Pregnancy in a Case of Chronic Myeloid Leukemia: A Case Report*

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ABSTRACT

Chronic Myeloid Leukemia, a chronic hematopoietic stem cell disorder, is uncommon among younger age group such as pregnant patients. Due to the rarity of this condition in pregnancy, there are no randomized controlled trials to address the optimal management of this condition. We are presented with a 26 year old patient, who had an unplanned pregnancy in the advanced phase of the disease. Due to the risk to the mother in delaying treatment, she was continued on Imatinib, a tyrosine kinase inhibitor, which is a known fetal teratogen. Her pregnancy was carried to term. The patient delivered via spontaneous vaginal delivery to a live, neonate, with findings of hydrocele and syndactyly on the 4th and 5th digit of the right foot. Due to the maternal disease progression, she presented with postpartum hemorrhage, in contrast to an augmented procoagulant state among normal pregnancies. Obstetric adjunctive measures, such as intrauterine balloon tamponade and uterine artery ligation, were done. The patient was discharged stable.

Keywords: chronic myeloid leukemia, imatinib, postpartum hemorrhage, pregnancy

INTRODUCTION

Chronic Myeloid Leukemia (CML) is associated with the fusion of two genes: BCR (on chromosome 22) and ABL1 (on chromosome 9) resulting in the BCR-ABL1 fusion gene. This condition signals uncontrolled production of granulocytes, resulting in decrease of healthy blood cells in the bone marrow. Hence, symptoms are usually associated with anemia & leukocytosis. The diagnosis of leukemia in pregnancy is more complicated than in a non-pregnant state due to its non-specific symptoms, which are also attributed to pregnancy.

For patients presenting in the advanced phases, the risk to the mother in delaying treatment is higher. In the first trimester, consideration must be given to terminating the pregnancy, and immediate treatment is warranted. In the second or third trimester, it may be possible to deliver the baby earlier. The first line therapy is Imatinib, a tyrosine kinase inhibitor, which is a known teratogen. It does not only target BCR-ABL tyrosine kinase, but also several other proteins that are known to have functions that may be important in gonadal development, implantation, and fetal development.

In advanced phases of CML, occurrence of bleeding is not uncommon, and may be due to abnormal quantity or quality of thrombocyte.

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OBJECTIVES

Main Objective:

To present a case of an unplanned pregnancy in a patient in the advanced phase of Chronic Myeloid Leukemia

Specific Objectives:

- To report a rare case of Chronic Myeloid Leukemia in pregnancy
- To report the clinical presentation of a patient in advanced phases of Chronic Myeloid Leukemia
- To present the approach to management of a patient with Chronic Myeloid Leukemia in pregnancy
- To present a suggested algorithm for the management of patients who are planning an elective pregnancy
- To present the possible pregnancy outcomes of patients in advanced phases of Chronic Myeloid Leukemia

CASE REPORT

This is the case of a 26-year old patient, Gravida 3 Para 2 (2002), admitted at 36 weeks 5 days Age of Gestation (AOG).

The patient was diagnosed with Chronic Myeloid Leukemia (CML) four years prior to admission, initially presenting with generalized body weakness and undocumented fever. At that time, she presented with pallor. Other physical examination findings were normal. Upon diagnostic work-up, complete blood count (CBC) revealed anemia, leukocytosis, and thrombocytopenia, with left shifted differential count. Ultrasound of the whole abdomen revealed splenomegaly. Hence, she was worked up for probable hematologic disorder, such as Flow Cytometry, Bone Marrow Biopsy, and Fluorescence in situ hybridization (FISH). The results were compatible with a myeloproliferative neoplasm, and indicated Chronic Myeloid Leukemia, in Chronic Phase. The patient was started on Hydroxyurea 500 mg/capsule, 1 capsule once daily, and Nilotinib 150 mg/tablet, 2 tablets twice daily. She was compliant with her medications for a year. However due to financial constraints, she eventually discontinued her medications. She was asymptomatic and no follow-up consultation was done. She had her first and second pregnancies two and four years after being diagnosed, respectively. She had irregular prenatal consultations at a lying-in clinic for both pregnancies, and did not disclose her history of CML. Both pregnancies were carried to term, and delivered via spontaneous vaginal delivery at a lying-in clinic. She had an unremarkable labor and delivery, and was discharged 2 days postpartum.

