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Acute Promyelocytic Leukima in Pregnancy Presenting as DIC - A Case Report and Review of Literature

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Abstract

Acute promyelocytic leukemia is a unique subset of acute myeloid leukemias characterised by the proliferation of neoplastic promyelocytes bearing chromosomal translocation t (15;17). Although APML accounts for nearly 13% of acute myeloblastic leukemia cases, it usually affects young adults and hence increasing the possibility of its occurrence during pregnancy. But to arrive at a diagnosis of leukemia in pregnancy, one should need a high index of suspicion. As most cases of acute promyelocytic leukemia present with coagulopathy, a peripheral smear study in pregnant women with similar picture can help in timely diagnosis and appropriate management. Here we discuss the case of a pregnant lady who had been diagnosed with APML in pregnancy in the second trimester and her clinical outcome.

Keywords: Acute promyelocytic leukemia, Pregnancy, PML-RARα, ATRA, Peripheral Smear, DIC

Introduction

Acute promyelocytic leukemia is a unique subset of acute myeloid leukemias characterised by the proliferation of neoplastic promyelocytes bearing chromosomal translocation t (15;17). Although APML accounts for nearly 13% of acute myeloblastic leukemia cases, it usually affects young adults and hence increasing the possibility of its occurrence during pregnancy. APML in pregnancy is both an oncologic as well as obstetric emergency as the patient may suddenly go in for disseminated intravascular coagulopathy. Emergence of anthracycline based chemotherapy and all trans retinoic acid has greatly changed the therapeutic course of APML, however the management protocol in pregnancy remains controversial. Here we discuss the case of a pregnant lady who had been diagnosed with APML in pregnancy in the second trimester and her clinical outcome.

Case Report

A G4P3L3 lady, previous 3 CS, at 24 weeks of gestation presented with fever with chills and reduced fetal movements for 2 days duration. She was a known case of gestational hypertension on antihypertensives. She had also given history of recurrent abscesses in her axilla, thighs, and teeth over past 2 weeks. On evaluation, she had bicytopenia with neutrophilia and leucocytosis. USG showed features of intrauterine fetal demise. On admission to ICU, she was in DIC. Investigations showed pancytopenia with blast cells, abnormal renal function, and coagulation profile. **Table 1** shows her laboratory parameters at the time of admission to ICU.

Table 1: Laboratory parameters at the time of admission

Lab parameter	Value	Lab parameter	Value
Hemoglobin	6.7 mg/dL (anemia)	Serum Uric acid	8.6 mg/dL (high)
Total WBC count	31500/mm3 (leucocytosis)	Urine protein	3+
Differential count	N9, L7, M84, blast cells+	Serum electrolytes	Normal
Platelet count	41000/mm3 (thrombocytopenia)	Serum Fibrinogen	77.8 mg/dL (low)
Liver function test	Normal	D- Dimer	8.1 (positive)
Blood Urea	30.7 mg/dL	PT-INR	13.8/1.24 (high)
Serum Creatinine	1.03 mg/dL	aPTT	33.5 (high)

Peripheral smear (**Figure 1, 2**) showed proliferation of myeloid precursors with increased blast cells. The leucocytes showed abundant coarse granules in the cells, deeply cleaved nuclei, and presence of auer rods suggestive of acute promyelocytic leukemia. There was strong myeloperoxidase positivity. The smear also showed anisopoikilocytosis and reduced platelet counts.

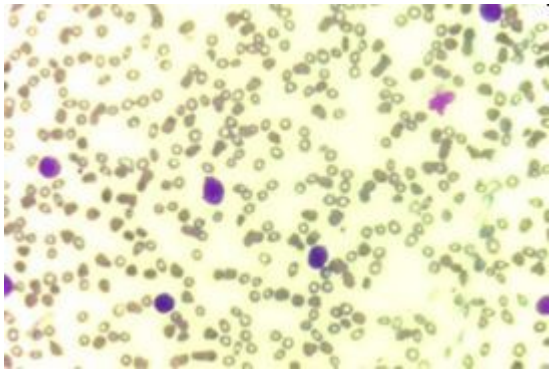

Figure 1: Peripheral smear showing predominance of abnormal promyelocytes suggestive of APML.

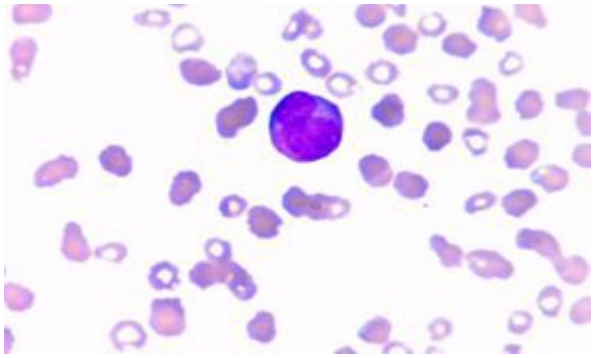

Figure 2: High power field of peripheral smear showing abnormal promyelocyte.

