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A Case of BCR-ABL Negative T-Cell Acute Lymphoblastic Leukemia (ALL) in an Obese Pregnant 36-year-old Primigravida at 17 Weeks Gestation

Melinda Madden[1], Rachel Truong[2], Christine Greves[3] and SJ Carlan[4*]

[1]Department of Infectious Disease, Orlando Regional Medical Center Orlando, Florida, USA

[2]Department of Internal Medicine, Orlando Regional Medical Center Orlando, Florida, USA

[3]Department of Obstetrics and Gynecology, Orlando Regional Medical Center Orlando, Florida, USA

[4]Department of Ob Gyn Division of Academic Affairs and Research, Orlando Regional Medical Center Orlando, Florida, USA

[*]**Corresponding author:** SJ Carlan, Department of Ob Gyn Division of Academic Affairs and Research, Orlando Regional Medical Center Orlando, Florida, USA. E-mail: stevecarlan@gmail.com

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Abstract

Background: Acute lymphocytic leukemia, also known as acute lymphoblastic leukemia, is a rapidly progressive proliferation of leukocyte precursors that can be fatal within a few months from onset if left untreated. Acute lymphocytic leukemia is further divided into the sub-types B-cell acute lymphocytic leukemia and T-cell acute lymphoblastic leukemia depending on the lineage of the cancerous cells. Both types can very rarely present in pregnant patients, complicating treatment options due to concern for harm to the fetus or mother.

Case Report: Here we present the case of a 36-year-old primigravida diagnosed with T-cell acute lymphoblastic leukemia at 17 weeks gestation. A routine complete blood count found marked leukocytosis with blasts at white blood cells (WBC) 58 x 103/uL and blasts 66%. Her bone marrow biopsy revealed T lymphoblastic leukemia/lymphoma with leukemic blasts occupying 80% of the marrow space and accounting for 90% of cells. Genetic testing of the white blood cells from her blood sample was negative for BCR-ABL1 fusion (Philadelphia chromosome). She underwent a second-trimester pregnancy termination, was started on a pediatric-inspired acute lymphocytic leukemia treatment regimen and went into remission.

Conclusion: To our knowledge, this case is the first reported case of Philadelphia chromosome-negative T-cell acute lymphoblastic leukemia in a woman of advanced maternal age treated with the older adolescents and young adults regimen for acute lymphocytic leukemia. The availability of first and second-trimester pregnancy termination procedures is a medical necessity in the management of gestational malignant hematologic neoplasia that is illustrated in this case.

Keywords: Pregnancy; Philadelphia chromosome; Precursor cell lymphoblastic leukemia-lymphoma; Precursor t-cell lymphoblastic leukemia-lymphoma; Female

Background

Acute lymphoblastic leukemia (ALL), also known as acute lymphoblastic leukemia, is an especially rare diagnosis amongst pregnant patients, with an incidence rate estimated at 1 case in 75,000-100,000 pregnancies [1]. Treatment must be initiated immediately should such an un-fortunate diagnosis be made, as delay has been shown to lead to worsened prognosis and could cause several complications to the pregnancy, such as leucostasis, thrombosis, and disseminated intravascular coagulation [1]. When choosing treatment, multiple prognostic factors, including but not limited to the patient's comorbidities, the possible termination of the pregnancy, and the cy-togenetic abnormalities of the disease must be considered to choose the best treatment as quickly as possible.

One specific abnormality that could impact the choice of treatment is the BCR-ABL1 fu-sion gene, also known as the Philadelphia chromosome (Ph) or t (9;22). It is primarily associated with chronic myelogenous leukemia but can be seen in ALL [2]. Recommended treatment for ALL in Ph-negative patients with significant comorbidities includes low, moderate, and high-intensity induction therapy with steroids in combination with chemotherapy treatments plus maintenance therapy [3]. However, evidence has emerged through the Cancer and Leukemia Group B 10403 (CALGB 10403) trial that a treatment regimen normally administered to pediatric ALL patients shows promise in the older adolescents and young adults (AYA) aged 17-39 years old with Ph negative ALL [4]. Here we report a case of Philadelphia chromosome-negative ALL in a 36-year-old primigravida at 17 weeks gestation who would later receive the pediatric ALL treatment regimen. This case is, to our knowledge, the first reported case of Philadelphia chro-mosome-negative T-ALL in an obese woman of advanced maternal age who received the CALGB 10403 treatment regimen. This report aims to explore the difficult ethical and medical considera-tions that a physician must undergo should a patient with significant comorbidities and a high-risk pregnancy present with ALL.

Case Presentation

A 36-year-old morbidly obese primigravida at 17 weeks gestation was referred from an outside hematology and oncology center for evaluation. A routine complete blood count (CBC) found marked leukocytosis with blasts at white blood cells (WBC) 58 x 103/uL and blasts 66%, (normal range WBC 4.4-10.5 x 103/uL). The patient denied any headaches, vision changes, fa-tigue, pain, or bleeding and had no personal or family history of any hematologic malignancy. Her physical examination was benign and vital signs were stable, and her other prenatal labs were within normal limits. Her body mass index was measured at 42 kg/m^2.