Two years prior to admission, the patient experienced abdominal fullness, which prompted her to seek consultation with a hematologist. Upon diagnostic work-up, there was noted progression of disease to Accelerated Phase diagnosed by complete blood count, and peripheral blood smear. Her medication was revised to Imatinib 400 mg/tablet, 1 tab once daily, which she took regularly until her unplanned third pregnancy.

One year prior to admission, the patient became pregnant, but did not immediately seek prenatal consultation. At 8 weeks 3 days AOG, she sought follow up consultation with her hematologist. Due to the risk to the mother in delaying CML treatment in the advanced phase of the disease. All possible fetal & maternal complications were discussed to the patient, as well as treatment options and plan. The patient decided to continue with her pregnancy. The patient was continued on Imatinib. At 21 weeks AOG, she had her first prenatal consultation with a private obstetrician in Rizal. CBC revealed anemia (Hemoglobin: 99 g/L, Hematocrit: 0.31), leukocytosis (WBC: 79.26 x 10^9/L) and thrombocytosis (Platelet count: 1123 x 10^9/L). The rest of the diagnostics requested were normal. She had irregular prenatal consultations. Due to high risk pregnancy, she was

advised consultation with a perinatologist, which she did at 35 weeks 2 days AOG. She was advised labor and delivery at a tertiary hospital. Third trimester ultrasound done revealed an incidental finding of hydrocoele on the left fetal scrotum. No other anomalies were noted at this time. She had 2 prenatal consultations prior to admission.

Few hours prior to admission, the patient had irregular uterine contractions. Physical examination revealed normal vital signs, but with an enlarged spleen measuring 18 x 12 cm. On internal examination, cervix was dilated to 6 cm, 50% effaced, intact bag of water, cephalic, station -2. The patient was admitted for trial of labor. CBC upon admission revealed anemia (Hemoglobin: 96 g/L, Hematocrit: 0.29), leukocytosis (WBC: 179.4 x 10^9/L) and thrombocytosis (Platelet count: 1222 x 10^9/L). She had an unremarkable labor course, and delivered via spontaneous vaginal delivery, to a live, term, singleton, male, birth weight 2860g, APGAR score 9,9, Maturity Index 37 weeks, appropriate for gestational age. There was minimal blood loss intrapartum. The uterus was maintained well-contracted. The patient then underwent postpartum bilateral salpingectomy. Upon re-examination post-operatively, blood clots were evacuated from the vagina, amounting to approximately 800 mL. Due to the blood loss, the patient was transfused with 1 unit of packed red blood cells (PRBC). Post-operative medications were Oxytocin drip, Methylergometrine Maleate, Tranexamic Acid, Cefuroxime, and Ketorolac.

On the second hospital day, there was moderate vaginal bleeding consuming 4 diapers per day. On examination, vital signs revealed tachycardia and fever. She had pale palpebral conjunctivae, and pale lips. There were clear breath sounds on chest auscultation. The uterus was well contracted. Serial pelvic examination, and reinspection of the vaginal canal, and cervix were done. There is accumulation of blood clots in the vaginal canal. On re-examination, retained placental fragments was ruled out. CBC revealed anemia (Hemoglobin: 85 g/L, Hematocrit: 0.24), leukocytosis (WBC: 204.5 x 10^9/L) and thrombocytosis (Platelet count: 1196 x 10^9/L). Urinalysis revealed 4-8 pus cells/hpf, and negative esterase. Chest radiograph revealed no significant cardiopulmonary findings. Hematology service ordered to hold blood transfusion. Hydroxyurea was increased to 500 mg/capsule, 2 capsules twice daily.

