Chronic Natural Killer Cell Lymphocytosis: A Descriptive Clinical Study

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We review the clinical manifestations and long-term outlook of patients with chronic natural killer (NK) cell lymphocytosis. After reviewing more than 1,500 peripheral blood lymphoid flow cytometry reports and molecular genetic data from patients with suspected large granular lymphocyte (LGL) proliferation, we identified 10 patients (median age at diagnosis, 60 years; range, 35 to 76 years; male:female ratio, 3:2) with persistent (greater than 6 months) increase in phenotypically determined NK cells (CD3−CD16+). Southern blot analysis performed on 9 patients showed no clonal T-cell receptor gene rearrangements. Disease duration was measured from time of initial recognition of LGL or NK cell excess (greater than 40% of the lymphocyte fraction). Clinical data from these 10 patients were compared with those from 68 patients with T-cell LGL (T-LGL) leukemia. Currently, all patients are alive (median disease duration, 5 years; range, 0.8 to 8 years). Associated disease manifestations included pure red blood cell aplasia, recurrent neutropenia, recurrent neutropenic sepsis, and vasculitic syndromes, all of which were responsive to immunosuppressive therapy. No patient had palpable lymphadenopathy or splenomegaly. Compared with the patients with T-LGL leukemia, patients with chronic NK cell leukemia had similar lymphocyte counts, associated conditions, treatment responses, and survival but had less neutropenia and anemia.

Quantitative abnormalities of large granular lymphocytes (LGLs) are not uncommon and may represent a transient phenomenon associated with viral infections or a chronic lymphoproliferative disorder characterized by chronic neutropenia.1,2 The lymphocytes in proliferations of LGLs carry the phenotypic characteristics of either T cells (CD3+CD16+) or natural killer (NK) cells (CD3−CD16+).3,4 In the former subset, clonality can be determined by T-cell antigen receptor gene rearrangement studies,5 which are not applicable to NK cells.6

On the basis of the phenotypic profiles and the clonal nature of the expanded lymphocyte population, the following terms have been proposed.2 LGL proliferations of T cells with demonstrable clonal T-cell antigen receptor gene rearrangements are referred to as "T-LGL leukemia." LGL proliferations of NK cells with clonal cytogenetic abnormalities are referred to as "NK-LGL leukemia/lymphoma." Clinically, T-LGL leukemia is usually an indolent chronic condition associated with neutropenia and responsive to immunosuppressive therapy.7,8 By contrast, NK-LGL leukemia/lymphoma is an aggressive lymphoproliferative disorder with multiorgan involvement and short survival times.2,8 LGL proliferations of NK cells cannot always be classified as NK-LGL leukemia/lymphoma. In our experience and that of others, a persistent increase in peripheral NK cells is often associated with a more indolent chronic disease similar to T-LGL leukemia.6,8-11 Unlike the case with NK-LGL leukemia/lymphoma, the clonal nature of chronic NK cell lymphocytosis is a matter of controversy.5,8,11,12 Herein, we describe the clinical spectrum and long-term outcome associated with chronic NK cell lymphocytosis.

Materials and Methods

Patients were identified from several sources including a review of more than 1,500 peripheral blood (PB) lymphoid flow cytometry reports obtained at our institution during the last 5 years and a review of molecular genetic data obtained from patients with suspected proliferations of LGLs. Patients were considered to have chronic NK cell lymphocytosis after demonstration of persistent (greater than 6 months) NK cell excess (evaluated with lymphoid flow cytometry) or LGL excess (evaluated with PB smear and subsequently phenotyped as NK cell excess by lymphoid flow cytometry). In addition, eligibility for this study included the absence of viral infections and medications known to influence lymphocyte subset distribution and number.

NK cells normally constitute approximately 15% of the mononuclear cells in PB. Therefore, a proportion exceeding the mean value by 2 standard deviations (40%) was used as a cutoff value to define excess LGL or NK cell populations. NK cells were defined as non-T and non-B lymphocytes expressing NK cell antigen markers (CD3−CD16+). Mononuclear cell phenotypic analysis, NK cell cytotoxicity assays, NK cell cultures, and T-cell antigen receptor gene rearrangement studies were performed according to previously described methods.14,15 An immunoperoxidase stain for CD57 (Leu-7, another NK cell marker) was used to identify NK cells in bone marrow (BM) biopsy specimens.

Study patients were analyzed for presenting clinical and laboratory features, clinical course, treatment outcome, and associated disease manifestations (Table 1). Survival was measured from the time an excessive NK cell fraction or LGL population was initially recognized in a PB smear. Treatment response measurements included complete remission (resolution of symptoms and normalization of blood cell counts and NK cell fractions in PB) and partial remission (resolution of symptoms or cytopenia together with a greater than 50% decrement in lymphocytosis without documented normalization of NK cell fraction).

