Adult-Onset Cyclic Neutropenia Is Associated With Increased Large Granular Lymphocytes

By Thomas P. Loughran, Jr, Edward A. Clark, Thomas H. Price, and William P. Hammond

Human cyclic neutropenia occurs in adults as well as children. Clinical illness is similar in the childhood and adult diseases, but distinctly different modes of onset suggest heterogeneity in its pathophysiology. We studied seven patients with cyclic neutropenia, three with disease acquired in adulthood, and four with the childhood-onset disorder. All three patients with adult-onset cyclic neutropenia had increased numbers of circulating large granular lymphocytes (LGL), whereas the four children with cyclic neutropenia had normal LGL counts. LGL from patients with adult-onset cyclic neutropenia expressed cell surface antigens HNK-1 (three of three patients) and IgG Fc receptors (two of three patients), although natural killer activity was low. Two of these patients were treated with alternate-day steroids, resulting in decreased LGL counts and abrogation of neutrophil cycling. We suggest that adult-onset cyclic neutropenia may be distinguished from the childhood-onset form of the disease by increased numbers of LGL. Furthermore, increased LGL may identify a subset of patients with cyclic neutropenia who respond to steroid therapy.

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HUMAN CYCLIC NEUTROPENIA is a rare disorder characterized by regular predictable oscillations of the blood neutrophil count. Fever, malaise, aphthous stomatitis, and mucous membrane infections occur at the time of the neutrophil nadir. Manifestations of this disease usually begin in childhood, although in about 25% of patients the first symptoms occur after age 20. Therapy such as androgens and splenectomy has been modestly successful in a few patients but has not reliably resulted in a correction of the cycling. Lithium, although abrogating cycling in the grey collie model of cyclic neutropenia, has not been uniformly efficacious in human disease. Corticosteroid therapy, however, has been shown to correct neutrophil cycling in a few patients with the adult-onset form of the disorder.

The etiology of cyclic neutropenia is not known, although the defect appears to reside at the stem cell level. Studies in patients with the adult-onset form of this disease may provide insight into the pathogenesis of this disorder. Recently a syndrome of chronic neutropenia associated with excess large granular lymphocytes (LGL) has been identified. We have shown that in some of these patients this disease results from a clonal expansion of LGL. In this report, we describe an association between excess numbers of circulating LGL and the adult-onset form of cyclic neutropenia.

MATERIALS AND METHODS

Patients. All patients with the exception of patient 3 were referred to us for evaluation of neutropenia and were studied at the Clinical Research Center at the University Hospital on protocols approved by the Human Subjects Review Committee of the University of Washington. Patient 3 was recruited for study through the National Institutes of Health (NIH) Clinical Center: slides of bone marrow obtained prior to steroid therapy were obtained from the NIH, whereas blood for surface marker studies was obtained through her private physician.

All three patients with adult-onset cyclic neutropenia had recurrent symptoms of fever, malaise, aphthous stomatitis, and occasional local infections. Clinical illness in patient 1 began in 1970 at the age of 59 when a complete blood cell count (CBC) showed neutropenia and absolute lymphocytosis. CBC with differential count had been normal in 1968 when she underwent distal pancreatectomy and splenectomy for chronic pancreatitis. The diagnosis of cyclic neutropenia was established in 1975. A trial of lithium carbonate in 1979 was unsuccessful, as described previously. She continues to experience periodic fevers, malaise, and aphthous stomatitis; she has declined treatment with alternate-day prednisone. Patient 2 was well until 1962 when at the age of 45 symptoms began to occur at approximately monthly intervals. A diagnosis of cyclic neutropenia was established in 1975, and a trial of alternate-day prednisone (50 mg) resulted in correction of neutrophil cycling. She currently remains well, receiving 20 mg prednisone every other day. Cyclic neutropenia was diagnosed in patient 3 at the age of 65. She has been the subject of previous studies of cyclic neutropenia performed at the NIH. A trial of alternate-day prednisone resulted in abrogation of neutrophil cycling and the clinical manifestations of her disease. She still receives prednisone, 10 mg daily, and has suffered multiple complications of steroid therapy including bleeding gastric ulcer, osteoporosis resulting in fracture of the right hip, and diabetes mellitus.

