

Preventive Role of Atopy in Lung Cancer

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Incidence of atopic disease, serum and sputum IgE, and sputum IgA levels were studied in lung cancer patients, and compared with those in lung benign disease patients and normal controls. A significantly lower prevalence of personal atopic history was observed in the cancer group in comparison with the other two experimental groups. Patients with lung cancer showed significantly higher serum IgE levels than benign-disease and normal control individuals. At the same time, patients with epidermoid lung carcinoma had significantly increased levels of serum IgE and sputum IgA than those with lung adenocarcinoma. © 1986 Academic Press, Inc.

INTRODUCTION

The existence of an inverse relationship between allergic diseases, particularly bronchial asthma, and the susceptibility to develop cancer has been repeatedly proposed (1-3). However, contradictory data about such relationship have been published (4-6).

From the experimental point of view, there are also evidences for a role of allergic sensitivity in cancer (7,8). Furthermore, IgE-class antibodies with anti-tumor specificity have been observed in mice (9), rats (10,11), and human beings (12-14), but the *in vivo* significance of such antibodies is not yet known.

Increased serum IgE levels have been reported in Hodgkin lymphoma and lung cancer, but no reports exist about IgE in secretions. Hallgren observed that serum IgE had a prognostic significance in lung cancer, since patients with non-elevated IgE showed a favorable prognosis (15).

To study the possible effect of the atopic condition in cancer development, we have chosen lung cancer as a model for various reasons:

(1) The respiratory tract represents a particularly interesting system for research in oncology and immunology, because of its permanent contact with immunogenic and also with potentially oncogenic substances present in the environment, and due to the frequent occurrence in it of immediate hypersensitivity reactions which are clinically manifested as bronchial asthma.

(2) Through different approaches it has been shown that lung cancer is immunogenic. Antigens associated with lung neoplasms have been identified and monoclonal antibodies reactive with them have been produced (16). On the other hand, antibody activity against lung tumor cells but not against normal lung cells has been found in bronchial lavages from lung carcinoma patients (17), and immunoglobulin from lung cancer eluates and effusions bind to lung carcinoma cells

but neither to normal lung cells nor to cells from tumors of other tissues. Effusions from other tumors do not react with lung cancer cells in vitro (18–19).

In this paper we present our results on the evaluation of the influence of atopic history, serum and sputum IgE in lung cancer patients.

MATERIALS AND METHODS

Patients. Forty-eight lung cancer patients admitted to the Hospital Simon Bolívar (female 18, male 30), with an average age 59.6 years range (42–75), as well as 33 patients with benign lung diseases (female 14, male 19), average age 51.1 years (range 25–78), and 50 age- and sex-matched normal individuals were studied. Patients and controls were questioned about the presence of a past or present personal history of genetically determined atopic diseases (eczema, rhinitis, or asthma), by at least two physicians. Other allergic diseases such as urticaria, contact dermatitis, or drug, food, or insect hypersensitivity were not included in this study.

The histologic classification of the tumors was done according to the World Health Organization (20). Twenty-two patients had adenocarcinoma, 19 epidermoid carcinoma, 2 oat cell carcinoma, 2 large cell carcinoma, 1 clear cell carcinoma, 1 pleural mesotelioma, and 1 bronchial carcinoid. Clinical staging was done through the T.N.M. classification (21). Thirty-eight patients had advanced disease (stage IV), 4 were in stage III, 4 in stage II and 2 in stage I. The group with benign pulmonary disease included 11 patients with pulmonary tuberculosis, 11 with chronic obstructive pulmonary disease, 5 with acute pneumonia, 3 with paracoccidioidomycosis, 2 with idiopathic pulmonary fibrosis, and 1 with tracheal stenosis.

Sera and sputum. Blood sera were obtained before any treatment, and stored at -70°C until study. For sputum immunoglobulin studies, comparisons were made between patients with benign lung disease and lung malignancy, since it was not possible to obtain a comparable sample from normal controls.

Sputum samples were expectorated into plastic cups, homogenized with 1:10 volume of 0.01 M EDTA, pH 8.0, centrifuged at 1.000g at room temperature, and the supernatants were frozen at -70°C until study (22). Bloody sputum samples were discarded.

Immunoglobulin A (IgA). IgA levels in sputum were measured by means of radial immunodiffusion in low level plates (Kallestad Laboratories Inc., Austin, Tex.), according to Mancini's technique (23).

Immunoglobulin E (IgE). Total serum and sputum IgE was determined by the paper radioimmunosorbent test (Phadebas IgE PRIST, Pharmacia Diagnostics AB, Uppsala, Sweden). All the samples were studied in duplicate. Results are expressed as log IgE (IU/ml). For sputum IgE, results are also presented as the ratio sputum IgE (IU/ml)/sputum IgA (mg%).

