

A STUDY OF ALLERGY IN PATIENTS WITH MALIGNANT LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA

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In a study of 229 patients with malignant lymphoma and chronic lymphocytic leukemia, an investigation of allergic symptomatology and immunoglobulin levels was conducted. Patients with chronic lymphocytic leukemia demonstrated a decreased incidence of allergic symptomatology which could be correlated with diminution of serum IgE levels. Of interest was the observation that some patients with lymphoma lost their symptoms of allergy prior to onset of the malignancy. History of allergic symptoms was elicited with equal frequency in both patients with malignancy and control population.

"ACQUIRED" IMMUNOLOGIC DEFICIENCIES have been observed in patients with malignant lymphoma and chronic lymphocytic leukemia (CLL).^{3, 4, 18} Allergy, while not an immunologic deficiency per se, as another manifestation of the immune imbalance has not been studied in these patients. The prevalence of allergic symptoms in patients with Hodgkin's disease (HD) is about the same as that for the general population,⁶ but allergy has not been studied in patients with CLL, reticulum cell sarcoma (RCS), or lymphosarcoma (LSA).

In this report, the results of a study of allergic symptoms in 229 patients with malignant lymphoma and CLL are presented. Correlations are made between allergic symptoms and quantitative levels of IgG, IgM, IgA, and IgE in allergic patients and in age and sex-

matched controls. An estimate of serum IgE was obtained in 10 patients with CLL and in 10 controls by skin testing with anti-IgE.

METHODS

Patient data: A total of 229 patients were interviewed. Ninety-eight patients had HD, 53 had LSA, 33 had RCS, and 45 had CLL. Pathologic diagnoses had been obtained on all of the patients.

Patients were asked whether they had ever had hives, asthma, hay fever, contact dermatitis, angioneurotic edema, food allergy, childhood eczema, or drug reactions. They were also asked whether or not they had ever been treated for their allergic symptoms and whether their symptoms had changed in severity either before or after acquiring their lymphoma. Minor or transient allergic episodes were not counted.

Gamma globulins: Serum IgG, IgA, and IgM concentrations were determined by immunodiffusion technique on sera from all of the patients who gave histories of allergy and from age and sex-matched controls. Sera from 26 of the patients who gave histories of allergy were screened for elevations in serum IgE by immunodiffusion against anti-IgE. The method was capable of detecting levels of IgE greater than 1000 ng per ml of serum.

Skin tests: A solution of guinea pig antihuman IgE globulin was used; 0.05 ml of a 1:2000 dilution was injected intracutaneously in 10 randomly-selected nonallergic patients

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with CLL. An equal volume of guinea pig serum diluted 1:1000 was used as a control. Skin tests were read after 10–15 minutes and declared positive if the subject developed a wheal more than 1 cm in diameter and a flare more than 3 cm in diameter. Pruritus was often associated. Age and sex-matched control patients with retinal detachments or cataracts and no other major medical problems were also tested.

Additional data on patients: The date of onset of the malignant lymphoma for each of the allergic patients was obtained from the patients' records. Radiation therapy, antimetabolites, and steroids both singly and in combination had been administered to nearly all of the patients. These treatments along with the dates on which they were given were recorded.

Control patients: Ninety-six patients with a variety of ophthalmologic and orthopedic conditions, including fractures, retinal detachments, corneal abrasions, and cataracts, were asked whether they had ever had allergic symptoms. The patients' ages ranged from 17 to 84 years. These patients were placed in 3 categories depending on their ages and sex in order to correspond to the HD patients (mean age 37), the RCS patients (mean age 54), and the LSA and CLL patients (mean ages 65 and 67 years, respectively).

Statistical methods: P values for comparing the prevalence of allergic symptoms in the various groups of patients and controls were computed with chi-square tests using 2×2 tables. A modification of Student's t-test was used to compare the gamma globulin concentrations in the serum of the lymphoma patients with concentrations from age and sex-matched controls.

