Chronic T-Cell Lymphocytosis With Neutropenia: Report of a Case Studied With Monoclonal Antibody

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A 55-yr-old man presented with an 8-yr history of lymphocytosis, neutropenia, and infection. There was moderate splenomegaly without lymphadenopathy, and lymphocytosis of the blood (15,000–41,200/cu mm) and bone marrow (30%): the latter also revealed no granulocytes more mature than the myelocyte. A diagnosis of leukemia could not be made from microscopic examination of the liver, spleen, or bone marrow. The circulating lymphocytes were T cells of the cytotoxic-suppressor subset with characteristic surface markers. They formed rosettes with unsensitized sheep erythrocytes (E rosettes), reacted with an antithymocyte heteroantiserum, were positive for the receptor for the Fc portion of IgG, and were devoid of surface immunoglobin. When examined with a panel of monoclonal antibodies, these cells reacted with OKT3, a monoclonal that identifies peripheral T cells, OKT11, which identifies the sheep cell receptor, and OKT5 and OKT8, which identify the cytotoxic suppressor subset of T cells, but not with OKT4, which identifies the inducer/helper subset. These lymphocytes also displayed a high level of antibody-dependent cytotoxicity, but natural killer activity could not be demonstrated. This indolent disorder closely resembles that of 7 patients with lymphocytosis and neutropenia described in the recent medical literature, but sharply contrasts with the more frequently reported cases of T-cell chronic lymphocytic leukemia. Since it is unclear that the present case represents a neoplastic proliferation, the noncommittal term "chronic T-cell lymphocytosis with neutropenia" is proposed for the condition. In view of the neutropenia and the benign course, cytotoxic treatment appropriate for B- and T-cell chronic lymphocytic leukemia should be undertaken only with circumspection. The new condition can be suspected from the clinical picture and can be diagnosed with conventional lymphocyte surface marker techniques and commercially available monoclonal antibodies.

TECHNIQUES that identify lymphocyte lineage allow detection of rare T-cell disorders that are difficult to distinguish morphologically from the common B-cell proliferations of small lymphocytes [chronic lymphocytic leukemia (B-CLL) and chronic lymphosarcoma cell leukemia].[1] We report a patient with marked and long-standing increase of T lymphocytes and associated neutropenia. This case does not resemble the usual picture of T-cell chronic lymphocytic leukemia (T-CLL)[2-5] or of cutaneous T-cell lymphoma (CTCL),[6-8] but is closely similar to several patients with T-cell lymphocytosis and neutropenia who have been the subject of recent reports from the United States[9,10] and Holland.[11] In the present case, a panel of monoclonal antibodies[12-14] was employed to demonstrate restriction of the T-lymphocyte proliferation to the cytotoxic-suppressor subset. Despite the subset restriction, the nonprogressive nature of the disorder makes it uncertain that the condition is neoplastic. While this entity is uncommon, its recognition has important prognostic and therapeutic implications.

CASE REPORT

C., a 55-yr-old man, was first seen in December 1972 when he presented with an abscess below the right mandible, an infiltrate in the right upper lobe, moderate splenomegaly, and stiffness, pain, and swelling of the proximal interphalangeal joints. The white blood count was 2100/cu mm, with a differential count of 2% neutrophils, 95% small lymphocytes, and 3% monocytes. Bone marrow examination on two occasions revealed 26% and 31% mature lymphocytes, a maturation "arrest" in the neutrophil series with no cells beyond the myelocytes stage, adequate megakaryocytes, and normal red cell maturation. Rheumatoid factor was detected at a level of 1:128, and an immunoelectrophoresis revealed a polyclonal increase of IgG and IgA with normal IgM. A splenectomy was performed. Microscopic examination revealed a nonspecific increase of mononuclear cells in the white pulp, and a moderate infiltrate of small lymphocytes in the sinus areas of the liver was observed in a biopsy done at the same time. The patient was symptomatic over the ensuing 8 yr, although examination of the bone marrow remained unchanged. The white blood count was 7100/cu mm immediately after splenectomy with 84% small lymphocytes but without mature neutrophils. In the past year, lymphocyte counts have fluctuated between 15,500 and 41,200/cu mm, the hematocrit between 37% and 42%, and the platelet count between 288,000 and 400,000/cu mm. The differential blood count has varied from 89% to 98% lymphocytes, 0% to 2% neutrophils, with the remaining cells monocytes and eosinophils. The predominant cell is a small lymphocyte with some azurophilic granulation and cytoplasm, which is positive with the acid phosphatase stain, but otherwise unremarkable in appearance. Karyotype analysis with G banding technique of a 4-day culture of peripheral blood lymphocytes after phytohemagglutinin stimulation revealed a normal 46, XY pattern.

