Clinical Spectrum of Clonal Proliferations of T-Large Granular Lymphocytes: A T-Cell Clonopathy of Undetermined Significance?

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We identified 68 patients with clonal T-large granular lymphocyte (T-LGL) proliferations who were seen at the Mayo Clinic between 1984 and 1992. Nineteen (28%) were asymptomatic at diagnosis, while the rest experienced fatigue (60%), B-symptoms (12%), and recurrent infections (15%). Associated comorbid conditions included rheumatoid arthritis (RA) in 26%. Severe anemia (hemoglobin [Hb] < 8g/dL) and neutopenia (absolute neutrophil count [ANC] <500/μL) were seen in 19% and 40% of patients, respectively. Immunophenotypic studies showed CD3$^+$, CD8$^+$ phenotype in the majority (72%). Twenty-one patients (31%) have required no therapy, and remain relatively stable with a median follow-up period of 50 months. Treatment was required at either diagnosis (36 patients) or at subsequent follow-up (11 patients). Initial response rates were similar in patients treated with cyclophosphamide (CTX) with or without prednisone (69%), or prednisone alone (73%). Overall, 61 patients (90%) are alive with a median follow-up of 44 months. Actuarial median survival of this entire cohort is 161 months. The presence of anemia or symptoms does not appear to correlate with the tumor burden. In patients requiring therapy, a lower ANC and the presence of B-symptoms/infection were independently associated with a significantly lower probability of achieving a molecular or hematologic complete remission (H-CR). Intermittent immunosuppressive therapy is effective in achieving durable responses in a number of patients. T-LGL proliferations are associated with a favorable prognosis and response to therapy. However, significant heterogeneity exists in clinical presentation and associated comorbid conditions. These disorders should be included in the differential diagnosis of patients with unexplained cytopenias, particularly in the setting of RA and other autoimmune disorders. Analogous to the situation with monoclonal gammopathies, a term such as T-cell clonopathy of undetermined significance (TCUS) may be more appropriate to describe these patients.

LARGE GRANULAR lymphocytes (LGL) are a morphologically distinct lymphoid subset comprising 10% to 15% of peripheral blood mononuclear cells.[1] LGL belong to one of two major lineages: CD3$^-$ LGL are natural killer (NK) cells, while CD3$^+$ LGL likely represent in vivo activated cytotoxic T cells.[2,3] It is now recognized that persistent expansions of LGL may be clonally derived from either of their normal counterparts, ie, CD3$^+$ LGL (T-LGL), or CD3$^-$ LGL (NK-LGL).[3,4] Confusion in the literature partly stems from the variety of terms used to describe this entity.[5,6] In 1990, the Morphologic, Immunologic, Cytogenetic (MIC) Cooperative study group recommended that LGL leukemia replace T-cell chronic lymphocytic leukemia (T-CLL) as a subgroup of chronic T-cell lymphoproliferative disorders.[7] While the clonal nature of CD3$^-$ LGL proliferations remains controversial,[8] clonality can easily be established in the more common T-LGL proliferations by detection of clonal rearrangement of the T-cell receptor (TCR). Recent reviews have suggested that clonal LGL proliferations be classified as either T-LGL leukemia (CD3$^+$) or NK-LGL leukemia (CD3$^-$), based on their origin.[3] However, controversy persists, particularly with reference to the use of the word leukemia, because clonality does not necessarily mean malignancy.[9] Recent studies have suggested that clonal LGL proliferations, particularly those of T-LGL, may be more common than once thought.[10] Even so, there is limited information regarding the natural history and clinical behavior of patients with clonal LGL proliferations. Most of the published literature is based on case reports or small series of patients with limited clinical follow-up,[10-15] thus, there are few guidelines for the treating clinician regarding management of these patients. We analyzed the clinical characteristics of patients with clonal proliferations of CD3$^+$ LGL seen at the Mayo Clinic from 1984 to 1992, and studied the clinical presentation, natural history, and prognostic features in this group of patients. To our knowledge, this is the largest single-institution experience with this disorder, and illustrates the clinical spectrum of clonal T-LGL proliferations.