RESULTS

Prevalence of allergy: The results are summarized in Table 1. Excluding drug allergy, the prevalence of allergy in HD patients was slightly higher at 19% than that already reported⁶ but was not statistically different from the prevalence of 21% obtained for the control group. The prevalence of allergy in LSA and RCS was also slightly higher than in the control groups, but again not significant. Of the 45 patients with CLL who were interviewed, only 2 patients, or 4.5%, had ever had allergic symptoms, excluding drug reactions, and this was significantly lower than the prevalence of allergy in the patients with HD ($P < 0.05$). The number of allergic patients with CLL was less than the number of allergic individuals in an age and sex-matched control group, but the numbers were too small to compare statistically.

Changes in allergic symptoms: A large number of lymphoma patients said that their allergic symptoms had decreased or disappeared at least one year prior to the time of the study; however the numbers were too small to analyze statistically (Table 2). Patients in this table were excluded if they had been treated specifically for their allergies.

Drug reactions: Of all patients interviewed, 21% gave a history of drug reaction (Table 3). Penicillin reactions were most frequent. The prevalence of drug reactions in LSA was quite high (32%), while drug reactions were less frequent among the patients with HD, RCS, and CLL.

Effect of treatment of lymphoma on allergy: Table 4 gives more detailed data concerning allergy in the patients, and it includes infor-

TABLE 1. Allergy in Patients with Malignant Lymphoma and Chronic Lymphocytic Leukemia

Diagnosis	No. interviewed	No. with allergy	Percent of total
Hodgkin's disease	98	19	19%
Hodgkin's controls	42	9	21%
Lymphosarcoma	53	8	15%
Lymphosarcoma controls	41	5	12%
Reticulum cell sarcoma	33	6	18%
Reticulum controls	34	6	17%
Chronic lymphocytic leukemia	45	2	4.5%
Chronic leukemia controls	41	5	12%
Total with cancer	229	35	15%
Total controls (none counted twice)	61	12	20%

TABLE 2. Patients with Lymphoma and Chronic Leukemia Whose Allergic Symptoms Decreased or Disappeared at Least One Year Prior to the Study

Diagnosis	Total allergic	Symptoms decreased	Percent decreased
Hodgkin's disease	16	9	56%
Hodgkin's controls	9	1	11%
Lymphosarcoma	6	5	83%
Lymphosarcoma controls	5	2	40%
Reticulum cell sarcoma	6	5	83%
Reticulum controls	6	3	50%
Chronic lymphocytic leukemia	2	1	50%
Chronic leukemia controls	5	2	40%
Total with cancer	30	20	67%
Total controls (none counted twice)	12	3	25%

mation about treatment and length of time since the onset of symptoms of the lymphoma. Of the 35 patients who had allergy, 18 still had symptoms at the time of the survey, while the others no longer had symptoms of allergy. Ten of the patients said their symptoms had decreased or stopped altogether after treatment for the lymphoma had begun, and 4 said that symptoms had stopped before treatments for the lymphoma but after the onset of symptoms from the lymphoma. Of all the patients who claimed to be allergic, only 5 said that their allergic symptoms were the same as they had always been, and only one said that his symptoms were worse.

It appeared that the lymphoma may have had some effect on the patient's allergic condition. Whether this effect was secondary to the treatment for the lymphoma or whether it was secondary to changes induced by the lymphoma itself is not easily discerned, because nearly all of the patients had been given radiotherapy, steroids, antimetabolites, or a combination of lympholytic agents. Patient B.S. had severe hay fever and also had episodes of angioneurotic edema on eating certain types of foods; her allergic symptoms subsided at the same time she began to have symptoms from lymphosarcoma in her spine.

Gamma globulins: Serum IgG, IgA, and

IgM concentrations in the patients with lymphoma who gave histories of allergy are shown in Figs. 1-3. When compared with age and sex-matched controls, serum IgG was significantly lower in patients with LSA. In patients with HD, serum IgA and IgM were both significantly lower than in the controls. Three of the patients with CLL (none of whom gave histories of allergy) had extremely low levels of IgM (7.7, 7.3, and 20.0 mg/100 ml). Interestingly, serum IgM levels were significantly lower in the control patients older than 47 years when compared with controls younger than 47 years ($0.05 > P$).