Patients 4 to 7 with childhood-onset cyclic neutropenia also had classic features of the disease: regularly recurring episodes of fever, malaise, aphthous stomatitis, and cervical lymphadenopathy. Patients 4 and 6 were previously reported by us; patient 4 died of necrotizing clostridial enterocolitis at age 11. Patient 5 presented with a lung abscess; she had severe periodontitis, as did patient 6. All four patients with childhood-onset cyclic neutropenia had cycle lengths between 19 and 21 days, all had monocytosis during neutropenia, and three had cyclic fluctuations of either platelet or reticulocyte counts.

Patients 8 to 10 with chronic neutropenia had histories of recurrent infections similar to those of patients with cyclic neutropenia. Patients 8 and 10 were referred by their physicians because of the severity of their infections. They had otherwise normal blood counts and fit the diagnostic category of chronic idiopathic neutropenia. Patient 9 was also anemic and thrombocytopenic; he had had documented neutropenia and severe recurrent skin infections for at least 10 years. These patients served as one control group, whereas ten healthy volunteers served as the normal control group.

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Blood counts. The diagnosis of cyclic neutropenia was established by performing blood counts a minimum of three times per week for at least 6 weeks as previously described. Patients with chronic neutropenia had serial blood counts similarly performed for a minimum of 4 weeks to document the absence of cycling. WBC counts were done on EDTA-anticoagulated specimens using a Coulter counter and total neutrophil counts (bands plus neutrophils) calculated from the WBC and a 100-cell differential count. LGL were identified by their characteristic morphology on Wright-Giemsa stains, ie, larger size and smaller nuclear cytoplasmic ratio than typical lymphocytes as well as prominent azurophilic granules. Total LGL counts were calculated by multiplying the total lymphocyte count by the percentage of LGL (of at least 100 cells counted) obtained in the differential lymphocyte count. Differential counts were performed by one observer (T.P.L.) on coded specimens to prevent biased reporting. Five hundred-cell bone marrow differential counts were performed by a single observer (T.H.P.).

Lymphocyte studies. Peripheral blood mononuclear cells were isolated by Ficol-Hypaque density gradient centrifugation and studied for expression of cell surface antigens using an Epics 5 flow cytometer with direct one-color and two-color analysis using a panel of fluorescein-conjugated or R-phycocerythin-conjugated monoclonal antibodies (MoAb) as previously described. The antigens recognized by these MoAb are described using the current World Health Organization international nomenclature. The following MoAb, verified by International Workshop analyses, were kindly provided by Dr Jeff Ledbetter (Genetic Systems, Seattle): G19-4 anti-CD3 (T3) and G10-1 anti-CD8 (T8). Dr Toru Abo (University of Alabama, Birmingham) provided HNK-1. The Fc-1 MoAb recognizes IgG Fc receptors (CD16) found on natural killer (NK) cells and does not recognize IgG Fc receptors expressed on monocytes. NK activity of peripheral blood mononuclear cells was determined using a Cr-labeled K562 erythroleukemia cell line as a target in a four-hour assay as previously described for our laboratory. Effector:target ratios were 6.25:1, 12.5:1, 25:1, and 50:1; lytic units for 30% killing of 10⁶ target cells were derived from a graph of log₁₀ effector/target ratio v the percent specific lysis plotted on semilog paper. Cytogenetic studies were done on peripheral blood mononuclear cells from patients 1 and 3 cultured either with or without phytohemagglutinin as previously described.