MATERIALS AND METHODS

Patient population. Clonal proliferations of T-LGL were defined as an increase (>2 SD) in absolute or percent of LGL/T cells bearing NK-associated determinants in the peripheral blood together with detection of clonal rearrangement of TCR using Southern analysis for TCR beta and gamma. We identified 68 patients with clonal T-LGL proliferations seen at the Mayo Clinic between 1984 and 1992, after review of clinic records and molecular genetic studies for TCR rearrangement. A detailed retrospective analysis was performed on these patients. Most of these patients have been followed at our institution, often in cooperation with a local physician. There were no defined follow-up intervals for assessment of toxicity or response. However, most patients did return to Mayo at 6- to 12-month intervals, depending on their clinical course.

Response criteria. Hematologic complete remission (H-CR) was defined as the complete normalization of blood counts, including absolute and percentage numbers of LGLs. Molecular complete remission (M-CR) was defined as the disappearance of a clonal population of LGL, as detected by Southern assay in addition to documentation of H-CR. Hematologic partial remission (H-PR) was defined as a greater than 50% improvement in deviation of blood counts from normal without complete normalization of blood counts. In case of anemia, a greater than 50% reduction in transfusion requirements, or a greater than 2-g/dL increment in hemoglobin was felt to satisfy the criteria for H-PR. Minor response (MR) was defined as any clinical/symptomatic response not meeting the above criteria.

Hematopathology studies. A Wright-Giemsa–stained peripheral

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Submitted February 28, 1994; accepted May 10, 1994.

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0006-4971/94/8405-0025$3.00/0

blood smear for detection of LGLs was performed and reviewed. A differential percent LGL as a percentage of lymphocytes was obtained and absolute LGL count was calculated. Normal ranges for LGL in peripheral blood were (±2 SD) established in 100 normal controls as 15% ± 10% (absolute LGL count, 300 ± 200/μL). In the majority of patients, a bone marrow examination was also performed at diagnosis. Immunophenotypic studies on the peripheral blood were performed using immunocytochemical techniques with a panel of antibodies consisting of CD2, CD3, CD4, CD8, CD20, and CD57. Detailed flow cytometric analysis was performed at diagnosis only in a minority of patients.

TCR gene rearrangement studies. Molecular studies for detection of clonal rearrangement of TCR were performed using Southern analysis using probes for J beta 1, J beta 2 (TCR beta), and TCR gamma using previously described methods.[16] The extent of each clone was quantitated based on the relative intensity of the rearranged band compared with the germline band, and classified as major or minor clone.

Other laboratory studies. Other laboratory studies were performed at the discretion of the treating clinician. These included rheumatoid factor, antinuclear antibody, antiplatelet antibody, antigranulocyte antibody, lactate dehydrogenase (LDH), Coomb's test, serum chemistries, and imaging studies for assessment of splenomegaly. Antinuclear and antiplatelet antibody assays were performed using an immunofluorescence based assay.

Statistical analysis. Nonparametric analysis was performed using the Mann-Whitney test when two groups were compared. The Kruskall-Wallis test was used when three or more groups were compared. Univariate and multivariate analyses were performed using simple and multiple regressional analysis, respectively. Overall survival was calculated from the date of diagnosis of LGL leukemia. Actuarial survival was calculated using the method of Kaplan and Meier.[17]

RESULTS

We identified 68 patients with clonal T-LGL proliferations for this analysis. Patient characteristics are shown in Table 1. Median age for the entire cohort was 61 years (range, 23 to 85 years). Nineteen (28%) patients were asymptomatic at diagnosis. The most common symptoms at diagnosis were mild to moderate fatigue and constitutional symptoms, which were noted in 60% of patients (Table 2). Despite the frequency of severe neutropenia, recurrent or significant infections were seen in only 10 (15%) patients at diagnosis. Eight patients experienced B-symptoms (fever, night sweats, >10% weight loss), while excessive bleeding was noted in only four (6%) patients. Three patients had recurrent mouth sores in association with neutropenia (neutropenic angina). The median duration of symptoms before diagnosis was 9 months for all patients. Only five patients were diagnosed within 1 month of onset of symptoms, while 30 patients had symptoms lasting longer than 6 months.

