Human Cyclic Neutropenia Transferred by Allogeneic Bone Marrow Grafting


Human cyclic neutropenia shows many features in common with the animal model of cyclic neutropenia in grey collie dogs. Until now, however, evidence was lacking that cyclic neutropenia in man as in the dog is caused by a defect in a transplanted hematopoietic stem cell. A patient is presented who, while undergoing bone marrow transplantation as treatment for acute lymphoblastic leukemia in relapse, acquired cyclic neutropenia from her histocompatible sibling donor.

During the past decade, bone marrow transplantation has become an accepted therapy for several serious bone marrow disorders. Usually a healthy histocompatible sibling serves as the bone marrow donor. However, in rare instances where no suitable alternative was available, persons with significant medical problems have been marrow donors. For example, bone marrow transplantations from a patient with Gaucher’s disease into a sibling with severe aplastic anemia have been performed. Neither donor suffered any adverse effect. We report an allogeneic bone marrow transplantation from a sibling suffering from cyclic neutropenia into a patient with relapsed acute lymphoblastic leukemia. This clinical observation provides a unique opportunity to demonstrate that the stem cell abnormality in human cyclic neutropenia can be transferred by allogeneic marrow grafting.

Case Report

The propositus (Unique Patient Number 119; shown as III, in Fig. 1) was a 3.75-yr-old white female when acute lymphoblastic leukemia was diagnosed in May 1978. On presentation, the white blood cell count was 155,000/μl with 94% blasts that were PAS positive. Bone marrow aspiration demonstrated complete replacement of marrow by leukemic blasts immunologically characterized as a non-T/non-B type. There was no evidence of extramedullary leukemia.

The patient’s family history was remarkable in that at least 7 members of her family were reported to have cyclic neutropenia. A pedigree is presented in Fig. 1. Cyclic neutropenia was documented in the patient’s sisters during the first year of life. The patient herself was studied during the first and second year of life with sequential blood counts over at least 2 mo and did not show cycling of her neutrophil counts. The distribution of cases in this family is compatible with autosomal dominant inheritance.

The remission induction treatment included prednisone, vincristine, cyclophosphamide, cytosine arabinoside, and L-asparaginase. A complete remission was attained. Prophylaxis against central nervous system leukemia consisted of intrathecal methotrexate and cranial irradiation. Subsequently, the patient received rotational reinduction chemotherapy. After 2.5 yr of continuous remission, treatment was stopped. In May 1981, 6 mo after therapy had been discontinued, the patient had the first bone marrow relapse. Reinduction was successfully established with vincristine, prednisone, L-asparaginase, and hydroxydaunomycin. Tissue typing revealed that the eldest sister (shown as III, in Fig. 1) was fully HLA compatible and MLC nonreactive with the patient. This sibling was known to have cyclic neutropenia but symptomatically her illness was not severe. Because of the grave prognosis associated with relapsed acute lymphoblastic leukemia, it was decided to proceed with marrow ablation and allogeneic marrow transplantation. A bone marrow aspiration performed at the time of admission for transplantation (July 1981) revealed that the patient was in early second relapse; approximately 25% of her bone marrow cells were leukemic blasts. Preparatory to marrow transplantation, the patient received cytosine arabinoside 5 mg/kg on days −7 and −3, the epipodophyllotoxin compound VM 26 10 mg/kg on day −5, vincristine 0.02 mg/kg and 1000 rad total body irradiation (single dose) on day −1. This therapy represents a pilot study for patients with relapsed acute lymphoblastic leukemia. On day 0, the day of marrow transplantation, 2.8 × 10^6 nucleated cells were harvested from the posterior iliac crests of the marrow donor and administered intravenously to the recipient. At this time, the marrow donor was neutropenic. Posttransplant care was carried out as previously described. The clinical course during the aplastic phase was benign, and the patient was discharged 30 days after marrow transplantation. Only mild (grade 1) skin graft-versus-host disease was present during the third week after transplantation, and by day +105, methotrexate and prednisone (administered for graft-versus-host disease prevention and therapy) were discontinued. Bone marrow aspirations performed on days +15, +30, +100, +180, and +273 were still hypocellular but revealed no evidence of recurrent leukemia. Engraftment was confirmed by red cell antigen analysis, demonstrating that the recipient had converted to donor-type antigen pattern (Kell negative to Kell positive). Red cell typing was performed 120 days after the last RBC transfusion. The patient’s hematocrit and platelet counts returned to normal and do not cycle. However, serial white blood cell counts showed that she remained leukopenic (so far highest total white blood cell count 3200/μl) and that she had acquired cyclic neutropenia. She is currently 11.5 mo

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Supported in part by NCI Grant CA 30206. Dr. Hammond is supported by NIH Grant AM 18951.

Submitted May 6, 1982; accepted July 6, 1982.

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0006-4971/82/6006-0050$01.00/0

Blood, Vol. 60, No. 6 (December), 1982 1263
Human cyclic neutropenia is a rare disease in which regularly recurrent episodes of fever, malaise, aphthous stomatitis, and cervical adenopathy occur every 19–22 days in association with neutropenia. Genetic analysis of case clusters in families shows patterns consistent with either autosomal dominant or autosomal recessive inheritance, suggesting heterogeneity in the pathophysiology of this disorder in man. Studies of patients with cyclic neutropenia showed that neutrophils have a normal survival in the circulation and that periodic interruption of marrow cell production causes cycling of the neutrophil counts. Demonstration

![Figure 1](image1.png)

**Fig. 1.** A pedigree showing the propositus who had acute lymphoblastic leukemia (III) and 15 family members, 7 of whom have cyclic neutropenia. Open symbols, unaffected individuals; dark symbols, individuals with cyclic neutropenia. BMT, bone marrow transplantation.

