Acute Myeloblastic Leukaemia in a Patient with Downs Syndrome and Sickle Cell Anaemia: A Case Report

Chika Duru**, Crosdale Pughikumo and Oyediji Adeyemi

1 Department of Paediatrics and Child Health, Niger Delta University Teaching Hospital, Okolobri, Bayelsa State, Nigeria
2 Department of Haematology, Niger Delta University Teaching Hospital, Okolobri, Bayelsa State, Nigeria

Introduction

Downs syndrome (DS) is the most common postnatally viable chromosomal anomaly. It has an incidence of about 1 in 700 live births [1]. Certain malignancies occur more frequently in persons with Downs syndrome compared to others. They include leukemias, gonadal and extragonadal germ cell tumours and retinoblastomas [2,3].

Children and adolescents with Downs Syndrome have a 10-30 fold increased incidence of leukaemia [1]. This suggests an important role for some chromosome 21 genes located in leukaemogenesis [2]. Notably, the AML 1 gene, a critical regulator of normal haematopoeisis located at 21q22 is involved in 25% of childhood acute Lymphoblastic Leukaemia(ALL) and 15% of acute Myeloblastic Leukaemia (AML) [2,3].

The age of onset for leukaemia in Downs syndrome is bimodal, peaking first in the newborn period and again at 3-6 years. Congenital leukaemia also occurs with increased frequency in Downs syndrome and is characterized by a preponderance of AML as in non-Downs syndrome children [3-5].

AML in Downs syndrome almost exclusively presents before the age of 4 years and the commonest type is acute megakaryoblastic leukaemia (AMkL) which is extremely rare in non-Downs syndrome children [1,3,5]. Recent reports indicate that Down syndrome children with AML especially AMkL have exceptionally high cure rates with event free survival (EFS) rates ranging from 80-100%.This is in contrast to EFS less than 35% for non-Downs syndrome children [6,7].

The sickle cell haemoglobin (HbS) is caused by a point mutation in the beta haemoglobin gene located on chromosome 11.8 Sickle cell disease (SCD) results from the inheritance from both parents of the sickle haemoglobin (HbS) or of HbS and another pathologic variant haemoglobin such as Haemoglobin C (HbS+C) and beta thalassemia (HbS+β-thalassemia) [8,9].

Sickle cell disease is the commonest genetic disorder and sickle cell anaemia (HbSS) is very frequently seen in Africa [9]. The incidence of SCD is about 48 per thousand live births in Africa [8,9]. In Nigeria, about 150,000 babies are born with sickle cell anaemia yearly [9]. There are several individual case reports documenting the occurrence of malignancy in patients with SCD worldwide [10-18]. A small series of collection of cases of malignancy in SCD have also been reported [19,20].

In an institutional study by Dawkins et al., [21] the cancer incidence in SCD was 1.74 per thousand years. Schultz and Ware 22 in a multi-institutional study found 52 cases of malignancy in 16,613 Sickle cell disease cases; fourteen patients had haematological malignancies, two of which were AML. Karyotypic analysis of some of the cases revealed alterations in chromosomes [5,7,17,21].

A few cases of SCD with AML have been reported [10,12,19,22]. While it is not improbable that the commonest chromosomal abnormality may coexist with the commonest genetic disorder, in reality it is extremely rare. In our literature search, only one case report of Downs syndrome and HbS/β-thalassemia was reported in Chicago [23].

The appearance of AML in a patient with coexistent Downs Syndrome and sickle cell disease was not seen in our literature search. We hereby present a case of this triple combination, probably the first reported in medical literature, highlighting the challenges in diagnosis and management.

Case Report

The patient KA presented to the paediatric department of the Niger Delta University Teaching Hospital Okolobri Bayelsa State in Nigeria at the age of 4 months. He presented with a history of visible abdominal movement and swelling and failure to thrive since birth, fever and cough of 1 day duration.

There was a positive history of delayed passage of meconium at birth. He is the fourth child of a 35 years old mother in a monogamous non-consanguineous union.

On presentation, the child was pale, febrile with dysmorphic features- flat occiput, webbed neck, flattened nasal bridge, low set ears, wide spaced nipples, simian crease, short digits, protruding tongue, wide space between the big toe and second digit and whitish specks in both eyes (Figure 1). He had a distended abdomen with visible peristaltic movement and tenderness on palpation with hepatomegaly and splenomegaly both of 6 cm below the right and left costal margins respectively. He was in respiratory distress with a respiratory rate of 44 cpm and a heart rate of 140 bpm with normal heart sounds and no murmur.

An assessment of possible Downs syndrome with Hirschsprungs disease, Bronchopneumonia and bilateral congenital cataract was made. A complete blood count done on admission revealed a Packed Cell Volume (PCV) of 17.9%, Platelets count-74×10¹²/l, Total White cell count (WBC)-5.4×10¹⁰/l, WBC differential count: neutrophils-25%, lymphocytes-66%, monocytes-6% and eosinophils-3%. He was transfused with fresh whole blood and commenced on intravenous broad spectrum antibiotics.