Even though deficiencies of IgG, IgA, and IgM were demonstrated in some of the patients with lymphoma and CLL, there was little correlation between the immune globulin deficiencies and decreases in allergic symptoms after the onset of symptoms from the lymphoma or leukemia, although there was a significant decrease in IgM in 4 young patients who said their allergic symptoms had decreased.

V.B., one of the patients with a pathologic diagnosis of LSA, had macroglobulinemia; she had a serum IgM concentration of 1.2 g/100 ml. She also had hay fever and was treated for this with pollen injections at about the same time she acquired the lymphoma. Her hay

TABLE 3. Incidence of Drug Reactions in Patients with Malignant Lymphoma and Chronic Leukemia

Diagnosis	No. interviewed	No. with allergy (drug)	Percent of total
Hodgkin's disease	98	16	16%
Lymphosarcoma	53	17	32%
Reticulum cell sarcoma	33	8	24%
Chronic lymphocytic leukemia	45	7	16%
TOTAL	229	48	21%

TABLE 4. Clinical Course of Malignancy and Relationship of Allergic Symptoms and of Gamma Globulins

Patient	Age	DX	Onset	Treatment	Allergy	Change in Allergic Symptoms	Sex
P.B.	36	HD	1960	RT'60, MHZ'65, VB'65, LK'67	HF, Ast	HF stopped '63, ast stopped '61	F
P.K.	24	HD	1967	RT'67	HF	Treated age 15, symp. disappeared	M
C.P.	25	HD	1964	RT'65	HF	HF only 2 yrs; decreased '68	M
T.N.	28	HD	1967	RT'67	Hives since '64	Decreased '66	M
V.S.	34	HD	1965	S'65, RT, VB '66, LK'67	HF since '54	No change	M
E.B.	45	HD	1962	RT'62, NM'63, RT'64, '65, VB'67	Hives	None since age 15	F
K.V.	18	HD	1965	RT'66	HF	No change	M
S.S.	64	HD	1948	RT'48	Hives	None since '58	M
E.P.	36	HD	1957	RT'57, '58, '60, '62; LK'61, S'65	HF since '58	Worse	F
R.C.	42	HD	1952	S'52, '60, RT'55, '58	HF	None since '57	M
A.P.	66	HD	1966	RT'66	Ast. since '48	No change	M
R.C.	25	HD	1963	NM'64, RT'64	HF since '65	?	M
L.S.	28	HD	1963	NM'63, LK, VB'64, MHZ'67	HF, Ang. Ed.	Treated '51-'58, none since '58	M
B.F.	32	HD	1967	VB'67, LK'67	Hives	No change	F
C.M.	22	HD	1960	RT'61, VB'63, '66, NM'62, VB'63	Hives, ecz., HF treated	No symptoms since childhood	M
B.M.	19	HD	1964	NM'64, RT'64	Hives since '56	Symp. decreased '66	M
A.V.	47	HD	1938	RT'38, '50	Hives	None since '42	M
J.M.	39	HD	1967	VB, RT'68	HF	Symp. decreased '65	M
J.B.	24	HD	1964	RT'64	Ecz. HF	Symp. decreased '65	M
B.S.	57	LSA	1961	S'66, LK'67	HF, Ang. Ed.	No symp. since '60	F
J.A.	57	LSA	1966	RT'66, '67; TT, P32'67	Hives '60-'63	No symptoms	M
M.M.	47	LSA	1955	RT'56, '64, S'66	Hives since '40	No change	F
L.I.	63	LSA	1959	RT'59, '61, S'62	HF since '28	Treated '45, '64, symp. decreased '66	F
V.B.	58	LSA	1955	C'64, Splenectomy '64	HF	Treated '55 and symp. disappeared	F
M.M.	28	LSA	1963	S'65	HF	None since '54	F
J.R.	59	LSA	1963	RT'63, '66, S, C'66	Cats	Six-month episode '60	M
C.R.	76	CLL	1965	None	HF	Symp. decreased '66	M
P.C.	74	CLL	1954	None	HF	?	M
R.R.	27	RCS	1965	C'67	HF'51-'57	None now	M
L.B.	72	RCS	1958	RT'58, '59, NM'58	Animal allergy	?	F
C.L.	74	RCS	1931	RT'33, S'62	HF	Decreased '63	F
T.K.	46	RCS	1961	LK'67	HF '58-'61	None since '61	M
M.A.	27	RCS	1961	RT'62	Ecz. as child	No recent symptoms	F
G.M.	60	RCS	1949	RT'50	HF	No symp. since '63	F