On the third hospital day, there was persistence of heavy vaginal bleeding, consuming 7 fully-soaked diapers per day. On examination, there was persistence of tachycardia and fever. She had pale palpebral conjunctivae, and pale lips. There were clear breath sounds on chest auscultation. The uterus was well contracted. CBC revealed anemia (Hemoglobin: 63 g/L, Hematocrit: 0.20), leukocytosis (WBC: 191 x 10^9/L) and thrombocytosis (Platelet count: 1272 x 10^9/L). Coagulation tests, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), were normal. Hematology service ordered blood transfusion of 2 units PRBC. Transvaginal ultrasound (Appendix 1) done revealed a *slightly enlarged, well contracted uterus (measuring 10.6 x 7.7 x 11.2 cm); thickened endometrium (measuring 2.0 cm, described as hyperechoic, endometrial midline not defined, with regular endometrial-myometrial junction, and no cystic areas; minimal color on Doppler flow),* compatible with postpartum findings.

As adjunctive procedures to help arrest postpartum hemorrhage, intrauterine balloon tamponade and uterine artery ligation were done. A sterile glove was used as an improvised balloon, and instilled approximately 300 mL of plain normal saline solution (PNSS). The balloon was inflated in the uterus, until the uterus became firm. Transvaginal uterine artery ligation was done.

On the fourth hospital day, vaginal bleeding stopped with the balloon tamponade in place. On examination, there was persistence of tachycardia and fever. There was decrease in pallor noted. There were clear breath sounds on chest auscultation. The uterus was well contracted. CBC still revealed anemia (Hemoglobin: 70 g/L, Hematocrit: 0.22), leukocytosis (WBC: 148.6 x 10^9/L) and thrombocytosis (Platelet count: 1127 x 10^9/L). The intrauterine balloon tamponade was subsequently removed. The patient was closely monitored.

On the fifth hospital day, there was vaginal spotting, with no increase in amount after removal of balloon tamponade. On examination, there was resolution of fever. The patient had pink palpebral conjunctivae, and pink lips. The uterus was well contracted. CBC revealed anemia (Hemoglobin: 89 g/L, Hematocrit: 0.29), leukocytosis (WBC: 142.1 x 10^9/L) and thrombocytosis (Platelet count: 1040 x 10^9/L). The patient was closely monitored. The rest of the hospital stay was unremarkable, and the patient was discharged on the seventh hospital day.

The patient was advised not to breastfeed. Although in some literatures, imatinib is demonstrated not to reach therapeutic concentrations in an infant's blood during breastfeeding[1], there is still lack of clinical evidence in infants, and the excellent alternative of bottle feeding supports this recommendation. The patient was likewise advised to continue regular consultations with her hematologist.

CASE DISCUSSION

Chronic Myeloid Leukemia (CML) is a chronic hematopoietic stem cell disorder driven by the BCR-ABL1 chimeric gene product – a constitutively active tyrosine kinase resulting from a reciprocal balanced translocation. It is associated with the fusion of two genes: BCR (on chromosome 22) and ABL1 (on chromosome 9) resulting in the BCR-ABL1 fusion gene. It signals the bone marrow to produce too many white blood cells (WBC).[2] Uncontrolled production of mature and maturing granulocytes, predominantly neutrophils, but also basophils and eosinophils. As a result, the number of healthy blood cells in the bone marrow is usually lower than normal.[3]

CML has no identified risk factors or cause. It is probably a genetic abnormality, and is not an inherited disease. Exposure to high-dose ionizing radiation increases the incidence, with a mode of increased incidence that ranges from 4-11 years in different exposed populations.[2] The patient has no personal history of exposure to radiation, nor a family history of hematologic disorders.

CML accounts for approximately 15% of all cases of leukemia. Its annual incidence is 1.5 cases per 100,000 individuals. It presents as approximately 10% cases of pregnancy-associated leukemia. Leukemia in pregnancy is rare, and is estimated to occur in only 1 in 75,000 to 100,000 pregnancies, although its incidence is poorly documented. The median age at diagnosis is 55-65 years.[3] Hence, it is uncommon in children, and younger age group, such as pregnant patients.

