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Incidence of Cancer in 98 Patients with Common Varied Immunodeficiency[1]

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Ninety-eight patients with common varied immunodeficiency have been observed for periods of 1–13 years. In 1986, 78 were alive, 19 had died, and 1 could not be located. Eleven patients in the group had developed cancer; two patients had had two cancers. Of the total number of neoplastic malignancies, seven were non-Hodgkin's lymphoma, one patient had a Waldenstrom's macroglobulinemia, and nine of the patients who developed cancer were female. Cancer developed in the fifth or sixth decade of life for 10 of the 11 patients. These data show an 8- to 13-fold increase in cancer in general for patients who have this immunodeficiency and a 438-fold increase in lymphoma for females.

KEY WORDS: Cancer; hypogammaglobulinemia; common varied immunodeficiency; lymphoma.

INTRODUCTION

Patients with severe primary immunodeficiency diseases have an increased incidence of cancer. For example, of 301 cases of Wiskott–Aldrich syndrome, 36 developed cancer (12%) (1). Similar data for ataxia telangiectasia show an incidence of 8.8 to 11.7% (2). While these rare, severe, and distinctive immunodeficiency syndromes have a defined incidence of neoplasia, comparable data concerning the frequency of cancer have been difficult to gather for the less rare and milder primary congenital immunodeficiency diseases such as common variable immunodeficiency (CVI, adult onset, or acquired hypogammaglobulinemia). While this immunodeficiency is often recognized in childhood, the diagnosis may not be made until the third or fourth decade of life because the syndrome is clinically heterogeneous (3). Therefore, patients having this disorder may receive care from pediatricians, internists, or specialists in immunology, pulmonary medicine, rheumatology, or oncology. Possibly for this reason, no large series of patients have been available in the United States for statistical analyses. However, a recent report from Great Britain shows a fivefold increase in cancer in a population of 220 CVI patients, due mainly to an increased incidence of stomach cancer and lymphoma (4).

In the present study, we report that 11 of 98 patients (11.2%) with CVI followed at our medical center developed at least one cancer during observation periods of up to 13 years. Of the total number of cancers (13) which have appeared, seven were non-Hodgkin's lymphoma, one was a Waldenstrom's macroglobulinemia, and all but two of the hypogammaglobulinemic patients in this group were female.

PATIENTS AND METHODS

The Immunodeficiency Clinic was originally established at Memorial Hospital in 1973 by Dr. R. A. Good, and adult and pediatric patients with CVI were continuously referred for analysis and treatment until 1986, when this clinic was relocated at the Mount Sinai Medical Center. The diagnosis of CVI was made by standard criteria (3). In order to

[1]Since the submission of this report, an additional female patient, aged 55 years, has developed Stage I, nodular lymphoma in the parotid gland.

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have a numerically defined population for study, this report is restricted to patients with CVI who were registered and attended the Immunodeficiency Clinic at Memorial Hospital from 1973 until January 1986. Therefore, for the purposes of this report, we excluded (i) patients less than age 2 years and/or transient hypogammaglobulinemia, (ii) antibody deficiency but no hypogammaglobulinemia, (iii) sex-linked (Bruton-type) agammaglobulinemia, (iv) hypogammaglobulinemia and thymoma, and (v) immunoglobulin deficiency due to intestinal loss. In order to exclude patients who were hypogammaglobulinemic due to cancer, patients who had been diagnosed as having cancer either before or 2 years after the diagnosis of hypogammaglobulinemia was established were also excluded.

The 98 CVI patients studied were of ages 3–71 years at the first evaluation. There were 47 females and 51 males. To determine the clinical condition of each individual in 1986, patients not currently attending the clinic were contacted and interviewed using a standard questionnaire. In most cases, the patient's current physician was also interviewed. For those who had died, the cause of death was ascertained by contacting the attending physician and, in five cases, by examination of the autopsy report. The pathology slides for each patient who had developed a lymphoid malignancy were reviewed by one of us (PL).

Most patients had received immunoglobulin replacement therapy as intramuscular or intravenous immunoglobulin; two patients had received plasma.

