Malignant Clonal Expansion of Large Granular Lymphocytes With a Leu-11+, Leu-7− Surface Phenotype: In Vitro Responsiveness of Malignant Cells to Recombinant Human Interleukin 2


A 14-year-old Japanese female with neutropenia showed malignant proliferation of the large granular lymphocytes (LGLs). These LGLs were E rosette+ and Fc(lgG) receptor+ and therefore are referred to as Tγ lymphocytes. They were also Leu-11+ and OKT11+; however, they were clearly negative for Leu-7, OKT3, OKT8, OKM1, and HNK-1 antigens as well as for terminal deoxynucleotidyl transferase activity. Karyotype analysis revealed 47, XXX. The LGLs showed no rearrangement of T cell receptor Cγ genes. The natural killer (NK) cell activity against K562 target cells was low, but was significantly augmented after transferase activity. Karyotype analysis revealed 47, XXX. The LGLs showed no rearrangement of T cell receptor Cγ genes. The natural killer (NK) cell activity against K562 target cells was low, but was significantly augmented after stimulation by recombinant human interleukin 2 (IL 2) in contrast to minimal NK boosting by recombinant human γ-interferon (γ-IFN). Such a unique responsive ability to lymphokines was quite similar to that noted in fetal and cord blood cells. These LGLs also demonstrated a considerable increase in antibody-dependent cell-mediated cytoxicity (ADCC) and lymphokine-activated killer (LAK) activity after a short incubation with IL 2. Although in a resting stage they showed no IL 2 receptor expression as examined by anti-Tac antibody, Tac antigen appeared after IL 2 treatment followed by a marked increase in γ-interferon antibody incorporation and a remarkable production of γ-IFN. To investigate the mechanism of neutropenia, in vitro IL 2-stimulated coculture studies of these cells with normal bone marrow cells were performed. Colony formation of myeloid progenitors (CFU-C) was significantly suppressed. In addition, the conditioned medium from IL 2-stimulated LGLs indicated a remarkable suppression of CFU-C. These results suggest that these LGLs with a Leu-11+, Leu-7− surface phenotype might belong to a unique subset of pre-NK cells that are functionally and phenotypically similar to those represented at any early stage of human ontogeny and that they strongly express Tac antigen under the influence of IL 2 administration, followed by remarkable cell proliferation and γ-IFN production.

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CASE REPORT

On Aug 19, 1985, a 14-year-old Japanese female was admitted to the Japanese Red Cross Hospital in Kanazawa because of a high fever that had lasted ten days. She was physically well developed for her age. Family history was noncontributory. The examination revealed hepatomegaly 4 cm below the right costal margin and splenomegaly 1 cm below the left costal margin. Laboratory results disclosed the following values: hemoglobin (Hb), 10.0 g/dL; RBC, 3,500,000/µL; and WBC, 11,400/µL with 1% granulocytes and 99% lymphocytes. The platelet count was 90,000/µL. Serum chemistry levels were as follows: SGOT, 95 IU/L; SGPT, 46 IU/L; and lactic dehydrogenase (LDH), 439 IU/L. During her hospitalization, the high fever continued despite antibiotic treatment and a moderate dose of prednisone.