Key to abbreviations: Ast.: Asthma; C: Cytosan; CLL: Chronic lymphocytic leukemia; DX: Diagnosis; Ecz: Eczema; HD: Hodgkin's disease; HF: Hay fever; LK: Leukeran; LSA: Lymphosarcoma; MHZ: Methylhydrazine; NM: Nitrogen mustard; RCS: Reticulum cell sarcoma; RT: Radiation therapy; S: Steroids; TT: Thiotepe; VB: Vinblastine.

fever symptoms disappeared 10 years after she acquired the lymphoma and before she had been treated for it with Cytosan (cyclophosphamide, Mead Johnson) and splenectomy.

Screening for IgE globulin was done on sera from 26 of the patients with lymphoma who gave histories of allergy. In all the patients, quantitative IgE was less than 1,000 ng per ml, the normal level being 100–700 ng per ml.¹²

Anti-IgE skin tests: The decreased prevalence of allergy among the patients with CLL prompted us to look for deficiencies of IgE in these patients. Ten patients were tested with guinea pig antihuman IgE, and 10 age and sex-matched controls were tested. The results are summarized in Table 5. Seven out of the 10 patients with CLL showed decreased levels of IgE, while 8 of the 10 controls demonstrated levels in the normal range.

To test the possibility that the negative skin reaction was due to lack of histamine release or inability to respond to histamine, we performed a Prausnitz-Küstner test on one of the patients. Patient E.O. did not react to the 1:2000 dilution of anti-IgE, and she reacted only minimally to the 1:1000 dilution. She was given intracutaneously 0.05 ml of a 1:200 dilution of ragweed hypersensitive serum. Twenty-four hours later she was challenged at the sensitized site and at a nonsensitized site with 0.05 ml of ragweed antigen. She gave a strongly positive response at the sensitized site but no response at the nonsensitized site. This result was in agreement with an identical experiment done on patients with CLL by Weed in 1965.²¹

DISCUSSION

The results of this study indicate that there is little relationship between the prevalence of allergy and the development of HD, RCS, or LSA in the patients studied; however, particularly in patients with HD, the malignant process or the therapy given for the malignancy may modify the allergic response, since many of the cancer patients lost their allergic symptoms during the course of the disease.

On the other hand, the study did demonstrate a decreased prevalence of allergy among the patients with CLL, and this decrease was accompanied in these patients by decreased levels of IgE. The role of circulating IgE in the allergic diathesis is not fully understood, but Johansson has shown that serum IgE is in-