Table 1. Patient Characteristics

Characteristics	Patients No.	Patients %
Male	34	50
Female	34	50
Age at diagnosis (yrs)		
≤40	7	10
40-60	26	38
60-80	32	47
>80	3	4

Table 2. Signs and Symptoms

	Patients No.	Patients %
Symptoms (n = 49)		
Constitutional	41	60
B-symptoms	8	12
Infections	10	15
Bleeding	4	6
Oral ulcers	3	4
Neuropathy	3	4
Physical examination		
Splenomegaly	13	19
Lymphadenopathy	2	3
Hepatomegaly	1	1
Neuropathy	3	4
Rash	1	1

Associated comorbid conditions for this cohort of patients are shown in Table 3. As is well recognized, rheumatoid arthritis (RA) was the most common associated condition, seen in 26% of patients. Hemolysis was seen in six patients, which was Coomb's positive in only one patient. Five patients had pure red blood cell aplasia (PRCA) at diagnosis, based on bone marrow histologic finding. Three patients had associated neuropathy, which included mononeuritis multiplex, mixed sensorimotor, and autonomic neuropathy in one patient each. Five patients (7%) had associated solid tumors, which included two patients with lung cancer and one patient each with testicular, colon, and prostate cancer. Associated endocrinopathy was seen in five patients, which included one patient with type I polyendocrinopathy, two with Hashimoto's thyroiditis, one with Grave's disease, and one with concurrent Cushing's disease and hyperparathyroidism. Other associated conditions seen in this cohort of patients included two patients with Sjögren's syndrome and one patient with vasculitic syndrome of unclear etiology. Five patients were noted to have associated myelodysplasia. The diagnosis of myelodysplasia was based on morphologic evidence of trilineage dysplasia on bone marrow examination, and presence of cytopenias. Cytogenetic studies were per-

Table 3. Comorbid Condition

Comorbid Condition (n = 45)	Patients* No.	Patients* %
Rheumatoid arthritis	18	26
Hemolysis	6	9
Red blood cell aplasia	5	7
Myelodysplastic syndrome	5	7
Neuropathy	3	4
Solid tumors	5	7
Endocrinopathy	5	7
MGUS	5	7

* Patients may have more than one comorbid condition.

Table 4. Hematologic Findings

Findings	Patients No.	Patients %
Anemia (Hb <11.5 g/dL)	35	51
Severe anemia (Hb <8 g/dL)	13	19
Oval macrocytosis (MCV >101 fL)	17	23
Thrombocytopenia (platelets $<150 \times 10^6/\mu L$)	14	20
Severe thrombocytopenia (platelets $<20 \times 10^6/\mu L$)	1	1
Neutropenia (ANC <1,500/μL)	50	74
Severe neutropenia (ANC <500/μL)	27	40
Absolute lymphocytosis (ALC >5,000/μL)	20	29
Bone marrow findings (n = 63)		
Nondiagnostic	35	55
Lymphoproliferative process	16	25
Myelodysplasia	5	7
PRCA	5	8
Maturational arrest	2	3
Cytogenetics (n = 61)		
Normal	57	91
Abnormal	5	9

formed in all five and were abnormal (both 5q−) in two patients.

Other than joint findings of RA, physical examination was abnormal in only 18 (26%) patients (Table 2). The most common abnormality was the presence of splenomegaly in 13 patients (19%). In five of these patients, only a spleen tip was palpable, and six of these patients had associated RA. None of the patients had massive splenomegaly. Lymphadenopathy was rare, noted in only two patients.

Table 4 summarizes the hematologic findings in these patients. The most remarkable abnormality was frequent and severe neutropenia. The median leukocyte count for the cohort was 4,500/μL (range, 400 to 37,000) and the median absolute neutrophil count (ANC) was 760/μL. Absolute neutropenia (ANC < 1,500/μL) was seen in 50 (74%) patients. Twenty-seven (40%) patients had severe neutropenia (ANC < 500/μL). The median hemoglobin (Hb) level was 11.2 g/dL (range, 3.6 to 15.1), and anemia (Hb < 11.5 g/dL) was seen in 35 patients. Severe (Hb < 8 g/dL) or transfusion-dependent anemia was seen in 13 (19%) patients. Oval macrocytosis with mean corpuscular volume (MCV) greater than 101 fL was seen in 17 (23%) patients. In all of these patients, serum B12 and folate determinations were within normal limits. Absolute lymphocytosis (ALC > 5,000/μL) was seen in only 20 patients. In contrast to anemia and neutropenia, thrombocytopenia (platelet count < 150,000/μL) was rare, seen in only 12 (17%) patients. Only one patient had severe thrombocytopenia (platelet count < 20,000/μL). Manual differential on the peripheral blood smear was performed on 64 patients to quantitate the percent LGL of all lymphocytes. The median absolute LGL count was 1,350/μL (range, 108 to 10,858/μL). Fifty-seven (89%) patients had a percentage LGL ≥25%. Thirteen patients had absolute LGL counts less than 500/μL. In four patients, both absolute and percentage LGL were normal, and an increase in cytotoxic suppressor T cells alone was noted. Bone marrow biopsy was performed at diagnosis in 63 patients, and findings were nondiagnostic in 35 (55%) patients. Some increase in lymphoid elements was noted in 37 (59%) patients, although definite evidence of a lymphoproliferative process in the marrow was noted in only 16 (25%) patients. The most common pattern of lymphoid involvement was interstitial and can, therefore, be easily missed. Five patients had morphologic evidence of PRCA in the marrow, while five patients (7%) had trilineage dysplasia, suggestive of myelodysplastic syndrome. Cytogenetics without lymphoid mitogens were performed in 62 patients and were normal in 57 (91%). Five patients with abnormal cytogenetics included two with 5q−, and one with trisomy 3, inversion 12, and Turner phenotype each.

