Management of pregnancy-associated acute leukemia

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Summary

Since leukocystosis and anemia are common findings in pregnancy, pathological alterations in hematopoesis, such as leukemias, can sometimes proceed undetected. Chemotherapy during pregnancy carries the risk of teratogenic effects on the fetus, and there is little data to guide chemotherapeutic regimens for leukemia during pregnancy. The following paper describes our experience in treating two women with acute leukemia during pregnancy and the immediate postpartum period, and reviews the relevant literature.

Key words: Acute leukemia; Chemotherapy; Pregnancy.

Introduction

In Taiwan, annual mortality rates for leukemia are approximately 3.28 per 100,000 people (722 cases of death per year), with 2.77 per 100,000 people (297 cases of death per year) when addressing the female population alone. The peak incidence of acute lymphoblastic leukemia (ALL) occurs at three to four years of age, and the incidence steadily decreases after nine years of age. ALL is rare after the age of 40 years of age. In contrast, the incidence of acute myelogenous leukemia (AML) gradually increases with age; and the median age of AML patients is 60 years.

The sequelae of acute leukemia include nonspecific fatigue, weakness, CNS involvement (headache, nausea, vomiting, blurred vision, or cranial nerve dysfunction), bone pain, abdominal fullness (hepatosplenomegaly in ALL), oliguria (dehydration, uric acid nephropathy), and obstipation. Physical signs that can be elicited on examination include pallor, petechiae, purpura, sternal tenderness, lymphadenopathy, hepatomegaly, meningismus, gingival hyperplasia, bleeding, and signs of infection.

Radiation exposure is a leukemogenic factor and can result in development of ALL, AML, or chronic myelogenous leukemia (CML). The incidence of leukemia increases in direct proportion to the cumulative dose of radiation, with doses greater than 100 cGy associated with the development of leukemias. In addition to radiation exposure, carcinogens associated with leukemia include benzene, toluene, alkylating agents (particularly associated with AML) arsenides, phenylbutazone, and chloramphenicol.

While leukemia is rare [1, 2], anemia is a common finding in pregnancy, with the most common cause attributed to iron deficiency anemia (IDA). In fact, over 50% of pregnant women in developing countries suffer from IDA [3], a diagnosis that is associated with poor pregnancy outcome if present in the first trimester [4]. Leukocytosis may also appear in normal pregnancy [5]. As a result, development of leukemia may sometimes proceed undetected. In the following paper two cases of pregnancy-associated acute leukemia are described and the relevant literature is reviewed.

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Case Report

Case 1

A 28-year-old primgravida patient presented at 13 weeks of gestation complaining of two weeks of non-specific fatigue and weakness. Routine blood testing revealed anemia and leukocytosis. (WBC count: 13,460, Hgb: 9.3, MCV: 90.2, platelet count: 145,000) in contrast to her normal counts that were documented on medical records from two years prior. The patient was referred for hematology consultation at out institution, where examination of the peripheral smear revealed blasts and immature cells (Table 1). The patient denied exposure to benzene or radiation and had no family history of hematologic abnormalities. There was no prior history of major disease except for pelvic endometriosis (treated with electrocautery) and intra-abdominal adhesions (treated by laparascopic lysis) six years prior.

The patient was admitted to the hospital for further work-up and treatment. CBC revealed normochromic normocytic anemia and leukocytosis, with 37% immature blasts. (Table 1). Bone marrow aspirate and biopsy examination revealed a hypercellular marrow with decreased erythroid and megakaryocytes cells and marked increase of blast cells characterized by small size and scant cytoplasm. Special staining of bone marrow revealed the following characteristics and markers: peroxidase(-), PAS(+)3%, acid phosphatase(-), IA(+), CD19(+), CD20(-), CD7(-), CIG(-), SIG(-), CD10(-), and normal chromosome study. A diagnosis of B-cell acute lymphoblastic leukemia (ALL) was reached via the bone marrow cytology and immunohistochemical stains.

