Parker et al., J Clin Case Rep 2012, 2:7
DOI: 10.4172/2165-7920.1000133

Journal of Clinical Case Reports

Case Report Open Access

A Case of a Young Girl with Myelodysplastic Syndrome (MDS), Dysmorphic Features, Short Stature, and Developmental Delay – Is there a Link?

Torrey M Parker[1,4], Mylene Bassal[1,2,4], Robert Klaassen[1,2,4], Sarah M Nikkel[1,3,4], Michaela Cada[1,2,4] and Donna L Johnston[1,2,4]*

[1]*Department of Pediatrics, Children's Hospital of Eastern Ontario, Canada*
[2]*Division of Hematology Oncology, University of Ottawa, Ottawa, Ontario, Canada*
[3]*Department of Medical Genetics, University of Ottawa, Ottawa, Ontario, Canada*
[4]*University of Ottawa, Ottawa, Ontario, Canada*

Abstract

Myelodysplastic Syndrome (MDS) is a problem of ineffective hematopoesis, due to a clonal disorder of the hematopoetic stem cells. MDS is rare in children and considered premalignant as it often progresses to leukemia over time. There are known inherited predisposing conditions to MDS that have been reported in the literature. We describe the case of a 12-year-old girl with multiple dysmorphic features, short stature, and developmental delay with a new diagnosis of MDS (RAEB) with no confirmed genetic diagnosis linking all these features together. We propose that her underlying syndromic diagnosis may have predisposed her to MDS.

Keywords: MDS; Genetic syndrome

Introduction

Myelodysplastic Sydrome (MDS) is a clonal disorder of hematopoesis that frequently progresses to leukemia. MDS is rare in children and more commonly seen in adults. Many children with MDS have associated abnormalities such as pre-existing bone marrow failure, congenital abnormalities, or inherited bone marrow failure syndromes, which predispose them to the development of Acute Myeloid Leukemia (AML) and other cancers. Children with primary MDS may have underlying predisposing genetic defects; however, available evidence is limited and derived mainly from small studies and case reports [1]. We describe a case of a 12-year girl with an unknown syndrome, short stature, multiple dysmorphic features, and developmental delay all of which may be related to her developing MDS (RAEB).

Case Report

A 12-year-old girl with an undiagnosed syndrome presented to our hospital with a 6-month history of decreased energy, appetite and oral intake with a 3-kilogram weight loss. She also had a one-week history of intermittent non-bilious emesis and tactile temperature. She had three episodes of mild epistaxis. Her review of systems was otherwise unremarkable. She was born at 32+3 weeks to a gravida one healthy mother who had an uncomplicated pregnancy and delivery. Her birth weight was 1410 g. Her head ultrasound at birth showed non-specific subependymal cysts and bilateral lateral ventricle dilatation. A follow-up MRI at age 4 years showed thickening of the genu of corpus callosum.

In neonatal follow-up, she was found to have dysmorphic features, which included: upslanting palpebral fissures, hypertelorism, a petite nose, bilateral clinodactyly of the fifth digits, small hands, brittle nails, and abnormally small teeth. She did not have evidence of leukoplakia or café-au-lait spots and/or hypo- or hyper-pigmented areas. She was seen by genetics at 14 months of age. Her chromosome microarray (44K oligonucleotides) analyses were normal. Sequencing of the C7 of 11 gene associated with non-photosensitive trichothiodystrophy was negative. Light microscopy of her hair was unremarkable. With age, her constellation of features progressed to include: short stature (minus four standard deviations), wooly hair, sensitive skin, and learning difficulties. She had delayed gross and fine motor skills. She had normal speech and intellectual capacity, but problems with information processing.