Neutrophil antibody studies. Tests for serum leukocytoclastinating antibodies were performed according to the method of McCullough et al. Neutrophil-associated immunoglobulin and serum or plasma neutrophil-binding immunoglobulin were determined by indirect immunofluorescence using a modification of the method of Verheught et al. Patient or normal target neutrophils were purified by Hypaque-Ficoll sedimentation and fixed with 1% parafformaldehyde. Neutrophil-associated immunoglobulin (direct test) was determined by flow microfluorometry after incubation of the cells with fluorescein isothiocyanate (FITC) goat antihuman IgG (or IgM) (Tago, Burlingame, Calif). Results were quantitated using peak fluorescence channel numbers and expressed as a multiple of average values for normal neutrophils. For determination of plasma/serum neutrophil-binding immunoglobulin (indirect test), normal neutrophils were incubated with test sera, washed, and surface immunoglobulin determined as before. For the indirect test, results are expressed as a multiple of values seen when target cells are incubated with autologous serum.

RESULTS

Cyclic neutropenia was well documented by frequent serial blood counts in seven patients. Of the patients with adult-onset cyclic neutropenia, patient 1 was studied on several occasions over a 10-year period; cycle length has remained constant at 20 days. Patient 3 has also been studied on several occasions over at least 14 years; cycle length has remained constant at 21 to 22 days. Blood counts obtained on patient 2 over a 10-month period before and after receiving prednisone therapy are shown in Fig 1. The cycle length was somewhat longer, with an average of 27 days. Alternate-day prednisone therapy eventually resulted in correction of cycling and stabilization of neutrophil counts at levels greater than 2,000/µL. Similar results of prednisone therapy have been reported previously for patient 3.

All three patients with adult-onset cyclic neutropenia had a marked increase in circulating LGL at the time of diagnosis (Table 1), values similar to those observed in patients with LGL leukemia. To determine whether an elevated LGL count was a nonspecific finding secondary to neutropenia and recurrent infections, we determined LGL counts in other groups of neutropenic patients. As shown in Table 1, three patients with chronic neutropenia and four children with cyclic neutropenia had LGL counts within the normal range. Clinical remission of adult-onset cyclic neutropenia was associated with a reduction in numbers of LGL in the two patients treated with alternate-day steroids (Table 1). Results of bone marrow differential counts in patients with adult-onset cyclic neutropenia are shown in Table 2. All three patients had increased numbers of mature-appearing narrow lymphocytes. In addition, characteristic findings of cyclic neutropenia were seen in serial marrow examinations from patient 1. During neutropenia, myeloid precursor cells predominated, whereas during the neutrophil recovery phase an expansion of the myeloid postmitotic pool was observed. Of interest, microscopic examination of the spleen of patient 1, obtained prior to clinical onset of cyclic neutropenia, revealed lymphoid infiltration of splenic red pulp cords, a finding similar to that reported in patients with LGL leukemia.

Figure 2 shows serial LGL, lymphocyte, and neutrophil counts obtained from patient 1 during a 26-day period.
Table 1. Clinical and Hematologic Features of Neutropenic Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>WBC</th>
<th>Neutrophils</th>
<th>Lymphocytes</th>
<th>Percentage of LGL</th>
<th>Total LGL</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult-onset cyclic neutropenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>74</td>
<td>F</td>
<td>9,900</td>
<td>0–1,984*</td>
<td>8,415</td>
<td>73</td>
<td>6,143</td>
<td>Severe fever, aphthous stomatitis, malaise</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid therapy</td>
<td></td>
<td></td>
<td>7,600</td>
<td>5,092</td>
<td>1,672</td>
<td>82</td>
<td>1,037</td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td></td>
<td></td>
<td>80</td>
<td>7,800</td>
<td>0–3,800</td>
<td>4,900</td>
<td>83</td>
<td>4,067</td>
</tr>
</tbody>
</table>

| Childhood-onset cyclic neutropenia |     |     |     |             |             |                  |           |                  |
| 4       | 11  | M   | 2,500 | 25–2,882 | 1,380 | 16 | 221 | Died of cervical sepsis and enterocolitis |
| 5       | 19  | F   | 5,500 | 0–1,353 | 3,465 | 13 | 450 | Right lung disease, severe periodontal disease |
| 6       | 10  | M   | 3,900 | 0–1,628 | 1,860 | 16 | 298 | Otitis media, aphthous stomatitis |
| 7       | 8   | F   | 5,500 | 0–1,944 | 4,015 | 9 | 381 | Otitis media, fever |

