A Morphologic and Immunologic Study of the Large Granular Lymphocyte in Neutropenia With T Lymphocytosis


We report four patients with expansion of a unique population of lymphocytes that is consistently associated with neutropenia. Two patients also had rheumatoid arthritis and autoantibodies. The lymphocytes contained many cytoplasmic azurophilic granules, which possessed strong acid phosphatase activity. Multiple cytoplasmic parallel tubular arrays were observed ultrastructurally. These granular lymphocytes showed the T suppressor/cytotoxic cell phenotype (E+, OKT3+, OKT8+, OKT4-, OKM1-, OK11-) and exhibited antibody-dependent cell-mediated cytotoxic activity but little or no natural killer cytotoxicity.

A NUMBER OF REPORTS have described patients with lymphocytosis associated with severe neutropenia that was out of proportion to the degree of marrow lymphocytic infiltration. In reports with an adequate morphological description, the cells have the characteristics of large granular lymphocytes (LGL). The peripheral blood LGL in normal individuals appears to contain much of the antibody-dependent cell-mediated cytotoxic and natural killer cell activity. Most of these cells express Fc receptors and about half of them form heat labile sheep red cell rosettes.

Detailed surface marker analyses of highly purified peripheral blood LGL show significant heterogeneity, suggesting that there may be multiple subpopulations within the LGL fraction. In patients with LGL lymphocytosis and neutropenia, the LGL are much more homogeneous with regard to surface characteristics and function. They may represent expansion of a subpopulation of normal peripheral blood LGL and provide a good opportunity for detailed study of the characteristics of such a subpopulation. We have studied four patients with LGL lymphocytosis in whom the cell surface phenotype was that usually attributed to T suppressor/cytotoxic (Ts) cells. We present the clinical features of these patients and compare the morphological and immunologic properties of their cells to LGL and Ts cells of normal individuals.

MATERIALS AND METHODS

Peripheral Blood Mononuclear Cell Preparations

Peripheral blood mononuclear cells (PBMC) were isolated by Ficoll-Hypaque density gradient centrifugation. Additional cells (PBMs) from two patients were obtained by leukapheresis using a cell separator (IBM, Model 2997) and stored frozen at -80°C in 10% dimethylsulfoxide (DMSO). Thawed cells had a viability of between 80% and 90%.

Macrophages were depleted by adherence to plastic petri dishes or by the use of carbonyl iron. Lympocytes with the T helper cell phenotype (Th) were removed by reacting peripheral blood lymphocytes with OKT4 antibody and allowing the cells to adhere to plastic dishes coated with affinity-purified goat anti-mouse IgG antibody. The nonadherent cells, depleted of Th cells, were obtained for further study. Lymphocytes with the T suppressor/cytotoxic cell phenotype (Ts) were enriched by reacting the cells with OKT8 monoclonal antibody, adhering them to anti-mouse IgG antibody-coated plastic dishes, and recovering the adherent fraction. The cell populations so obtained were assayed for Ts cells as detailed below.

Surface Marker Analysis

Sheep erythrocyte rosette (E rosette) formation was assessed by incubating lymphoid cells with neuraminidase-treated sheep erythrocytes. Rosettes were counted after 2-hr incubation at 4°C. Cells bearing receptors for IgG Fc fragments (FcR) were assayed using rabbit IgG-sensitized ox erythrocytes. Surface immunoglobulin-bearing cells were detected using peroxidase-conjugated antibody to human immunoglobulins. T cell subsets were determined using an indirect immunoperoxidase technique, employing monoclonal antibodies against peripheral blood T cells (OKT3), the helper/inducer subset (OKT4), and the suppressor/cytotoxic subset (OKT8). In experiments where a cell population had been treated with a monoclonal antibody for enrichment or depletion purposes, assaying for other cell surface antigens was carried out using biotinylated monoclonal antibodies and peroxidase-conjugated avidin to avoid interference by the monoclonal antibody initially employed for cell separation. OKM1 and OK11 were used to detect an antigen found on myelomonocytic cells and the HLA-DR antigen, respectively, by an indirect immunofluorescence technique. In all experiments, cryopreserved peripheral blood mononuclear cells obtained from leukapheresis of a normal healthy person were used as control. Raji cells

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were used as a positive control in the determination of the HLA-DR antigen.