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Table 1. Surface Markers* in Lymphocytosis of the Cytotoxic-Suppressor Subset of T Cells and in a Case of the Cutaneous T-Cell Lymphoma

	Surface Immunoglobulin				Rosettes				Antithymus	Monoclonal Antibodies†										
	G	M	K	λ	E	IgMEAC	IgGEA	IgGOx	Heteroantiserum	T1	T3	T4	T5	T6	T8	T9	T10	T11	M1	I1
Patient C	3	0	3	3	95	0	33	41	92	3	79	5	79	0	87	2	1	83	4	16
Cutaneous T-Cell lymphoma	0	0	0	0	71	4	1	0	84	91	85	89	1	0	3	0	0		0	0

*All results are expressed in percent.

†The following monoclonal antisera were employed: OKT1, all T cells; OKT3, peripheral T cells; OKT4, inducer/helper T cells; OKT6, common thymocytes; OKT5 and OKT8, cytotoxic–suppressor T cells; OKT9, early thymocyte; OKT10, early thymocyte; OKT11, sheep cell receptor; OKI1, Ia-like antigen; OKM1, monocyte, granulocyte.

MATERIALS AND METHODS

Lymphocyte Preparation and Patient Selection

Purified lymphocytes were prepared from defibrinated blood with a Ficoll-Hypaque gradient.[15] The viability of cells studied in this report exceeded 90% as determined by trypan blue dye exclusion. The diagnosis of cutaneous T-cell lymphoma in the comparison case was based on erythroderma, a lymphocyte count of 22,000/cu mm, and characteristic convoluted morphology of the cell nuclei.[16]

Surface Marker Analysis With Hybridoma Antisera

Nonfluoresceinated monoclonal mouse hybridoma antisera were obtained from Ortho Pharmaceutical Corp., Raritan, N.J., as lyophilized ascites protein.[12–14] Lymphocytes (10^6) in 0.05 ml of medium 199 were incubated with 0.05 ml (10 μg/ml) of each of the following mouse hybridoma antisera: OKT1 (all T cells), OKT3 (peripheral T cells), OKT4 (inducer/helper T cells), OKT6 (common thymocytes), OKT5 and OKT8 (suppressor-cytotoxic T cells), OKT9 (early thymocytes), OKT10 (early thymocytes), OKT11 (sheep cell receptor), OKM1 (monocytes and granulocytes), and OKI1 (Ia-like antigen). After a 30-min incubation at 37°C, the lymphoid cells were washed twice at room temperature with phosphate-buffered saline (pH 7.4), and then reincubated for 60 min at the same temperature with 0.05 ml of a 1:5 dilution of fluorescein-conjugated goat anti-mouse gamma globulin antiserum [$F(ab')_2$ fraction obtained from N.L. Cappel Laboratories, Cochranville, Pa.]. The cells were again washed twice, suspended in phosphate-buffered glycerine, placed on a slide, overlayed with a cover slip, and examined with a Zeiss ultraviolet microscope equipped with an Osram HBD 200 mercury arc lamp and a fluorescein isothiocyanate 495 nm interference primary filter. A minimum of 200 lymphocytes were examined.

Conventional Lymphocyte Surface Markers

Cell surface immunoglobulin was determined with fluorescein-conjugated goat antisera specific for the IgG and IgM heavy chains of human immunoglobulin, and for the kappa and lambda light chains as previously described.[15,17] The fluorescence microscope was also employed to evaluate thymus-related surface antigens making use of the globulin fraction of a rabbit antiserum to human fetal thymus absorbed with A-positive erythrocytes and chronic lymphocytic leukemia cells.[18]

Spontaneous rosette formation with sheep erythrocytes (E rosettes) was assessed by adding a suspension of lymphoid cells to sheep cells in the presence of 9% absorbed and inactivated AB serum.[19] The mixture was incubated for 10 min at 37°C, centrifuged at room temperature, and incubated for at least 2 hr at 4°C. Fc receptor was assayed with sheep and ox erythrocytes coated, respectively, with the IgG fraction of a rabbit anti-sheep and anti-bovine cell stroma antiserum (IgGEA and IgGOx rosettes) employing a 45-min incubation at 37°C.[20] Complement receptor was detected with sheep erythrocytes sensitized by the addition of the IgM fraction of a rabbit anti-sheep cell stroma antiserum and mouse complement employing a similar incubation (IgMEAC rosettes).[21]