Table 5 shows the serologic abnormalities noted in these patients. Rheumatoid factor was the most common abnormality, detected in 24 of the 39 patients (61%) tested. Eighteen of these patients had clinical evidence of RA as noted above. Antinuclear antibodies were positive in 22 (44%) of 50 patients tested. Abnormal Coomb's test was noted in only seven of 51 patients tested (14%) and, of these, only one had clinical evidence of hemolysis. Antiplatelet antibodies were tested in 12 patients with thrombocytopenia, and were positive in three (25%). Serum protein electrophoresis was performed in 63 patients, and showed polyclonal hyperglobulinemia in three patients (5%) and monoclonal gammopathy in five patients (8%). Monoclonal proteins in these patients were IgG kappa in three patients, and IgG lambda, IgM lambda in one patient each. Antineutrophil antibodies were tested in 24 patients with neutropenia, and were positive in five (20%). Elevated serum LDH was noted in 10 of 30 patients tested.

Immunophenotypic studies confirmed a T-cell phenotype in all patients ($CD2^+$, $CD3^+$). The most common phenotype was CD2, $CD3^+$, $CD4^-$, $CD8^+$ (T-suppressor) phenotype in 49 (72%) patients. In the remaining patients, the phenotype was not further characterized. As noted previously, detailed multiparameter flow cytometric analysis was performed in only nine patients at diagnosis. This may contribute to our inability to characterize the phenotype in these remaining patients. We were unable to identify any significant clinical differences in the $CD8^+$ cohort when compared with the entire group, with reference to clinical presentation or prognosis. By definition, all patients had evidence of clonal rearrangement of the TCR, as detected by Southern analysis. The rearranged band was felt to represent a major (33 patients) or minor (35 patients) clonal population, based on the relative intensities of the germline and the rearranged band.

Table 5. Serologic Findings

Findings	Patients No.	Patients %
Rheumatoid factor	24/39	61
Antinuclear antibody	22/50	44
Increased LDH	10/30	33
Positive Coomb's test	7/51	14
Antiplatelet antibody	3/12	25
Antineutrophil antibody	5/24	20
Monoclonal gammopathy	5/63	8
Polyclonal hyperglobulinemia	3/63	5

Table 6. Initial Therapy

		H-CR		M-CR		H-PR		MR		RR	
Therapy	No.	No.	%	No.	%	No.	%	No.	%	No.	%
Prednisone	15	4	26	—		7	46	—		11/15	73
CTX ± Pred	16	3	19	3	19	4	25	1	6	11/16	69
Splenectomy	8	1	12	—		3	37	1	12	5/8	62
MTX + Pred	2	1	50	1	50	—		—		2/2	100
Others	6	—		—		2	33	—		2/6	33
Total	47	9	19	4	9	16	34	2	4	31/47	66

Abbreviations: RR, response rate; Pred, prednisone. See text for definitions.