**Cytotoxicity Assays**

Antibody-dependent cell-mediated cytotoxicity (ADCC) and natural killer (NK) activity were measured by a cytotoxicity assay using ^51^Cr-labeled targets. Rabbit IgG-sensitized chicken erythrocytes were used as ADCC targets, and K562 cells were used in NK assays. The amount of ^51^Cr released into the supernatant was determined after 4 hr or 18 hr of incubation at 37°C in a 5% CO2/air mixture. The percent cytotoxicity was calculated according to the following formula:

\[
\text{Percent cytotoxicity} = \left( \frac{\text{cpm (test wells)} - \text{cpm (spontaneous release)}}{\text{cpm (maximum release)} - \text{cpm (spontaneous release)}} \right) \times 100
\]

Maximum release was determined by freeze-thawing the target cells. To eliminate the contribution of monocytes in the ADCC assays, monocytes were removed with carbonyl iron before testing. Peripheral blood mononuclear cells from normal donors and, in some experiments, cryopreserved human splenic lymphocytes were used as controls for the assays. Negative controls for the ADCC assays consisted of tests performed without added antibody or effector cells.

**Mitogen and Antigen Stimulation**

Stimulation with the mitogens phytohemagglutinin (PHA), concanavalin A (Con-A), and pokeweed mitogen (PWM) and the recall antigens SKSD, candida, and tetanus toxoid was performed as described previously. To assess the helper or suppressor activity, various concentrations of patient peripheral blood mononuclear cells (PBMs), unirradiated or irradiated with 1,000 rad or 3,000 rad, were added to PBMs from normal healthy donors stimulated by the various mitogens. The effect of the addition of patient PBMs on tritiated thymidine uptake by normal cells was then determined.

**Mixed Leukocyte Culture (MLC)**

In one-way MLC experiments, responder cells were mixed with irradiated (3,000 rad) stimulator cells in triplicate in a 96-well cluster tray. Each well contained 2.5 x 10^5 responder cells and an equal number of stimulator cells in 200 μl of RPMI 1640 with 10% pooled human AB serum. In two-way MLC experiments, neither population of cells was irradiated. The effect of patient cells on the MLC response was assayed by adding various concentrations of patient cells to MLC between two normal individuals. All cultures were incubated for 5 days at 37°C in 5% CO2 and harvested after a 4-hr pulse with tritiated thymidine.

**Phagocytosis Assay**

One hundred microliters of cells, at 10^4 cells/ml in RPMI 1640 with 5% fetal calf serum, was mixed with 10 μl of a 0.9 μm diameter latex bead suspension (Polysciences, Warrington, PA) at 10^5 beads/ml in a plastic culture tube (Falcon 2063). The tube was incubated for 45 min at 37°C in a 5% CO2/air mixture. The cells were then washed 3 times to remove free latex particles. Cytocentrifuged preparations were made, stained with Wright's stain, and examined for intracytoplasmic latex particles in LGL.

**Morphologic Examination**

Trephine and marrow aspiration biopsies were obtained from the posterior iliac crest and processed as described. Marrow smears were stained for acid phosphatase (ACP), alpha-naphthyl acetate esterase (ANAE), and periodic-acid Schiff activities. Cells for transmission electron microscopy were fixed in 1.25% glutaraldehyde in Millonig's buffer, postfixed in 1.25% osmium tetroxide, dehydrated in Millonig's buffer, and embedded in Maraglas. The thin sections stained with uranyl acetate and lead citrate.

**RESULTS**

Table 1 summarizes the relevant clinical features and laboratory findings of the four patients. All four patients had neutropenia and marrow lymphocytosis and a marked increase in peripheral blood LGL. Two patients had rheumatoid arthritis and autoantibodies. Serum immunoglobulin levels were either normal or high. Skin sepsis was the most frequent complication.

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<thead>
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<th>Clinical and Laboratory Findings</th>
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<td><strong>Sex/age</strong></td>
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<tr>
<td><strong>Splenomegaly</strong></td>
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<td><strong>Associated diseases</strong></td>
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<td>Chronic neutropenia, pyoderma gangrenosum</td>
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<td>Chronic neutropenia, rheumatoid arthritis</td>
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<td>261,000</td>
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<td>52</td>
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<tr>
<td><strong>Marrow granulopoiesis</strong></td>
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<td>Moderate hypocellularity arrested at myelocyte stage</td>
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<td><strong>Serum immunoglobulins</strong></td>
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and septicemia occurred in patient 2. Mild splenomegaly was detected clinically in the two patients with rheumatoid arthritis, whereas lymphadenopathy and hepatomegaly were absent. Patient 4 developed palpable cervical and groin lymph nodes later. There was no evidence of organ dysfunction due to lymphoid infiltration during a follow-up period of 1–4 yr. Patient 4 died after 4 yr due to intestinal infarction, the cause of which was not clear. Patient 2 showed a gradual decrease in his lymphocyte count, an increase in Th/Ts ratio, and a parallel improvement in his neutropenia and anemia over a 13-mo period. None of the other patients showed a spontaneous remission of either the lymphocytosis or the neutropenia. Treatment with prednisone in two patients also did not result in any objective improvement.

