Lymphoblastic Leukemia with Marked Eosinophilia: A Report of Two Cases

By Gary Spitzer and O. Margaret Garson

Two cases of acute lymphoblastic leukemia with eosinophilia are described. The degree of eosinophilia was such that at presentation, a provisional diagnosis of eosinophilic leukemia was made. Cytogenetic evidence is presented, indicating that the eosinophilia is reactive to the leukemic process rather than part of it. A mechanism for the production of the eosinophilia is discussed, and it is suggested, on the basis of our findings, that acute eosinophilic leukemia may be of rarer occurrence than is already accepted.

Acute eosinophilic leukemia is a rare disease and, when it does occur, is considered to be a variant of granulocytic leukemia. This paper reports two cases of acute leukemia accompanied by very marked eosinophilia. At presentation, both patients were considered to have acute eosinophilic leukemia. However, hematologic evidence showed the leukemia to be lymphoblastic, and cytogenetic studies indicated that the eosinophilia was reactive in nature.

CASE REPORT

Case 1

L.B., a 14-yr-old white female, presented in June 1969 with a history of a paintul lower jaw for several days, followed by central chest pain that was aggravated by breathing. Blood examination was performed in a diagnostic laboratory, and on the basis of this, she was referred to St. Vincent’s Hospital with a provisional diagnosis of acute eosinophilic leukemia. On admission, examination showed an alert girl with a blood pressure of 100/80 mm Hg, pulse rate of 104/min, and a temperature of 36.7°C. A purpuric rash was present over the anterior chest, abdomen, and arms, and there was a mild degree of sternal tenderness. A firm, nontender spleen was palpable 1 cm below the left costal margin, but there was no enlargement of lymph nodes or liver detected. There was no past history of parasitic infections or allergic disease.

Full blood examination on admission revealed a hemoglobin of 13.0 g/100 ml, platelet count 86,000/cu mm, white cell count 132,000/cu mm with 76% mature eosinophils, 4% eosinophilic metamyelocytes, 3% eosinophilic myelocytes, 9% mature neutrophils, 3% blasts, and 5% lymphocytes. Some of the eosinophils showed variation in the staining of the granules. Bone marrow aspiration showed a hypercellular marrow consisting mainly of blast cells and mature eosinophils. The blast cells showed a high nuclear-cytoplasmic ratio, one to two nucleoli per cell, and minimal cytoplasmic granulation and were, therefore, considered to be lymphoblasts (Fig. 1). There was a marked decrease in erythroid cells and megakaryocytes. The marrow differential count was 52% lymphoblasts, 4% mature neutrophils, 40% mature eosinophils, 1% eosinophilic metamyelocytes, 1% eosinophilic myelocytes, and 2% lymphocytes. Cytochemistry showed the blast cells to be peroxidase negative, and there was obvious block positivity with PAS.
Fig. 1. Case 1. Bone marrow smear showing lymphoblasts, eosinophil precursors, and eosinophils. Jenner-Giemsa stain.

The total protein was 6.0 g/100 ml, albumin 3.2 g/100 ml, total globulin 2.8 g/100 ml, γ-globulin 0.35 g/100 ml. LE cells and antinuclear factor could not be demonstrated. The electrocardiogram was noted to be abnormal with T wave inversion in limb leads 2, 3, avf, and all the chest leads. Examination of the stools for ova and parasites was negative.

A diagnosis of acute lymphoblastic leukemia was made, and it was considered that the eosinophilia was probably reactive in nature. She was treated with vincristine, prednisolone, and daunorubicin; this last agent was ceased after the first injection because of an increase in the T wave inversion in the electrocardiogram. A hematologic remission was achieved with the disappearance of lymphoblasts from both the peripheral blood and marrow, and at the same time the eosinophil count returned to normal. Maintenance therapy with 6-mercaptopurine and intermittent courses of vincristine and prednisolone was administered for 11 mo until March 1970. A rise in the peripheral eosinophil count from 250 to 2000/cu mm was then observed, and this was followed by an increase in the total white cell count consisting mainly of lymphoblasts. A further course of combination therapy with vincristine and prednisolone resulted in a brief remission, but after only 2 mo the eosinophil count again rose, and bone marrow examination showed evidence of relapse. The marrow was hypercellular with a differential count of 24% lymphoblasts, 3% promyelocytes, 5% myelocytes, 1% metamyelocytes, 22% mature neutrophils, 3% eosinophilic myelocytes, 3% eosinophilic metamyelocytes, 4% mature eosinophils, 11% lymphocytes, and 24% normoblasts. Treatment was changed to cytosine arabinoside and prednisolone, and a further remission obtained.

Maintenance therapy with 6-mercaptopurine was continued until December 1970, when there was a further relapse preceded by an increased peripheral eosinophil count. Remission was then obtained with cytosine arabinoside and vincristine. However, despite more intensive maintenance therapy using intermittent courses of cytosine arabinoside, vincristine, and prednisolone, a final relapse occurred in April 1971, approximately 2 yr after her initial presentation.