Approximately 30% of patients are asymptomatic at the time of diagnosis. The disease is discovered coincidentally when an elevated WBC is noted upon prenatal evaluation.[4]

Symptoms are gradual in onset, and may include easy fatigability, abdominal discomfort, early satiety, and many other symptoms associated with anemia & leukocytosis. Unfortunately, women with cancer have non-specific symptoms which also are attributed to pregnancy. Hence, the diagnosis of a disease such as leukemia in pregnancy is more complicated

than in non-pregnant women, since anemia, leukocytosis and thrombocytopenia are common in pregnant women.

The diagnostic criteria for leukemia in pregnant women are the same as for the normal population. Apart from the history and physical examination, diagnostic work-up may include: complete blood count (CBC), peripheral blood smear (PBS), flow cytometry, bone marrow aspiration, and fluorescence in situ hybridization (FISH).[2]

There is no staging system in CML. However, itt has three (3) phases, the Chronic, Accelerated and Blast Phases.[2] Phases are based mainly on the number of immature WBC (blasts) in the blood or bone marrow. The natural history of the disease is to evolve into an Accelerated Phase, in which cytopenias develop and response to Chronic Phase therapy is lost. In general, Chronic Phase has a higher probability of survival. Whereas, advanced phases such as Accelerated and Blast Phases, have more symptoms, and has higher resistance to therapy. Pregnancy, however, does not alter the normal course of CML.[5]

Since pregnancy is rare in CML, there are no randomized controlled trials to address the optimal management of this condition.[6,7] At the present time, there is no consensus on how to manage different pregnancy situations in CML. But there is a suggested algorithm for the management of pregnancy in patients with CML who are on treatment with Imatinib (Appendix 2).[1]

For patients presenting in the advanced phases, such as the patient, the risk to the mother in delaying treatment is higher. In the Accelerated Phase, during the first trimester, consideration must be given to terminating the pregnancy, and immediate treatment is warranted.[6]

Imatinib or second-generation tyrosine kinase inhibitor (TKI) can be used after pregnancy termination. For patients diagnosed in the second or third trimester, it may be possible to deliver the baby earlier. In these cases, sensitive and compassionate counseling of the parents, and careful examination of all possibilities, is mandatory. Treatment options and plan were discussed to the patient. The patient decided to continue with her pregnancy, and the patient was continued on Imatinib[1,7]

In the Blast Phase, chemotherapy is recommended. In Chronic Phase, prepubertal patients may be started immediately on TKI. Whereas, for post pubertal patients, they are counseled about the risks and benefits of TKI on fertility & pregnancy, such as impaired functions in gonadal development, implantation, and fetal development.[1] They may be offered sperm or oocyte cryopreservation.[8] Then, TKI may be started.[1,7]

For post pubertal patients in Chronic Phase already under TKI therapy, and with unplanned pregnancy or diagnosis of CML in pregnancy, they are counseled about the risks and benefits of TKIs on pregnancy. They are also advised to stop TKI. During the first trimester, leukapheresis is a treatment option, since persistence of abnormally high blood counts increases the chance of obstetric complications including thrombosis, bleeding, placental insufficiency, and intrauterine growth restriction. Leukapheresis as a cytoreductive measure is a temporizing procedure, however, with no curative potential or lasting effect, and availability of this procedure is limited.[6] In the second and third trimester, leukapheresis & interferon alpha (IFNα) are considered. IFNα is considered safe for the fetus,[5] however, has a slower and less certain ability compared with TKI to induce control of abnormal blood counts, and therefore, may not be a

sufficient treatment for high leukemic burden at CML onset.[1,7]

For patients in the Chronic Phase planning an elective pregnancy, TKI may be discontinued if patient is in complete or major molecular response (CMR / MMR) for ≥ 2 years.