In all patients, the lymphocytes showed a similar morphology. They were medium-sized cells with moderate to abundant pale blue cytoplasm, containing many azurophilic granules (Fig. 1). The nucleus was usually round or oval with clumped chromatin and slightly eccentric. The cells were PAS negative and strongly acid phosphatase positive. Most were negative for ANAE activity. Electron microscopy showed that the LGL had many membrane-bound structures in their cytoplasm. These structures were identical to the parallel tubular arrays described by McKenna et al.2 (Fig. 2). Granules with an electron-dense core were rarely encountered.

Table 2 summarizes the surface marker studies on the peripheral blood lymphocytes of these four patients. These cells had a uniform phenotype: E+, OKT3+, OKT8+, OKT4−, and slg(−). Cells from three patients were tested for OKM1 and HLA-DR antigens, and most of the cells were negative. Cells bearing Fc receptors for IgG were increased in all patients tested. The LGL did not adhere to plastic surfaces and did not demonstrate phagocytic activity. Cells from all three patients tested showed ADCC activity that was not abolished by depletion of monocytes by plastic adherence or carbonyl iron (Fig. 3).
NK activity against K562 was weak or absent, even after 18 hr of culture (Fig. 4).

PBM from patients 2 and 3 did not respond to any of the three recall antigens. Whereas PBM from patient 3 responded to all 3 mitogens, cells from patient 2 responded only to PHA. The mitogenic responses were generally lower than those of normal controls (Table 3). To determine whether the response was due to the small number of OKT4+ cells present or to OKT8+ cells, an OKT4-depleted population and an OKT8-enriched population were assayed for PHA and Con-A stimulation. In patient 2, with populations of cells containing less than 1% T4+ cells and over 95% T8+ cells, the response to PHA was unchanged, whereas the response to Con-A was less than 2% of the normal control (Table 3). In patient 3, the OKT4-depleted and OKT8-enriched cells were unable to respond to either PHA or Con-A. Addition of plastic adherent cells to the cultures did not restore their responsiveness.

To investigate whether the LGL could function as suppressor cells in mitogenic responses, allogeneic cells were cultured with various concentrations of irradiated and nonirradiated LGL from patients 2 and 3 in the presence of PHA, Con-A, and PWM. Figure 5 shows that cells from patient 3 did not have any significant inhibitory effect on the mitogenic responses of allogeneic lymphocytes. Similar results were obtained with cells from patient 2 (data not shown). Increasing the concentration of irradiated LGL added to the culture resulted in a decrease in the proliferative response to mitogenic stimulation (Fig. 6). The same effect was observed even when irradiated autologous cells were used instead of cells from the patient, arguing against any specific suppressor effect exerted by the patient's cells.

Peripheral blood mononuclear cells from patients 2 and 3 responded in MLC (Table 4), though the responses were usually weaker than MLC between normal individuals. Most normal individuals could mount an MLC against patient's irradiated cells. To investigate whether unirradiated PBM could function as suppressor cells in MLC, a two-way MLC was set up between patient cells and normal donor cells and the results compared with those of a one-way MLC.
Tritiated thymidine uptake was significantly higher in the two-way MLC (Table 5). Various numbers of unirradiated PBM from patient 2 and 3 were also added to MLC between two normal individuals. No suppression of the MLC was observed (Fig. 7).

DISCUSSION

Large granular lymphocytes are present in the peripheral blood of normal individuals and their number increases with age. They constitute about 22% of the peripheral blood lymphocytes in persons over age 30.\(^1\) Most of the NK and ADCC activities reside in this population of cells.\(^2\) About 50% of LGL form sheep red cell rosettes at 4°C, and most of them bear Fc receptors.\(^7\) A recent study of the surface antigens on LGL reveals considerable heterogeneity.\(^8\) This may indicate that there are multiple subpopulations among the LGL or that a single population of cells can express various surface characteristics corresponding to different functional or developmental states. The identifi-
cation of patients with a proliferation of LGL provides an unparalleled opportunity to study these cells, as large quantities of relatively pure LGL may be obtained readily. Moreover, the LGL in these patients might represent an expansion of a normally minor or pure subset of cells which would be difficult to obtain in adequate quantity for study in normal individuals.

Surface marker studies showed that the LGL from our four patients were homogeneous with respect to their membrane antigens (E+, OKT3+, OKT8+, OKT4+, slg—). The LGL of three of the patients studied were also OKM1— and HLA-DR—. This homogeneity contrasts sharply with the heterogeneity of LGL isolated from the peripheral blood of normal individuals.

Furthermore, although ADCC activity was demonstrated, there was minimal or no NK activity against K562. The similarities of the morphological, surface marker, and functional characteristics indicate that all four patients had a proliferation of a similar population of cells, probably corresponding to a minor subset of LGL in normal peripheral blood. Whether this subset of LGL is really devoid of NK activity must await further testing with more NK targets.