Finally, the clinical data from patients with chronic NK cell lymphocytosis were compared with the data from 68 patients with T-LGL leukemia observed at our institution during the study period. The Mann-Whitney statistic was used to compare age distributions, hemoglobin values, absolute neutrophil counts, white blood cell counts, and absolute lymphocyte counts. The χ2 statistic was used to compare symptom or disease associations.

Results

Patient selection. A total of 10 patients with chronic NK cell lymphocytosis were identified. Detailed immunophenotypic studies were performed in all patients (NK cells in PB: median cell fraction, 68%; range, 42% to 83%). In addition,
molecular genetic studies were performed in all but 1 patient and showed no clonal T-cell antigen receptor gene rearrangements.

Patient characteristics and physical findings. The median age of the patients was 60 years (range, 35 to 76 years), and the male-to-female ratio was 3:2. The median duration of disease was 5 years (range, 0.8 to 8 years; see Table 1). None of the patients had palpable lymphadenopathy or splenomegaly at diagnosis, and palpable splenomegaly developed in only 1 patient during the course of the disease.

Associated disease manifestations and symptoms. At the time of initial immunophenotypic analysis, associated disease manifestations included pure red blood cell (RBC) aplasia (1 patient), recurrent neutropenia, recurrent neutropenic fever sometimes associated with pneumonia or bacterial cellulitis (2 patients), and vasculitis syndromes (3 patients; see Table 1). Of the 4 other patients, 3 were asymptomatic and 1 had severe constitutional symptoms, with quantitative decrease in erythropoiesis. Both granulopoiesis and megakaryopoiesis were increased, and there was a left-shifted erythropoiesis with maturation arrest. The vasculitis syndromes included urticarial vasculitis, acute interstitial nephritis, and cutaneous polyarteritis nodosa. The patient with acute interstitial nephritis had a renal biopsy specimen that showed acute necrotizing glomerulonephritis. The patient with urticaria had slightly indurated erythematous patches measuring 0.5 to 1 cm. The skin biopsy specimen showed leukocytoclastic vasculitis with eosinophilic granule debris. The patient with cutaneous polyarteritis nodosa had persistent livedo and painful leg ulcers. The biopsy specimen showed neutrophilic vascular inflammation consistent with periarteritis nodosa with impetiginization. Comorbid conditions included rheumatoid arthritis in 1 patient (patient no. 10) and severe diabetic neuropathy in another (patient no. 8).

Laboratory findings. In addition to the required CD3(CD16* phenotype, the NK cells displayed a CD2(CD8* phenotype in all cases. HLA-DR was expressed in all but 1 patient (patient no. 9); CD7 was expressed in 8 of the 10 patients (patients no. 1 and 10; CD7*; see Table 1). A total of 2 patients had anemia attributable to chronic NK cell lymphocytosis, and 1 was transfusion-dependent (patient no. 6; see Table 1). Two patients had mild progressive thrombocytopenia (patients no. 1 and 9). Neutropenia (absolute neutrophil count less than 1,500/μL) was observed in 3 patients (Table 1). The median white blood cell and absolute lymphocyte counts were 8,850/μL (range, 2,200 to 15,300) and 4,900/μL (range, 1,000 to 7,500), respectively.

The PB smear showed excess LGLs in all but 1 patient (median LGL fraction in patients with excess LGLs was 60%; range, 48% to 74%; see Figs 1A and B). NK cell excess in the 1 patient without obvious LGL excess in PB was shown by immunophenotypic analysis (patient no. 6). BM from 7 patients was examined, and the pattern of LGL infiltration was always interstitial and was not easily recognizable. Immunoperoxidase staining of BM biopsy specimens with CD57 (Leu-7) was useful in visualizing the interstitial LGL infiltration (Fig 1C). Occasionally, a few non-NK cell lymphoid aggregates were noted (Fig 1D). In addition, pure RBC aplasia and myeloid maturation arrest were seen in patients no. 6 and 10, respectively. Cytogenetic studies were performed in 5 patients and showed no clonal abnormalities.

Additional laboratory studies included negative results on granulocyte antibody tests in the 3 patients with neutropenia, negative findings on cell-bound platelet antibody test in 1 patient with thrombocytopenia, polyclonal gammaglobulinemia in 3 patients, and normal findings on liver function.