As on previous occasions, this relapse was preceded by a rise in the eosinophil count. Physical examination at this time showed a petechial rash over arms and legs. The spleen was palpable 1 cm below the left costal margin, and the liver was palpable 3 cm below the right costal margin. The tourniquet test was negative. Full blood examination showed hemoglobin 11.0 g/100 ml, platelet count 60,000/cu mm, and white cell count of 70,000/cu mm with 10% blasts. The bone marrow was hypercellular and was composed mainly of lymphoblasts and eosinophils that were mainly mature. Combinations of cytosine arabinoside, thioguanine, prednisolone, vincristine, and asparaginase failed to achieve remission. Marked pancytopenia developed, and terminally a pulmonary fungal infection was suspected that did not respond to amphotericin therapy. She died in June 1971, 2 yr after diagnosis.

At autopsy, widespread acute fungal infection was found, as evidenced by the presence of small rounded areas of necrosis containing septate branching fungi consistent with aspergillosis in the lungs, mediastinum, and brain. Throughout both chambers of the heart there were small necrotic areas with surrounding congestion, mainly involving the endocardial surface, but in some places extending to involve the subendocardial muscle. These did not contain fungi.
Histologically, areas of endocardial thickening with overlying fibrin were identified throughout the heart. The marrow was markedly hypocellular, and there was little residual evidence of acute leukemia.

Case 2

M.C., a 16-yr-old Italian girl, was admitted in March 1972 with a history of 1-mo malaise and 3 days respiratory symptoms, consisting of dull central chest pain, cough, wheeze, and dyspnea. On the day before admission, she developed a purpuric rash over the chest, but the tourniquet test was negative. There was neither past history of parasitic infection nor any family history of allergy.

Physical examination showed an acutely ill, cyanotic young girl with a blood pressure of 90/70 mm Hg, pulse rate of 136/min, respiratory rate of 42/min, and a temperature of 38.9°C. Purpura was present over the chest. There were no enlarged lymph nodes, and the liver and spleen were not palpable. Examination of the chest revealed bilateral basal crepitations, but no cardiac abnormality was detected.

Full blood examination showed a hemoglobin of 10.2 g/100 ml, platelet count of 58,000/cu mm, and white cell count of 15,000/cu mm with a differential count of 20% mature eosinophils, 1% eosinophilic myelocytes, 1% eosinophil metamyelocytes, 35% mature neutrophils, 9% neutrophil metamyelocytes, 9% neutrophil myelocytes, 2% promyelocytes, 3% lymphoblasts, and 20% mature lymphocytes. Marrow aspiration showed a hypercellular marrow; the predominant cell was a small lymphoblast that was weakly PAS positive. These microlymphoblasts had a high nuclear-cytoplasmic ratio and contained an occasional nucleolus per cell (Fig. 2).

The marrow differential count showed lymphoblasts 74%, lymphocytes, 17%, mature eosinophils 5%, eosinophilic metamyelocytes 1%, eosinophilic myelocytes 2%, and normoblasts 1%.

The total protein was 5.86 g/100 ml, albumin 3.4 g/100 ml, total globulin 2.46 g/100 ml, γ-globulin 1.2 g/100 ml. Serum electrolytes and liver function tests were normal, as was the serum lysozyme at 6.0 μg/ml (normal range 2.8–11.3 μg/ml). The infectious mononucleosis screening test, ox cell hemolysin titer, hepatitis-associated antigen, and repeated estimations of toxoplasma, mycoplasma, psittacosis, and cytomegalovirus antibody titers failed to show any abnormality.

X-ray of the chest showed a diffuse reticular pattern throughout the lungs maximal at the bases. The arterial blood gases showed a PO2 of 42 mm Hg, PCO2 38 mm Hg, and pH 7.41. The electrocardiogram was abnormal with ST depression and T wave inversion in the anterior chest leads. Blood, sputum, and urine cultures for both bacteria and fungi were negative, and a stool culture and microscopy failed to detect any pathogenic bacteria or ova and parasites.

A diagnosis of lymphoblastic leukemia with associated reactive eosinophilia was made, and she was commenced on combination cytotoxic therapy with cytosine arabinoside and thioguanine (the nature of the pulmonary pathology was not established). It did not respond to the administration of penicillin and ampicillin but resolved during simultaneous treatment with Bactrim (trimethoprim and sulfamethoxazole) and cytotoxic drugs, including corticosteroids. Remission of the leukemic process was achieved after 2 mo, with disappearance of the lymphoblasts and eosinophils from blood and bone marrow. At the time of this report, the patient is still in remission 6 mo after diagnosis.
Table 1. Bone Marrow Chromosome Findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date of Examination</th>
<th>No. of Chromosomes Per Cell</th>
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<td>—</td>
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<td>47</td>
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<td></td>
<td>June 11, 1971</td>
<td>—</td>
<td>1</td>
<td>9</td>
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<td>2. M. C.</td>
<td>March 3, 1972</td>
<td>—</td>
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<td>3</td>
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<td></td>
<td>June 28, 1972</td>
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RESULTS