Following review by the haematologist, a peripheral blood film was done which showed moderate anisopoikilocytosis, polychromasia,

*Corresponding author: Chika Duru, Department of Paediatrics and Child Health, Niger Delta University Teaching Hospital, Okolobri, Bayelsa State, Nigeria, E-mail: chikamerenu@yahoo.com

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target cells and occasional sickle cells. There was relative lymphocytosis with some poorly characterised large cells? Blasts (Figure 2). An impression of Downs syndrome with Sickle Cell disease was made to rule out Acute leukaemia. Requests were made for haemoglobin electrophoresis, bone marrow aspiration (BMA) and serum electrolytes, urea, creatinine and uric acid.

Haemoglobin electrophoresis done on admission and repeated later at 18 months of age confirmed HbSS. Serum potassium and sodium were normal while the Urea 2.0 mmol/l (2.4-6.0) and Creatinine 25 mmol/L (60-120) levels were low. Serum uric acid was elevated 520 μmol/L (120-420). Bone marrow aspiration revealed depressed erythropoiesis, myeloid hyperplasia with myeloblasts constituting about 70% of marrow nucleated cells. The myeloblasts were granulated with occasional Auer rods. Myeloid maturation arrest was also noted (Figures 3 and 4). An impression of acute myeloblastic leukaemia AML-M2 by morphology was made. There are no facilities in our institution for immunocytochemistry and karyotyping so we could not undertake immunologic classification and cytogenetic studies.

The parents were counselled on the nature of the child’s disease, management options and prognosis and the child was subsequently worked up for chemotherapy. Electrocardiogram done pre chemotherapy was normal. The patients age, background sickle cell disease, other associations like Hirschsprungs disease, susceptibility to infections and our low capacity for supportive care were major impediments to aggressive chemotherapy. So we instituted chemotherapy with the traditional regimen of Daunorubicin and Cytosine Arabinoside at slightly sub-optimal doses. This was preceded by intravenous hydration and oral allopurinol for 24 hours.

A repeat BMA after 21 days was done showed only partial remission by morphology, so a re-induction was undertaken using the same drugs at full doses. This was backed by haematological support and surveillance of treatment of infections which were quite frequent. Another BMA done after 21 days following this re-induction showed complete remission by morphology (Figures 5 and 6). Repeat serum electrolytes, urea, creatinine and uric acid showed normal values.

The patient then underwent consolidation therapy with the same drugs over the next four months. He showed remarkable response with appreciable weight gain. He was transfused with whole blood six times during the course of his treatment and also treated for recurrent cutaneous and respiratory infections.

Presently, our patient is twenty months old and clinically stable following completion of chemotherapy. He is on routine haematinics and antimalarial preventive therapy and is presently being followed up
Discussion

The association between Down's syndrome (DS) and malignancy has been established for over 90 years, but no definite relationship between Sickle cell disease (SCD) and malignancy has been established. Only one report of DS coexisting with SCD was seen in our literature search [23].

Our patient has Down's syndrome, SCD and AML-M2 by morphology using the French-American-British (FAB) classification. AML-M2 is associated with the translocation t(8;21) [24]. The presence of an extra chromosome 21 probably increases the chance of having this translocation. We could not rule out other chromosomal abnormalities in this patient because there are no facilities for karyotyping.

A major diagnostic challenge in DS patients with acute leukemia is posed by the presence of transient myeloproliferative disorder (TMD), also called transient leukemia. It occurs in about 10% of DS patients [2]. TMD is usually recognised by the presence of megakaryoblasts in the peripheral blood, liver and bone marrow. Typically, most cases present at birth or shortly after and remit by three months, though a few cases persist beyond this [2,25,26]. After spontaneous remission of TMD, 10-30% of cases develop AML after 1-30 months [25,26]. Our patient was diagnosed at the age of 4 months, had no megakaryoblasts in the peripheral blood and the bone marrow blasts had obvious granulocytic maturation.

Knowing the rapidly fatal nature of AML 24 but mindful of the complexities, we commenced chemotherapy cautiously. We were also encouraged by the reports of favourable outcome of chemotherapy in patients with Downs Syndrome and AML with minimal or no cardiotoxicity with antracyclines [6,7].

The presence of sickle cells in the peripheral blood film (PBF) of this patient was a surprising discovery. This is similar to the findings of Paydas [27] where the PBF findings were the first and most important step in the detection of SCD in 4 out of 5 cases of Sickle cell anaemia with haematological neoplasia.

Our patients response to chemotherapy was remarkable with haematological remission. This is in line with several reports of highly favourable outcome in the use of chemotherapy in DS children with AML [3,6,7,28].

The patient's age at diagnosis (4 months) is a good prognostic factor, as AML in DS children occurring above the age of two years have poor outcomes [29]. In a study by Garris et al. [29] DS patients with AML occurring before the age of two years had a better prognosis. Taga et al. [30] also reported a poor outcome in Japanese DS children with AML occurring above the age of four years. This case highlights the challenges in the diagnosis and management of DS children with SCD complicated by AML, but the treatment can be quite rewarding even in resource-poor settings.

References


Figure 6: Bone marrow aspirate showing complete remission (high power).


