Down Syndrome with Myelodysplasia of Megakaryoblastic Lineage

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The association between Down syndrome and acute myelogenous leukemia (AML) has been well documented.[1,2,3] AML in Down syndrome is usually a specific type of megakaryoblastic leukemia (M7, AMKL).[1] A myelodysplastic syndrome generally precedes this malignancy. Down syndrome patients with AMKL have a much better prognosis than other children with AML.[5]

A case study of a 22-month-old female with Down syndrome and myelodysplastic syndrome of a megakaryoblastic lineage is presented here. Upon admission to a pediatric hematology/oncology clinic, flow cytometry results reported a distinct population of phenotypically abnormal myeloblasts expressing myeloid antigens and the immature cell markers.

The patient was placed on a national research group study and began chemotherapy treatment. To date she has received two courses of cytarabine (ara-c) and daunorubicin therapy, which were tolerated well, and is awaiting her third course. Her blood counts stabilize for a while after treatments and her prognosis is good.

ABBREVATIONS: AMKL = acute megakaryoblastic leukemia; AML = acute myelogenous leukemia; BMT= bone marrow transplant; CBC = complete blood count; CMV = cytomegalovirus; RSV = respiratory syncytial virus; TAM = transient abnormal myelopoiesis.

INDEX TERMS: acute megakaryoblastic leukemia (M7, AMKL); acute myelogenous leukemia (AML); Down syndrome.

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The association between Down syndrome and AML has been well documented for nearly 70 years.[1,2,3] Children with Down syndrome have a tenfold to 20-fold increased risk of developing AML over those who do not carry the extra chromosome 21.[2] It is estimated that about two percent of children presenting with pediatric leukemia have Down syndrome.[4] AML in Down syndrome is usually a specific type of acute megakaryoblastic leukemia (M7, AMKL).[1] AMKL is very rare in the general population. A myelodysplastic syndrome generally precedes this malignancy. Myelodysplastic syndrome is a disease in which the bone marrow does not function normally and is sometimes referred to as preleukemia or "smoldering leukemia". Chances are high for a Down syndrome patient with myelodysplastic syndrome to differentiate into AMKL.[1]

CASE PRESENTATION

The patient is a 22-month-old white female with Down syndrome. She appeared to be in a normal state of health with a past medical history of asthma and respiratory syncytial virus (RSV) for which she was being treated with Pulmicort and Xopenex nebulizers when needed. At birth, she was an uncomplicated 37 week delivery with a negative echocardiogram. She lives at home with her mother, father, and three year old sister. There are no sick contacts at home, and she does not attend daycare. She was taken to her local physician after her mother noticed that she was pale with decreased activity and seemed to be easily fatigued. A complete blood count (CBC) reported a white blood cell count of 5400/uL, hemoglobin 4.2g/dL, hematocrit 12.4%, and a platelet

count of 8000/uL. A differential showed a predominance of lymphocytes and a few blasts. She was promptly referred to a pediatric hematology/oncology clinic for myelodysplasia with severe anemia and thrombocytopenia.

At the pediatric oncology clinic a physical examination revealed a positive umbilical hernia and pinpoint petechia on her lower extremities and left forearm. All other vital signs proved unremarkable. She then received transfusions of packed red blood cells and platelets. The peripheral blood smear revealed a predominance of small, mature lymphocytes. There were a few blasts with round to oval nuclei, partially condensed chromatin, several tiny prominent nucleoli, and blue cytoplasm. Only occasional platelets were seen. The red cell morphology showed anisocytosis, poikilocytosis with occasional teardrop cells, spherocytes, ovalocytes, and a few schistocytes. There were also several mononuclear cells with oval nuclei, blue cytoplasm, and irregularities in shape that appeared to be monocytes. Her CBC and differential results from the pediatric hematology/oncology laboratory are shown in Table 1.

A battery of tests ensued including bone marrow biopsies taken from the right and left posterior iliac spine. The biopsies were reviewed using para-aminosalicylic acid and haematoxylin and eosin stains. Marked megakaryocytic hyperplasia and reticulin fibrosis were noted along with marked erythroid and myeloid hypoplasia. Small lymphoid aggregates were also seen. Reticulin fibrosis is common in AMKL.

