.81	* * 291.6 ± 61.97	131.8 ± 60.54	* * 7.64 ± 5.62	* * 66.32 ± 32.65
	40	IV	1484.8 ± 412.24	* * 322.6 ± 69.53	120.5 ± 42.18	* * 8.58 ± 6.85	* * 72.80 ± 33.72

All values are mean ± SD * = $P < 0.01$; * * = $P < 0.001$
(Comparisons were done with the values of normal control subjects)

Table 4. Effect of treatment on serum immunoglobulin levels

Group of subjects	IgG mg%	IgA mg%	IgM mg%	IgD mg%	IgE µg%
Patients 6 months after surgery and/or radiotherapy and clinically cured ($n = 67$)	1485.8 ± 427.96 (1497.7 ± 450.85)	218.7 ± 50.45 (277.9 ± 53.74)	121.5 ± 34.71 (124.3 ± 38.72)	4.75 ± 2.98 (7.01 ± 3.95)	* 14.66 ± 9.54 (57.89 ± 43.42)
Patients still receiving chemocherapy and having residual lesions ($n = 23$)	1508.7 ± 318.32 (1541.4 ± 392.82)	** 298.4 ± 39.16 (311.7 ± 43.63)	117.6 ± 32.04 (120.5 ± 38.72)	** 8.06 ± 6.33 (9.46 ± 7.58)	** 72.82 ± 31.14 (89.64 ± 52.63)
Normal healthy controls ($n = 100$)	1521.4 ± 372.70	206.5 ± 31.17	127.2 ± 37.39	4.06 ± 3.91	9.35 ± 8.42

n = number of subjects
All values are mean ± SD
* = $P < 0.01$
** = $P < 0.001$
The figures in paranthesis indicate the Ig levels of the same group of patients at the beginning of the study (Comparisons were done with values of normal control subjects)

Results

The results of the investigation are given in Table 2. It can be noted that in benign lesions only IgE showed a significant rise compared to normal controls ($P < 0.01$). Serum IgG was normal in carcinoma of the breast and oral cavity whereas in carcinoma of the uterine cervix it was found to be elevated ($P < 0.01$). IgA and IgE were significantly elevated in all the three types of cancers ($P < 0.001$). There was no difference in serum IgM levels in any of the patients. The rise in IgD was significant in carcinoma of the uterine cervix and breast ($P < 0.001$). The changes in serum immunoglobulin levels in cancers at different clinical stages are shown in Table 3. The rise in serum IgG was significant only in cancer of the uterine cervix, and that from stage 2 onwards. IgA and IgE were significantly elevated in all patients and in all stages ($P < 0.001$), IgM was unaltered in all stages whereas IgD was found to be elevated significantly in stages 3 and 4. The changes in serum immunoglublin levels with regard to cure of the disease are given in Table 4. The patients who were clinically cured showed a rise only in IgE fractions whereas the patients who were still receiving chemotherapy had very high levels of IgA, IgD and IgE ($P < 0.001$).

Discussion

The present study clearly indicates that there are elevations in the levels of serum immunoglobulins in carcinoma of the oral cavity, breast and uterine cervix. A rise in serum IgG in patients suffering from carcinoma of the uterine cervix was reported as early as 1971 by Vasudevan et al. [22], and repeated by others [1]. Our findings are in agreement with their reports. We observed a significant rise in IgG in stages 3 and 4 of cervical cancer and the values were found to increase as the stage of the disease advanced. The high IgG levels in carcinoma of the uterine cervix may be due to the high incidence of anti-viral antibodies in these patients [10]. The levels of IgG in oral and breast cancers have been reported to be normal [9, 16, 19], elevated [1, 3] or even decreased [18]. We observed no change in the serum levels of IgG either in oral cancer patients or in breast cancer patients at any stage.

Elevated levels of IgA have been reported in breast cancer [4, 11, 14, 18] in oral cancer [9, 11, 19] and in carcinoma of uterine cervix [1, 4, 11, 22]. We observed elevated levels of IgA in all types of cancers and in all stages. The levels of IgA were found to increase with advance in clinical stage. The IgA level thus seems to be a good indicator of the clinical status of the patient, as it returned to normal in patients who were clinically cured and remained elevated in patients who were still receiving treatment.

Serum IgM levels have been reported to be elevated in oral cancer [9]. But we observed no change in the IgM fraction in any of the cancer patients, which is in agreement with most previous reports [1, 11, 16, 19].

Serum IgD levels have been reported to be decreased in breast cancer [14] and unaltered in oral cancer [19], however we observed an elevation in serum IgD levels in all types of cancers especially in stages 3 and 4. The serum IgD levels remained elevated in patients with residual disease, but the values returned to normal, in patients who were clinically cured. No studies were conducted in the earlier reports with regard to immunoglobulin levels in treated patients.

Very few reports are available regarding IgE levels in cancer patients. A rise in serum IgE in oral cancer was reported earlier [17, 19, 20], but no change was observed in breast cancer [16]. We observed elevated IgE values in all types and stages of cancer. This rise in IgE may reflect a defect in cell mediated immunity [24]. Further, we observed that the IgE levels were very high in patients with residual lesions.