On Sept 4, the patient was transferred to the Kanazawa University Hospital for assessment and treatment. At that time, hepatomegaly measured 4.5 cm and splenomegaly 9.5 cm. No significant lymph node swelling was observed. A complete blood count showed the following values: Hb, 11.5 g/dL; RBC, 4,270,000/µL; and WBC...
14,300/μL with 5% granulocytes and 95% lymphocytes. The platelet count was 119,000/μL. A May-Grünwald-Giemsa-(MGG)-stained peripheral blood smear demonstrated a predominance of large lymphocytes (84%) 15 to 20 μm in diameter, with abundant cytoplasm and sparse intracytoplasmic granules (Fig 1A). Bone marrow aspiration also revealed increased numbers of abnormal large granular lymphocytes (LGLs) with 42% nucleated cells. Blood chemistries showed the following data: total bilirubin, 0.60 mg/dL; SGOT, 71 IU/L; SGPT, 28 IU/L; LDH, 695 IU/L; γ-glutamyl transpeptidase (γ-GTP), 195 IU/L; BUN, 14 mg/dL; creatinine, 0.9 mg/dL; and uric acid, 4.5 mg/dL. Albumin and cholinesterase levels were normal. Tests for rheumatoid arthritis and lupus cryoglobulinemia were also negative. The Coombs' test was negative. Polyclonal hypergammaglobulinemia was demonstrated (IgG, 2,082 mg/dL; IgA, 626 mg/dL; and IgM 267 mg/dL). The C3c and C4 levels were 121 mg/dL and 69 mg/dL, respectively. Antibodies to Epstein-Barr virus (EBV) as detected by indirect immunofluorescence techniques showed the following titers: EBV capsid antigen (VCA) IgG, 320; IgM, 10; early antigen (EA), 80; and EB nuclear antigen (EBNA), 160. The titer of antibody to cytomegalovirus was within the normal range. The tests for hepatitis B surface antigen (HBSAg) and anti-HBSAg antibodies were negative. Although treatment with prednisone (60 mg/d) continued and a pulse therapy of methyl prednisone (1,000 mg/d × 3) was also given after informed consent, the high fever persisted. The WBC count gradually increased to 126,000/μL. (LGLs, 80%) at the end of September. The LDH level also increased to 16,216 IU/L. A second bone marrow aspiration after informed consent showed a further increase in the numbers of abnormal LGLs (79%). Blood levels of γ-IFN were checked twice in the clinical course by radioimmunoassay. The levels were 27.2 U/mL on Sept 6 and 5.3 U/mL on October 1, both of which were markedly increased as compared with normal controls (less than 0.2 U/mL). However, the presence of IL 2 in plasma could not be identified by a sensitive radioimmunoassay method using a monoclonal antibody against human IL 2, L6. L6 (kindly performed by Dr Ide, Shionogi & Co. Ltd, Osaka, Japan). At the beginning of Oct, a remarkable swelling of the bilateral cervical lymph nodes was noted. Full doses of anticancer drugs (vincristine, doxorubicin, cyclophosphamide, and cytosine arabinoside) were started, but the WBC count further increased to 200,000/μL. (LGLs, 90%). Chromosome analysis of the LGLs using a G-banding technique revealed an abnormal 47, XXX pattern. When Southern blot techniques were used, the LGLs were not found to rearrange the T cell receptor Cβ genes. The patient died on Oct 12 of a hemorrhagic tendency caused by disseminated intravascular coagulation. Autopsy was refused.

**MATERIALS AND METHODS**

**Surface markers.** Peripheral blood mononuclear cells (PBMCs) from the patient and normal donors who had given informed consent were isolated by Lymphoprep (Nygaard and Co, Oslo) gradient centrifugation as described elsewhere. The expression of receptors for SRBCs (ER) and Fc receptors for IgG (Fc IgGRI) were determined by the rosetting method using either SRBCs or chicken RBCs sensitized with rabbit IgG antibody against chicken RBCs. PBMCs were studied with a panel of monoclonal antibodies: OKT3 (Ortho Diagnostic Systems, Raritan, NJ), which reacts with mature T cells; OKT11 (Ortho), which binds to SRBC receptors; OKT4 and OKT8 (Ortho), which selectively bind to lymphocyte subsets containing cells with helper and suppressor/cytotoxic activity, respectively; OKM1 (Ortho), which identifies an antigen expressed on cells from the myelomonocytic lineage and some LGLs; OKT10 (Ortho), which reacts with the majority of thymocytes and activated T cells and has been reported to recognize some LGLs; Anti-HLA-DR (Becton Dickinson Monoclonal Center, Inc, Mountain View, Calif), which reacts with Ia-like antigens; Leu-7 (Becton Dickinson), which binds to LGLs and about 20% of PBMCs; NKH-1 (Coulter Immunology, Hialeah, Fla), which identifies NK cells but not neutrophils; and Leu-11 (Becton Dickinson), which reacts with the Fc IgGRI of NK cells and neutrophils. We also used anti- Tac antibody (provided by Dr Waldmann, National Cancer Institute, Bethesda, Md), which recognizes an IL 2 receptor–related antigen. Monoclonal antibodies were used in a direct or an indirect immunofluorescence technique, and the surface markers were analyzed by using a fluorescence-activated cell analyzer (Ortho Spectrum III, Ortho Diagnostics, Westwood, Mass).

**Recombinant human IL 2.** IL 2 was a product of S.A. Biogen, Geneva. This IL 2 preparation had a titer of 22 × 10^3 U/mL with a
specific activity of $1.15 \times 10^4$ U/mg of protein (one unit being the amount of IL 2 giving 50% of the maximal $^3H$-thymidine $[^3H]$-Tdr incorporation into the NK-7 clone assay as described by Suzuki et al.