Table 1. Initial presentation CBC/differential data

Test	Result	Reference
WBC	5.3 x 10^9/L	4.5 – 17.5 x 10^9/L
RBC	3.18 x 10^{12}/L	3.7 – 5.3 x 10^{12}/L
HGB	10.6 g/dL	10.5 g/dL – 16.0 g/dL
HCT	28.8%	33% – 49%
MCV	90.4 fl	70 fl – 102 fl
MCH	33 pg	22 pg – 35 pg
MCHC	37%	30% – 37%
RDW	15.0	11.5 – 14.5
RETIC	2.4%	0.8% – 1.2%
PLATELETS	69 x 10^9/L	150 – 400 x 10^9/L
SEGS	14%	42% – 75%
LYMPHS	79%	25% – 46%
MONOS	5%	0% – 6%
BLASTS	2%	0% - 0%

Cytogenetic studies were also performed. Chromosome analysis from cultured bone marrow cells revealed the presence of an abnormal, mosaic pattern consistent with a neoplastic process. Using Giemsa banding techniques, 20 metaphase cells were examined and all of them contained an extra chromosome 21(trisomy 21). In addition, seven of the 20 cells contained an additional isochromosome 8q resulting in an 8q tetrasomy. The trisomy 21 is a constitutional abnormality because the patient was already known to have Down syndrome. Isochromosome 8q is not known to be diagnostic of any specific neoplasia but is probably the result of some dysplastic event occurring in the bone marrow.

A clinical flow cytometry laboratory performed cytometric immunophenotyping of a bone marrow aspirate from the patient. The results showed that the specimen contained a mixture of cell types with a relative lymphocytosis. The laboratory reported a distinct population of phenotypically abnormal myeloblasts expressing myeloid antigens and the immature cell markers CD34 and CD117(c – kit). CD61, which stains positively in disease states of AMKL and also stains positive for blasts in transient myeloproliferative disorder, demonstrated a weak 1+. However, it is important to note that in AMKL CD13, CD33, and CD 71 all stain variable, and all were positive on this patient. In addition, CD14 and CD64 stained negative which is also suggestive of AMKL. [6] Results of myeloid related CD markers are seen in Table 2.

The pathology report described the patient's bone marrow to be abnormal. Marked megakaryocytic hyperplasia and reticulin fibrosis were noted along with marked erythroid and myeloid hypoplasia. A diagnosis of acute leukemia could **not** be made because no clusters of blasts were detected. However, clinical correlation was recommended. Her condition was diagnosed as Down syndrome with myelodysplastic syndrome and severe cytopenias.

TREATMENT

The patient was given irradiated apheresed leukocyte reduced platelets on four separate occasions during her initial hospital stay. She also was transfused with 100cc of irradiated cytomegalovirus negative packed red blood cells on three separate occasions. She was placed on a national research group study

and began chemotherapy treatment. Complying with protocol, she received Cytarabine (ara-C) and daunorubicin for four days and also ara-C intrathecally (IT) medications. The patient tolerated the chemotherapy well with few side effects. She was given speech therapy, physical therapy, and occupational therapy following her treatment. A post-treatment physical examination showed her to be playful and active, and all vital signs were within normal limits. Her blood counts appeared to stabilize and a CBC indicated a WBC of 3750/uL, hemoglobin 11.7g/dL, hematocrit 31.8% and a platelet count of 100,000/uL. She was discharged and scheduled to return two weeks later for a second course of chemotherapy.

DISCUSSION

It is believed that many cases of AMKL in Down syndrome may have been misclassified as undifferentiated AML (M0), so the incidence might actually be much higher than previously believed. The median age at diagnosis for AMKL is 22 to 23 months of age.[7] Down syndrome patients with AMKL have a much better prognosis than other children with AML.[5] The majority of Down syndrome patients with AML/AMKL can be cured and seem to have a considerable advantage over non-Down syndrome children. A four year event-free survival approaching 75% has been documented.[7] Non-Down syndrome patients who are fortunate enough to receive a bone marrow transplant have about a 50% survival rate as opposed to a rate of only 35% for those who do not receive a bone marrow transplant.

