PRELIMINARY REPORT

Complement-Fixing Antivirus Antibodies in Patients with Leukemia

By SHEILA MCBEATH AND D. G. HARNDEN

NOT ALL ANIMALS carrying an oncogenic virus develop the tumor associated with this virus.[1] Further, it has been shown that polyoma virus is widely distributed in mouse populations in which polyoma-induced tumors are rare or do not occur at all.[2] The possibility exists, therefore, that a virus which is potentially oncogenic in man may be widely distributed in human populations, either as a pathogen or as a passenger virus, and yet be the cause of a malignancy on only rare occasions. For this reason, it was decided to screen the sera of patients with leukemia to determine whether the frequency of occurrence of antibodies against common viruses differed significantly between these patients and matched controls. It has been shown that in chronic lymphatic leukemia, the circulating antibody to viral antigens is diminished[3] while in acute leukemia and chronic myeloid leukemia, this response is normal or even enhanced.[4,5] The present report gives the result of observations on one hundred patients with chronic myeloid leukemia or acute leukemia of any cell type; cases of chronic lymphatic leukemia were not included in the study.

METHODS

Blood from leukemic patients was collected and the serum separated and stored at −70 C. until required. Samples were obtained from 57 cases of chronic myeloid leukemia of whom 13 were in the acute phase of the disease when the sample was taken, and from 43 cases of acute leukemia of several different cell types. Of these 100 patients, 59 had received treatment and 43 were untreated. One control subject matched for age and sex was selected for each patient. Serum from these controls, none of whom was known to have a malignancy or an infectious disease was stored at −70 C. until required. All the sera were screened against the complement-fixing antigen of influenza A, influenza B, influenza C, sendai virus, respiratory syncitial virus, adenovirus, mumps S, mumps V, measles, herpes simplex, psittacosis, *Rickettsia burneti,* and *Mycoplasma pneumoniae,* which were obtained from the Central Public Health Laboratory, London, England.

Complement-fixation tests were carried out in batches of approximately 20 sera (10 patients and 10 matched controls) using the technic of Bradstreet and Taylor.[6] The tests were scored blind by two observers. Sera which gave 50 per cent lysis or less at a titer of 1/16 were considered positive.

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Table 1.

	Total Cases	Number Positive at a Dilution of 1/16														
		Influenza A	Influenza B	Influenza C	Respiratory Sendai	Respiratory Syncitial	Respiratory Adeno	Mumps S	Mumps V	Measles	Herpes Simplex	Psittacosis	*Rickettsia burneti*	*Mycoplasma pneumoniae*	Total Positives
Chronic myeloid leukemia		18	15	26	13	13	9	3	15	11	17	3	2	6	151
Control	44	26	9	23	17	13	19	3	11	13	21	7	1	6	169
Chronic myeloid leukemia → acute		5	3	3	3	2	4	2	6	3	6	0	0	3	40
Control	13	9	3	6	4	3	6	2	4	6	5	1	1	3	53
Acute leukemia		18	3	19	14	12	14	2	13	9	22	4	0	2	132
Control	43	19	7	18	11	7	22	3	13	11	19	3	1	3	137
All leukemias		41	21	48	30	27	27	7	34	23	45	7	2	11	323
Controls	100	54	19	47	32	23	47	8	28	30	45	11	3	12	349

Table 2.

			No. of Cases	No. of Subjects Positive for Adenovirus at 1/16
Chronic myeloid leukemia	Treated	Patient	24	7
		Control	24	10
	Untreated	Patient	20	2
		Control	20	9
Chronic myeloid leukemia (acute phase)	Treated	Patient	10	3
		Control	10	4
	Untreated	Patient	3	1
		Control	3	2
Acute	Treated	Patient	25	9
		Control	25	15
	Untreated	Patient	18	5
		Control	18	7
Total	Treated	Patient	59	19
		Control	59	29
	Untreated	Patient	41	8
		Control	41	18

Results

The results are presented in Table 1. In this table, the treated and untreated patients have been grouped together since independent analysis showed that, although there were slightly fewer positives in the treated patients, the difference between the two groups was not significant.