Bone marrow study (**Figure 3, 4**) showed highly cellular marrow with myeloid proliferation (predominantly abnormal promyelocytes).

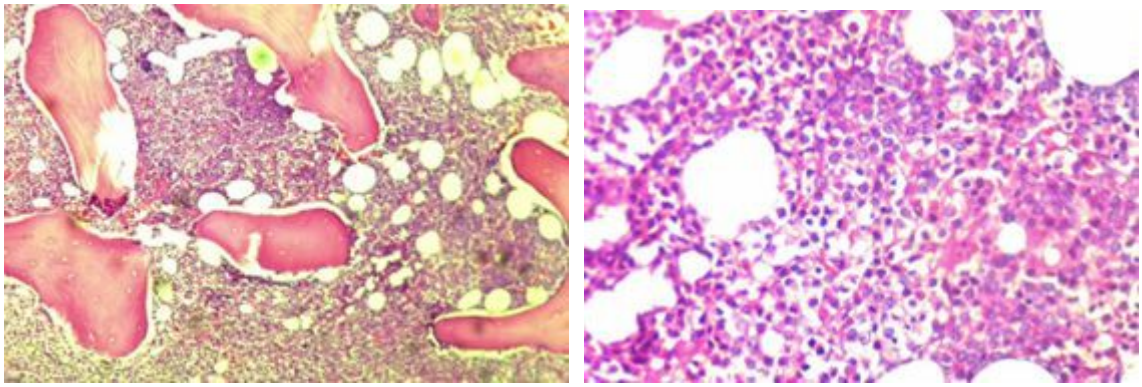

Figure 3, 4: Bone marrow study demonstrating myeloid proliferation.

Flow cytometry was positive for CD13, CD33, CD64 and myeloperoxidase. PML RARα was tested positive (signals for PML-RARα NCN for BCR 1 were detected in the leukocytes). In the background of a final diagnosis of acute promyelocytic leukemia (High risk as per Sanz criteria), she was started on all trans retinoic acid (45mg/m2/kg), blood and blood products, MgSO4 and antihypertensives. She underwent emergency hysterotomy after the first dose of ATRA and delivered a male IUD baby of 560 grams. Postoperatively, she was on mechanical ventilation. Even after stopping sedation, her sensorium remained poor. Her renal function worsened (S. creatinine- 3.17mg/dL), had decreased urine output, high uric acid levels (10.8 mg/dL), Phosphatemia (S. Phosphate- 9mmol/L) and low serum calcium levels (7.7mg/dL). Thus, based on Cairo Bishop Scoring system, she was diagnosed to have developed tumour lysis syndrome and was started on Rasburicase, Hydroxyurea and Febuxostat. Her serial CBC showed elevated leucocytosis and developed generalised edema and fever, which was thought to be due to differentiation syndrome in response to ATRA and hence the drug was discontinued. Chemotherapy with mitoxantrone (10mg/m2) was initiated. Her total counts started to fall post mitoxantrone, however on postoperative day 8, she had worsening acute kidney injury and hemodialysis was initiated. She also developed ventilator associated pneumonia in between and antibiotics were escalated. Her sensorium remained poor and MRI brain was suggestive of leukencephalopathy. Total of 212 blood products (12 Packed red cells, 90 platelet concentrates, 16 cryoprecipitates and 94 fresh frozen plasma) were transfused during the hospital stay. She went into worsening shock and hypoxia with a clinical picture of septicemia and advanced malignancy. On POD 14, she expired following bradycardia and asystole.

Discussion

Acute promyelocytic leukemia (APML) is a subtype of acute myeloid leukemia. It is characterised by the proliferation of neoplastic promyelocytes bearing the balanced translocation t (15;17). [1] Leukemia affects 1 in 75,000 pregnancies. However, the exact incidence of APML in pregnancy is unknown. However as APML is commonly seen around a median age of 40 years, the probability of its incidence to occur among pregnant women increases as compared to other myeloid neoplasms [2].

Etiology

The cytogenetic abnormality present in APML is the balanced translocation t (15;17). It results in the fusion of the retinoic acid receptor alpha (RARα) gene located on chromosome 17 with the promyelocytic leukemia (PML) gene located on chromosome 15. The resultant PML-RARα fusion protein causes a differentiation and maturation arrest in the myeloid lineage which leads to incessant proliferation of abnormal promyelocytes in the peripheral smear and bone marrow [3].