| Chronic neutropenia |     |     |     |             |             |                  |           |                  |
| 8       | 20  | F   | 2,800 | 244–902 | 2,016 | 6 | 121 | Occasional skin infections |
| 9       | 22  | M   | 2,500 | 243–945 | 1,750 | 4 | 70 | Severe recurrent skin infections, glomerulitis |
| 10      |     |     | 21  | 2,500 | 73–1,402 | 1,472 | 7 | 103 | Severe aphthous stomatitis |

| Normal† |     |     |     |             |             |                  |           |                  |
| n = 10  |     |     | 37±14 | 5M/5F | 5.920±1.999 | 3.654±1.563 | 2.221±832 | 11±6 | 223±99 |
| (22–58) |     |     |       |       | (1.100–5.500) | (1.333–5.035) | (1.300–4.275) | (5–24) | (104–482) |
| n = 42  |     |     | — | 27M/15F | — | — | 14±4 | 245±108 |
| (14–80) |     |     |       |       |       |       | (5–24) | (1120–620) |

*Ranges indicate fluctuations from nadirs to peak values.
†Normal values were obtained in our laboratory on ten healthy volunteers. The top line gives the mean ± SD; the bottom line gives the range in parentheses. LGL values are compared with those obtained on 42 healthy controls in another laboratory.

WBC, neutrophils, lymphocytes, and total LGL are cells/μL. Hematocrit and platelet counts were normal in all patients except patient 9, whose hematocrit value was 31% and platelet count was 104,000 cells/μL.

Surface marker studies of peripheral blood mononuclear cells from all three patients revealed some phenotypic characteristics of NK cells. All patients had increased numbers of HNK-1+ cells; in addition, two patients had LGL that expressed IgG Fc receptors (Table 3). Two-color analysis showed that HNK-1+ cells from patient 1 coexpressed CD3 and CD8 and lacked expression of IgG Fc receptors (CD16).

Results of two-color analyses of peripheral blood mononuclear cells from patients 2 and 3 obtained while both patients were receiving steroid therapy were more heterogeneous. In both patients the majority of HNK-1+ cells lacked expression of either CD3, CD8, or CD16, although 20% to 43% of HNK-1+ cells did express these other markers (Table 3). In spite of elevated numbers of mononuclear cells bearing NK-associated antigens, the NK activity in all three patients was markedly reduced (<0.001 lytic units for patients 1 to 3, compared with 5.5, 10.4, and 2.2 lytic units obtained for normal concurrent controls for patients 1 to 3, respectively).

Cytogenetic studies showed normal karyotypes in phytohemagglutinin-stimulated peripheral blood mononuclear cell cultures from patient 1 and in unstimulated peripheral blood mononuclear cell cultures from patient 3. There were no analyzable metaphases in unstimulated peripheral blood mononuclear cell cultures from patient 1.

Results of neutrophil antibody studies are shown in Table 4. Leukoagglutination studies were negative in all three patients.

Table 2. Bone Marrow Differential Counts

<table>
<thead>
<tr>
<th>Patients</th>
<th>Counts 1 (No. 1)</th>
<th>Counts 2 (No. 2)</th>
<th>2</th>
<th>3</th>
<th>Normal*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid</td>
<td>9.8</td>
<td>15.2</td>
<td>27.4</td>
<td>34.0</td>
<td>15.0–36.2</td>
</tr>
<tr>
<td>Myeloblast</td>
<td>0.4</td>
<td>0.2</td>
<td>1.3</td>
<td>1.9</td>
<td>0.3–1.7</td>
</tr>
<tr>
<td>Promyelocyte</td>
<td>7.8</td>
<td>0.9</td>
<td>1.7</td>
<td>3.5</td>
<td>1.9–4.7</td>
</tr>
<tr>
<td>Myelocyte</td>
<td>1.2</td>
<td>6.5</td>
<td>1.5</td>
<td>8.5</td>
<td>8.5–16.9</td>
</tr>
<tr>
<td>Metamyelocyte</td>
<td>0.9</td>
<td>4.3</td>
<td>0.9</td>
<td>4.4</td>
<td>7.1–24.7</td>
</tr>
<tr>
<td>Bands + segments</td>
<td>0.9</td>
<td>24.6</td>
<td>6.3</td>
<td>8.5</td>
<td>13.2–26.4</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>61.9</td>
<td>39.9</td>
<td>46.5</td>
<td>29.4</td>
<td>8.6–23.8</td>
</tr>
<tr>
<td>Other</td>
<td>17.1</td>
<td>8.4</td>
<td>14.4</td>
<td>9.8</td>
<td>—</td>
</tr>
<tr>
<td>Blood PMN</td>
<td>0</td>
<td>1,540</td>
<td>900</td>
<td>NA</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; PMN, polymorphonuclear cells.