One such unit is equivalent to 4.5 units of a reference Jurkat IL 2 standard provided by the Biological Response Modifiers Program of the National Cancer Institute.

**Response to lymphokines.** Proliferative responses of PBMCs from the patient and normal donors to phytohemagglutinin (PHA-P, 0.1%, Difco, Laboratories, Detroit) and recombinant IL 2 (25 U/mL) were assessed in triplicate by $[^3H]$-Tdr incorporation as previously described. In brief, various concentrations of effector cells were suspended in RPMI 1640 medium (GIBCO, Grand Island, NY) containing 300 ug/mL L-glutamine, 200 U/mL penicillin, 10 ug/mL gentamicin, 25 mmol/L HEPES buffer (GIBCO), and 5% fetal bovine serum (FBS, M.A. Bioproducts,Walkersville, Md). In some experiments, to study the role of $\gamma$-IFN (provided by Shionogi & Co, Ltd) and IL 2 in the augmentation of NK cell activity, cells were pretreated with 25 U/mL IL 2 or 1,000 U/mL $\gamma$-IFN for 18 hours prior to assay. Cells were added to triplicate cultures of $10^4$ $^{35}Cl$-labeled K562 cells in 0.2 mL vol in V-bottomed microtiter plates (Nunk, Kamstrup, Denmark). After centrifugation at 25 g for eight minutes, the cells were incubated for four hours at 37 $^\circ$C in a humidified 5% CO2 atmosphere. The supernatants were harvested and stored at $-20^\circ$C until used. To examine the effects of the supernatants on CFU-C, graded amounts of the supernatants were added to the CFU-C assay system just described. To determine the category of IFN to which the activity of the supernatants was attributable, we performed a neutralization study using an anti-$\gamma$-IFN antibody and a specific antiserum to human $\alpha$-IFN (Interferon Sciences, Inc, New Brunswick, NJ). IL 2-stimulated cell supernatants were treated with an excess of each antibody at 37 $^\circ$C for one hour prior to CFU-C assay.

**RESULTS**

**Morphologic characteristics.** MGG-stained smears showed that the morphologic characteristics of the proliferative cells from this patient were quite similar to LGLs. They looked relatively large (15 to 20 $\mu$m in diameter), with a high cytoplasm-to-nucleus ratio and sparse azurophilic granules in the cytoplasm (Fig 1A). Nuclei were round, and nucleoli were rarely observed. Double-nucleated cells were noted rarely. An electron microscopic analysis revealed prominent cytoplasmic granulogenesis and cytoplasmic inclusion bodies. Parallel tubular arrays that were characteristic of normal human $T\gamma$ lymphocytes were also indicated. Cytochemical analysis revealed that they were all negative for esterase, peroxidase, acid phosphatase, terminal deoxynucleotidyl transferase, and asialo GM1 activities.

**Surface markers.** Immunologic analysis using a panel of monoclonal antibodies showed that these LGLs had receptors for SRBCs and Fc receptors for IgG that were identified by rosetting with both SRBCs and chicken RBCs (Fig 1B). In addition, these cells had only a OKT11 antigen among a series of $T$ cell–related antigens, OKT11 and Leu-11 antigens as NK cell–related antigens, and OKT10 and IgA-like antigens as activated $T$ cell–related antigens. However, of interest, there was no expression of Leu-7, OKT3, OKT8, or OKM1 antigen on the surface of the LGLs (Fig 2A and B).

**NK cell activity.** Figure 3 shows NK cell activities in the patient's LGLs against K562 target cells as compared with those in sorted Leu-11+ cells from adult PBMCs and cord blood cells. The spontaneous NK cell activity of the patient's LGLs was much lower than that in the adult control, but was significantly augmented after treatment with IL 2 to almost the same level as that in adult Leu-11+ cells at various effector/target cell ratios. In contrast, after stimulation by $\gamma$-IFN, no marked increase of the NK activity was demonstrated. Such a characteristic ability of different responsiveness to these lymphokines was quite similar to that shown in the control cord blood Leu-11+ cells. The LGLs were tested...
Fig 2. (A, B) Surface markers of the patient's LGLs.

for their ability to bind and kill K562 target cells in a single-cell cytotoxicity assay in agarose (Fig 1C). About 25% of the patient's LGLs had a binding capability to K562 target cells, and the relative proportion of target-bound cells was increased to approximately 43% after treatment with IL 2. The proportion of dead cells among these conjugates was also increased from 28% of the patient's LGLs to 75% after IL 2 stimulation.

