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Outcome of Pregnancy in Rare Case of Chronic Myeloid Leukemia Diagnosed at 24 Weeks of Gestation

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Abstract:- The management of chronic myelogenous leukemia during pregnancy requires balancing the health of both mother and fetus. We report a case of a 22-year-old female who was diagnosed with chronic myelogenous leukemia (CML) at 24 weeks gestation and who had an atypical chromosome t(9;22;11) (q34;q11.2;q13) translocation. She was managed with PEG-IFNa through the remainder of the pregnancy and the disease remained stable; she delivered a normal male child. Treatment with dasatinib was initiated 1 week after delivery on patient's request and she went into complete hematologic remission after 1 month of therapy. We discuss the course of the disease and various treatment modalities available for CML during pregnancy.

I. INTRODUCTION

Chronic myelogenous leukemia (CML) is a chronic myeloproliferative disorder defined by the presence of a chimeric gene, *BCR::ABL*. CML accounts for 7% to 15% of all cases of leukemia in adults. In western countries the median age of CML patients is about 57 years. In Asia the median age at diagnosis is <50 years, reflecting in part the lower median age of the population.[1] There is slight male predominance. There is no association with geographic distribution or race. The etiology of CML is unknown. High-dose radiation exposure is a well-established environmental risk factor. No genetic predisposition is thought to play any role in pathogenesis of CML. *BCR::ABL* is created by a reciprocal translocation of genetic material between the long arm of chromosome 9 (containing the proto-oncogene c-abl) and the long arm of chromosome 22 (containing the bcr gene). This is the Philadelphia chromosome, and it is correctly annotated t(9;22) (q34.1;q11.21). The translocation results in constitutive upregulation of tyrosine kinase activity of abl, which triggers downstream transduction pathways of a signaling cascade of oncogenic events.

Patients usually present in the initial chronic phase, exhibiting a cluster of specific clinical and laboratory features. More than half of patients with CML diagnosed in the chronic phase are asymptomatic. The median time to the development of terminal blast phase is 3 to 6 years. The disease typically progresses through slow evolution into an accelerated phase and then blast phase, but it can transform rapidly directly into the blast phase.

The therapeutic landscape of chronic myeloid leukemia (CML) has profoundly changed over the past few years. Most patients with chronic phase (CP) now have a normal life expectancy. Another goal is achieving a stable deep molecular response (DMR) and discontinuing medication for treatment-free remission (TFR). First-line treatment is a tyrosine kinase inhibitor (TKI; imatinib brand or generic, dasatinib, nilotinib, and bosutinib are available first-line). Allogeneic transplantation continues to be a therapeutic option particularly for advanced phase CML. Treatment discontinuation may be considered in patients with durable DMR with the goal of achieving TFR.[1] The occurrence of CML during pregnancy poses a unique clinical challenge for physicians treating these patients and requires balancing concerns between maternal survival and fetal health in both the short- and long-term. Interferon-alpha is a safe option due to its safety profile while TKI's are not given because of their teratogenic potential.[2]

II. CASE

We report the case of a 20 year female G1P0 in 2nd trimester (at 24 weeks of gestation) presented withleukocytosis, left shift, thrombocytosis and splenomegaly on her regular pregnancy checkup. She was suspected for CML and was investigated for it, the findings of which are seen in table 1.

Hemoglobin	9.5 %
Total leukocyte count	46300/Cumm
Platelet count	12.14 Lakh/Cu mm
Neutrophil	66%
Lymphocyte	05%
Eosinophil	02%
Monocyte	05%

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Basophils	07%
Myelocytes + Metamyelocytes	14%
Blast	1%
Spleen	5cm BCM
Blasts on Bone Marrow Biopsy	2.3%
BCR-ABL (P210)	51.964% IS
Sokal	1.04 (intermediate risk)
ELTS	0.8053 (low risk)

Table 1 : Pre-treatment initiation investigations for suspected CML

Patient was diagnosed with Chronic Myeloid Leukemia in Chronic Phase and put on Interferon-alpha 2b 3 mu/day 3 times/week to be taken until delivery.