The median follow-up for all patients is 44 months (range, 7 to 161 months). Twenty-one (31%) patients have required no therapy, and remain relatively asymptomatic, with a median duration of follow-up of approximately 50 months (range, 8 to 131 months). Forty-seven patients (69%) have required therapy, either at initial presentation (36 patients), or during subsequent follow-up. Patients with asymptomatic cytopenias were generally followed until symptomatic progression. The most common indications for initiating therapy were symptomatic anemia (18 patients), B-symptoms (12 patients), or recurrent neutropenic infections (nine patients). The indications of therapy in the remaining eight patients were RA (two patients), symptomatic splenomegaly (four patients), immune thrombocytopenia (one patient), and neuropathy (one patient). No specific ANC cutoff was used as an indication for therapy. The median ANC in patients requiring therapy for recurrent infections was 670/μL, and was not significantly different from that in the entire cohort (760/μL). Among patients with symptomatic anemia requiring therapy, 13 were transfusion-dependent, while five were not. Initial therapy and responses are summarized in Table 6. Fifteen patients were treated with prednisone alone, while sixteen patients received oral cyclophosphamide (CTX) with or without prednisone. The doses were 40 to 60 mg/d of prednisone and 25 to 100 mg/d of CTX. Following an initial response to therapy, prednisone taper was attempted. The schedule for prednisone taper was as per the treating physician, and not on a defined protocol. Alternate-day maintainance regimens using low-dose prednisone regimens at doses ranging from 10 to 30 mg have been successful in some patients with durable responses. The median duration of initial therapy with either prednisone or CTX was 12 months. While the overall response rates were similar, CTX with or without prednisone was associated with a longer duration of response (34+ *v* 12 months), higher rate of M-CR (19% *v* 0%), and lower toxicity (18% *v* 40%) than prednisone alone. Treatment-related toxicity was predominantly related to long-term corticosteroids, and 20% of patients receiving prednisone alone experienced at least moderate toxicity. Six of 11 responses with CTX ± prednisone are currently unmaintained, while only three of 11 responses with prednisone have been durable. Splenectomy was performed in seven patients with moderate splenomegaly, and in one with immune thrombocytopenia. Two patients received methotrexate (MTX) and prednisone, predominantly dictated by the presence of concomitant active RA, and both responded to therapy. Other therapies included pyridoxine (two patients); cyclophosphamide, vincristine, and prednisone (CVP; two patients); chlorambucil (one patient); and danazol (one patient). Overall response to initial therapy was 66%, and median duration of response was 32 months. The data for response to initial therapy based on the indication for therapy are shown in Table 7. Patients treated for presence of B-symptoms as the indication for therapy had a lower proportion of complete remissions to initial therapy and, in these patients, a higher response rate to prednisone was noted. However, we would urge caution in the interpretation of such exploratory subset analyses in a relatively small data set. Twenty-seven patients have received further therapy for relapsed (n = 16) or refractory (n = 11) disease (Table 8). As expected, response to second-line therapy was slightly lower in patients refractory to first-line therapy (7/11, 63%) than in those relapsing after an initial response (13/16, 81%).

Response to second-line therapy was seen in three of five patients refractory to initial therapy with CTX (prednisone H-CR, H-PR; and granulocyte colony-stimulating factor [G-CSF], H-PR), and two of four patients refractory to prednisone (CTX, H-CR; and G-CSF, H-PR). The most common therapy in the setting of relapsed disease was oral CTX plus prednisone, which was effective in 13 (81%) patients, and nine (70%) of these responses are currently unmaintained. Other therapies that were effective at the time of first relapse were G-CSF (one patient, H-PR), MTX plus prednisone (one patient, H-CR), and cyclosporine plus high-dose corticosteroids (one patient, MR). Nine patients have received various third-line therapies, including fludarabine, G-CSF, and danazol. One of two patients treated with fludarabine for relapsed disease had a H-CR, while two of three patients receiving

Table 7. Initial Therapy (analysis by indication of therapy)

Indication	Therapy	No.	H-CR	M-CR	H-PR	MR	RR
Anemia	CTX ± Pred	9	3	2	2	1	8/9
(n = 18)	Pred	5	—	3	1	—	4/5
	Other*	4	—	—	1	—	1/4
B Symptoms	CTX ± Pred	5	—	1	1	—	2/5
(n = 12)	Pred	5	—	—	3	—	3/5
	Other	2	—	—	1	—	1/2
Infection	CTX ± Pred	2	—	—	1	—	1/2
(n = 9)	Pred	5	—	1	2	—	3/5
	Other	2	—	—	2	—	2/2

* Other, splenectomy, pyridoxine, CVP, danazol.