**LAK activity.** LAK activity of these LGLs was assessed by using four different kinds of cell lines as NK-resistant tumor cells as shown in Fig 4. A remarkable enhancement of IL 2–induced LAK activities was exhibited at various effector/target ratios, suggesting that these LGLs have a wide spectrum of target specificity.

**ADCC.** ADCC of the patient's LGLs was compared with that of normal adult PBMCs at different effector/target ratios. The patient's LGLs had approximately two- to threefold higher levels of ADCC (80%) than the control adult PBMCs (30%) at an effector/target ratio of 20/1.

**Response to lymphokines and IFN production.** Proliferative response of the patient's LGLs to PHA-P and IL 2 was measured by ³H-TdR incorporation. As compared with the control adult PBMCs, the patient's LGLs showed a remarkable increase of ³H-TdR uptake by the stimulation of IL 2, whereas PHA-P was less effective on the patient's LGLs than the adult PBMCs (Table 1). In addition, a significant increase of IFN production was demonstrated, especially by the influence of IL 2 administration (Table 2). Characterization of IFN produced by the LGLs was examined by heat and pH stability tests. A marked reduction of IFN titers after the treatment with both hot water (56 °C) and acid solution (pH 2) was shown, suggesting that the γ type of IFN was contained in the supernatants of the PHA-P– and IL 2–stimulated cultured media. In concordance with the increase of γ-IFN activity in the supernatants, intracellular γ-IFN produced by IL 2 was clearly demonstrated by an immunohistochemical technique using a monoclonal anti–γ-IFN antibody (Fig 1D). IL 2–containing cells were not identified immunohistochemically even after exogenous IL 2 stimulation.

**Tac antigen expression.** Figure 5 shows the ability of Tac antigen expression on the patient's LGLs after IL 2 stimulation. They expressed marginal amounts of Tac antigen on their surfaces in a resting stage, and the proportion of
 Tac+ cells was not increased by PHA-P stimulation. However, when these LGLs were cultured with IL 2, they exhibited a rapid (even within 12 hours of incubation) and significant augmentation of the expression of Tac antigen in contrast to control adult PBMCs. γ-IFN induced no significant increase in Tac antigen expression on the patient’s LGLs.

**CFU-C assay.** Severe neutropenia was shown throughout the clinical course of this patient. Thus, we next studied suppressive effects of the patient’s LGLs on normal bone marrow CFU-C formation. The patient’s bone marrow (LGLs, 42%) showed a significantly decreased number of CFU-C (29/10^3 BMMCs) as compared with normal controls (131 ± 46 [mean ± SD] /10^3 BMMCs). No suppressive effect of LGLs on normal bone marrow CFU-C formation without stimulation of IL 2 was shown, whereas a remarkable suppressive effect on CFU-C was demonstrated under the influence of IL 2 administration (Table 3). Furthermore, the IL 2-induced cell supernatants exhibited a dose-dependent suppressive effect on CFU-C formation (Table 4). As shown in Table 5, the suppressive activity of the supernatants was markedly abolished with anti-γ-IFN, but not anti-α-IFN, antibody treatment, suggesting that γ-IFN could be greatly involved in the suppression of granulopoiesis.

**DISCUSSION**

In the present study, we described a patient with abnormal clonal expansion of LGLs and neutropenia. As these proliferative cells demonstrated ER+ and Fc(IgG)R+ phenotypes, they were referred to as T'y lymphocytes. Recently, a number of cases of abnormal proliferation of Tγ lymphocytes (Tγ lymphoproliferative diseases, Tγ-LPD) have been reported10-14 (for review see refs 5, 32, and 35), and most cases were not aggressive, although the majority of the patients had recurrent bacterial infections requiring antibiotic therapy. In contrast, our patients showed a very rapid expansion of Tγ lymphocytes. The patient’s Tγ lymphocytes were similar to normal LGLs although they were much larger in size (more than 15 μm in diameter) and scanty in granules. They were positive for OKT11 and Leu-11 antigens. However, interestingly, they were negative for Leu-7, OKT3, and OKT8 antigens, which were expressed in most of the previously reported cases with Tγ-LPD. Such unique morphologic and phenotypic properties allows us to consider the lineage of these LGLs from which they abnormally expanded. Abo et al17 recently characterized three subpopulations of human LGLs from blood and lymphoid tissues using HNK-1 (Leu-7) and Leu-11 monoclonal antibodies. Each subpopulation (HNK-1+ Leu-11−, HNK-1− Leu-11+ and HNK-1− Leu-11−) had a different NK cell activity. Among these three subsets, the HNK-1+ subset lacking the Leu-11 appeared to be the most immature form of LGLs and had minimal NK cell activity, whereas the HNK-1− Leu-11−...
subpopulation had a higher level of NK activity and was considered a more mature subset. Based on the expressions of Leu-11 and Leu-7 (HNK-1) antigens, the LGLs from our patient (Leu-11+, Leu-7−) seem to belong to a rather mature subset of NK cells. This speculation, however, is questionable because the patient’s LGLs do not have sufficient spontaneous NK cell activity nor do they express OKT3 or OKT8 antigens, which have been reported to be expressed in mature NK cells.