Patient took interferon-alpha 2b for 13 weeks and had a normal full term delivery. Baby was healthy, weighed 2.6 kg and no malformations were seen. Investigations to assess the status of her CML were done after delivery and seen in table 2.

Hemoglobin	9.9 %
Total leukocyte count	26900/Cumm
Platelet count	17.68 Lakh/Cu mm
Neutrophil	60%
Lymphocyte	05%
Eosinophil	04%
Monocyte	04%
Basophils	07%
Myelocytes + Metamyelocytes	20%
Blast	0%
Spleen	5 cm BCM
Sokal	1.59 (high risk)
ELTS	0.6393 (low risk)

Table 2 : Post-delivery investigations to assess CML status

Patient was counselled to continue Interferon-alpha 2b even after pregnancy to facilitate exclusive breast feeding to infant but she asked to be put on standard therapy for CML and was thus given Dasatinib 100mg/day OD and achieved complete hematologic remission after one month of therapy.

III. DISCUSSION

CML in pregnancy is a rare condition, with an annual incidence of 1 per 100,000 pregnancies. The disease during pregnancy has been traditionally managed conservatively by leukapheresis, hydroxyurea and interferonbecause it has an initial chronic phase that may not require an immediate therapy and pregnancy per se does not affect CML. The therapeutic management of CML in pregnant women with TKIs often poses substantial challenges to both patients and their physicians.[3]

Our patient was not put on TKI therapy due to its teratogenic potential. This is supported by various studies. Like in Pye et al's. study, of 180 women exposed to imatinib during pregnancy, outcome data are available for 125 (69%). Of those with known outcomes, 50% delivered normal infants and 28% underwent elective terminations, 3 following the identification of abnormalities. There were a total of 12 infants in whom abnormalities were identified.[4]

Our patient was given interferon-alpha 2b for CML during the course of her pregnancy. The results of a study by Brojeni et al suggested that IFN-alphaα does not significantly increase the risk of major malformation, miscarriage, stillbirth or preterm delivery above general population rates.[5]

Leukapheresis in pregnant CML patients is generally used in cases with severe hyperleukocytosis which was not observed in our patient at any instance and was thus not considered anytime during the course of her pregnancy. Hydroxyurea was also not used due to its teratogenic profile and no need for any other therapy was noticed since the patient was relatively well controlled on interferon therapy.

Our patient was observed to have controlled CML after pregnancy and was thus suggested and counseled to continue Interferon-alpha 2b even after pregnancy to facilitate exclusive breast feeding to infant since TKIs are secreted in breast milk thus it is not advisable to give an actively feeding mother TKIs such as Dasatinib. But the patient wasn't much comfortable with continuing IFN-alpha due to its flu-like side effects and also wanted to take the best therapy possible for her, for the CML. So she asked to be put on standard therapy for CML and was started on Dasatinib 100mg/day OD whilst the patient was simultaneously referred to the Pediatrics department for the proper nursing of her newborn.

Dasatinib is a multi-targeted kinase inhibitor of bcr/abl and Src kinases that has 100- to 300-fold higher activity than imatinib.[6]

Our patient was observed to have complete hematologic remission after 1 month of dasatinib therapy.

IV. CONCLUSION

CML occurrence during pregnancy is noted to be a rare phenomenon and warrants careful therapeutic planning due to the relative risk of embryotoxicity of TKIs, which is considered as first-line therapy in CML on one hand, but the good efficacy and treatment success rates of the same on the other hand. Interferon-alpha 2b 3 mu/day 3 times/week is noted to be a safe option in pregnant CML patients managed without TKIs. Our study supports this fact with its observed positive outcome of both the pregnancy and fetus.

Conflicts of Interest -

No conflicts of interest declared.

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