Some Down syndrome children develop transient abnormal myelopoiesis (TAM) at or soon after birth. TAM is generally unique to Down syndrome and produces a blood and bone marrow picture that is indistinguishable from leukemia.[8] TAM spontaneously resolves within three to four weeks. Down syndrome neonates presenting with these symptoms are left untreated and monitored closely to see if the condition goes away. Only if the condition does not spontaneously resolve can the patient be diagnosed with AML and begin a treatment regimen. Approximately 20% to 30% of patients with TAM will develop AML at some point later in life.[7]

CASE RESOLUTION

The patient returned to the pediatric oncology clinic as scheduled for her second course of chemotherapy. Upon admission, she presented with a fever of 101.7 °F and moderate nasopharyngeal congestion. She was placed on broad-spectrum antibiotics pending the result of cultures. Cultures returned negative and her condition was determined to be of viral origin. Her condition improved during her hospital stay and she received blood product transfusions to support her platelet and erythrocyte count. It was determined that her second course of chemotherapy be postponed until the upper respiratory tract infection had resolved. She was given an additional transfusion of one half of a unit of CMV negative, apheresis, and irradiated platelets to boost her platelet count and was then sent home.

Table 2. Myeloid CD markers

CD Marker	Result
CD11b	3+
CD13 (LeuM7	pos
CD14 (LeuM3)	neg
CD15 (LeuM1)	neg
CD33 (LeuM9)	pos
CD34 (My10)	2+
CD45 (HLE)	pos
CD61 (gp3a)	1+
CD64	neg
CD71	pos
CD117	pos
HLA-DR	neg

Table 3. Post-treatment CBC data

Test	Result	Reference
WBC	3.9 x 10^9/L	4.5 – 17.5 x 10^9/L
RBC	3.02 x 10^{12}/L	3.7 – 5.3 x 10^{12}/L
HGB	9.8 g/dL	10.5 g/dL– 16.0 g/dL
HCT	29.1%	33% – 49%
RDW	20.0*	11.5 – 14.5
RETICS	7.9 %	0.8% – 1.2 %
PLATELETS	174 x 10^9 /L	150 – 400 x 10^9 /L
SEGS	85%	42% – 75 %
BANDS	2%	0% – 9 %
LYMPHS	10%	25%– 46 %
MONOS	3%	0% – 6 %

*Slight to moderate poikilocytosis and anisocytosis were also indicated.

Three weeks later the patient returned in healthy condition to resume her second round of chemotherapy. A bone marrow aspirate, lumbar puncture, and administration of intrathecal Ara-C were performed and treatment proceeded without difficulty for a course of five days. She tolerated the second course remarkably well with only mild, brief emesis shortly after the onset of her treatment. She exhibited no significant nausea, vomiting, or intolerance, and remained playful and interactive. A post chemotherapy assessment determined her to be in no apparent distress and all of her vital signs were within normal limits. She was discharged with instructions to return in one week to evaluate her peripheral blood picture.

Complete blood counts and manual differentials were performed weekly after completion of her second course of chemotherapy. Her CBC/differential at one month post second treatment produced the results in Table 3.

Currently, the patient is preparing to begin her third course of chemotherapy. Her blood counts are being monitored on a weekly basis and she will continue to receive chemotherapy treatments for an unspecified length of time. Each case is unique to the individual and the treatment regimen may require modification as different situations arise. She also continues to receive blood product transfusions as needed to help stabilize her red blood cell and platelet counts. She continues to be very active and playful which is encouraging to both her parents and her physician. Fortunately, her disease was caught at an early stage before it had time to progress into AML (M7), which is a significant benefit. Early detection is paramount to the recovery process of any malignancy. In addition, given the fact that the vast majority of Down syndrome patients completely recover from AML and myelodysplastic syndrome, it is believed that her prognosis is good.

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