For 12 out of the 13 antigens tested there is a good concordance between the number of leukemic sera positive at a dilution of 1/16 and the number of positive control sera. This confirms previous observations that the circulating antibody response to viral antigens is not seriously impaired in acute leukemia or chronic myeloid leukemia.[4,5] There is, however, an apparent deficiency of leukemic sera which are positive for adenovirus. A statistical analysis of these data using a direct comparison of the matched pairs shows that, while the figures for adenovirus considered separately are significant at the 1 per cent level, the probability of getting one such result out of 13 is 0.12 and cannot therefore be considered significant.

The grouping together of several different leukemic types might have tended to obscure differences. Closer examination of the figures for adenovirus (Table 2) shows a lack of leukemic patients positive for adenovirus in all groups, but this is most marked for untreated patients with chronic myeloid leukemia (2 out of 20 positives as compared with 9 out of 20 positives for the controls). In an attempt to clarify this point, additional samples were obtained from some of the patients already studied, and further untreated cases of chronic myeloid leukemia were sought. Of the original 20 patients, only 8 were available for re-examination and all had now been treated. All 8 were originally negative and this result was confirmed. Seven new untreated patients with chronic myeloid leukemia were located, and, of these, 3 were positive for adenovirus while 5

out of 7 controls were positive, giving a total of 5 out of 27 positives as compared with 13 out of 27 for the controls. It is clear that this does not add to the significance of the result.

Discussion

Millian et al.[3] have screened the sera of patients with chronic lymphatic leukemia, reticulum cell sarcoma, lymphosarcoma, and Hodgkin's disease for antibodies against a number of common viral and rickettsial complement-fixing antigens. For chronic lymphatic leukemia, the proportion of patients with a significant amount of antibody was consistently lower than in the controls, but there was no significant correlation with one particular virus. There was, however, a significant deficiency of complement-fixing antibodies to adenovirus in patients with Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma. On the other hand, Murphy et al.[7,8] have found that three times as many leukemic adults have neutralizing antibodies to adenovirus 4 as do normal adults, but that this is not true for antibodies to adenovirus 12. Further study of complement-fixing antibodies, neutralizing antibodies, and antibodies against T antigens, as suggested by Lewis et al.[9] will be necessary to clarify this situation.

It is of interest, however, that Potter and Schild[10] report that adenovirus 12 and 18 are only midly antigenic in man as compared with adenovirus 1 and 5, while Van Hoosier et al.[11] report only an infrequent specific complement-fixing antibody response in mice with adenovirus type 12–induced tumors and suggest that the tumor may be absorbing antibody so that circulating levels are undetectable. These two observations suggest that a deficiency of antibodies to a specific virus in patients with neoplastic disease could be important in trying to determine whether the relationship between the virus and the disease is significant in terms of the etiology of the disease.

Summary

The sera from 100 patients with chronic myeloid leukemia or acute leukemia and from 100 matched controls were screened for antibodies against a number of common viral and rickettsial antigens. No over-all depression of immune response to these antigens was noted. For 12 out of 13 antigens, there was good correspondence between patients and controls but a deficiency of leukemic patients with antibodies against adenovirus, though not formally significant, seems worthy of further study.

SUMMARIO IN INTERLINGUA

Le seros ab 100 patientes con chronic leucemia myeloide o con leucemia acute e ab 100 appareate subjectos de controlo esseva examinate pro le presentia in illos de anticorpores contra un numero de commun antigenos viral e rickettsial. Nulle depression general del responsa immunologic a ille antigenos esseva notate. Pro 12 de 13 antigenos le correspondentia inter patientes e subjectos de controlo esseva bon. Le facto que un reducite numero de patientes leucemic habeva anticorpore anti adenovirus pare meritar un investigation additional ben que illo non esseva technicamente significative.

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