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CASE REPORT

Relapse of Acute Lymphoblastic Leukemia in Pregnancy: Survival Following Chemoirradiation and Autologous Transfer of Interleukin-2-Activated Stem Cells

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Four cases of relapse of acute lymphoblastic leukemia (ALL) in pregnancy have been reported previously. During the past 2 decades, ALL has become curable in a majority of children, many of whom have entered their reproductive years. Thus, additional occurrences of relapsing ALL during pregnancy can be anticipated. We present the fifth case in the English-language medical literature of recurrent ALL in pregnancy. A 20-year-old woman with ALL experienced a relapse during the third trimester of her first pregnancy. Reinduction therapy was started with vincristine and prednisone and the baby was delivered 3 weeks later. Umbilical cord blood was collected and stored. The patient then received intensive chemotherapy with whole body radiotherapy and autologous peripheral blood stem cell rescue. The ALL has been in second remission for 22 months. Our patient is the only current survivor of a relapse of ALL during pregnancy. In addition, the collection of umbilical cord blood from a pregnant woman with leukemia has not been reported previously. © 1999 Academic Press

Key Words: leukemia; pregnancy; relapse; umbilical cord blood harvest.

INTRODUCTION

Acute leukemia is estimated to complicate fewer than 1 per 100,000 pregnancies annually [1]. Although pregnancy does not appear to alter the course of the disease, leukemia may have a detrimental effect on the fetus, in that both the disease and the chemotherapy administered to the mother have been associated with prematurity and, rarely, fetal death [2, 3]. The diagnosis of acute leukemia in pregnancy mandates immediate treatment, with maternal health being given prime consider-

ation. This approach is supported by reports of mean survival time in untreated patients of only 2 months, too brief to permit the delay required for a clinically meaningful enhancement of fetal maturity in many cases [4, 5]. Even when therapy is instituted during pregnancy, long-term maternal prognosis has in the past been poor. In one of the largest single institution series of primary leukemia complicating pregnancy, Pizzuto and colleagues reported in 1980 nine women who were treated during pregnancy, none of whom survived longer than 3 years after delivery [6]. At present, with modern chemotherapy, better supportive measures, and the availability of bone marrow transplantation, an improved prognosis is predictable; however, because leukemia infrequently complicates pregnancy, recent survival data are lacking.

We present here a case of acute lymphoblastic leukemia (ALL) which relapsed early in the third trimester of pregnancy. To our knowledge, this report describes the youngest patient to experience a relapse during pregnancy and is only the fifth such case in the English-language medical literature. We also describe for the first time the collection of umbilical cord blood from the fetus of a woman with leukemia.

CASE HISTORY

While living in an orphanage in Ensenada, Mexico, a 17-year-old female complained of abdominal pain and severe fatigue in May 1993. She was found to have a leukocyte count of $35 \times 10^9/L$ and a hemoglobin of 7 g/dl. A bone marrow aspiration was consistent with acute leukemia. She was given a course of high-dose cytosine arabinoside and was referred to the City of Hope Medical Center as a candidate for allogeneic bone marrow transplantation. Her entry into the United States on a medical visa was facilitated by the Door of Faith organization of Laguna Niguel, California.

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At the City of Hope, a bone marrow biopsy demonstrated a predominance of lymphoblasts, classified as French-American-British Cooperative Working Group FAB L-2. Flow cytometry study revealed a pre-B phenotype expressing CD10, CD34, terminal deoxynucleotidyl transferase, and HLA DR. No significant numerical or structural chromosomal abnormality was found. Analysis of cerebrospinal fluid demonstrated no evidence of central nervous system involvement.

The patient was treated with induction chemotherapy consisting of prednisone, vincristine, L-asparaginase, and daunorubicin. Remission was documented by a repeat bone marrow biopsy in July 1993. She then received consolidation chemotherapy with methotrexate and cytosine arabinoside and central nervous system prophylaxis with intrathecal methotrexate. Maintenance chemotherapy consisted of cyclophosphamide, vincristine, cytosine arabinoside, and prednisone. All chemotherapy was electively discontinued in March 1996, 34 months after diagnosis. Serial bone marrow aspirations and spinal fluid examinations had demonstrated continuous remission.

The patient conceived her first pregnancy in August 1996. At 32 weeks gestation, 11 months after cessation of maintenance chemotherapy, she presented for routine prenatal care complaining of fatigue and generalized malaise. Physical examination showed no lymphadenopathy or hepatosplenomegaly. Monthly complete blood counts had been within normal limits since chemotherapy had been discontinued, but now demonstrated a white blood count of $31 \times 10^9/L$, a platelet count of $60 \times 10^9/L$, and 80% lymphoblasts in the peripheral blood smear (Fig. 1A). A bone marrow biopsy confirmed relapse of ALL (Fig. 1B). Immunophenotyping of the lymphoblasts demonstrated expression of CALLA and CD34. The cerebrospinal fluid was normal.

