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Case Report
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Low Dose Single Agent Chemotherapy Cured a Child with Down Syndrome and Acute Myeloid Leukemia

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Abstract

Patient with Down syndrome (trisomy 21) have more than 10 time increasing risk Of acute leukemia with more than 1% of children with down syndrome will develop Acute Myeloid Leukemia (AML), this increase risk occur primarily in children with Down Syndrome (DS) under the age of 10 years.

Among patients with DS, AML most commonly occur between 1 to 4 years old age, megakaryocytic AML (M7) which is uncommon subtype of AML mostly affecting patients with DS.

We reported a patient with Down syndrome who developed AML M2 (Myeloblastic without maturation) at the age of 2 years who was treated by single agent low dose Cytarabine (Ara-C) chemotherapy because of associated cardiac comorbidity for 24 months, currently she is 4 years off chemotherapy and on complete remission.

Keywords: Down syndrome; Trisomy 21; Acute myeloid leukemia; Low dose chemotherapy; Atrioventricular Septal Defect (AVSD)

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Introduction

Down syndrome or constitutional trisomy 21 was linked to leukemia for the first time in a case report published in 1930 [1].

Since then, Down syndrome has been recognized as one of the most important leukemia-predisposing syndromes and patients with Down syndrome and leukemia have unique clinical features and significant differences in treatment response and toxicity profiles compared to patients without Down syndrome [2].

We reported a patient with Down syndrome and AVSD developed AML M1 which was successfully treated by low dose single agent chemotherapy to prevent potential anthracycline induced cardiotoxicity.

Case Presentation

A 24 months old female was referred to us by a pediatrician neurosurgeon for further assessment and treatment.

The patient was a known case of Down syndrome with large Atrioventricular Septal Defect (AVSD) or what is called endocardial cushion defect with right to left shunt that causing heart failure.

She was presented suddenly with intermittent fever for 3 weeks which was not responding to antipyretic and several courses of antibiotic, progressive pallor, cutaneous bleeding. She was on anti-failure drug (Enalapril tablet 2.5 mg and furosemide 5 mg per day); she was vaccinated according to her age. There is no consanguinity of parents, neither family history of malignancy nor similar condition. In addition to the characteristic physical stigmata of Down syndrome (delayed physical growth, microcephaly, low seated ears, poor muscle tone, grade 4 pan-systolic murmur and other

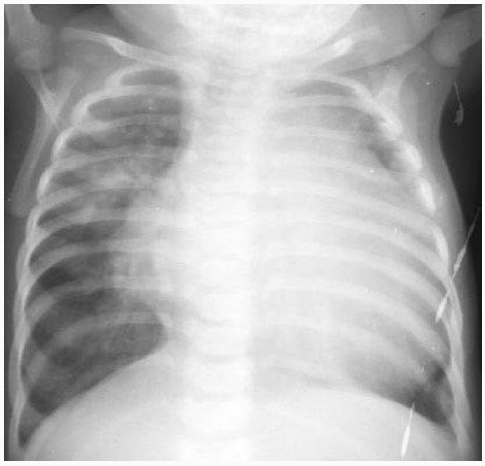

Figure 1: Posterior Anterior (PA): Chest X-ray demonstrates cardiomegaly, and increased pulmonary vascular markings.

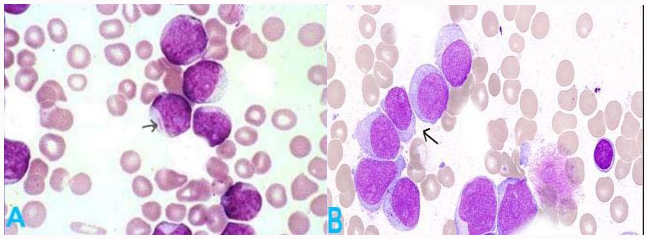

Figure 2: A) Blood film shows blast with Auer rod (black arrow), B) Bone marrow aspirate revealed involvement by a myeloid neoplasm of atypical immature cells with irregular nuclei and delicate chromatin (black arrow) by Giemsa Stain (original magnification 1000x).

feature of DS), examination revealed fever, pallor, skin ecchymosis, generalized lymphadenopathy and hepatosplenomegaly.

Laboratory investigations include liver function tests, renal function tests, serum electrolytes (potassium, sodium, calcium, phosphorus); serum uric acid and coagulation profile (PT and PTT), all were normal.

Cerebrospinal Fluid cytology (CSF) Cytology was negative for malignant cell.

Chest X-ray showed cardiomegaly with Echocardiography revealed (Figure 1).

Right ventricular hypertrophy and Ejection Fraction (EF) of 40%.

Complete blood count showed hemoglobin was 7.1 g/dl; the platelet count was 11,000/ml, and a leukocyte count of 21,000/ml with 43% neutrophils, 44% lymphocytes, 2% monocytes, 0.5% basophils, 0% eosinophil with 12% blasts cell with Auer rode (Figure 2A). Bone marrow aspirate revealed 90% myoblasts with minimal maturation (M1 FAB morphology) Figure 2B.

Blasts immunohistochemistry stains shows positive MPO, positive CD34, negative CD68 and positive CD33 (Figure 3A to 3D).