Table 8. Therapy at Relapse

		H-CR		M-CR		H-PR		MR		RR	
Therapy	No.	No.	%	No.	%	No.	%	No.	%	No.	%
CTX ± Pred	16	5		1		7		—		13/16	81
Pred	5	3		—		1		—		4/5	80
Others	6	1		—		1		1		3/6	50
Total	27	9	33	1	4	9	33	1	4	20/27	74

G-CSF responded to therapy (both H-PR). Sixty-one patients (90%) are currently alive, with a median follow-up of 44 months, with 18 patients (26%) being in unmaintained H-CR (four patients, M-CR). Actuarial median survival of the entire cohort is 161 months (Fig 1). Of seven patients who are dead, the cause of death was felt to be disease-related in five patients (four infectious complications, one bleeding). Other causes of death were respiratory failure from chronic obstructive lung disease, and lung cancer in one patient each. One additional patient has recently developed acute myeloid leukemia without significant prior alkylator exposure, and is still alive.

Detailed analysis of presenting clinical and laboratory features was performed to identify prognostic factors in these patients. We were unable to find any prognostic factors predictive of overall survival in this cohort. This may relate to the length of follow-up, and the number of events, rather than lack of any relevant prognostic factors. Of the patients requiring therapy, the probability of achieving a CR was inversely associated with the presence of severe neutropenia (ANC, 500/μL) (P = .03) and B-symptoms or infections (P = .04). On multivariate analysis, both of these features were independently associated with probability of CR. No such association was noted with presence of anemia (P = .46), ALC (P = .66), percentage LGL (P = .60), or presence of major/minor clone as detected by Southern analysis (P = .15). There was no correlation between presence/severity of anemia and ALC (P = .43), percentage LGL (P = .15), or presence of major/minor clone (P = .06). Similarly, no correlation was noted between presence of symptoms and ALC (P = .06), percentage LGL (P = .35), or detection of major/minor clone (P = .15). There was no correlation between need for therapy and percentage LGL (P = .49), ALC (P = .41), or detection of major/minor clone (P = .58) as markers for disease burden. Comparison of the cohorts requiring no therapy versus therapy at follow-up showed no differences with reference to ANC (P = .37), ALC (P = .31), percentage LGL (P = .9), platelet count (P = .61), or major/minor clone (P = .9). As expected, presence of anemia was significantly associated with the need for subsequent therapy (P = .005), because transfusion-dependent anemia was considered to be an indication for therapy.

DISCUSSION

Recent literature trends suggest increased awareness of LGL proliferative states.[3,10] It has been recognized that proliferations of LGL may be transient or chronic in nature. Chronic/persistent LGL proliferations may, in turn, be clonal or chronic reactive (nonclonal). While the clonal nature of chronic NK-LGL proliferations is controversial,[9] clonality can be easily established in the more common T-LGL proliferations by detection of clonal rearrangement of the TCR. While at least 129 total patients with T-LGL proliferations have been described in more than 40 reports,[3] data regarding natural history and clinical course of these patients are lim-

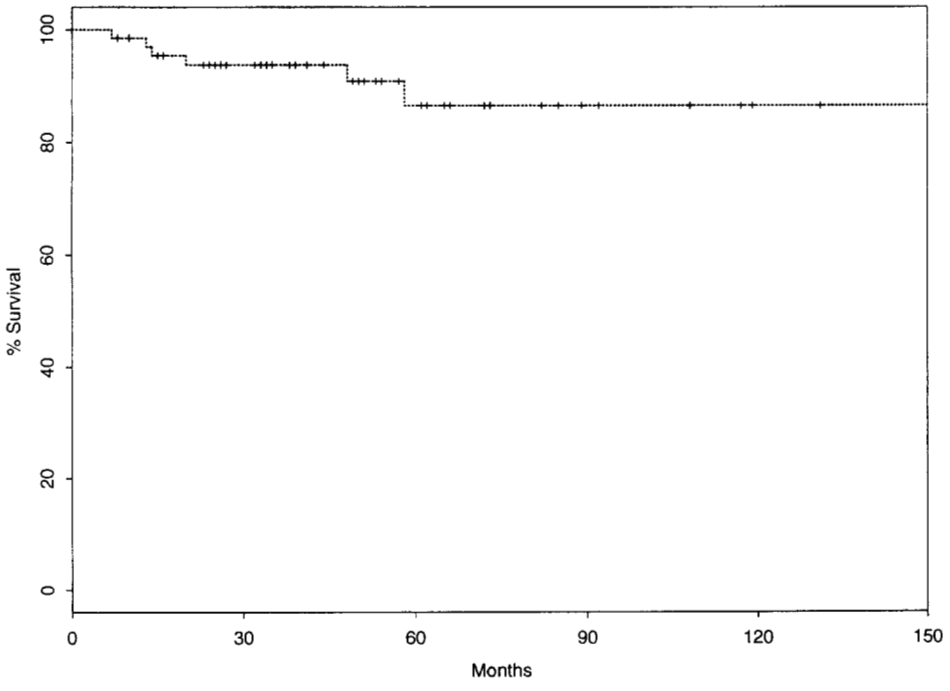

Fig 1. Kaplan-Meier plot showing actuarial overall survival for the entire cohort.