At 33 weeks gestation, reinduction chemotherapy was started with vincristine and prednisone. After two doses of vincristine the leukocyte count fell to $2 \times 10^9/L$ and circulating lymphoblasts were no longer identified. Antepartum fetal surveillance by ultrasonography and fetal heart rate nonstress testing revealed no evidence of fetal or placental anomalies or placental insufficiency.

To prevent exposure of the fetus to additional, more aggressive chemotherapy, at 35 weeks gestation, labor was induced with intravaginal prostaglandin at the University of California, Irvine, Medical Center and a viable male infant weighing 2648 g was delivered. With the patient's informed consent, 80 mL of umbilical cord blood was collected in heparinized saline and cryopreserved at the City of Hope Medical Center. Pathologic evaluation of the placenta showed no evidence of metastatic disease.

One month after delivery, the patient received consolidation therapy at the City of Hope with high-dose ifosfamide, etoposide, L-asparaginase, vincristine, and intrathecal methotrexate. She experienced transient pancytopenia, gram-negative sepsis, and a mild episode of cardiopulmonary failure.

After HLA typing failed to identify any matched siblings,

FIG. 1. Relapse of acute lymphoblastic leukemia. (A) Peripheral smear: Circulating immature lymphoblasts with high nuclear-to-cytoplasmic ratio (arrows). (B) Bone marrow biopsy: Replacement of marrow by lymphoblasts.

she received a primed peripheral blood stem cell autologous transplant: Following administration of granulocyte colony-stimulating factor, the patient's peripheral blood was harvested and CD34⁺ progenitor cells were isolated and activated with interleukin-2 (IL-2). The conditioning regimen included total body irradiation, high-dose cyclophosphamide, and etoposide (Table 1). She then underwent hematopoietic rescue with her own activated stem cells and has remained in remission for 22 months without further therapy. Except for amenorrhea, minor renal dysfunction, and mild cardiomyopathy, she is clinically well. Her baby is healthy and is growing and developing normally.

DISCUSSION

Approximately 28% of acute leukemias diagnosed during pregnancy have been classified as ALL [2]. ALL is a malignant disorder resulting from the clonal proliferation of lymphoid precursors with arrested maturation. The disease can originate

TABLE 1
Conditioning Regimen for Autologous Stem Cell Transplant

Day minus 9:	Admission to bone marrow transplant unit
Day minus 8–5:	Fractionated total body irradiation: 3 Gy/day
Day minus 4:	VP-16 (60 mg/kg)
Day minus 2:	Cyclophosphamide (100 mg/kg)
Day minus 1:	Thawing and IL-2 activation of autologous peripheral stem cells
Day 0:	Reinfusion of IL-2-treated peripheral stem cells
	Nucleated cells: $5.29 \times 10^8/\text{kg}$
	CD34+: $11.31 \times 10^6/\text{kg}$

in lymphoid cells of B-cell or T-cell origin. ALL was among the first malignancies to be cured in the majority of children (60–70%) [7]. In adults and adolescents, however, ALL is curable in only 20–40% of patients [1]. Poor prognostic factors include age >10 years, leukocyte count $>10,000/\text{mm}^3$, a high percentage of circulating lymphoblasts, pseudodiploid cytogenetics, CD34 expression, and the presence of the multidrug resistance-associated protein P-170 [7].

When the diagnosis of ALL is made during pregnancy, treatment of the mother should begin without delay, so as not to compromise her chance for remission or possible cure. Because exposure to chemotherapy early in pregnancy poses a risk of teratogenesis to the fetus [8], therapeutic termination may be considered during the first and early second trimester. In the latter half of pregnancy, fetal exposure to antineoplastic agents carries risks of intrauterine growth restriction and fetal bone marrow toxicity [5]. Antepartum surveillance with ultrasonography to identify gross fetoplacental abnormalities or growth restriction and fetal heart rate testing to document fetal well-being and exclude sinusoidal rhythms resulting from anemia are required. After delivery, potential delayed effects resulting from intrauterine exposure to chemotherapy include poor growth, subnormal intellectual function, loss of reproductive capacity, compromised immunologic status, and the development of secondary malignancies [9], emphasizing the need for long-term follow-up of these children.

In pregnant patients with leukemia, fetal risks may go beyond exposure to chemotherapy and dependence on a maternal host weakened by disease or treatment-related side effects. Hematologic malignancies rank second only to malignant melanoma with respect to the frequency of metastases to the products of conception. Placental and fetal tissue metastases have been reported, as has one case each of missed abortion and fetal leukemia arising from vertical transmission [10–12]. While many chemotherapeutic agents used in the treatment of leukemia are known to cross the placenta, it is not known whether fetal metastases are effectively treated by maternal chemotherapy. The fetus may theoretically also be predisposed to the subsequent development of leukemia by inheritance from the mother of genetic mutations [13].