At her presentation at age 12, in addition to her aforementioned dysmorphic features and physical findings, she had an enlarged liver at 2 cm below the costal margin but no splenomegaly. Her cardiovascular and respiratory exams were unremarkable. Her White Blood Cell count (WBC) 5.74 x 10^9 cells/L, absolute neutrophil count 4.11 x 10^9 cells/L, platelets 57 x10^9 cells/L; hemoglobin 84 g/L; MCV 94.9 fl; reticulocytes 64 x 10^9 cells/L. Her LDH was 1131 U/L; uric acid 117 umol/L; and ESR 70 mm/hr. Her peripheral blood smear showed 4% blasts. She had a structurally normal heart with a pericardial effusion (with no blasts) that required drainage by day 7 of hospitalization.

Her initial bone marrow aspirate demonstrated 15% blasts. Bone marrow immunophenotyping revealed that 38% of cells were an abnormal population showing variable expression of CD10, CD13, CD15, CD33, CD36, HLA-DR, CD41, CD61 and MPO, and negative for CD34, CD19, and surface CD3. These findings were suggestive of Myelodysplastic Syndrome (MDS) with excess blasts but could not exclude progression to acute myeloid leukemia (AML). Bone marrow biopsy was consistent with MDS showing a hyper cellular marrow and a typical localization of immature precursors. Bone marrow karotype confirmed 46, XX. Fluorescent *in situ* Hybridization (FISH) revealed no evidence of monosomy 5 or 7, or BCR/ABL. Her chromosome breakage studies, genetic testing of exon 2 of the SBDS gene and telomere length was normal. The final diagnosis was MDS with refractory anemia with excess blasts (RAEB).

***Corresponding authors:** Donna L Johnston, Division of Hematology-Oncology, Children's Hospital of Eastern Ontario (CHEO), 401 Smyth Road, Ottawa, Ontario, K1H 8L1, Canada, Tel: 613-737-7600 ext 2210; Fax: 613 738-4828; E-mail: djohnston@cheo.on.ca

Received March 29, 2012; **Accepted** April 18, 2012; **Published** April 28, 2012

Citation: Parker TM, Bassal M, Klaassen R, Nikkel SM, Cada M, et al. (2012) A Case of a Young Girl with Myelodysplastic Syndrome (MDS), Dysmorphic Features, Short Stature, and Developmental Delay – Is there a Link? J Clin Case Rep 2:133. doi:10.4172/2165-7920.1000133

She was given one dose of intrathecal cytarabine at the time of her bone marrow. She was then treated with 2 cycles of azacytidine at a dose of 75 mg/m^2/per day for 7 days every 21 days. The second bone marrow aspirate and biopsy done following the two cycles of azacytidine were again consistent with RAEB with 8% excess myeloid blasts and megakaryocytic dysplasia. As she had only mild improvement with azacytidine therapy, she underwent a 6/6 HLA matched unrelated donor umbilical cord stem cell transplant. She was conditioned with targeted intravenous busulfan for 4 days, cyclophosphamide 50 mg/kg/day for 4 days, and Anti Thymocyte Globulin (ATG) 2.5 mg/kg daily for 3 days, which was well tolerated.

Discussion

MDS in children is a rare and more common in adults. The morphologic, cytogenetic and genetic abnormalities, and how these lead to childhood MDS are poorly understood. Allogeneic hematopoietic stem cell transplantation (HSCT) is often the only option with a realistic chance at cure [1]. It is often difficult to predict how children will tolerate this therapy, especially if they have other congenital anomalies, pre-existing organ dysfunction or decreased ability to tolerate toxic therapy, as seen in children with Fanconi anemia and dyskeratosis congenita. Those children with inherited bone marrow failure syndromes and even those with unclassifiable bone marrow failure syndromes may have a predisposition for other malignancies, the risk of which is not eliminated by HSCT [2].

Published series of childhood MDS estimate that 30% of the patients have associated genetic syndromes [3-7], however, an exact association is difficult to know due to the possibility of under diagnosis [4-6]. The pathophysiology of childhood MDS and its association with chromosomal and genetic abnormalities are not well understood and may reflect unique biological factors that may contribute to dyshaematopoeisis [6,7].