After being informed as to the teratogenic effects of chemotherapy during the first trimester, the patient elected to terminate the pregnancy via dilatation and curettage. Induction chemotherapy was initiated on November 13, 1999 and consisted of prednisolone 70 mg/m^2 qd for 25 days, vincristine 1.4 mg/m^2 qw (per week) for 4 doses, and daunorubicin 60 mg/m^2

on D1-D3. Complete remission was demonstrated by bone marrow blood examination. The patient received cranial prophylaxis with radiation (2400 rads) and methotrexate (15 mg intrathecal injection). Maintenance chemotherapy with 6-MP and MTX was administered over a one-year period. The patient remained in good health until relapse in September 2001. The patient was subsequently treated with salvage chemotherapy (Ara-C and Mitoxantrone on D1-D4). Unfortunately, the patient developed sepsis and acute renal failure and expired approximately 18 months after the initial diagnosis of acute leukemia.

Case 2

A 30-year-old primigravida patient was referred to our Hematology Department by her local clinic after presenting with intermittent fever, bilateral ankle twitching and leukocytosis four months after full-term delivery by cesarean section. CBC revealed leukocytosis and normochromic normocytic anemia, and examination of the peripheral smear revealed blasts and immature cells (Table 2). The patient denied exposure to benzene or radiation, and there was no family history of hematologic abnormalities. The patient was admitted for further work-up and treatment, and bone marrow aspirate and biopsy revealed hypercellularity with almost total replacement of the normal marrow cells and trabeculae with uniform, monotonous blasts (> 80%), associated with scant cytoplasm and frequent mitoses. Special staining of bone marrow revealed the following characteristics and markers: peroxidase(-), PAS(-), acid phosphatase(+), IA(+), CD34(+), CD2(+), CD3(-), CD7(-), CIG(-), SIG(-), CD10(-), CD 20(+/-), and chromosome studies were normal. Based on bone marrow biopsy, bone marrow aspirate, and immunohistochemical stains, a diagnosis of B-precursor acute lymphoblastic leukemia (ALL) was reached. Induction chemotherapy was initiated on March 8, 1999 and consisted of prednisolone 70 mg/m^2 qd for 25 days, vincristine 1.4 mg/m^2 per week for 4 doses, and daunorubicin 60 mg/m^2 on D1-D3. During induction chemotherapy, the immature cells gradually disappeared (Table 2), and complete remission was confirmed via bone marrow blood examination after completion of induction chemotherapy. The patient received cranial prophylaxis with radiation (2400 rads) and methotrexate (15 mg intrathecal injection). Maintenance chemotherapy with 6-MP and MTX was administered over a one-year period. The patient remained in good health until relapse in March 2001. Further chemotherapy was performed using Ara-C and Mitoxantrone on D1-D4. The patient continues with regular follow-up, albeit with a poor prognosis.

Discussion

Disruption of different hematopoetic cell lines occurs in leukemic patients, resulting in abnormalities in production of erythrocytes (90% normocytic, normochromic anemia), leukocytes (leukocytosis in 60% of cases, normal WBC in 15%, and leukopenia in 25%) and platelets (thrombocytopenias in 90%). The two cases discussed in this study evinced such hematologic abnormalities, including leukocytosis, normocytic anemia, and decreased platelet counts.

When reviewing the medical records of the 4,100 pregnant patients that were cared for at Tri-Service General Hospital over the last three years, only two cases of acute leukemia were diagnosed. Zuazu et al. reviewed 48 pregnant women diagnosed with leukemia or lymphoma collected from ten hospitals [6] and reported that 64% of the pregnancies went to term, 9% resulted in spontaneous abortion, 5% resulted in premature births, and one case of malformation of the offspring occurred. However, these outcomes were not significantly different than the general population of pregnant women. There was one case of late relapse from acute lymphoblastic leukemia

Table 1. — *Laboratory blood analysis of Case 1.*

Date	WBC 1000/ul	N/L/M%	Nucleated RBCs 100/WBC	Blasts	Young cell	Hgb	Platelets 1000/ul	Reticulocytes %	Meta-myelocytes %	Remarks
3/11/00 Before induction C/T	13.46	33/28/0	3	0	37	8.9	145	1.6	1	Anisocytosis, Baso. Seppling RBC, Baso. RBC; Platelets: decrease, adequate
19/12/00 Post induction C/T	3.37	90/5/3	0	0	0	8.6	194	1.5	1	Anisocytosis
11/01/01 Post CNS prophylaxis	5.06	63/24/12	0	0	0	12.3	382k	2.5	0	Anisocytosis, tear drop cell