Functional analysis of the responsiveness to IL 2 and γ-IFN is another useful method for studying the lineage of the LGLs. The NK cell activity of the patient’s LGLs against K562 target cells was low but was significantly augmented by the stimulation of IL 2 in contrast to γ-IFN. In previous studies, Ueno et al. tested the ontogenic changes in the lymphokine responsiveness of human NK cells by using PBMCs from fetuses, premature infants, and full-term neonates as compared with adults. PBMCs from fetuses at early gestational ages showed minimal NK cell activity even after pretreatment with γ-IFN. In contrast, IL 2 induced a marked NK cell activity. On the other hand, PBMCs from full-term neonates showed a low level of NK cell activity but a considerable NK boosting by both γ-IFN and IL 2. From these data, ontogenic pre-NK cells from very early stages of human life were suggested to be divided into γ-IFN-sensitive and IL 2-sensitive subpopulations. Although it is not known whether these cell subsets belong to different cell lineages or different maturational stages of the same cell lineage, the patient’s LGLs, which showed IL 2 but not γ-IFN sensitivity, might belong to a subset similar to fetal pre-NK cells. Furthermore, although Leu-7+ cells were negligible in cord blood, the relative proportion of Leu-11+ cells was shown to be equal to that in adult PBMCs by Seki et al. They selected for a Leu-11+ cell population by a cell sorting technique and demonstrated that the spontaneous NK cell activity of Leu-11+ cells in cord blood was low but was significantly augmented under the influence of IL 2 administration. The abnormal LGLs from the patient, which have a similar phenotype to the NK cells in cord blood (Leu-11+ Leu-7−), also had a similar responsiveness to the lymphokines. This fact strongly suggests that the patient’s LGLs may have originated from the pre-NK cell subset during maturational stages.

Table 3. Effects of the Patient’s LGLs on CFU-C Growth

<table>
<thead>
<tr>
<th>Bone Marrow Cells (i/mL)</th>
<th>Effector Cells (i/mL)</th>
<th>IL 2 (25 U/mL)</th>
<th>CFU-C (i/10⁵ Cells)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x 10⁶</td>
<td>−</td>
<td>−</td>
<td>254</td>
<td>100</td>
</tr>
<tr>
<td>1 x 10⁵</td>
<td>−</td>
<td>+</td>
<td>262</td>
<td>103</td>
</tr>
<tr>
<td>Patient’s LGLs</td>
<td>1 x 10⁶</td>
<td>1 x 10⁶</td>
<td>262</td>
<td>103</td>
</tr>
<tr>
<td>1 x 10⁵</td>
<td>2 x 10⁵</td>
<td>−</td>
<td>324</td>
<td>128</td>
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<tr>
<td>1 x 10⁵</td>
<td>1 x 10⁵</td>
<td>+</td>
<td>57</td>
<td>22.4</td>
</tr>
<tr>
<td>1 x 10⁵</td>
<td>2 x 10⁵</td>
<td>+</td>
<td>43</td>
<td>16.9</td>
</tr>
</tbody>
</table>

Control PBMCs

| 1 x 10⁵                   | 1 x 10⁶               | −             | 327                 | 129        |
| 1 x 10⁵                   | 2 x 10⁵               | −             | 335                 | 132        |
| 1 x 10⁵                   | 1 x 10⁵               | +             | 254                 | 100        |
| 1 x 10⁵                   | 2 x 10⁵               | +             | 274                 | 108        |

The patient’s LGLs were mixed with normal BMMCs and preincubated for 18 hours at 37 °C with or without IL 2 (25 U/mL). After incubation, the cell mixture was plated in 0.35% agar for the CFU-C assay. The number of colonies are expressed as mean values in triplicate cultures. Data from one of three similar experiments are presented.