Our case is the first report of cord blood collection in a pregnancy complicated by leukemia. Recent reports have dem-

onstrated the utility of human cord blood as a source of transplantable hematopoietic stem cells to treat patients with a number of blood, genetic, and metabolic disorders and to reconstitute hematopoiesis after myeloablative therapy for hematologic malignancies [14, 15]. The long-term storage of cord blood would enable the child to receive an autologous transplant should one of these conditions occur later in life. This is a particularly relevant consideration given the theoretical risk of leukemia resulting from *in utero* chemotherapy exposure, vertical transmission during gestation, or inheritance of genetic or chromosomal aberrations.

The availability of cord blood also presents the possibility of a future transplant for the mother, who is at high risk for another relapse. Our patient's HLA type matched that of the cord blood at only three of six loci. Although results with HLA-mismatched cord blood transplants have been encouraging, cord blood probably has a weak graft-versus-leukemia effect. We therefore opted in this case for hematopoietic rescue by stem cells from the patient's peripheral blood rather than from the cord blood.

Transplantation of cord blood carries the potential risk of transferring vertically transmitted leukemic cells to the recipient, a risk that would presumably reflect maternal disease burden at the time of cord blood harvest. Assessing the safety of such a transplant ultimately may be assisted by molecular techniques currently able to detect malignant cells at densities lower than one per million in some types of leukemia. Furthermore, molecular techniques capable of purging malignant cells from fetal cord blood have not been reported, but may be feasible in the future.

The present case is the fifth in the English-language medical literature, and only the second in the United States, of a patient with ALL which relapsed during pregnancy. Although the relapse may have been a chance event, mechanisms attributable to the immunologic and hormonal changes of pregnancy have been postulated. Specifically, immunologic derangement may result in a loss of control of minimal residual disease, while placental growth factors may stimulate quiescent leukemic cells to replicate [16].

The clinical features of our patient and those of the four cases previously reported in the literature [17–20] are summarized in Table 2. Although the number of cases is small, it appears that most relapses occur in the second trimester of pregnancy, with our patient's relapse occurring in the third trimester being distinctly unusual. An extraordinarily wide range in the interval between diagnosis and relapse (14 months to 19 years) has been observed. Also of note is the fact that all five patients were treated between 2 weeks and 4.5 months with cytotoxic chemotherapy with the fetus still *in utero*. While one patient whose treatment began in the first trimester later underwent an elective abortion, four other patients, including our own, subsequently delivered healthy and normal infants. Unfortunately, the maternal outcome was not as favorable: Although all patients except one entered complete remission,

TABLE 2
Literature Review: Relapses of Acute Lymphoblastic Leukemia during Pregnancy

Author	Country	Age ^a (years)	Interval to relapse (years)	Gestational age ^b (months)	Duration of treatment ^c (months)	Response to therapy ^d	Outcome [baby/mother (months)]
Dara [17]	United States	26	1.2	5	3	CR	Healthy/DOD 10
Reynoso [18]	Canada	3	19	4	4.5	CR	Healthy/DOD 11
Brinckner [19]	Denmark	10	17	3	6	CR	Abortion/DOD 20
Camera [20]	Italy	21	4	4	3	PR	Healthy/DOD 12
Present	United States	17	3.5	7	0.75	CR	Healthy/NED 22

Note. Each of the first three patients experienced a second relapse following pregnancy termination/delivery. Follow-up and outcome information of the cases cited in references 17 and 19 was kindly provided by Drs L. M. Slater and H. Brinckner, respectively. DOD, dead of disease following relapse; NED, no evidence of disease.

^a Age at primary diagnosis of leukemia (i.e., prior to pregnancy and leukemic relapse).

^b Duration of pregnancy at time of diagnosis of leukemic relapse.

^c Duration of treatment with fetus *in utero*.

^d Response to therapy during pregnancy: CR, complete remission; PR, partial remission.

our patient is currently the only survivor, the others having died of their disease in under 2 years.

In summary, relapse of leukemia in pregnancy is a rare but potentially devastating event for mother and baby. The leukemia is an immediate threat to maternal survival and as such demands early therapy. For the fetus, if termination of early pregnancy is not elected or if delivery must be postponed because of prematurity, close surveillance is required, given the possible adverse impact of the disease and its treatment, both *in utero* and subsequently. The potential uses of cord blood should be discussed with the patient and harvesting of the blood strongly encouraged. Since with standard therapy, patients in whom leukemia has relapsed are at very high risk for treatment failure and death, early referral should be made to a cancer center for consideration of specialized treatment protocols.

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