Table 2. — *Laboratory blood analysis of Case 2.*

Date	WBC 1000/ul	N/L/M%	Nucleated RBCs 100/WBC	Blasts	Young cell	Hgb	Platelet 1000/ul	Reticulocytes %	Meta-myelocytes %	Remarks
8/3/99 Before induction C/T	45.99	3/10/0	0	30	56	8.9	114	0.3	0	Anisocytosis, Baso. RBC, normochromic, tear drop cell
8/4/99 Post induction C/T	21.94	81/2/1	0	0	0	10.9	338	1.0	5	Anisocytosis, Baso. Stippling RBC, Baso. RBC, slight hypochromic, tear-drop cell
27/4/99 Post CNS prophylaxis	4.70	88/5/6	0	0	0	9.8	229	0.8	0	Anisocytosis, normochromic

Baso: basophilic.

Table 3. — *Literature concerning pregnant women with acute leukemia.*

Author, year	No. of cases	Patient's outcome	Fetal outcome
Zuazu J., 1991	56 pregnancies with leukemia or lymphoma	No mortality during pregnancy or postpartum	1. 9% resulted in spontaneous abortion, and 5% resulted in premature births 2. No fetal loss during the first year after chemotherapy 3. Only one malformation
Caligiuri M.A., 1989	40 AML in pregnancy, 20 ALL in pregnancy	Chemotherapy was performed. AML: 72% complete remission ALL: 76% complete remission	1. Chemotherapy treatment during pregnancy 2. 13 fetus in first trimester, 8 premature and 2 spontaneous abortion
Camera A., 1996	A woman with ALL had a relapse during pregnancy	The patient died of refractory leukemia 9 months after delivery	A cesarean section was performed at the end of the 7th month, with the delivery of a normal male infant
Aviles A. *et al.*, 1988	17 mothers with acute leukemia received chemotherapy during pregnancy	No mortality during pregnancy or postpartum	Chemotherapy was given during the pregnancy, including 11 cases during the first trimester. No fetal malformations or late side-effects were found
Hansen W.F. *et al.*, 2001	A 24-year-old pregnant woman with acute lymphocytic leukemia	The patient completed 3 cycles of intensive multiagent chemotherapy	1. Transient oligohydramnios in each cycle, decrease fetal growth rate 2. A normal male infant was delivered at 36 weeks

during the 17th week of gestation, but it did not contribute to pregnancy-related relapse [7].

Since it appears that leukemia does not affect the pregnancy outcome, elective termination of pregnancy remains controversial [6, 8] Caligiuri *et al.* analyzed retrospective series and case reports of pregnant women with leukemia and suggested that elective termination of pregnancy is not necessary [9]. They concluded that standard chemotherapy could be safely administered during the second and third trimesters provided that the antifolates (e.g. methotrexate), being particularly teratogenic, were avoided. However, they also commented that the risk for placental injury, sepsis, and spontaneous abortion or premature birth was undoubtedly increased in women who experience periodic episodes of myelosuppression that accompany leukemia treatment. Sadural *et al.* stated that the benefit of immediate treatment must be weighed against toxicity to the fetus in cases in which elective termination of pregnancy is not performed [8]. In contrast, Maloisel *et al.* [10] advocated that termination of the pregnancy in the first trimester resulted in the best outcome for the woman and fetus. McLain reviewed five case reports of acute or chronic leukemia in pregnancy [1] and found that chemotherapy and radiation during the second and third trimesters did not commonly result in gross abnormalities. However, radiation therapy has late carcinogenic effects and the long-term morbidity and mortality of infants exposed to radiation in utero is not known.