### Table 1. Clinical Features of 10 Patients With Chronic NK Cell Lymphocytosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Associated Disease</th>
<th>Hgb (g/dL)</th>
<th>WBC (no. /μL)</th>
<th>ANC (no. /μL)</th>
<th>NK (%)</th>
<th>Therapy</th>
<th>Response</th>
<th>Survival (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>M</td>
<td>None</td>
<td>13</td>
<td>2,800</td>
<td>520</td>
<td>64</td>
<td>None</td>
<td>NA</td>
<td>1.5+</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>F</td>
<td>Neutropenia, anemia</td>
<td>8.2</td>
<td>5,400</td>
<td>240</td>
<td>68</td>
<td>Pred, CTX</td>
<td>NR</td>
<td>5.5+</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>M</td>
<td>Severe constitutional symptoms</td>
<td>16.4</td>
<td>15,300</td>
<td>7,500</td>
<td>83</td>
<td>Pred, CTX</td>
<td>NR</td>
<td>2+</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>F</td>
<td>Skin vasculitis</td>
<td>13.1</td>
<td>11,000</td>
<td>2,500</td>
<td>75</td>
<td>Pred</td>
<td>PR</td>
<td>5-</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>M</td>
<td>Fever and AGN</td>
<td>12</td>
<td>8,900</td>
<td>3,500</td>
<td>42</td>
<td>Pred</td>
<td>PR</td>
<td>8-</td>
</tr>
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<td>6</td>
<td>64</td>
<td>F</td>
<td>PRCA</td>
<td>7.7</td>
<td>2,900</td>
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<td>66</td>
<td>Pred, Aza</td>
<td>PR</td>
<td>6-</td>
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<td>7</td>
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<td>M</td>
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<td>15.8</td>
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<td>4+</td>
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<td>8</td>
<td>58</td>
<td>M</td>
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<td>16.5</td>
<td>8,900</td>
<td>2,900</td>
<td>68</td>
<td>None</td>
<td>NA</td>
<td>0.8+</td>
</tr>
<tr>
<td>9</td>
<td>76</td>
<td>F</td>
<td>Skin vasculitis</td>
<td>15.9</td>
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<td>5,300</td>
<td>74</td>
<td>NSAIDs</td>
<td>NR</td>
<td>7+</td>
</tr>
<tr>
<td>10</td>
<td>66</td>
<td>M</td>
<td>Cyclic</td>
<td>10.2</td>
<td>2,200</td>
<td>100</td>
<td>51</td>
<td>CTX</td>
<td>PR</td>
<td>2.5+</td>
</tr>
</tbody>
</table>

**Abbreviations:** AGN, acute glomerulonephritis; ANC, absolute neutrophil count; Aza, azathioprine; CR, complete remission; CTX, oral cyclophosphamide; Hgb, hemoglobin; NA, not applicable; NK, NK cells; NR, no response; NSAIDs, nonsteroidal antiinflammatory agents; PR, partial remission; PRCA, pure RBC aplasia; PRED, prednisone; WBC, white blood cell count.
tests in all patients. Rheumatoid factor assay and antinuclear antibody test were performed in 5 and 6 patients, respectively, and the results were positive only in the patient with rheumatoid arthritis (patient no. 10).

Cytotoxicity assays were performed in 2 patients (patients no. 2 and 3) and showed marked activity in both direct NK cell-mediated cytotoxicity and antibody-dependent cellular cytotoxicity. In addition, the NK cells from 1 of these 2 patients (patient no. 2) had altered in vitro growth requirements, suggesting that these cells did not represent a polyclonally expanded population of normal NK cells. Subsequent X-linked DNA analysis in this patient showed a monoclonal pattern of X-chromosome inactivation.13

Treatment outcome. Six patients required immunosuppressive therapy for vasculitic syndromes (2 patients), symptomatic neutropenia (2 patients), pure RBC aplasia (1 patient), or constitutional symptoms (1 patient; see Table 1). In the 2 patients with vasculitic syndromes, corticosteroid therapy resulted in amelioration of symptoms and signs of vasculitis. In addition, both patients had documented partial hematologic remissions.

Treatment with corticosteroids failed to resolve the symptomatic neutropenia in patient no. 2, but hematologic complete remission was achieved with cyclophosphamide administered orally. Patient no. 10 was receiving treatment with prednisone for rheumatoid arthritis when recurrent neutropenic fevers developed. The patient had partial remission with cyclophosphamide administered orally. Similarly, the patient with pure RBC aplasia had partial remission with corticosteroid treatment and subsequently achieved a durable complete remission with azathioprine. Despite treatment that lasted for only 1 to 11 months, cytopenia has not recurred in these 3 patients, who have been followed up for 1, 4, and more than 5 years. Neither the symptoms nor the laboratory abnormalities responded to either corticosteroids or cyclophosphamide in the patient with constitutional symptoms.

Comparison with patients with T-LGL leukemia. During the study period, we also saw a series of 68 consecutive patients with T-LGL leukemia.16 We compared several clinical variables, including presenting clinical features, laboratory findings, treatment outcome, and survival, between patients with chronic NK cell lymphocytosis and those with T-LGL leukemia. No significant differences were observed with regard to age, sex, symptoms, white blood cell count (P = .14), absolute lymphocyte counts (P = .37), treatment responses, or survival. In contrast, patients with chronic NK cell lymphocytosis showed less neutropenia (P = .03) and anemia (P = .06).