Laboratory Testing

Serum immunoglobulins were quantitated by radial immunodiffusion and examined for monoclonal proteins by immunoelectrophoresis. Antibody deficiency was additionally verified in many cases by determining the titer of isohemagglutinins, by Schick testing, or by quantitation of antibody responses to diphtheria and tetanus and/or immunization with pneumococcal vaccine. Enumeration of T and B cells (5) and the lymphocyte proliferative response to mitogens, antigens, and allogeneic cells (6) was performed on the first clinic visit for the majority of patients. Fluorescence microscopy was performed on peripheral blood and, in some cases, on bone marrow or tumor cells, in order to determine the percentage of cells bearing various immunoglobulin isotypes (5).

Statistical Analyses

The expected number of cases of cancer for all sites and for lymphoma (excluding Hodgkin's disease and myeloma) for our patient group was determined by calculating the number of person-years at risk for each 5-year age interval for both male and female patients and applying standard tables for age-specific cancer incidences for New York State (7). The expected number of cases was then compared to the number of cancers observed to provide a standard incidence ratio (SIR), where SIR = 100% × observed/expected (8).

Table I. Cancers Identified

Patient No.	Sex	Date of diagnosis of immunodeficiency	Date of diagnosis of cancer	Age at diagnosis of cancer (years)	Tissue diagnosis
1	F	1971	1982	12	Diffuse large-cell lymphoma
2	F	1977	1981	(1) 48	Diffuse large-cell lymph.
				(2) 53	Squamous carcinoma
3	M	1971	1983	52	Adenocarcinoma ×2
4	F	1983	1985	(1) 50	Carcinoma
				(2) 56	Diffuse, small cleaved-cell lymphoma
5	F	1969	1978	54	Diffuse, mixed small- and large-cell lymphoma
6	F	1958	1973	50	Diffuse, mixed small- and large-cell lymphoma
7	F	1976	1982	57	Adenocarcinoma
8	M	1972	1978	63	Plasma-cell infiltrate
9	F	1973	1986	66	Adenocarcinoma
10	F	1970	1980	67	Diffuse large-cell lymphoma
11	F	1972	1978	71	Diffuse large-cell lymphoma

Table I. Continued.

Patient No.	Initial location	Treatment	Other conditions	Outcome
1	Liver, spleen	Chemotherapy	Parotid abscess, rec. pneumonia	Died 1983
2	(1) Proximal jejunum (2) Vagina	Surgical resection, radiotherapy	Nodular lymphoid hyperplasia	Alive, no cancer
3	Colon	Surgical resection × 2 of adenomatous polyps	Recurrent bronchitis, sinusitis, RUL lobectomy, s/p cholecystectomy, nodular lymphoid hyperplasia	Alive, no cancer
4	(1) Cervix (2) Pelvis	Surgical resection, chemotherapy	Nodular lymphoid hyperplasia, protein-losing enteropathy	Alive, on chemotherapy
5	Right inguinal node	Surgical resection, chemotherapy	Primary biliary cirrhosis, rheumatoid arthritis	Alive, no cancer
6	Pelvic retroperitoneum; recurrence, buccal mucosa and submandibular area	Chemotherapy	Previous recurrent pneumonia, lobe resection, hemolytic anemia	Died 1980
7	Ovary	Surgical resection, chemotherapy	Recurrent pneumonia sinusitis, bronchiectasis, psoriasis	Died 1985
8	Bone marrow	Plasmapheresis, chemotherapy	Prior recurrent pneumonias, meningitis, splenectomy, hyperviscosity syndrome	Died 1981
9	Stomach	Surgical resection	Recurrent sinusitis, bronchitis, linitis plastica	Alive, post-surgery
10	Supraclavicular area, abdomen	Chemotherapy	Hemolytic anemia	Died 1980
11	Lymph nodes, lungs	Chemotherapy		Died 1979

RESULTS

Of the total of 98 CVI patients seen from 1973 to 1986, 78 were alive in 1986, 19 had died, and 1 could not be located. The total number of years for observation of these patients was 631. Of the group of 97 patients who could be traced, 11 individuals had developed at least one cancer (Table I). Ten were female and two were male. For the group of 86 patients who had not developed cancer, 37 were female and 49 were male.