There are known predisposing conditions to MDS that have been reported in the literature including: Down syndrome, Kostmann syndrome, Noonan syndrome [4], Fanconi anemia, Dyskeratosis congenita, Trisomy 18, Neurofibromatosis type 1, Shwachman-Diamond syndrome, and familial leukemia syndromes [1,7,8]. There has been case reports of MDS that may be associated with Naxos disease [7], Dandy-Walker syndrome, Lowe syndrome [7], and Wolf-Hirschhorn syndrome [9]. MDS associated with Down syndrome and Noonan syndrome has a more favourable prognosis and may require only supportive care. MDS associated with Fanconi anemia often requires bone marrow transplant and can have a poor prognosis [6].

Our case describes a young girl with multiple dysmorphic features, short stature, and developmental delay with a recent diagnosis of MDS (RAEB) with no confirmed genetic diagnosis linking all these features. This could be considered as an unclassifiable inherited bone marrow failure syndrome, which is associated with multilineage cytopenias with physical malformations [2]. It is difficult to know whether there is an underlying genetic abnormality that may be responsible for the progression to MDS or merely a coincidence as has been suggested by Sharathkumar [9]. Interestingly, Passmore [4] described a small number of patients with MDS with an undiagnosed genetic syndrome with associated abnormalities including: short stature, microcephaly, developmental delay, xanthomata, and xanthogranulomata. There is growing evidence that there are patients with as of yet unclassified inherited bone marrow failure syndromes, which predispose them to MDS/AML or other malignancies [2].

Future research is needed to recognize the underlying process involved in childhood MDS and to understand whether there is in fact a link to certain genetic conditions. It is plausible that underlying genetic abnormalities may have a significant impact on management. It is beneficial for clinicians to be aware that certain genetic abnormalities/syndromes may be associated with childhood MDS in order to aid in early detection, which in turn may have an impact on overall survival.

References

1. Hasle H, Niemeyer CM (2011) Advances in the prognostication and management of advanced MDS in children. Br J Haematol 154: 185-195.
2. Teo JT, Klaassen R, Fernandez CV, Yanofsky R, Wu J, et al. (2008) Clinical and genetic analysis of unclassifiable inherited bone marrow failure syndromes. Pediatrics 122: e139-e148.
3. Bader-Meunier B, Mielot F, Tchernia G, Buisine J, Delsol G, et al. (1996) Myelodysplastic syndromes in childhood: Report of 49 patients from a French multicentre study. French Society of Paediatric Haematology and Immunology. Br J Haematol 92: 344-350.
4. Passmore SJ, Hann IM, Stiller CA, Ramani P, Swansbury GJ, et al. (1995) Pediatric myelodysplasia: A study of 68 children and a new prognostic scoring system. Blood 85: 1742-1750.
5. Luna-Fineman S, Shannon KM, Atwater SK, Davis J, Masterson M, et al. (1999) Myelodysplastic and myeloproliferative disorders of childhood: a study of 167 patients. Blood 93: 459-466.
6. Polychronopoulou S, Panagiotou JP, Kossiva L, Mavrou A, Anagnostou D, et al. (2004) Clinical and morphological features of paediatric myelodysplastic syndromes: A review of 34 cases. Acta Paediatr 93: 1015-1023.
7. Polychronopoulou S, Tsatsopoulou A, Papadhimitriou SI, Panagiotou JP, Anastasakis A, et al. (2002) Myelodysplasia and Naxos disease: A novel pathogenetic association? Leukemia 16: 2335-2337.
8. Emanuel PD (1999) Myelodysplasia and myeloproliferative disorders in childhood: An update. Br J Haematol 105: 852-863.
9. Sharathkumar A, Kirby M, Freedman M, Abdelhameen M, Chitayat D, et al. (2003) Malignant hematological disorders in children with Wolf-Hirschhorn syndrome. Am J Med Genet Part A 119: 194-199.