*A 95% confidence range.

Results expressed as a percentage, 500 cells counted.
patients. There was no evidence for circulating antineutrophil antibodies in either patient 1 or 3; in contrast, both IgG and IgM antibodies were demonstrated in the serum of patient 2. High levels of neutrophil-associated IgM were documented in patient 2; this patient also had elevated serum levels of IgM (808 mg/dL). In addition, there was a slight increase in neutrophil-associated IgG in patient 3. Of note, patient 3 had previously been shown to have a normal neutrophil survival.24

DISCUSSION

This study suggests that adult-onset cyclic neutropenia may be distinguished morphologically from the more common childhood-onset cyclic neutropenia by the presence of increased numbers of circulating LGL. All three patients with the adult-onset disorder met clinical and hematologic criteria for cyclic neutropenia: (1) recurrent symptoms of fever, malaise, aphthous stomatitis, and occasional superficial infections and (2) periodic episodes of profound neutropenia associated with reciprocal mononcytosis. In patients 1 and 3 the cycle length was within the 20- to 22-day cycle period seen in 85% of patients with cyclic neutropenia,1 whereas the cycle length in patient 2 was a bit longer (27 days). Furthermore, the cycle lengths of individual patients were very stable when studied at intervals of several years, a feature of classic cyclic neutropenia.1,2

Results of lymphocyte surface antigen phenotyping in these patients with acquired cyclic neutropenia revealed some heterogeneity. Mononuclear cells from the only patient studied in an untreated state (patient 1) were CD3+, CD8+, HNK-1+, CD16−. The other two patients also had increased numbers of HNK-1+ cells; approximately 40% of these cells also expressed IgG Fc receptors, a surface antigen normally associated with active NK cells.34−37 Of note, NK activity of peripheral blood mononuclear cells from all three patients was very low, a finding previously noted in most patients with large granular lymphocytosis and chronic neutropenia.2,23

No prior studies of LGL in adult-onset cyclic neutropenia have been reported. Lymphocyte subpopulations have been studied in three children with cyclic neutropenia,12,38 but LGL were examined in only one of these patients.38 In that report, LGL (defined as HNK-1+ cells) fluctuated from 0.7% to 7.5% of the total blood lymphocytes; using this data, we estimate that absolute LGL numbers were always below 300/μL, consistent with our finding of normal LGL counts in the childhood disorder.

The syndrome of chronic neutropenia associated with excess LGL was first described in 1977 and has recently been reviewed.35 We showed previously that in at least some of these patients this disorder represents a leukemia of LGL that is characterized by autoimmune manifestations and infiltration of splenic red pulp, hepatic sinusoids, and bone marrow by immature NK cells.23 Although cycling of neutrophil counts did not occur in patients with LGL leukemia (unpublished observations), the three patients with adult-onset cyclic neutropenia we report here do share features of that disease: (1) excess LGL that express some NK surface antigens yet have little NK activity and (2) lymphocytic infiltration of splenic red pulp cords and possibly bone marrow. In contrast, our patients with adult-onset cyclic neutropenia did not have arthritis or positive tests for antinuclear antibody or rheumatoid factor, common features of LGL leukemia.2,23 Furthermore, they have had extraordinarily prolonged illnesses ranging from 8 to 14 years, demonstrating a remarkable stability of the disorder.