Diagnosis

Although APML can present with various nonspecific symptoms, presence of a severe hemorrhagic syndrome or coagulopathy is the striking feature. Thromboplastin activity in the promyelocytic granules is the trigger for the activation of coagulation cascade [4]. A complete blood count measurement, peripheral smear and bone marrow study aid the diagnosis of APML. However a cytogenetic analysis and demonstration of the hybrid PML-RARa fusion gene is the confirmatory test [5].

Management

APML usually presents with a picture of disseminated intravascular coagulopathy (DIC), thus making it an obstetric as well as oncologic emergency. The management of the disease in pregnancy is a particularly challenging task for the obstetrician as there is high risk of maternal mortality and morbidity. A multidisciplinary team which includes an obstetrician, oncologist, hematologist and neonatologist should be involved in the treating panel [1,5].

In general, treatment of acute leukemia is divided into three phases, namely induction, maintenance, and consolidation phase. According to the current practice guidelines, induction therapy in high risk APML usually consist of all trans-retinoic acid (ATRA), Arsenic trioxide and an anthracycline (Idarubicin/Daunorubicin/Mitoxantrone) given either sequentially or simultaneously. Combination therapy was associated with a lower relapse rate. Once morphologic complete remission (less than 5% bone marrow blasts) is achieved, consolidation therapy with ATRA/Arsenic trioxide is initiated up to six cycles. To assess the response, a bone marrow biopsy is done 4-6 weeks after the start of treatment. Maintenance therapy consists of 6-mercaptopurine and methotrexate in combination with ATRA, which is usually given for a period of 2 years [5,6].

Addition of ATRA to conventional anthracycline-based chemotherapy had resulted in a great impact on the course of the disease as it reduces the onset of DIC. This new drug has also resulted in a complete and durable remission in more than 90% of the patients [2,7]. The major underlying pathology of APML is the hybrid gene. This fusion gene, however, confers great sensitivity to differentiating agents like ATRA and Arsenic trioxide. ATRA induces differentiation of the abnormal promyelocytes. It has shown to induce remission in APML with rapid dissolution of DIC, and that too with minimal bone marrow suppression.

Management in pregnancy

Treatment regime for each pregnant women have to be individualised based on their gestational age [1]. The factors to be considered before initiating therapy are risk of fetal loss, teratogenicity, aggressiveness of the neoplasm, marrow suppression in host, chances of cure and gestational age. It is generally observed that the fetal outcome improves with advancing gestational age [2]. Notable fetal complications are spontaneous abortions, teratogenicity, prematurity, preterm labour and respiratory distress syndrome. So keeping all these in mind, chemotherapy has to be initiated judiciously and in strict adherence to current protocols in these patients [1]. Treatment can be initiated without delay if there is a clinical suspicion of APML and need not wait for genetic confirmation [8].

Teratogenic effects of ATRA consists of retinoic acid embryopathy with malformations involving craniofacial, central nervous system, cardiovascular, thymic, otologic and other structures [2,5]. Although these effects are not well established, the current guidelines recommend against its use in first trimester [9]. If ATRA had been given in early gestation, it is advisable to offer therapeutic termination of pregnancy after complete remission of the disease [10]. However, ATRA and chemotherapy appear to have a reasonable safety profile in the second and third trimester of pregnancy. Early delivery or caesarean section may be advised if the fetus has attained viability

[2,11]. If chemotherapy is initiated post-delivery, breastfeeding is contraindicated.

Consoli et al., [2] have described three cases of APML diagnosed in pregnancy. All of them were started on ATRA followed by conventional chemotherapy and two of them had complete remission. One patient expired owing to differentiation syndrome which did not respond to treatment. Hoffman et al., [12] had also reported a case of APML and DIC diagnosed in second trimester of pregnancy. The patient was given conventional chemotherapy and labor was induced in view of intrauterine fetal demise. The patient had a turbulent course following delivery but achieved complete remission within a month. She relapsed later and underwent bone marrow transplantation, but eventually died due to varicella infection following the surgery.

Conclusion

Incidence of acute promyelocytic leukemia in pregnancy is very rare and a high index of suspicion should be there in patients presenting with refractory anemia or coagulopathy to establish the diagnosis. Hence a peripheral smear study is highly recommended in such cases. Once the diagnosis of APML is made, treatment should be initiated without any delay to achieve higher cure rate and to minimise maternal mortality and morbidity. The chemotherapy regimens, however, should be individualised based on the gestational age and risk of fetal hazards.

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