Statistical analysis. Student's *t* test was used to compare IgE levels between experimental groups. Percentages of frequency of atopy were compared by means of the two percentages equality test (24).

RESULTS

Prevalence of atopic diseases. Frequency of atopic diseases in the three experi-

TABLE 1
PREVALENCE OF PERSONAL ATOPIC HISTORY IN PATIENTS WITH PULMONARY DISEASES

Experimental group	n	Atopic/total	%	P value ^a
Normal controls	50	9/50	18.0	—
Benign lung disease	33	8/33	24.2	NS ^b
Lung cancer	48	3/48	6.2	0.05

^a Two percentages equality test.

^b NS: Not significant.

mental groups is presented in Table 1. It can be observed that a personal history of atopy was significantly less frequent in patients with lung cancer in comparison with those with benign lung disease or normal controls ($P < 0.05$).

Total serum IgE. Figure 1 shows the IgE levels in sera from patients with lung diseases and control individuals. Values of total IgE were significantly high for both benign disease group ($P < 0.01$) and lung cancer group ($P < 0.0005$) in comparison with normal subjects, although there was also a significant difference between benign and malignant groups ($P < 0.0005$). Average values (IU $\pm$ SEM) were: lung cancer 1.079 ± 193 ; benign lung disease 413 ± 69 ; normal controls 159 ± 35 . Total serum IgE levels were higher in patients with epidermoid carcinoma than in those with adenocarcinoma ($P < 0.025$), and remained high in patients with advanced disease (Stage IV) ($P < 0.0005$). Other clinical stages could not be compared because of the small number of patients.

Increased levels of serum IgE in the benign group were mainly due to the chronic obstructive pulmonary disease patients (673 ± 118 IU/ml), since patients with pulmonary tuberculosis showed lower values (274 ± 106 IU/ml) ($P < 0.025$).

Sputum IgE. IgE in sputum was compared between patients with lung cancer and pulmonary benign diseases, and results were expressed as the log of absolute values (IU/ml) or as the IgE/IgA ratio to avoid individual differences in secretion rate. There were no significant differences between benign and malignant groups.

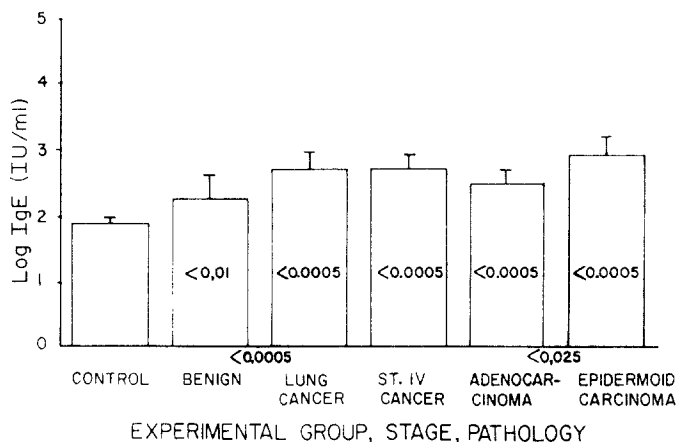


FIG. 1. Total serum IgE in benign and malignant pulmonary diseases.

TABLE 2
SPUTUM IgE IN LUNG DISEASES

Experimental group	<i>n</i>	Sputum IgE (log IU/ml)	<i>p</i> value ^a	IgE/IgA ratio	<i>p</i> value ^a
Benign lung disease	8	0.64 ± 0.3	—	0.113 ± 0.06	—
Lung cancer	21	1.39 ± 0.9	NS	0.65 ± 0.3	NS
Adenocarcinoma	10	1.51 ± 1.2	NS	0.23 ± 0.19	NS
Epidermoid carcinoma	8	1.45 ± 1.1	NS	1.38 ± 0.72	<0.0025

^a Student's *t* test.

but epidermoid carcinoma showed a significant increase of sputum IgE/IgA ratio when compared to benign patients or those with lung adenocarcinoma, as shown in Table 2.

Sputum IgA. There were no differences in sputum IgA levels between cancer and benign disease patients. Epidermoid carcinoma patients showed significantly higher levels of sputum IgA than adenocarcinoma patients (Table 3). On the other hand, sputum IgA was significantly decreased in atopic individuals from cancer ($P < 0.025$) and benign groups ($p < 0.0125$), as shown in Fig. 2.

DISCUSSION

The identification of risk or protective factors related to cancer development represents an important medical issue. In the present study we have found a lower incidence of atopic diseases in the lung cancer population when compared to normal individuals and patients with benign lung disease (Table 1), which confirms observations by other investigators, and suggests a protective role for anaphylactic hypersensitivity against tumor growth.