Chromosome studies were performed on direct bone marrow preparations using our modification of the method of Kiossoglou et al. (Table 1). Case 1 was studied prior to and during her final relapse. The marrow at the time of this relapse consisted mainly of lymphoblasts, eosinophilic precursors, and eosinophils. Two cell lines were found in the marrow preparations. One was an abnormal hypodiploid line with chromosome constitution, 45,XX,C−,D+,E+,F−,G−. This was considered to be the leukemic lymphoblast karyotype. The other cell line was normal 46, XX in constitution. It was noted that these mitoses with normal karyotypes were often overlaid by distinctive eosinophilic granules (Fig. 3), whereas the mitoses of abnormal karyotype were not (Fig. 4). These findings were interpreted as indicating that the normal karyotypes were derived from eosinophilic myelocytes.

Case 2 was studied at diagnosis, during therapy, and in remission. Initially, the cell lines were all hyperdiploid with chromosome counts ranging from 47 to 51 chromosomes per cell, the major cell line being 47,XX,A+,B−,C+,D−,G+. No eosinophilic granules were seen overlying any of the mitoses.

With response to therapy, the hyperdiploid mitoses disappeared leaving a 46 pseudodiploid cell line of constitution 46,XX,A+,B−,D−,C+, which was also the chromosome constitution found in the patient’s stimulated lymphocytes and skin culture. Cytogenetic studies of this patient and her family are to be the subject of a future report.

DISCUSSION

Two patients are reported who were initially thought to have acute eosinophilic leukemia but who were subsequently shown to have acute lymphoblastic leukemia with associated eosinophilia. No cause could be found for the eosinophilia other than the leukemia, and as the leukemia was identified as lympho-
blastic, it was considered unlikely that the eosinophilia was part of the leukemic proliferative process.

The cytogenetic findings in case 1 strongly support the view that the eosinophilia was not leukemic. The eosinophil precursors in the marrow were found to have a normal chromosome constitution, whereas the leukemic lymphoblasts possessed an abnormal aneuploid karyotype. This is evidence that the two cell lines did not arise from the one hemopoietic cell precursor and implies that the eosinophils were normal cells and not primarily leukemic in type. The eosinophilia was, therefore, considered to be reactive and, in the absence of any other cause of eosinophilia, was assumed to be a consequence of the leukemia. Additional evidence supporting this suggestion was the rise in peripheral eosinophil counts prior to the reappearance of lymphoblasts in each relapse shown by case 1.

The suggestion that there is an eosinophilic response to a leukemic clone is not surprising, as eosinophilia occurring in association with other malignancies is well documented.\(^5,6\) The fundamental mechanism for the reactive eosinophilia is unknown, but recent work of Basten et al. may be relevant.\(^7,10\) They have shown that in animals, using *Trichinella spiralis* injections as an antigen, an increased eosinophil production is mediated through thymic-processed lymphocytes. The eosinophilia did not occur in response to these injections if the animals were first thymectomized or given antilymphocytic globulin prior to the antigenic challenge. They postulated that these thymic-processed lymphocytes initiate the eosinophilia by a mechanism affecting an early stage in eosinophilic development.

It has been shown by Hamilton Fairley that leukemic blast cells, collected during relapse and stored, will stimulate in a mixed lymphocyte culture autologous lymphocytes taken during remission.\(^11,12\) This supports the findings of
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others that tumor-associated antigens exist on the cell surface of leukemic blast cells. It is conceivable in these cases that the appearance of a leukemic antigen initiates production of a population of immune thymus-dependent lymphocytes with a specific receptor for the leukemic antigen. This reaction could provide the trigger to induce synthesis and release of lymphokines, such as “eosinopoietic factor,” that would stimulate eosinophilic production and contribute to a cell-mediated response to the “tumor-specific antigen.”

Although these patients had lymphoblastic leukemia, they both showed clinical features similar to the “hyper-eosinophilic syndrome” of Hardy and Anderson and the “disseminated eosinophilic collagen disease” of Engfeldt and Zetterstrom. Both patients had electrocardiographic changes, and in case 1, endocardial and subendocardial changes similar to those described in such conditions were demonstrated at autopsy. Purpuric-like skin rashes were seen in both patients in the absence of a positive tourniquet test and with platelet counts above 58,000/cu mm. The nature of these rashes was uncertain, and both disappeared as the leukemia responded to treatment. Case 2 on presentation had severe respiratory distress with hypoxia and a reticular infiltrate on chest x-ray. No infectious agent was demonstrated to explain these respiratory findings. These clinical features could be a consequence of the intense eosinophilia or complications of the acute lymphoblastic leukemia.

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