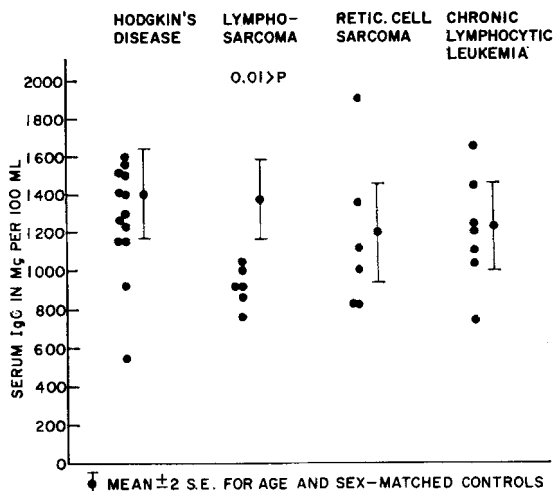


FIG. 1. Serum IgG levels in patients with lymphoma and chronic lymphocytic leukemia. Black dots indicate serum levels in individual patients. The vertical line at the right of each group of dots shows control values for each group.

creased in certain patients with allergic asthma,¹⁴ hay fever, and *Ascaris* infection.¹⁵

Since IgE has clearly been shown to be a major reaginic antibody, it is reasonable to associate diminished allergic symptomatology with decreased levels of this antibody fraction.

It is unlikely that the IgE deficiency demonstrated in some of the patients with CLL has any more significance than the other immune globulin deficiencies which may be associated with the disease. All of the deficiencies seen may be a result of the same underlying immu-

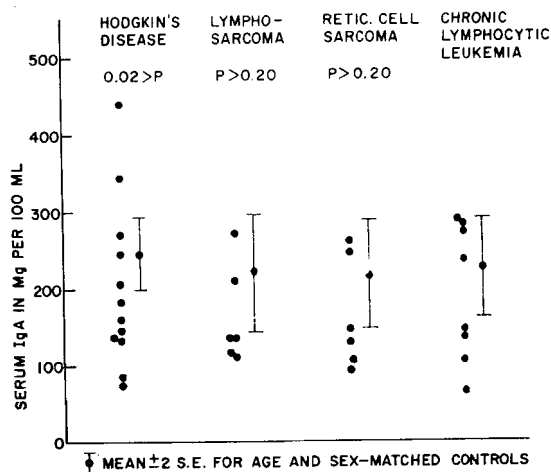


FIG. 2. Serum IgA levels in patients with lymphoma and chronic lymphocytic leukemia. Black dots indicate serum levels in individual patients. The vertical line at the right of each group of dots shows control values for each group.

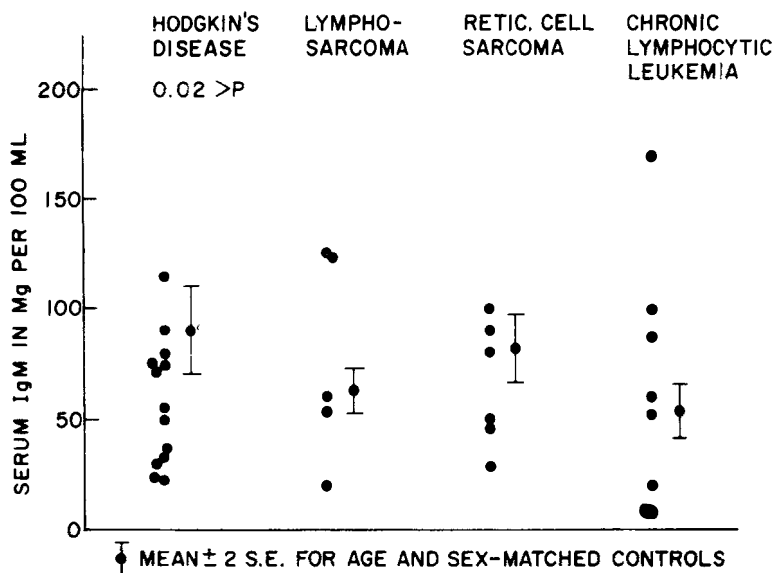


FIG. 3. Serum IgM levels in patients with lymphoma and chronic lymphocytic leukemia. Black dots indicate serum levels in individual patients. The vertical line at the right of each group of dots shows control values for each group.