Of the cancers, seven patients had non-Hodgkin's lymphoma, one had Waldenstrom's macroglobulinemia, one had an adenocarcinoma of the stomach, and one had an adenocarcinoma of the ovary, and one had two adenomatous polyps of the colon. For patients having non-Hodgkin's lymphoma, four were categorized as having diffuse large-cell, one as having diffuse, small cleaved-cell, and two as having diffuse lymphomas of mixed large- and small-cell morphology. Two patients with lymphoma also had a second cancer; one (case 2) developed carcinoma of the vagina 6 years after the lymphoma developed, and the other individual (case 4) had previously had Stage II cervical cancer.

Cancer developed in the fifth and sixth decades of life for 10 of the 11 individuals. For the group of 86 patients who had not developed cancer, the age range was 13 to 65 years, with an average age of 34 years. For the group of patients with cancer, the average length of survival after diagnosis was 2.4 years; patients who died did so as a result of widespread cancer. Five patients are alive in 1986, three of whom have been on no therapy for an average of 3.4 years. Thus in our group of patients, 6 deaths of 19 were due to cancer. (Other causes of death were as follows: respiratory insufficiency with or without cor pulmonale, 8; suicide, 2; fatal measles infection, 1; bone marrow aplasia, 1; and cerebrovascular accident, 1.)

Results of immunologic testing for the patients who developed cancer are shown in Table II. Varying degrees of serum hypogammaglobulinemia were observed. Three patients had had an increased

Table II. Results of Immunologic Testing and Cellular Immune Parameters for Patients Who Developed Cancer

Patient	Date	Serum immunoglobulins (mg/dl)[a]			Mononuclear cells (%)		Lymphocyte proliferation response (cpm)			
		IgG	IgA	IgM	T cells	B cells	PHA	Con A	PWM	MLC
1	5/81	162	2	26	51	16	9,575[b]	2,095[b]	2,340[b]	824[b]
2		105	34	5	—	—	—	—	—	—
3	1/77	8	5	0	88	4?	21,355	12,378	16,665	—
4	10/84	380	66	35	66	28.5[c]	28,250	14,670	13,795	2,200[b]
5[d]	4/69	600	0	960 (polyclonal)						
	7/69	400	0	660						
	1/71	640	0	440						
	4/78	479	0	702						
	12/80	214	0	96						
	9/82	273	0	72						
	4/85	188	24	53	8.2	5	14,980[b]	6,510[b]	1,460[b]	5,360[b]
6	4/73	80	0	160	89	16	1,426[b]	320[b]	315[b]	—
	4/74	310	30	330						
	1/78	287	8	992 (IgM k)						
	1/77	265	0	462						
	5/78	360	1	156						
7	12/76	100	0	0	87.5	2	15,917	2,382[b]	2,168[b]	4,516[b]
	9/77	237	<8	1						16,452[b]
8	3/78	276	95	3,420 (IgM k)	70	8	14,203[b]	5,114[b]	2,861[b]	1,833[b]
	12/78	406	11	2,350						
	12/79	225	8	833						
	4/80	180	24	2,720						
9	1/73	177	0	5	73.5	10	21,000	11,700	8,500	—
10		200	20	11	97	0.5	22,038	15,578	2,718[b]	5,298[b]
11		354	20	116	82	12	4,755[b]	1,250[b]	3,725[b]	1,308[b]

[a]Normal ranges: IgG, 800–1800 mg/dl; IgA, 90–450; IgM, 90–300.
[b]Two standard deviations below the mean.
[c]B cells mark positive for IgM k.
[d]Tumor cells of patient 5 had surface IgM k.

serum IgM at some point before or at the time that the diagnosis of lymphoma was made; two of these IgM proteins were monoclonal IgM k. A fourth patient had an increased number of circulating and bone marrow B cells bearing IgM k. The lymphoma cells of this patient also bore these immunoglobulin markers.

Cellular immune parameters were investigated (Table II). Patients 1, 4–8, 10, and 11 were found to have moderate to severe T-cell defects in lymphocyte proliferative responses to mitogens and/or allogeneic cells. Patients 1, 4, 10, and 11 were evaluated within 2 years of the time that the diagnosis of malignancy was made, and patient 5 was not studied until some years after the affected lymph node had been resected.