The possible mechanisms involved in the prevention of neoplasm development by atopy are not known, but some speculation has been derived from the studies of Lynch and Salomon (7). They proposed that chemical mediators released by basophils and mast cells are able to induce changes in vascular permeability which would in turn facilitate the influx of immune humoral and cellular effectors into the tumor. An additional but no less important explanation comes from recent observations which confer a higher cytotoxic potential to the immediate hypersensitivity reactions. Different mast cell mediators have chemotactic activities for eosinophil and neutrophil leukocytes, cells which contain cytolytic substances

TABLE 3
SECRETORY IgA IN LUNG DISEASES

Experimental group	<i>n</i>	IgA (mg%)	<i>P</i> value ^a	
Benign disease	21	19.2 ± 3.4	—	
Lung cancer	43	30.4 ± 4.3	NS ^b	
Adenocarcinoma	21	20.6 ± 4.3	NS	
Epidermoid carcinoma	15	37.7 ± 8.8	<0.025	<0.05

^a Student's *t* test.

^b Not significant.

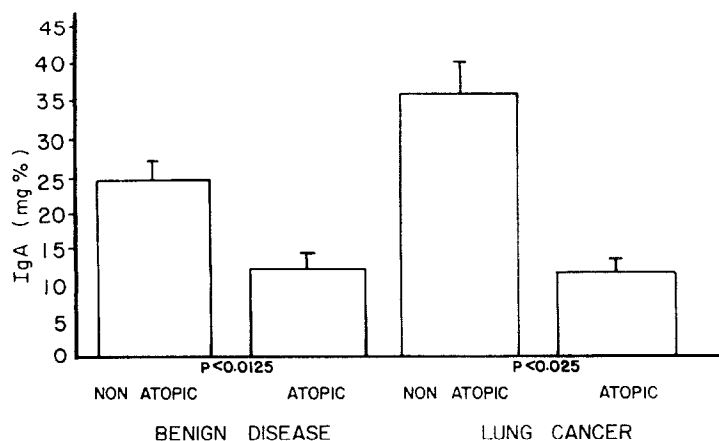


FIG. 2. Sputum IgA in pulmonary diseases according to atopic family history.

such as proteases and the eosinophil major basic protein. It has been shown that the major basic protein of the eosinophil granule has helminthotoxic properties, and is able to destroy tumor cells (25), whereas eosinophil peroxidase in conjunction with hydrogen peroxide and halides can damage tumor cells (26).

When the levels of total serum IgE were studied we observed significantly higher levels in lung cancer patients than in normal or benign-disease individuals (Fig. 1). A decreased cell-mediated immune response has been reported in patients with advanced lung cancer (27). Since it has been demonstrated that IgE production is exquisitely regulated by suppressor T cells (28), it could be speculated that patients with lung cancer could have deficient IgE-specific suppressor T cells, although to our knowledge, there is no evidence so far for such a defect.

An apparent discrepancy could be raised in that lung cancer patients in this report have a lower degree of clinical atopy together with higher serum IgE levels. However, it should be noted that the term "atopy" was first used by Cooke and Coca to define a genetically determined abnormal state of hypersensitivity (29), which is generally referred to as synonymous to IgE-mediated hypersensitivity disease. On the other hand, in tropical countries such as Venezuela, it has been shown that total IgE levels do not necessarily reflect an atopic state, being more frequently due to helminthiasis (30).

In our studies we have found higher levels of serum IgE, sputum IgA, and C1q-fixing circulating immune complexes (Orozco, A. *et al.*, unpublished observations), in epidermoid lung carcinoma as compared to lung adenocarcinoma. On the other hand, recent reports have shown a higher prevalence of cellular immunity abnormalities in epidermoid carcinoma of the lung (27). If confirmed, these observations in conjunction with ours would suggest a different immunogenicity of lung cancer depending on its histopathologic picture.

Finally, our results of lower IgA levels in sputum of atopic individuals from benign lung disease and lung cancer groups is in agreement with the description of increased prevalence of IgA deficiency in atopic individuals by Kauffman and Hobbs (31).

In short, our results confirm a lower incidence of lung cancer in atopic subjects, suggest abnormalities of IgE regulation in patients with advanced lung cancer and a higher immunogenicity for epidermoid carcinoma of the lung compared to lung adenocarcinoma in relation to the antibody-mediated immune responses.

ACKNOWLEDGMENTS

Supported by Fundación Venezolana de Inmunología. Technical advice by Arturo Alvarado, M.Sc., is greatly appreciated.

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Received December 2, 1985; accepted with revision June 12, 1986