Management is the same for that of an unplanned pregnancy, if there is loss of complete or major molecular response, such as no cells containing the Philadelphia chromosome by cytogenetic analysis, BCR-ABL1/ABL1 ratio is < 0.1%, or a 3-log reduction in quantitative PCR from pre-treatment baseline.[4]

All patients with CML need treatment. The patient is on Imatinib, which is the first line therapy for CML. This blocks the tyrosine kinase receptor, which somehow prevents the production of myeloblasts. Due to the advent of Imatinib, treatment has been dramatically improved in the last 15 years, reducing the annual mortality from 10-20% to about 2%. However, Imatinib is a known teratogen. It does not only target BCR-ABL tyrosine kinase, but also several other proteins that are known to have functions that may be important in gonadal development, implantation, and fetal development. There are a number of case reports of the fetal outcome of patients on Imatinib during pregnancy. It may cause miscarriage, low birth weight, and is associated with a number of congenital abnormalities. Congenital anomalies recorded were omphalocele, craniosynostosis, clinodactyly, polydactyly, hypospadias, renal & vertebral anomalies, etc.[1,6,7] For the patient, her baby has hydrocele, noted with a positive transillumination test, and syndactyly on the 4th and 5th digit of the right foot (Appendix 3).

Balancing the potential teratogenic risk to the fetus from Imatinib, against the risk to the mother if she discontinues treatment, is difficult. In this case, the principle of double effect was applied. The patient was informed of the possible fetal, as well as maternal complications, such as possible thrombotic or vaso-occlusive events (due to hypercoagulable state of pregnancy on top of her leukocytosis & thrombocytosis), possibility of hemorrhage during delivery, or even maternal death from all the possible complications. With all these explained, the patient decided to continue with her pregnancy, where principle of autonomy was applied.

After spontaneous vaginal delivery, the patient had postpartum hemorrhage. Possible causes such as Tone, Tissue, Trauma, and Thrombin were assessed.[9] Uterine atony (Tone), which is failure of the uterus to contract adequately after delivery, was ruled out by intermittent physical examination. The uterus was maintained well contracted. The patient was continued on oxytocin drip, and was given methylergometrine maleate to ensure uterine contractility. Retained placental tissues (Tissue) was ruled out with attempted manual evacuation, where no placental fragments were obtained. Transvaginal ultrasound was done to assess the endometrial cavity. Genital tract trauma (Trauma) was also ruled out on cervical and vaginal inspection since no hematoma was noted. Hence, coagulopathy (Thrombin) was highly considered, even if coagulation parameters were normal.

During normal pregnancy, both coagulation and fibrinolysis are augmented but remain balanced to maintain hemostasis. Extensive changes develop to create a procoagulant state. Some of these include appreciable increases in the plasma concentration of coagulation factors. In CML, occurrence of bleeding usually suggests disease progression such as in this patient in Advanced or Accelerated Phase, which is caused by abnormal quantity or quality of thrombocyte. Unlike in Chronic Phase

CML, bleeding is unusual due to the generally preserved function of platelets. There are some reported cases which presented with bleeding, but show almost normal results of clotting screening tests.[10] As a matter of fact, there are few rare defects which cannot be recognized by prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count in a hemorrhagic patient.

SUMMARY

Chronic Myeloid Leukemia in pregnancy is rare. All patients with CML need treatment, especially in the advanced phases of the disease. Balancing the potential teratogenic risk to the fetus from Imatinib, against the risk to the mother if she discontinues treatment, is difficult. In these cases, sensitive and compassionate counseling of the parents, and careful examination of all possibilities, is mandatory. Different pregnancy situations in CML may be managed, given the advances in treatment. Intrapartum and postpartum hemorrhage must always be anticipated, even with coagulation parameters, due to abnormal quantity or quality of thrombocyte, and a few rare defects in coagulation factors.

CONCLUSION

The patients with Chronic Myeloid Leukemia should be encouraged to pursue a normal life including planning a family, given advances in treatment. In CML in pregnancy, three factors must always be considered: the mother, the baby, the illness; all equally important and related.