Antibody-Dependent Cellular Cytotoxicity (ADCC), Natural Killer (NK) Activity, and Antineutrophil Antibodies

ADCC and NK activity were measured with K562 cells by the method of Ault and Weiner.[22] Antineutrophil antibodies were assayed with the *Staphylococcal* slide test of Harmon, Weitzman, and Stossel.[23]

RESULTS

Lymphocyte surface marker findings, obtained in patient C with both conventional techniques and a panel of monoclonal antibodies, are presented in Table 1. His circulating lymphocytes (absolute count 26,500/cu mm) are devoid of surface immunoglobulin and form rosettes with unsensitized sheep erythrocytes (E rosettes). Thus, the cells are unequivocally T lymphocytes. The absence of complement receptor (IgMEAC rosettes) and reactivity with an antithymus heteroantiserum provides additional support for this conclusion. These lymphocytes also bear the receptor for the Fc portion of IgG, which was detected with both sheep and ox erythrocytes coated with IgG (IgGEA and IgGOx rosettes). The monoclonal antibody results indicate that the lymphocytes of patient C belong to the cytotoxic-suppressor subset of T cells. Thus, they react with the monoclonal antibody OKT3 (Fig. 1, left), which detects all peripheral T cells, OKT11, which detects the sheep cell receptor, OKT5 and OKT8 (Fig. 1, right), which detect the cytotoxic-suppressor subset, and they fail to react with OKT4, which detects the inducer/helper subset. There is faint reactivity with OKI1, a monoclonal antibody to the Ia-like antigen.

For comparison, the results of similar studies performed in a case of cutaneous T-cell lymphoma are