nologic aberration. This study and others have shown that in patients with CLL there may be a deficiency of immune globulins. This is in contrast to the apparently intact cell-mediated immunity in patients with CLL. A recent careful study has demonstrated that most of these patients respond well to 2, 4-dinitrochlorobenzene sensitization. It is also likely that while a large percent of circulating lymphocytes show delayed PHA responsiveness in CLL, the total number of immunologically reactive cells in the circulation may be normal or increased.²

The frequent association of positive histories of allergy in patients with HD was noted

by Shier²⁰ and others. However, a study at Memorial-Sloan Kettering failed to reveal an increased prevalence of allergy among such patients.⁶ One report by Logan and Saker noted an increased prevalence of allergic histories in patients with cervical cancer and other malignancies,¹⁶ but the controls were not age and sex-matched. By contrast, Fisherman⁸ noted a marked decrease in the prevalence of allergy in patients with neoplasms of lung, uterus, breast, genitourinary tract, gastrointestinal tract, and skin. He found an increased prevalence of allergy in the group with ovarian carcinoma, but this group was too small to be statistically signif-

TABLE 5. Skin Test Results and Immunoglobulin Values in Patients with Chronic Lymphocytic Leukemia

Name	Age	Sex	Anti-IgE 1 : 2000	Anti-IgE 1 : 1000	Quantitative immunoglobulins Chronic Leukemia (mg/100 ml)		
					IgG	IgA	IgM
A.S.	64	M	0	+++	520	58	10
F.O.	69	M	0	N.T.	470	50	34
E.T.	62	F	0	+++	900	14	3
E.O.	62	F	0	+	504	84	153
H.W.	42	M	+	N.T.	234	28	8
J.K.	78	M	+	+++	770	127	38
M.G.	64	F	+	+++	724	39	14
D.B.	67	M	+++	N.T.	540	106	84
R.G.	71	M	+++	N.T.	1090	70	14
O.B.	54	M	+++	N.T.	630	163	26
Controls*			+++	N.T.			

* Age and sex-matched controls without leukemia.¹²

N.T. Not tested.

+++ Positive response.

+

0 Minimal response.

0 No response.

icant. In addition, a study by MacKay¹⁷ demonstrated a significantly decreased prevalence of allergy in 111 female cancer patients as compared with age and sex-matched controls, with no significant differences between breast, stomach, lung, and large bowel cancers. Yet a third study by Ure²² confirmed the inverse relationship between gynecologic malignancy and atopy. In view of the apparent inverse relationship between atopy and cancer, there has been recent revival of the hypothesis that immune mechanisms related to the allergic diathesis may also be involved in response to tumor-specific antigen,⁷ but confirmation of this theory must await much more experimental evidence.

Patients with CLL have a three-to four fold increase in the prevalence of secondary primary cancers and an eight- to thirteen-fold increase in skin cancers.^{1, 11} The known immunologic deficiency in these patients may promote the development of malignancy. Gunz¹¹ described a number of patients who developed CLL at the same time as they were found to have a second primary malignancy and cited several other well-documented reports of patients who went into spontaneous remission from their CLL while they developed progres-

sive and disseminated disease from a second malignancy. He went so far as to propose that the leukemia in these patients may be an abortive attempt to respond immunologically to tumor-specific antigen.

CLL may be compared to the group of congenital immunologic deficiency diseases which includes Bruton agammaglobulinemia, Swiss agammaglobulinemia, and Wiscott-Aldrich syndrome. The hereditary nature of CLL has been already suggested by the raised incidence of cancer in relatives of patients with CLL,¹⁰ the relatively numerous cases of "familial" CLL,¹⁹ and the report of deletion of chromosome material from G-group chromosomes in lymphocytes of patients with CLL.⁹ In both CLL and in the hereditary immunologic deficiency diseases, there is an increased chance that cancer will develop.⁵ The finding in this study that allergic symptoms are decreased throughout the lives of the patients with CLL might be explained by the fact that they may have an hereditary immunologic defect which makes its appearance only late in life with the development of hypogammaglobulinemia and the proliferation of an immunologically unreactive type of lymphocyte.

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