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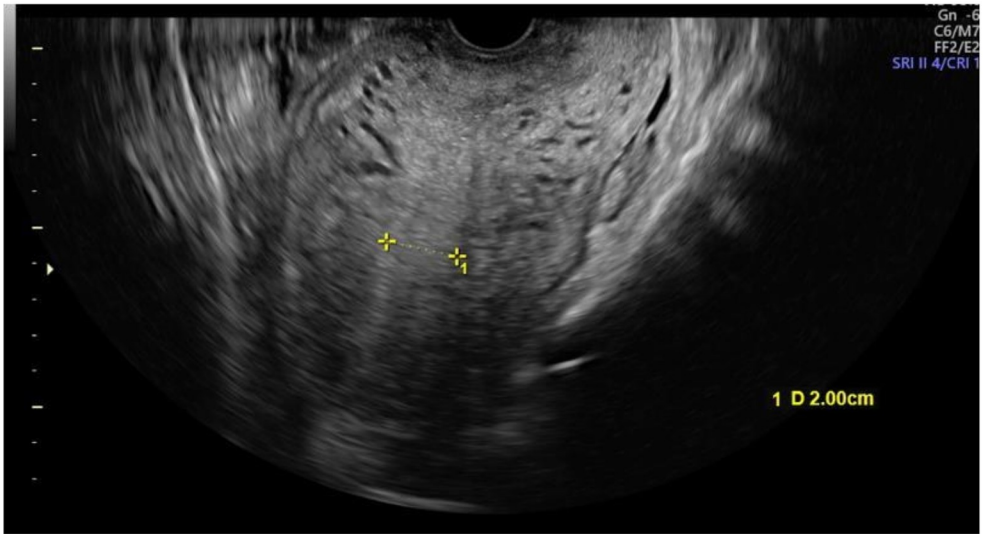
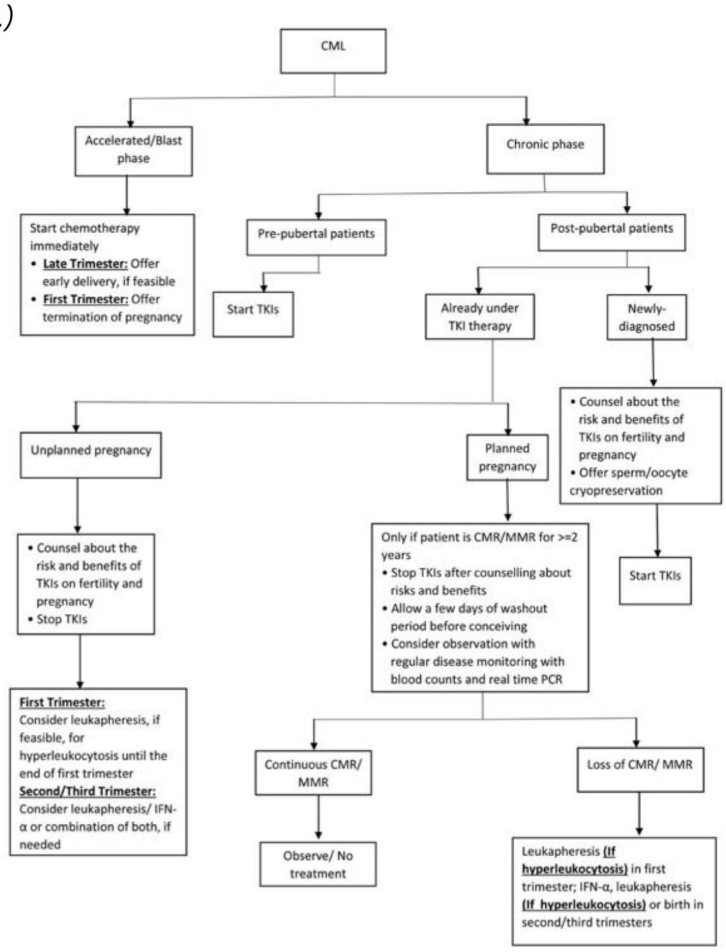
Appendices

Appendix 1: Transvaginal Ultrasound showing a thickened endometrium, measuring 2.0 cm, described as hyperechoic, endometrial midline not defined, with regular endometrial- myometrial junction, and no cystic areas; minimal color on Doppler flow



Appendix 2: Suggested Algorithm for Management of Patients with Chronic Myeloid Leukemia *(source: Bhandari A, Rolen K, Shah B. Management of Chronic Myelogenous Leukemia in Pregnancy. Anti-Cancer Research, 2015.)*



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