Analysis by flow cytometry as showed by Figure 4, the blasts were positive for, MPO, HLADR, CD7, CD13, CD33, CD34 and CD117 but negative for CD3, CD10, CD14 and CD15.

According to the bone marrow morphology, immunohistochemistry stains and immunophenotype by flow

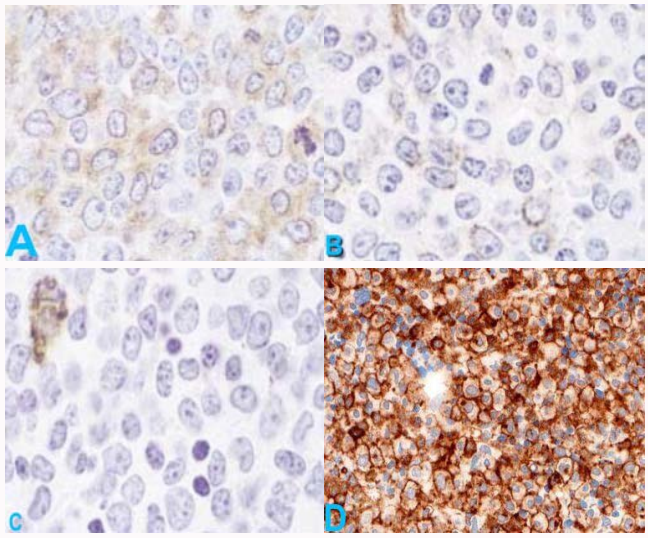

Figure 3: A) Immunohistochemistry Stains shows positive MPO, B) Positive CD34, C) Negative CD68 and D) Positive CD33.

cytometry the diagnosis was AML M1.

Cytogenetic analysis by karyotype of the blast cell showed trisomy 21 (DS) without any other chromosomal abnormality and she was categorized as a favorable risk group.

The patient was started on supportive care to prevent tumor lysis syndrome (Allopurinol, Hydration).

Because of her cardiac problem (heart failure with low baseline EF) and because of the potential cardiotoxicity by anthracycline chemotherapy, we discussed her condition with her family and we decided to started her on low dose single agent Cytarabine 10 mg/kg/dose twice daily by subcutaneous injection for 10 days per 28 days cycle as an outpatient palliative treatment.

After two uneventful courses the patient entered Complete Remission (CR) with negative Minimal Residual Disease (MRD).

We continued chemotherapy for 24 cycles (24 months) without any significant chemotherapy complication but unfortunately her cardiac problem progress, we stopped her chemotherapy and she underwent surgical correction for her atrioventricular septal defect.

Now she is 4 years off chemotherapy and she is hematologically in Complete Remission (CR) and doing well regarding her corrected atrioventricular septal defect.

Discussion

Children with trisomy 21/DS represent a clinically and genetically unique subset of pediatric patients with AML, with patients <4 years of age having a 500-fold increased risk of developing the disease [3].

Approximately 15% of pediatric AML cases occur in DS children. Acute Megakaryocytic Leukemia (AMkL; M7) is the most common French-American-British subtype of DS AML patients, other AML French-American-British subtypes have also been described in DS AML including M0, M1/M2, and M6 [2,4,5].

It is now recognized that DS children with AML have exceptionally high cure rates, which typically have been >80% [6,7].

In view of the high incidence of congenital cardiac defects in

DS children, potential concerns exist, particularly with the use of anthracyclines. A recent report from the Children's Oncology Group (COG) Study POG 9421 found an increased frequency of cardiac-related late effects, which used a total cumulative anthracycline (daunorubicin and mitoxantrone) dose of 375 mg/m^2, with 24% of DS patients developing cardiomyopathies [8].

In our case report, we presented 2 years old female DS patient who was a known case of heart failure due to an atrioventricular septal defect developed AML M1which initially manifested as intermittent fever, pallor, bleeding tendency, generalized lymphadenopathy with hepatosplenomegaly.

Complete blood picture revealed anemia, thrombocytopenia and leukocytosis.

BMA showed 95% blast which was confirmed by immunohistochemistry and flow cytometry as AML M1. Echocardiography was with low EF (40%).

Our patient underwent chemotherapy with low dose cytarabine as she was unfit for aggressive chemotherapy which was used to treated a patient with AML, she respond well to this low dosage therapy and underwent CR, we stopped the chemotherapy after 24 months because her cardiac problem which needed surgical correction. At the time this manuscript was prepared the patient was undergoing regular follow up for the last uneventful 4 years.

Conclusion

Acute myeloid leukemia should be considered in the differential diagnosis of DS patient's experiences cytopenia or leukocytosis. When acute leukemia is suspected clinically, a bone marrow aspirate for morphology, immunohistochemistry staining, and immunophenotypes by flow cytometry and cytogenetic should be performed.

Echocardiography is always important before starting anthracycline chemotherapy.

Chemotherapy is the treatment of choice for acute myeloid leukemia and usually including combination of two or more chemotherapeutic agent which including anthracycline. Notably, treating DS with AML with single agent cytarabine for a given time interval; depending on the response; May benefit patients who has a significant cardiac dysfunction but a large studies are needed to established it is efficacy in patient with DS and AML.

Acknowledgment

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