A repeat CBC two weeks later was remarkable for WBC 94.3 x 103/uL, blasts 82%, and moderate smudge cells with the peripheral smear showing predominantly immature blast cells with large nuclei. Pathology of the peripheral blood resulted in T-cell lymphoblastic leuke-mia/lymphoma. Her peripheral blood flow cytometry identified precursor T cells expressing CD34 and CD38 but negative for CD117. The cells expressed early T lineage markers, including CD2, CD5, CD7, and cytoplasmic CD3. They were negative for surface CD3, CD4, CD8, HLA-DR, markers of B-cell lineage, and myeloid markers. TdT+ lymphoid blasts comprised 85% of the analyzed white blood cells and co-expressed cytoplasmic CD3, CD2, CD5, CD7, CD34, and CD38 but were negative for surface CD3, HLA-DR, and myeloid markers. Mature lymphocytes, including polyclonal B-cells, NK cells, and immunophenotypically normal CD4+ and CD8+ T cells were decreased. Mature granulocytes were also markedly decreased. 85% of the white blood cells from her blood sample displayed weak CD45 and low side scatter consistent with blasts.

Karyotyping studies yielded 45, XX add (5) (q11.2), del 6 (q13q23), -7 [3]/, 45, XX add (5) (q22q35), del 6 (q13q23), -7 [3]/, and 46, XX [14], indicating a female who is a mosaic for a single missing chromosome and several additions and deletions of unknown significance. Further genetic testing was negative for BCR-ABL1 fusion (Philadelphia chromosome), MLL rearrangement, and MYC rearrangement. Her bone marrow biopsy revealed T lymphoblastic leukemia/lymphoma with leukemic blasts occupying 80% of the marrow space and accounting for 90% of cells. According to the 4th edition of WHO classification guidelines, our patient was diagnosed with early T-precursor ALL based on CD7 expression, lack of CD8 expression, and positivity for CD34.

The patient was recommended a second-trimester abortion before treatment due to the risk of mortality to both the patient and the fetus. She initially declined but later opted to undergo the procedure so she could begin treatment with a pediatric-inspired ALL treatment regimen as rec-ommended by CALGB 10403. Her induction phase was planned to be 4 weeks. Her treatment would begin with intrathecal injection of the antimetabolite cytarabine on Day 1, then subsequent doses of the anthracycline daunorubicin, the vinca alkaloid vincristine, the antimetabolite metho-trexate, the enzyme pegylated asparaginase, allopurinol, and prednisone as detailed in CALGB 10403. Further treatment course from there-specifically whether the patient would require ex-tended remission induction-would depend on her response to the initial induction course. She was transferred to another hospital outside of our healthcare system at her request to complete her treatment and achieve remission. She was consequently lost to follow-up.

Discussion

The choice of treatment for ALL in a pregnant patient presents a significant medical and ethical challenge that requires thorough discussion with the patient and the entire medical team about the patient's goals for her disease and her fetus. Rapid initial recognition of the disease therefore becomes an important cornerstone in tackling such a challenge. Characteristic clinical findings of all leukemia types include frequent infections, fatigue, malaise, weight loss, diarrhea, bruising, and shortness of breath. However, epistaxis, bleeding gums, abdominal pain, chest pain, nausea, and vomiting were more significant for acute leukemia than chronic leukemia [5]. De-pending on the immunophenotyping of the cancer cells, ALL can further be divided into B-cell acute lymphocytic leukemia (B-ALL) and T-cell acute lymphocytic leukemia (T-ALL) subtypes, with T-ALL representing only 25% of all leukemia cases [6]. Diagnosis is then confirmed via bone marrow biopsy or peripheral blood smear showing more than 20% blast cells [7]. Our 36-year-old patient with a medical history significant only for morbid obesity and a pregnancy of 17 weeks gestation lacked the typical clinical and physical exam findings of ALL. She was diagnosed with Ph-negative T-ALL due to an incidental finding on routine CBC, the findings of her bone marrow biopsy and her blood smear, and her genetic testing.

The patient's cytogenetic testing was negative for Ph, which plays a significant role in guiding her prognosis and therapy. Ph-positive patients have historically been noted to have worse survival outcomes but advent of tumor-kinase inhibitors has improved survival of such patients [2]. However, because of her complex karyotype (defined as at least 5 chromosomal abnormalities) and her being over 35 years old at the time of diagnosis, our patient's disease was considered at least intermediate risk [2].