Aviles *et al.* reviewed the status of 17 children born to mothers with acute leukemia who received chemotherapy during pregnancy [11], sometimes during the first trimester. Fetal malformations did not occur, and late side-effects were not demonstrated. Kawamura *et al.* gathered data via mail questionnaire from 43 parents who had undergone post-remission therapy [12]. No malformed babies resulted, and the average duration until delivery was 79 months after diagnosis and 49 months after the final post-remission therapy. Four of 38 parents of live offspring died (3 with relapse, 1 from other disease), and the other 34 parents were in complete remission. Maloisel *et al.* observed that use of chemotherapy in pregnant patients resulted in both objective disease remission and the subsequent delivery of normal infant [10]. However, Lishner *et al.* found that chemotherapy during the second and third trimesters could have nonteratogenic adverse effects, such as low birth weight [13]. Brell *et al.* stated that acute leukemia demands prompt cytotoxic chemotherapy to maximize the chances of maternal survival [14], but advocated against use of cytotoxic agents during the first trimester, when there is a 17% chance of fetal malformation (particularly with folate antagonists). Similar findings have been seen in pregnant patients with other types of cancer [15-17].

Data from animal models describe adverse effects on the fetus that may occur from chemotherapy. Significant amounts of 5-fluorouracil and mitomycin-c can cross the placenta and may result in fetal damage [18]. In patas monkeys, investigators demonstrated DNA damage and high adduct levels in fetal brains after cisplatin treatment [19]. In pregnant women treated with multiagent chemotherapy for acute leukemia, oligohydramnios and decreased fetal growth rate was noted [20]. Other case reports suggest that chemotherapy treatment during pregnancy may result in fetal growth restriction, low birth weight, preterm delivery, or myelosuppression, even if chemotherapy was administered in the 2nd and 3rd trimesters [21-24]. Sweet reported that radiation may be particularly problematic and that great caution should be paid to pregnant women who undergo radiation therapy for prophylactic purposes [25]. Finally, Aviles *et al.* observed 17 children born to mothers with acute leukemia who received chemotherapy during pregnancy. Chromosomal studies were unremarkable in the long-term survivors (age range 4 to 22 years). Further, no fetal malformations were found and late side-effects were not present [11].

McCredie *et al.* treated 543 adult leukemic patients with vincristine and prednisone [26]. Median durations of

complete remission and survival were 35 and 62 weeks, respectively, for patients with AML, and 47 and 75 weeks, respectively, for patients with ALL. Ho *et al.* reviewed 46 young adult patients with ALL that received chemotherapy from 1984 through 1997 [27]. The median duration of remission was 12 months (range 3-39 months), and the median overall survival time was 13 months (range 0.5-50 months). Styczynski *et al.* studied chemotherapy resistance in 23 adult ALL patients and 395 childhood ALL patients [28] and reported that adult common/pre-B-ALL were more resistant than childhood common/pre-B-ALL (n = 310) to treatment with prednisolone, dexamethasone, and daunorubicin. Lymphoblasts from adults proved to be relatively resistant to drugs commonly used in therapy. This finding could contribute to the poor prognosis of ALL seen in pregnant adults.

Conclusion

Leukemia is a rare event in a pregnant patient. While no specific symptoms or signs suggest a diagnosis of acute leukemia in pregnant women, the presence of normocytic anemia should raise the index of suspicion. There does not appear to be a causal relationship between pregnancy and acute leukemia, but the relatively few number of cases make associations diificult to detect.

When cure of leukemia in a pregnant woman is feasible, therapy should be initiated immediately. Elective termination of pregnancy during the 1st trimester should be considered, but chemotherapy treatment during the 2nd to 3rd trimester may not require termination as remission of acute leukemia and delivery of a normal infant seems likely. When maternal prognosis is poor, protection of the fetus can still be achieved by avoidance of radiation therapy during the 1st trimester. Long-term surveillance of children born to women treated with chemotherapy during pregnancy is still required to definitively rule out late adverse effects.

As in non-pregnant patients, the prognosis for adult-onset acute leukemia in pregnancy is poor, and the prognosis worsens if there is a delay in diagnosis or treatment. In the future, analysis of chemotherapy resistance profiles could be exploited to tailor individualized treatment with higher efficacy and lower toxicity to optimize prognosis for the patient and fetus.

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