Table 4. Effects of IL 2-Stimulated LGL Supernatants on CFU-C Growth

<table>
<thead>
<tr>
<th>Colony-Stimulating Factor (Mo-CM) Mixed With</th>
<th>CFU-C</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>502</td>
</tr>
<tr>
<td>Medium with IL 2 (10%)</td>
<td>565</td>
</tr>
<tr>
<td>Supernatant 2.5%</td>
<td>167</td>
</tr>
<tr>
<td>5%</td>
<td>163</td>
</tr>
<tr>
<td>10%</td>
<td>129</td>
</tr>
<tr>
<td>15%</td>
<td>105</td>
</tr>
</tbody>
</table>

IL 2-stimulated LGL supernatants were collected after 48 hours of incubation at 37 °C. Graded amounts of the supernatants indicated were added to the CFU-C assay system using Mo-CM as a source of colony-stimulating factor as described in Materials and Methods. The numbers of colonies are expressed as mean values in triplicate cultures. Data from one of three similar experiments are presented.
T'y-LPD. Some investigators suggested that NK cells and NK-like killing activity was noted by Yodoi et al who established a YT cell subset and a strong expression of Tac antigen after stimulation of CFU-C with IL 2.

Pathologic clonal proliferation of the LGLs in this patient was also suggested by the karyotype analysis that showed an abnormal 47, XXX pattern. However, these LGLs were not found to rearrange the T cell receptor Cβ genes with Southern blot techniques (data not shown). The heterogeneity of T'y-LPD in the organization of the Cβ genes has been shown by Rambaldi et al who demonstrated that the more frequently encountered cases of T3 + T'y-LPD showed clonal rearrangements (T3 + Cβ + T'y-LPD), whereas the less common T3 - T'y-LPD exhibit the germline Cβ configuration (T3 - Cβ - T'y-LPD). Our case (T3 - Cβ - ) confirms these findings.

Other unique functional capabilities caused by stimulation of the IL 2 of these LGLs were strong and rapid expression of Tac antigen followed by a marked cellular proliferation and a significantly increased production of γ-IFN. Although exogenous γ-IFN did not induce the expression of Tac antigen and there was no detectable IL 2 activity in cultured-conditioned medium or in blood, it is likely that the patient's LGLs do express Tac antigen and enhance their own abnormal growth via Tac antigen induction. A similar observation was made by Yodoi et al who established a YT cell line derived from a boy with thymic lymphoma. These cells had NK cell surface phenotypes and NK-like killing activity. YT cells, which marginally expressed Tac antigen, markedly increased the expression of Tac antigen after incubation with IL 2-containing conditioned medium from peripheral blood leukocytes or spleen cells, both of which were stimulated with PHA.

This patient had severe granulocytopenia (less than 500/μL) as did approximately half (46%) of the patients with activity. YT cells, which marginally expressed Tac antigen, cells had NK cell surface phenotypes and NK-like killing activity was noted by Yodoi et al who established a YT cell subset and a strong expression of Tac antigen after stimulation of CFU-C with IL 2.

CFU-C were noted to be more responsive to γ-IFN than other categories of IFNs such as α- (leukocyte) and β- (fibroblast) IFNs. Indeed, spontaneous or mitogen-stimulated γ-IFN production has been demonstrated by lymphocytes from several patients with T'y-LPD. The disease presented in this paper may be termed acute T'y-LPD because of the rapid clonal expansion of the T'y lymphocytes. We suggest that such an acute clinical course is related to the unique surface phenotype for a premature NK cell subset and a strong expression of Tac antigen after stimulation of IL 2. Although the lineage of the NK cells in this case still remains to be elucidated, such a leukemialike proliferation of LGLs serves as an experimental model for studying the ontogeny and function of LGLs in both immunoregulation and hematopoiesis. Finally, functional analysis for response to lymphokines as well as immunohistochemical studies of the intracellular expression of γ-IFN and IL 2 may be useful for examining the cell lineage and functional characteristics of abnormal proliferative lymphocytes.

ACKNOWLEDGMENT

We would like to thank Dr Waldmann (National Cancer Institute, Bethesda, Md) for providing the anti-Tac monoclonal antibody, Dr Le (New York University Medical Center, NY) for the anti-γ-IFN monoclonal antibody, and Dr Golde (UCLA, Los Angeles) for the Mo-CM as a source of colony-stimulating factor. We also thank Dr Kita (Mie University, Japan) for the analysis for T cell receptor Cβ genes.

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Malignant clonal expansion of large granular lymphocytes with a Leu-11+, Leu-7- surface phenotype: in vitro responsiveness of malignant cells to recombinant human interleukin 2