ited. The majority of these reports have included patients with both T- and NK-LGL proliferations, and TCR studies have been performed in only limited patients, making the existing data harder to interpret. To our knowledge, this series constitutes the largest single-institution survey to date on this group of patients.

LGL proliferations have been defined in previous reports as an increase in absolute number or percentage of LGL and/or phenotypically defined T cells bearing NK-associated determinants.[10-15] We have used a similar definition for this analysis but, in addition, have restricted this analysis to clonal proliferations as defined by TCR analysis. Because a number of patients may require therapy within 6 months of diagnosis, we did not require minimum duration of 6 months as a criteria. In addition, evidence of clonality serves to exclude reactive causes of LGL proliferation. Because a few patients with T-LGL alone may have significant leucopenia, an arbitrary cutoff value for absolute LGL count alone may not be appropriate. This analysis was restricted to clonal proliferations because these are more likely to be a homogenous and well-defined subset of patients.

Clinical features in this cohort bears several similarities to cases reported previously in the literature.[3,10-15] Median age of patients is generally in the sixth decade, with no sex predilection. Despite a possible referral bias toward symptomatic patients, up to a fourth of the patients were asymptomatic. More importantly, despite a high frequency of significant neutropenia, only a minority (15%) of patients had significant infections. T-LGL proliferations should, therefore, be included in the differential diagnosis of patients with unexplained neutropenia, and patients with suspected chronic idiopathic or benign neutropenia. Association of T-LGL proliferations with RA is well recognized.[18,19] These cases may thus resemble Felty's syndrome, with the clinical triad of RA, neutropenia, and splenomegaly. While previous studies have suggested that up to a third of patients with Felty's may have increased LGL,[18] recent studies suggest this may be greatly underestimated.[19] Similarly, the association with PRCA is well recognized, and numerous studies have shown direct inhibitory effects of LGL on erythropoiesis in vitro.[20]

Possible association with neuropathy noted in this cohort has not been previously noted. Most remarkable of these was a patient with mononeuritis multiplex, reported previously.[21] The exact etiology of neuropathy in these patients is unknown, and possible explanations include autoimmune etiology or direct effects related to LGL. Similarly, existence of endocrinopathies in these patients has not been previously noted. This may just be another manifestation of autoimmune phenomenon prevalent in these patients,[22] as typified by the patient with type I polyendocrinopathy. The presence of monoclonal gammopathy in a patient with T-LGL proliferation has been previously noted anecdotally,[22] and previous series have noted no such association. However, the presence of concurrent monoclonal gammopathy of undetermined significance (MGUS) in these patients is interesting, in light of the recent evidence of oligoclonal T-cell expansions in patients with myeloma.[23] Five patients in this series had clinical and morphologic features suggestive of associated myelodysplasia. The presence of trilineage dysplasia in the bone marrow of these patients does not necessarily imply another clonal process, particularly if the cytogenetics were normal. These patients characteristically had absence of abnormal ringed sideroblasts in the bone marrow, commonly seen in other patients with myelodysplastic syndrome. Nonetheless, awareness of this possible diagnostic pitfall is important because patients with unexplained cytopenias, macrocytic anemia, and nondiagnostic marrow may be mislabeled as having myelodysplastic syndrome.