Her pregnancy added an additional layer of ethical and medical com-plexity to her case. Per the National Comprehensive Cancer Network (NCCN) guidelines, treat-ment for ALL in Ph-negative patients AYA patients such as ours is the regimen recommended by CALGB 10403, which specifies an induction regimen of intrathecal cytarabine on Day 1, then subsequent doses of daunorubicin, vincristine, methotrexate, pegylated asparaginase, allopurinol, and prednisone. However, the recommended treatment regimen for a patient with substantial comorbidities such as our morbidly obese patient can also include the alkylating agent cyclo-phosphamide and the monoclonal antibody rituximab depending on the choice of treatment in-tensity [3]. Regardless of the regimen chosen, the NCCN recommends that all regimens should include central nervous system (CNS) prophylaxis, antimicrobial prophylaxis, and growth factors for support. In comparison, the pediatric-inspired regimen calls for significantly more intense dosing of glucocorticoids, vincristine, and L-asparaginase and a prolonged course of CNS prophylaxis [4]. For our patient, it was judged that the benefits of aggressive treatment with the pediatric-inspired regimen would be better for her in the long-term. However, the issue of her pregnancy would need to be thoroughly discussed with her prior to initiating treatment.

Our patient's pregnancy was already considered high-risk due to her advanced maternal age and her morbid obesity. It also posed a significant medical and ethical dilemma that required a very thorough discussion with the patient. When considering treatment options, including whether to terminate the pregnancy, it is important to consider the entire clinical picture of the patient and her developing fetus. A decision made too quickly or under significant pressure could place the patient and her fetus at further risk for complications. However, allowing the discussion to go on for too long could potentially lead to a delay of treatment, a consequence that cannot be afforded in the setting of a rapidly proliferating disease such as ALL. Seventeen cases of ALL diagnosed during pregnancy have been previously reported. Of these cases, 4 (24%) were Ph-positive, 14 (82%) were diagnosed with B-ALL, 6 (35%) were diagnosed during the second trimester, 3 (18%) were of advanced maternal age, and none opted to terminate the pregnancy before beginning treatment [8-15]. Our patient is unique among these 17 other cases due to a combination of her lack of Ph, advanced maternal age, and her T-ALL diagnosis. She also went through with the termination of her pregnancy prior to beginning treatment with the pediatric-inspired AYA regimen, a choice opposite from that of two women with Ph-negative B-ALL who received similar chemotherapy regimens [10,12].

It is often recommended to terminate the pregnancy during the embryonic period early in the first trimester because of the potentially harmful effects of chemotherapy on the developing fetus, such as spontaneous abortion, fetal death, and major malformations. However, during the second trimester and beyond, the primary risks are increased intrauterine growth restriction and low birthweight risk. Of note, out of 152 patients treated with different combinations of vincristine, daunorubicin, cyclophosphamide, asparaginase, and mercaptopurine, only 6 (4%) of neonates had detectable congenital abnormalities at birth [16]. Notably, out of 7 live births exposed to chemo-therapy in utero for treatment of acute leukemia, none had detectable congenital malformations. However, when compared to the 19 live births that remained unexposed to chemotherapy in utero, the exposed cohort had a higher rate of premature birth (P=0.030) and a low birth rate (P=0.049) [17].

When our patient with T-ALL chose to terminate the pregnancy and start treatment, the de-cision was made to start the pediatric-inspired regimen presented in CALGB 10403 based on its superior median event-free survival (EFS) rate of 78.1 months (95% CI 41.8 to not reached) and its disease-free survival (DFS) rate of 81.7 months (95% CI 58.4 months to not reached). These survival rates are significantly higher than the historical controls of 30 months (95% CI 22-38 months) and 34 months (95% CI 28-50 months). In addition, it should be noted that there was no significant difference in event-free survival between B and T-ALL subtypes or between the AYA age groups [4]. Future directions using these findings could include using the CALGB 10403 regimen as a foundation for further studies for ALL patients, leading to a possible shift in the approach to treating ALL.

The choice of using the pediatric-inspired ALL regimen in our patient following CALGB 10403 still faced some challenges. Stock et al found through the CALGB 10403 study that obesity contributed to significantly worse DFS (HR, 1.82; P=0.04) [4]. The reasoning for this may be multifactorial. Mouse models have shown that ALL treatment could be impaired by adipose tissue, as it can attract and shield leukemic cells from daunorubicin and vincristine [18]. Our patient's immunophenotype was compatible with that of the study's population, but as shown in the study, her morbid obesity could significantly worsen her treatment outcome. Despite these concerns, our team and the patient made the decision together to terminate her pregnancy and begin treatment with the pediatric-inspired regimen.

Conclusion

The decision of how to treat a pregnant woman with ALL, including whether to terminate the pregnancy, must be made together with the patient fully informed to start treatment as soon as possible. Based on the efficacy and improved outcomes for AYA patients treated with the pediat-ric-inspired regimen for ALL, there may be a mortality benefit for a woman aged 17-39, but her obesity status should be considered when considering treatment outcomes. The availability of first and second-trimester pregnancy termination procedures is a medical necessity that is illustrated in this case. A pregnant patient declining treatment for T-cell acute lymphoblastic leukemia because of pregnancy could be fatal, especially if the gestation is early. Treatment choices, monitoring, and outcomes can be affected if she continued the pregnancy complicating an already lethal neoplasm.

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