Lymphocytes from a number of patients with similar clinicopathologic features have been examined by transmission electron microscopy. They have characteristic cytoplasmic structures, called parallel tubular units, which resemble those of normal LGL and HLA-DR—. This homogeneity contrasts sharply with the heterogeneity of LGL isolated from the peripheral blood of normal individuals.

Normal peripheral blood T lymphocytes bearing the OKT5 or OKT8 antigens are unable to respond to recall antigens. They respond poorly to PHA but normally to Con-A and contain the T suppressor/cytotoxic cell subset. The peripheral blood mononuclear cells from patients 2 and 3 were able to respond to PHA, and those from patient 3 to Con-A and PWM as well. Depletion of OKT4+ cells or enrichment of OKT8+ cells abolished the ability of cells from patient 3 to respond to all the mitogens. The response to PHA by patient 2 was retained. Because the populations of cells tested were markedly depleted of OKT4+ cells and enriched in OKT8+ cells, at least a fraction of the OKT8+ cells appeared to be able to respond to PHA. The pattern of response to mitogens of these cells was, however, quite different from that expected of OKT8+ peripheral blood T cells from normal individuals. Addition of plastic-adherent cells to the cultures did not restore the response to mitogens or antigens.

We cocultured irradiated (1,000 rad and 3,000 rad)
and unirradiated cells from patients 2 and 3 with allogeneic lymphocytes stimulated with mitogens and could not demonstrate any significant suppressor activity. Our findings differ from those of Callard et al., who observed suppression of an allogeneic cell PHA response by lymphocytes from both of their patients. One of the patients had red cell aplasia rather than neutropenia, and the cells from their patients bore HLA-DR antigens, suggesting that they represented either the proliferation of a different subset of cells or that the cells were activated in some way. Lymphocytes from most normal donors responded well to irradiated PBM from our patients in MLC, suggesting the absence of suppressor cells to MLC response. To exclude the possibility of inactivation of suppressors due to irradiation, unirradiated PBM from the patients were used in a two-way MLC with normal donor cells. Various concentrations of unirradiated PBM from the patients were also added to an MLC between two normal individuals. There was no suppression observed in either system.

Rumke et al., recently reported two patients with features very similar to ours. They could not demonstrate suppression of PWM-induced immunoglobulin synthesis by the cells of these patients. Similar results were obtained by Callard et al. Though in vitro studies of the effect of LGL on immunoglobulin synthesis were not performed in our patients, the normal or high serum immunoglobulin levels argue against any in vivo suppression of the B cell system. The T8+ LGL appear to be a unique population of cells with characteristics different from other OKT8+ suppressor T lymphocytes.

There is a close association between lymphocytosis of OKT8+ LGL and neutropenia. Bagby has demonstrated that depletion of marrow OKT3+, OKT8+ cells from two patients with neutropenia led to an increase in colony-forming units (CFU-C) in vitro. It is tempting to speculate that the LGL in our patients may play a role in the pathogenesis of their neutropenia. A study of patients similar to ours by Linch et al., however, fails to show a suppressive effect of their lymphocytes on CFU-C. Further studies on the relationship between LGL and neutropenia are necessary.

It remains uncertain whether the OKT8+ lymphocytosis seen in these patients is the result of a neoplastic process or an immunoregulatory disturbance. The disease does not have an aggressive course and massive visceral and marrow involvement like some reported cases of chronic T cell lymphocytic leukemia. We have seen four additional patients with neutropenia and a markedly decreased Th/Ts ratio (0.19–0.48). Their total lymphocyte counts ranged from 820 to 4,712/cu mm, but there was always a marked increase in the proportion of large granular lymphocytes. This lymphocytosis, thus, appeared to be one end of the spectrum of changes that may be observed. These patients also showed little or no clinical progression of their disease during the period of observation. Of particular importance is the observation that patient 2 spontaneously normalized his peripheral blood granulocyte count in association with a drop of his lymphocyte count and reversion of the Th/Ts ratio to normal. The course of the disease in this patient supports the concept that the disorder may represent an immunoregulatory disturbance and that the expansion of the LGL population may be either a reactive epiphrenomenon or perhaps is involved in the etiology of this neutropenia. Cases of T cell proliferation similar to ours have been reported by other authors as T chronic lymphocytic leukemia or T lymphoproliferative disorder.

Most of these authors, however, stated that the possibility of a reactive process or an immunoregulatory disturbance could not be excluded. Until obvious malignant features or a clonal enzymatic or chromosomal marker are documented, a diagnosis of a neoplastic process cannot be made with certainty. A descriptive term for this disorder, such as T cell lymphocytosis with neutropenia, as suggested by Aisenberg et al., may be more appropriate.

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A morphologic and immunologic study of the large granular lymphocyte in neutropenia with T lymphocytosis

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