The most common hematologic abnormality in these patients is neutropenia, which is often severe. The incidence of neutropenia is unknown because there may be some referral bias in most series reported to date, including ours. Similarly, the mechanism of neutropenia is unknown. While LGL are known to have multiple effects on hematopoietic system, in vitro studies have generally failed to demonstrate any suppressive effect of LGL on granulopoiesis. The lack of correlation between cytopenias and surrogate markers of disease burden, as noted in our study, suggests lymphokine mediated rather than myelophthisic process. Bone marrow biopsy is often nondiagnostic, and when abnormal, shows a subtle interstitial increase in lymphoid infiltrate. In contrast to some previous reports, we did not observe maturational arrest to be a common bone marrow histologic finding in these patients.[11]

Careful evaluation of peripheral smear is critical in establishing the diagnosis of LGL proliferations. Occasionally, however, immunophenotypic studies may show clonally expanded T cells with NK-associated phenotype and lacking LGL morphology.[18] One of the limitations of our study is the lack of detailed immunophenotypic data, because multiparameter flow cytometry was performed in only a minority of patients at diagnosis. While various phenotypic classifications have been suggested for these patients,[4,24] their clinical utility is not established. While we do recommend flow cytometry to be a part of routine clinical evaluation of these patients, attempts at complex phenotypic classifications should be withheld until their clinical relevance, particularly from the standpoint of impact on prognosis and management, is evident.

Our data suggest that clonal proliferations of T-LGL are associated with a relatively favorable outcome and response to therapy. We were unable to identify any features predictive of poorer survival, although a previous multicenter study identified fever at diagnosis, low percent HNK-1–positive cells, and low LGL count as associated with worse outcome.[15] We did observe lower ANC and B-symptoms to be associated with a lower probability of achieving a CR, and it is possible that with further follow-up this may translate into survival differences. In contrast to previous impression of nonprogressive indolent disease,[15] a number of patients in recent series have eventually required therapy.[3] Unfortunately, there appear to be no predictive features at presentation to identify the subset not requiring therapy. Since a number of patients may have a relatively indolent course, we have elected to defer therapy until progressive or symptomatic disease.

Optimal therapy for these patients is unknown. However,

immunosuppressive therapy with CTX and/or prednisone is effective as initial therapy. While both prednisone and CTX appear comparable with reference to response rates, the latter appears to be better tolerated, and is associated with more durable remission. To limit the alkylator exposure, we have generally limited the duration of therapy to 12 months. Such intermittent therapy seems effective in obtaining durable remissions in a number of patients. Several other case reports and small series have also confirmed the efficacy of single-agent chemotherapy in this setting.[13,16,20,25] While combination chemotherapy has been tried in a few cases with aggressive disease, it has generally not been successful.[14] Perhaps because of similarity with Felty's syndrome, splenectomy has been attempted in a number of patients with historically poor response and occasional deterioration.[26] In our experience, splenectomy was most effective only in patients with evidence of immune cytopenias or significant splenomegaly. Because other therapies may be more effective and better tolerated, splenectomy in these patients should probably be considered only as second- or third-line therapy. Our experience, and that of others, suggests that low-dose MTX may also be effective in these patients,[3] particularly those with concomitant RA. Experience regarding use of growth factors in these patients is limited. However, a number of cases showing response to G-CSF have been reported.[27] These agents may be particularly useful in patients with active infections related to neutropenia at diagnosis. Similarly, data regarding use of purine nucleoside analogs are evolving.[28] Our experience with fludarabine suggests that this may also be an active agent (T.E. Witzig, unpublished data). In view of increased awareness and possible increasing frequency of this entity, there is a need for prospective evaluation of various therapeutic options, possibly as a collaborative effort.

While the clonal nature of T-LGL proliferations can be easily established by gene rearrangement studies, clonality does not necessarily imply malignancy. While some patients may do well without therapy, others appear to have progressive disease, eventually requiring therapy for symptomatic disease. The situation thus appears analogous to that in the case of monoclonal gammopathies,[29] with an indefinite (albeit higher) risk of transformation to a malignant process. Recent reports of findings of persistent clonal expansions of $CD8^+$ T cells in apparently normal elderly individuals[30] and clonal V-alpha 12.1^+ T-cell expansions in patients with uncomplicated RA[31] indeed argues for the benign nature of at least some of these proliferations. Recent data from the Yorkshire Leukemia Group also suggest that such clonal expansions may be more frequent than once thought, often with otherwise normal blood counts.[10] Additionally, the relatively favorable outcome of patients in our series supports the above hypothesis. Thus, the true significance of these clonally expanded T-cell populations remains unclear. We, therefore, propose use of the term T-cell clonopathy of undetermined significance to describe these disorders and emphasize the similarities to monoclonal gammopathies. Further prospectively designed studies are warranted to fully understand the clinical spectrum of TCUS.

ACKNOWLEDGMENT

The authors thank J. Grill, Division of Biostatistics, for his assistance with survival analysis.

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