Between day +100 and day +180 after transplantation, the patient and both her sisters had complete blood counts, including platelet and reticulocyte counts performed every second or third day. The absolute counts of neutrophil leukocytes of the three sisters, based on 100 white cell differential counts performed in the clinical hematology laboratory, are presented in Fig. 2. The granulocyte counts of all three cycled synchronously during the period of observation. Although relative monocytosis was present during the episodes of granulocytopenia, no compensatory cycling was noted. Platelet counts of the three sisters did not vary during neutropenia cycles, but the reticulocyte counts of the marrow donor clearly show a low amplitude cyclic fluctuation.

Follow-up examination between days +180 and +344 show that the transplant recipient continues to have cyclic neutropenia and leukopenia. Absolute neutrophil counts cycle between 50 and 1620/μl.

**DISCUSSION**

Human cyclic neutropenia is a rare disease in which regularly recurrent episodes of fever, malaise, aphthous stomatitis, and cervical adenopathy occur every 19–22 days in association with neutropenia. Genetic analysis of case clusters in families shows patterns consistent with either autosomal dominant or autosomal recessive inheritance, suggesting heterogeneity in the pathophysiology of this disorder in man. Studies of patients with cyclic neutropenia showed that neutrophils have a normal survival in the circulation and that periodic interruption of marrow cell production causes cycling of the neutrophil counts. Demonstration

![Figure 2](image2.png)

**Fig. 2.** Absolute neutrophil counts per microliter of the patient (lll.), who received an allogeneic bone marrow transplantation (solid lines), and of her two sisters, who have inherited cyclic neutropenia. III (dotted lines) and III (broken lines). III served as bone marrow donor.
that monocytes, lymphocytes, reticulocytes, and platelets also cycled in some patients suggested that this disease be called cyclic hematopoiesis, but direct demonstration of a stem cell abnormality in man has not been reported.

The discovery of an animal model of cyclic neutropenia in grey collie dogs led to a series of studies that demonstrated close parallels between the human and canine diseases. In the dogs, cycling of the neutrophil counts was shown to be due to a production defect and cycling of other blood cell counts was also demonstrated. Bone marrow transplantation experiments then showed that the cyclic hematopoiesis could be transferred to an unaffected littermate or conversely cured in an affected grey collie by appropriate bone marrow cell infusions. Thus, in dogs, cyclic neutropenia appears to be caused by a regulatory defect in hematopoiesis at the transplantable stem cell level.

It has been shown that cyclic neutropenia in dogs can be induced by chemotherapeutic agents such as cyclophosphamide. It may be speculated that the intense treatment required preparatory to bone marrow transplantation may have induced a similar phenomenon in our patient. For this reason, we have evaluated 122 consecutive patients who had received marrow transplants from healthy sibling donors as a treatment for acute leukemia in our program since 1976: 36 patients died between days -2 and +99 because of infection, bleeding, graft-versus-host disease, or recurrent leukemia and were not evaluated for white cell pattern in respect to cycling; 79 surviving patients had reached normal white blood cell counts by day +100 and remained within the normal range; an additional 7 patients were still leukopenic on day +100 but reached the normal white blood cell range in subsequent months. None of the patients who lived longer than 100 days after marrow grafting showed cyclic neutropenia. The reason for the persisting leukopenia in our patient, up to 11.5 mo after marrow transplantation, is not clear. The number of nucleated cells in the bone marrow inoculum she received certainly is well within the range normally contained in marrow grafts.

In the family reported here, cyclic neutropenia occurred in an autosomal dominant pattern and was transferred from one affected daughter to her unaffected sister by bone marrow transplantation. This extraordinary situation demonstrates that cyclic neutropenia in man, as in the grey collie dog, is caused by a defect in a transplantable hematopoietic stem cell.

Although healthy histocompatible siblings are preferred, a donor with a significant transmissible defect sometimes is the only available option. In this case, the recipient was a patient with acute lymphoblastic leukemia in second relapse who had no chance for long-term survival without bone marrow transplantation, so that the potential benefit clearly outweighed the risks of her developing cyclic neutropenia. However, because she was in relapse at the time of transplantation, her likelihood of developing another leukemic recurrence remains high.

ADDENDUM

The marrow graft recipient is now 15 mo after transplantation and continues to be in complete hematological remission. Her total white blood cell count has risen to 4600/μl. The amplitude of her neutrophil cycles currently ranges from 62 to 2350 μl and is in the same order of magnitude as in the two genetically affected sisters.

REFERENCES

2. Storb R, Thomas ED, Buckner CD, Clift RA, Deeg HF, Fefer A, Goodell BW, Sale GE, Sanders JE, Singer J, Stewart P, Widen AL: Marrow transplantation in acute leukemia. N Engl J Med 1976; 36 patients died between days -2 and +99 because of infection, bleeding, graft-versus-host disease, or recurrent leukemia and were not evaluated for white cell pattern in respect to cycling; 79 surviving patients had reached normal white blood cell counts by day +100 and remained within the normal range; an additional 7 patients were still leukopenic on day +100 but reached the normal white blood cell range in subsequent months. None of the patients who lived longer than 100 days after marrow grafting showed cyclic neutropenia. The reason for the persisting leukopenia in our patient, up to 11.5 mo after marrow transplantation, is not clear. The number of nucleated cells in the bone marrow inoculum she received certainly is well within the range normally contained in marrow grafts.

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