DISCUSSION

NK cells are defined operationally as a subpopulation of lymphocytes carrying the membrane phenotype, CD3-
CD16", and expressing nonmajor histocompatibility-restricted cytotoxicity without previous sensitization. Normal NK cells constitute approximately 1% of the PB mononuclear cell fraction. Morphologically, they appear similar to T-suppressor lymphocytes, with abundant cytoplasm and azurophilic cytoplasmic granules (Fig 1A). Because of this morphologic similarity, disorders of NK cell proliferation are categorized as a subset of LGL proliferative disorders, which also include T-cell disorders.

However, as shown by 1 of our patients and previously appreciated by others, NK cells are not always discernible as LGLs. Therefore, it might be more appropriate to use a less restrictive terminology such as "NK cell proliferative disorders." This has direct clinical relevance, because suspected NK cell disorders may need to be evaluated with both PB smear examinations and immunophenotypic analysis.

The amount of information available about the spectrum of clinical conditions associated with NK cell proliferations is limited. Similarly, the clonal nature of persistent NK cell proliferations is not always evident. Nevertheless, at least two clinical disorders characterized by persistent NK cell proliferations have been recognized. The first, operationally defined as "NK-LGL leukemia/lymphoma," affects relatively younger patients and is characterized by an acute systemic disease with multiorgan involvement, severe constitutional symptoms, and short survival. The clonal nature of this disease has been confirmed by the demonstration of clonal cytogenetic abnormalities or single episomal form of Epstein-Barr virus DNA in the leukemic cells. A causative role for Epstein-Barr virus in disease pathogenesis or transformation has been suggested.

The second NK cell disorder, which we refer to as "chronic NK cell lymphocytosis," has a more indolent disease course similar to that of T-LGL leukemia. Unlike NK-LGL leukemia/lymphoma, the results of cytogenetic studies are only occasionally abnormal. Similarly, T-cell antigen receptor gene rearrangement studies are not helpful in the clonal determination of chronic NK cell lymphocytosis. We showed monoclonality with X-linked DNA analysis in 1 of our patients, an observation supported by some but not by others. Regardless, in the majority of patients with chronic NK cell lymphocytosis, the clonal nature of the disorder is uncertain.

An overview of our experience with 10 patients with chronic NK cell lymphocytosis described herein indicates that patients with this disorder can expect prolonged survival but that their disease may be associated with life-threatening cytopenia or severe vasculitic syndrome. These complications were usually responsive to immunosuppressive therapy; cyclophosphamide administered orally was the most useful agent. Similar to earlier reports, 1 of our patients had severe constitutional symptoms (fatigue, arthralgias, night sweats, weight loss, fever) unresponsive to therapy. The heterogeneity in clinical manifestations may be related partly to the phenotypic and possibly functional diversity of the excess NK cell populations. Regardless, it may be clinically helpful to include chronic NK cell lymphocytosis in the differential diagnosis of unexplained cytopenias, vasculitic syndromes, and persistent constitutional symptoms.

The observed clinical remissions were associated with a significant decrease in the number of NK cells, suggesting a causative role in disease manifestation. NK cells have been shown to have a negative regulatory control on erythropoiesis and, thus, could suppress in vitro erythroid colony formation. Similarly, the associated neutropenia may be secondary to an interleukin-2–induced cell-mediated suppression of myeloid progenitors possibly involving γ-interferon. Alternatively, it may involve a functional deficiency of myeloid colony-stimulating factors mediated by humoral mechanisms. The latter supposition is supported by reports of successful treatment of T-LGL leukemia-associated neutropenia with colony-stimulating factors. Although abnormal B-cell function has not been studied in chronic NK cell lymphocytosis, their abnormal function that results in autoantibody production has been implicated in T-LGL leukemia as the pathogenetic basis for associated autoimmune diseases.

The durable remissions observed with cyclophosphamide taken orally are similar to those reported in patients with T-LGL leukemia. We previously reported on a successful immunosuppressive therapy with corticosteroids and azathioprine in a patient with pure RBC aplasia associated with chronic NK cell lymphocytosis. Although some patients responded to corticosteroid therapy, remission depended on continued administration of high doses of the drug.

Comparative clinical data between patients with chronic NK cell lymphocytosis and those with T-LGL leukemia showed similar epidemiologic and clinical features, including the spectrum of associated disease manifestations and survival. The only differences were lesser incidences of anemia and neutropenia in patients with chronic NK cell lymphocytosis and a higher incidence (26%) of rheumatoid arthritis in patients with T-LGL leukemia. Although acute transformation into a clinically more aggressive disease was not observed in our patients, it has been reported with chronic NK cell lymphocytosis.

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