### Table 4. Neutrophil Antibody Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Lgα</th>
<th>IgG</th>
<th>IgM</th>
<th>IgG</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>negative</td>
<td>ND</td>
<td>ND</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>negative</td>
<td>1.5</td>
<td>5.9</td>
<td>2.9</td>
<td>10.3</td>
</tr>
<tr>
<td>3</td>
<td>negative</td>
<td>2.0</td>
<td>0.9</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Normal†</td>
<td>—</td>
<td>0.1-1.9</td>
<td>0-1.4</td>
<td>0-2.4</td>
<td>0-1.8</td>
</tr>
</tbody>
</table>

Abbreviation: Lgα, leukoagglutination; ND, not determined.
*Results expressed as multiples of values for control cells.
†Results expressed as multiples of values for autologous serum.
‡A 95% confidence limit.
The etiology of cyclic neutropenia is not known. Previous marrow transplantation studies have suggested that this disorder is a result of a periodic failure of myelopoiesis occurring at the stem cell level. However, it may not be possible to generalize these studies performed in the autosomal recessive model disease of grey collie dogs or in human childhood-onset cyclic neutropenia to the adult-onset disease in humans. Kinetic studies, though, have shown normal neutrophil survival, fluctuating neutrophil reserves, and virtually absent myelocyte incorporation of 3H-thymidine during neutrophilia in both childhood-onset and adult-onset disease in humans.24,25 strongly suggesting a common final pathway for the neutropenia, namely periodic failure of production. In patients with LGL leukemia, on the other hand, there is some evidence that neutropenia is secondary to autoimmune peripheral destruction.26 In contrast to these findings, not all of our patients with adult-onset cyclic neutropenia had antineutrophil antibodies. Furthermore, normal neutrophil half-life was demonstrated previously in patient 3.27 These data suggest that the mechanism of neutropenia in patients with adult-onset cyclic neutropenia may differ from that observed in patients with LGL leukemia.

Perhaps of most interest was the dramatic clinical response to alternate-day steroid therapy. Both patients 2 and 3 had correction of neutrophil cycling; the other patient declined such treatment. Therapy was associated with stabilization of bone marrow neutrophil precursors and neutrophil marrow reserves in patient 3.15 Although LGL counts still remained greater than normal, clinical remission induced by prednisone was also associated with a reduction in numbers of LGL. Thus, it seems likely that increased LGL are involved in adult-onset cyclic neutropenia, either as a causative factor or as still another phenomenological component of cyclic fluctuations of stem cells. Whether LGL cycle in all untreated patients would be interesting to know but can not be determined from this study; in any event, the marked elevation of LGL levels in patients with adult-onset disease is in striking contrast to the normal levels in childhood-onset disease. Also of note, a lymphoid infiltration of splenic red pulp cords was documented in patient 1, 2 years before the clinical and hematologic onset of cyclic neutropenia. Furthermore, LGL are known to produce multiple regulatory factors,41,42 and it has been emphasized that cyclic neutropenia may be secondary to an abnormality in feedback regulation of hematopoiesis.43

Two other patients with cyclic neutropenia have been reported to respond to steroid therapy.44,45 Another patient had a temporary response to plasmapheresis.46 Documented improvement in neutrophil counts was also observed in at least three patients following splenectomy,5,7 in one patient undergoing splenectomy and receiving adrenocorticotropic hormone injections,8 in two patients receiving androgen therapy,4 and in one patient receiving lithium.9 All of these patients had the adult-onset form of cyclic neutropenia; lymphocyte morphology was not noted. In contrast, no successful therapy for childhood-onset cyclic neutropenia has been reported. The results of our study indicate that adult-onset cyclic neutropenia may be characterized by markedly increased LGL and suggest that the pathogenesis of this form of the disease may be different from the childhood-onset disorder. Furthermore, this form of the disease may be amenable to steroid or other therapy. Future studies on similar patients may provide further insight into the pathogenesis of cyclic neutropenia and the regulatory role of LGL in myelopoiesis.

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