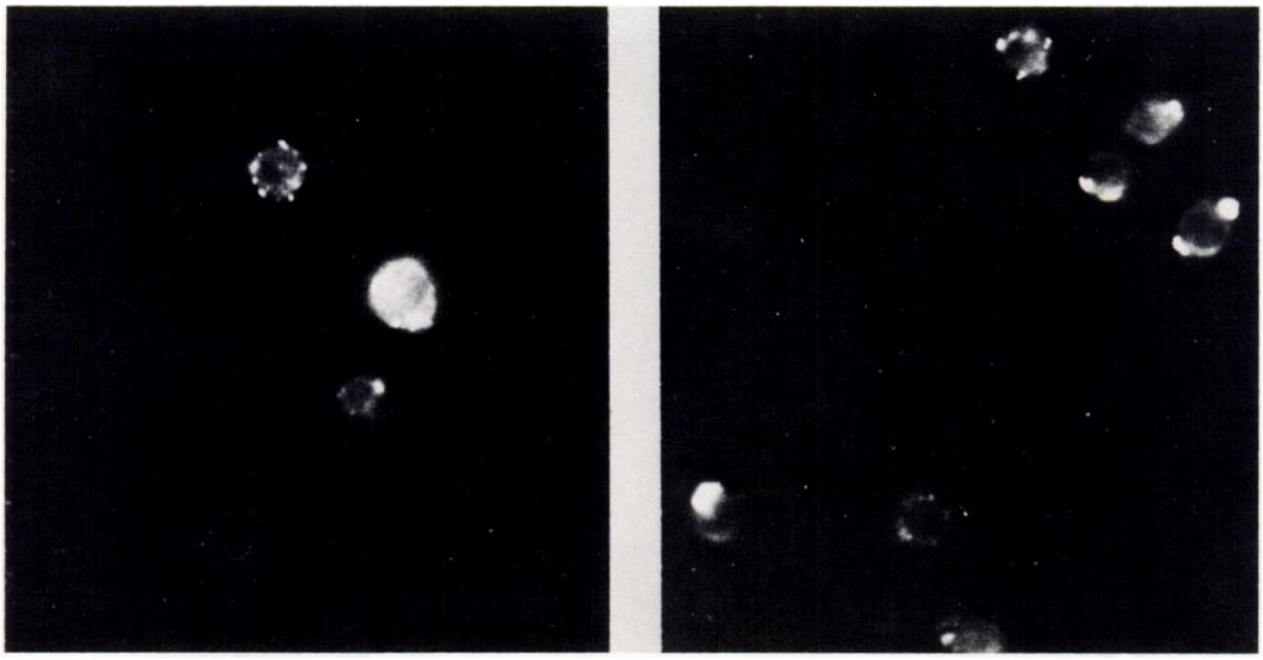

Fig. 1. Lymphocytes from patient C. after incubation with monoclonal mouse antibody OKT3, which detects human peripheral T cells (left), and OKT8, which detects the cytotoxic-suppressor subset of human T cells (right). All lymphocytes in both fields stain brightly following the addition of fluorescein-conjugated goat anti-mouse gamma globulin antiserum (initial magnification ×240).

included in Table 1. The circulating lymphocytes in that patient are also devoid of surface immunoglobulin and complement receptor, form rosettes with unsensitized sheep erythrocytes, and react with the antithymus heteroantiserum. However, the Sézary cells are of the inducer/helper subset, reactive with the monoclonal antibody OKT4 and unreactive with OKT5 and OKT8. The Sézary cells also differ from the lymphocytes of patient C by their lack of the Fc receptor.

Table 2 indicates that the lymphocytes from patient C have a very high level of antibody-dependent cellular cytotoxicity, but are devoid of natural killer activity. Antineutrophil antibodies could not be detected on two occasions employing the *Staphylococcal* slide test of Harmon, Weitzman, and Stossel (data not shown).[23]

Table 2. Antibody-Dependent Cellular Cytotoxicity and Natural Killer Activity of Lymphocytes From Patient C. With T-Cell Lymphocytosis

Effector Cell	Effector to Target Cell Ratio	Specific Lysis (%)
Natural Killing		
Patient C.	20:1	2.4 ± 1.0
	10:1	0.0 ± 1.0
	5:1	0.4 ± 1.0
Normal control	20:1	31.3 ± 2.5
	10:1	16.4 ± 2.2
	5:1	5.6 ± 1.9
Antibody-dependent cellular cytotoxicity		
Patient C.	20:1	92.8 ± 2.4
	10:1	84.4 ± 4.2
	5:1	82.0 ± 1.4
Normal control	20:1	54.3 ± 3.7
	10:1	34.7 ± 3.1
	5:1	23.3 ± 5.8

DISCUSSION

Proliferations of small T lymphocytes (surface immunoglobulin-negative, E-rosette-positive) are infrequent and heterogeneous. Cutaneous T-cell lymphoma (CTCL) and T-cell chronic lymphocytic leukemia (T-CLL) are the best defined. The first is characterized by erythroderma, and a lymphocytosis of helper T cells with convoluted cell nuclei.[6,8,16] The latter, T-CLL, usually presents with hepatosplenomegaly, anemia, and thrombocytopenia:[2-5] chromosome abnormalities are frequently found[24] and, like CTCL, skin lesions and T-cell nuclei of convoluted shape may be present. T-CLL pursues a short relentless course and is usually unresponsive to therapy. The present case bears little resemblance to either CTCL or T-CLL, nor is it similar to either the rare cases of T-cell lymphocytosis, which may accompany thymoma,[25] or to the occasional suppressor cell variants of T-cell acute lymphocytic leukemia.[26,27]

Recently, two Dutch patients with a chronic lymphocytosis of cytotoxic-suppressor T cells, neutropenia, and recurrent infection were described in whom the circulating cells were positive for the Fc receptor

Table 3. Clinical Features of Chronic T-Cell Lymphocytosis

Case	Age and Sex	Spleno-megaly	Lymph-adenopathy	Major Clinical Problem	Survival	Granulocytes (per cu mm)	Hemoglobin (g/100 ml)	Platelets (per cu mm)	Marrow Lymphocytes	Reference
1.	M, 19	+	–	Infection	5 yr	200	13.4	215,000	58%	6
2.	M, 25	+	–	Infection	10 yr	800	8.1	176,000	53%	6
3.	M, 58	+	–	None	8 mo	2,100	13.6	124,000	22%	6
4.	M, 75	±	–	Back pain†	2 yr	1,200	10.0	330,000	61%	6
5.	M, 58	–	–	Infection	20 yr*	300	Normal	Normal	Increased	8
6.	F, 67	+	–	Infection	20 yr	300	Normal	Normal	Increased	8
7.	M, 41	–	–	None	2 yr	Normal	13.2	395,000	30%	7
8.	M, 55	+	–	Infection†	8 yr	300	13.0	288,000	30%	This report

*Death from infection.