We have included a large number of patients in all groups. No studies have previously been reported with regard to immunoglobulin levels in cancer patients receiving therapy. Our study clearly indicates the usefulness of IgA, IgD and IgE especially for the prognosis of cancer. These three immunoglobulins were found to increase with progression of the disease, and to return to normal after clinical cure. Of these, IgA seems to be more promising as the rise always corresponded with the clinical staging and the results obtained by various groups seem to be the same. We feel that immunoglobulin levels together with the high affinity rosette forming cells as reported elsewhere [23], will serve as good markers for diagnosis and prognosis of cancer.

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References

1. Adelusi B, Salimonu LS (1981) Serum immunoglobulin concentrations in serum of patients with carcinoma of the cervix. Gynecol Oncol 11: 75
2. Blair PB, Lane M (1975) Non T cell killing of mammary tumour cells by spleen cells: Secretion of antibody and recruitment cells. J Immunol 115: 184
3. Gupta SC, Singh PA, Shukla HS, Mehrotra TN (1980) Serum immunoglobulin profile in patients with cancer cervix. Ind J Med Res 71: 893
4. Gupta SC, Singh PA, Shukla HS, Sinha SN, Mehrotra TN, Kumar S (1981) Serum immunoglobulins in carcinoma of various organs. Ind J Cancer 18: 277
5. Hellstrom I, Hellstrom KE, Strogen HO, Warner GA (1971) Demonstration of cell mediated immunity to neoplasms of various histological types. Int J Cancer 7: 1
6. Hellstrom I, Hellstrom KE, Strogen HO, Warner GA (1973) Increase in lymphocyte mediated tumour cell destruction by certain patient sera. Int J Cancer 12: 348
7. Hoffman DR (1973) Estimation of serum IgE by an Enzyme linked Immunosorbent Assay. J Allergy Clin Immunol 51: 303
8. Hudson MJK, Humphrey LJ, Mantz FA, Morse PA (1974) Correlation of circulating serum antibody to the histologic finding in breast cancer. Am J Surg 128: 756
9. Khanna NN, Das SN, Khanna S (1982) Serum immunoglobulins in squamous cell carcinomas of the oral cavity. J Surg Oncol 20: 46
10. Kumari TV, Shanmugam J, Prabha B, Vasudevan DM (1982) Prevalence of antibodies against Herpes Simplex and adenovirus in oral and cervical cancer patients. A preliminary report. Ind J Med Res 75: 590
11. Lee NY (1977) Quantitative changes of serum proteins and immunoglobulins in patients with solid cancer. J Surg Oncol 9: 179
12. Lehner T (1972) Cell mediated immune responses in oral diseases a review. J Oral Pathol 1: 39
13. Lichtenstein A, Zighelboim J, Dorey F, Brossman S, Fahey JL (1980) Comparison of immune derangements in patients with different malignancies. Cancer 45: 2090
14. Munzarova M, Trnka A, Malir A (1977) Serum immunoglobulins A, G, M, D and TNM classification in breast cancer. Br J Cancer 35: 488
15. Padmanabhan TK, Vasudevan DM (1982) A statistical analysis of cancers registered at the Regional cancer centre, Trivandrum. Ind J Cancer 18: 189
16. Pettingale KW, Merret TG, Tee DEH (1977) Prognostic value of serum levels of immunoglobulins (IgD, IgA, IgM, and IgE) in breast cancer: A preliminary study. Br J cancer 36: 550
17. Pidcock NB, Cooper EH, El-Asser AA, El-Sebai I (1984) Immunoglobulin A G and E levels in Egyptians with cancer. Influence of schistosomiasis. Int J Cancer 33: 771
18. Roberts MM, Bathgate EM, Stevenson A (1975) Serum immunoglobulin levels in patients with breast cancer. Cancer 36: 221
19. Scully C (1982) Immunological abnormalities in oral carcinoma and oral keratosis. J Maxcillofac Surg 10: 113
20. Serrou B, Dubois JB, Robinet Levy M (1975) IgE serum levels in cancer patients. Lancet I: 396
21. Sieinski W (1980) Immuno-histological patterns of immunoglobulins in dysplasias, benign neoplasms and carcinomas of the breast. Tumori 66: 699
22. Vasudevan DM, Balakrishnan K, Talwar GP (1971) Immunoglobulins in carcinomas of cervix. Ind J Med Res 59: 1653
23. Vijayakumar T, Vasudevan DM (1985) High affinity rosette forming cells in carcinoma of the oral cavity, uterine cervix and the breast. Cancer Lett 27: 339
24. Wanebo HJ, Pinsky CM, Beattie EJ, Oettgen HF (1978) Immunocompetence testing in patients with one of the four common operable cancer – A review, Clin Bullet 8: 15
25. Wang DY, Goodwin PR, Bullbrook RD, Hayward JL (1977) Plasma immunoglobulin levels in patients with breast cancer. Cancer 39: 2190
26. Weltman JK, Frackelton AR, Szaro RP, Rotman B (1976) A galactosidase immunosorbent test for human immunoglobulin E. J Allergy Clin Immunol 58: 426

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