DISCUSSION

The Immunodeficiency Cancer Registry has recorded 114 cases of malignancy in patients with CVI; of these, 55 were lymphoid and 59 were derived from other tissues (9, 10). While these data are useful for comparing the relative incidence of various tumors in this immunodeficiency disorder, they do not indicate the actual frequency of such cancers in hypogammaglobulinemic patients since the total population of patients observed is not known. Recently, of 220 patients with CVI observed in Great Britain, 14 developed cancer (6.4%). Of these, 7 were stomach cancer, 3 were lymphomas, 1 was cervical cancer, and 3 were derived from other tissues (4). By comparing these figures to the expected incidence of such neoplastic malignancies in the general population, it was determined that there was a 47-fold increase in stomach cancer, a 30-fold increase in lymphoma, and a 5-fold increase in all cancers.

A previous study of 46 patients with CVI in the United States recorded seven neoplasms (excluding the thymomas included in this report) (15%); of these, four were adenocarcinoma of the stomach and one was a lymphoma (11). In contrast, we have found that 11 individuals of a total group of 98 have developed cancer (11.2%) but that 8 of these (8.2%) involved lymphoid tissues.

Table III. Age-Adjusted Cancer Incidence

		Observed	Expected	O/E
Females	All sites	11	0.80	14
Males	All sites	2	0.25	8
Females	Lymphoma	7	0.016	438
Males	Lymphoma	0	0.011	0

Comparing these data to the age-adjusted expected incidence, the group of patients studied here had an 8-fold increase for males, a 13-fold increase for females for cancer in general, and a 438-fold increase for lymphomas for females (Table III). The reason for the greatly increased incidences of these diseases, particularly lymphoma, as compared to patients studied in the United Kingdom, is unknown. Although Memorial Hospital specializes in the treatment of cancer, the hypogammaglobulinemic patients included in this study were referred to Memorial Hospital not for this reason but for management of immunodeficiency. [In fact, we excluded two additional hypogammaglobulinemic patients with malignancies (adenocarcinoma of the stomach and Hodgkin's disease) who had been referred for cancer management during the study period.] However, it is possible that hypogammaglobulinemic patients with more severe immune defects were referred to this hospital; this factor could conceivably introduce a bias in favor of the higher incidence of malignancy in our patient group.

Among our group of 11 patients, 10 had been tested for cellular immunocompetence. Of these, 8 were found to have moderate to severe proliferative defects. In contrast, 29 of 69 (42%) of CVI patients without cancer had similar defects of cellular immunity. The differences for the incidence of cellular defects between patients with cancer and patients without cancer is statistically significant ($P > 0.05$, chi-square test). While this may indicate that defects of cell-mediated immunity are associated with the development of a neoplastic malignancy in hypogammaglobulinemic patients, evaluations of cellular immune status in some patients reported here were (i) performed within 2 years of the development of cancer, and the results could therefore be altered by the presence of occult lesions (cases 1, 4, 8, 10, and 11), or (ii) performed several years after chemotherapy for cancer had been completed (case 5), which could conceivably also alter the results. However, in general we have found that no effects of chemotherapy on immune responses would be expected at this point after treatment (12).

Two of the lymphomas secreted IgM k paraproteins and a third was a clonal expansion of nonsecreting, IgM k-bearing B cells. These results are in accordance with previous studies which show that B-cell lymphomas are predominant in Wiskott–Aldrich syndrome (13) and are a particular feature of immunosuppression (14, 15).

Previous investigators have suggested that the reported increased incidence of cancer in CVI was not sustained when adjusted for age and when an appropriate denominator for the total patient population studied was included (16). An additional objection has been that patients with lymphoma can be found to have hypogammaglobulinemia and that the inclusion of such cases in previous reports has inflated the reported incidence of cancer. However, having excluded these objections in this report, our data show that the overall incidence of malignancy in patients with CVI in the northeastern United States may be similar to that in patients with Wiskott–Aldrich syndrome or ataxia telangiectasia, although patients with CVI have a longer life expectancy and may not develop cancer until the latter decades of life. From our data, it appears possible that older patients with CVI and cellular immune defects may be more at risk for the development of cancer.

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