†Rheumatoid factor present.

of IgG and exhibited ADCC.[11] A third case with similar cell surface markers, but without neutropenia or infection, has been reported from the United States.[10] Finally, four additional patients with neutropenia and Fc-receptor-positive T cells were encountered in an analysis of chronic lymphocytic leukemia,[9] and it is probable that some of the patients in the early report of Brouet *et al.* were also similar.[2] Salient clinical and laboratory features of the 7 cases in the literature and of our own patient are outlined in Tables 3 and 4.

Thus, there is a subset of patients with chronic T-cell lymphocytosis who present with neutropenia, frequently complicated by infection. In contrast to T-CLL, skin involvement and karyotype abnormalities are not seen, and red cell and platelet production are usually intact. Moderate splenomegaly is the rule, and bone marrow examination reveals only a moderate infiltration of small lymphocytes and, in most instances, an arrest of granulocyte production at the myelocyte level. The absence of progression of this disorder over periods of observation in excess of 20 yr is remarkable and contrasts sharply with T-CLL. The surface marker findings are characteristic; E-rosette-positive, Fc-receptor-positive, and a high level of ADCC without NK activity. Our own case and one other[28] were reactive with the monoclonal antibodies OKT5 and OKT8, which identify the cytotoxic-suppressor subset of T lymphocytes, and unreactive with OKT4, which detects inducer/helper T cells.

Although earlier investigators, reasoning from the parallel observation that most B-cell lymphocytosis in the adult is B-CLL, have concluded that the new disorder is probably a neoplasm,[9,11] the evidence is not compelling. Thus, the indolent course with little progression, the modest lymphocyte elevation, the maintenance of platelet and red cell production, and the failure to document a malignant process by pathologic examination of bone marrow and other tissues, all favor a benign process. If, indeed, the process is not malignant, it is unclear whether neutropenia and lymphocytosis spring from a common derangement, or whether one or the other is primary. Perhaps the most plausible pathogenesis, one that would provide an explanation for neutropenia in the absence of antineutrophil antibody, is suppression of granulocyte production by cytotoxic-suppressor T lymphocytes. However, while there is evidence for interaction between red cell precursors and regulatory lymphocytes,[29,30] such a mechanism for neutropenia is speculative.

Until convincing evidence of the nature of the disorder presented by these patients is available, it seems best to refer to them with the noncontroversial term "chronic T-cell lymphocytosis with neutropenia." Regardless of whether or not the disorder is neoplastic, it is important that cases be recognized

Table 4. Lymphocyte Characteristics in Chronic T-Cell Lymphocytosis

Case No.	Lymphocytes (per cu mm)	B Cells* (%)	E-Rosettes (%)	Acid† Phosphatase	Fc Receptor (%)	ADCC†	NK†	Monoclonal Antibody (%)† OKT4	OKT5	OKT8
1	11,300	2	71	+						
2	25,900	5	50	+	95					
3	6,000	5	66	+	53					
4	10,600	1	50	+	83					
5	6,900	4	67		51	+		–		+
6	14,000	0	87		58	+		–		+
7	29,000	1	93	+	57	+	–			
8	26,500	5	95	+	41	+	–	5	79	87

*B cells are expressed as the sum of cells with kappa and with lambda light chain on the surface, except for cases 5 and 6, which are expressed as the cells positive for Ia-like antigen.

†ADCC, antibody-dependent cytotoxicity; NK, natural killer activity; and + positive, – negative. The case numbers are the same as in Table 3.

because of the prognostic and therapeutic implications. Thus, these individuals have a far better outlook than those with T-CLL, and it would be inappropriate to employ the standard alkylating agent-prednisone therapy of B-CLL for a disorder in which the principal problem is neutropenia. The new condition can be suspected from the clinical characteristics, and a presumptive diagnosis made when routine cell surface markers reveal lymphocytes that are devoid of surface immunoglobulin, form spontaneous rosettes with sheep erythrocytes, and are positive for the Fc receptor of IgG. Commercially available monoclonal antibodies readily identify T-cell subsets and should facilitate recognition of the condition. Future investigation will establish whether or not this subset-specific proliferation is clonal, the exact place of the cell in lymphocyte development, and the mechanism of the neutropenia.

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