

Myelodysplastic Syndrome in Childhood

Hina Bilal, Lubna Naseem and Nazia Siddiqui

Department of Pathology, Pakistan Institute of Medical Sciences Islamabad

Abstract

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders, characterized by cytopenias due to impaired blood cell production and hyper cellular and dysplastic bone marrow. The significance of MDS lies in the increased incidence of leukemic transformation. Many morphologic, immunophenotypic and genetic features observed in MDS in adults are also seen in childhood form of disease, but significant differences are reported especially in patients who do not have increased blasts in peripheral blood or bone marrow. Here we present a case of six years female, resident of Yemen, who presented to us with suspicion of aplastic anemia but later she was diagnosed as a case of MDS.

Key words: Childhood Myelodysplastic syndromes, cytopenias, dysplasia.

Introduction

Myelodysplastic syndromes (MDS) are a heterogenous group of hemopoietic clonal disorders characterized by ineffective hemopoiesis due to abnormal "dysplastic" cell morphology. These disorders have increase tendency to transform into acute leukemia. Genetic disorders and inherited bone marrow failure syndromes are often associated with childhood MDS. Various studies have shown that MDS in children is associated with an abnormal karyotype. Abnormal karyotype is present in 30%-50% of all children with MDS. Most of these are numerical anomalies of the chromosomes. Monosomy 7 is most common cytogenetic abnormality followed by trisomy 8 and trisomy 21.¹

There are no specific diagnostic criteria for MDS in children and many patients with refractory anemia are not diagnosed earlier. As a result, these patients developed complications without a diagnosis. Few children with chronic unresponsive anemia died of frank leukemia, due to natural progression of the

disease.²

Case presentation

Hemoglobin	9.8 g/dl
MCV	88.7 fL
Platelet count	36,000 /uL
Total leucocyte count	3,700 /uL
Absolute Lymphocyte count	3,330/uL
Absolute Neutrophil count	370/uL
Reticulocyte Count	0.5%

A six year-old Yemeni girl, presented to us, as a case of aplastic anemia. Her history dated back to early infancy when she was found to have anemia and thrombocytopenia. Initial work up was done in Yemen and the impression from bone marrow was that she had aplastic anemia. Since that time she was on regular blood and platelet transfusion. Clinically she

Contribution of Authors: Dr. Hina Bilal conceived the idea; study designed and carried out the main research work. Dr. Lubna Naseem supervised the research and Dr. Nazia Siddiqui helped in manuscript writing and search of references.

Correspondence: Dr. Hina Bilal
Department of Pathology, Pakistan Institute of Medical Sciences Islamabad
hinaaziz37@hotmail.com

Article Received: 13.08.2015
Accepted: 09.10.2015

was well, but all her growth parameters were below the 5th percentile for her age. She had no rudimentary or absent thumbs neither she had any x-ray changes, but she had subtle dysmorphic facial features; suggestive of Fanconis anemia. The rest of her systemic examination was normal.

Table II Lab investigations

AST	31.2U/L (0-50 U/L)
ALT	31.7U/L (0-41 U/L)
ALP	169.4U/L (up to 281U/L)
GGT	13.2U/L (5-61 U/L)
FERRITIN	2237ng/ml (7-142ng/ml)

Her blood complete picture showed pancytopenia with neutropenia and reticulocytopenia. Her alkaline phosphatase (ALP) level was raised along with markedly raised ferritin due to repeated blood transfusions.

Karyotyping: Her karyotyping showed normal female karyotype (46XX). No spontaneous breakage was seen. There was negative breakage induction.

Bone Marrow Aspiration: Bone marrow aspiration showed hypercellular smear. Erythropoiesis was hyperplastic. Maturation was normoblastic with megaloblastic change and dyserythropoiesis was seen (intercytoplasmic bridging, mitoses and karyorrhexis). Myelopoiesis was also hyperplastic. Maturation was normal and all cell stages were seen with dysmyelopoiesis (bizarre segmentation and cytoplasmic vacuolation). Megakaryopoiesis was adequate in cellularity with dysmegakariopoiesis (hypolobated megakaryocytes). Dysplasia was observed in all three cell lineages. Lymphocytes were increased i.e 36%.Stainable iron was increased in fragments. Siderocytes and sideroblasts were seen on iron stain.

Bone Marrow Trephine Biopsy: Showed hypercellular smear with some hypocellular areas and increased fat spaces. Erythroid precursors were patchily distributed. Myelopoiesis was moderate with left-shifted maturation. Megakaryopoiesis was

moderate with numerous mononuclear forms and abnormally separated nuclear lobes. Lymphocytes were increased. No collection of blast cells is noted.

Impression: Refractory Cytopenia with Multilineage Dysplasia.

Immunohistochemistry:

CD61: Positive in many of the micromegakaryocytes.

CD34: Negative.

On the findings of blood and bone marrow diagnosis of MDS was made. Her bone marrow transplantation was done but she could not survive due to transplant rejection and died after 35 days of bone marrow transplant.

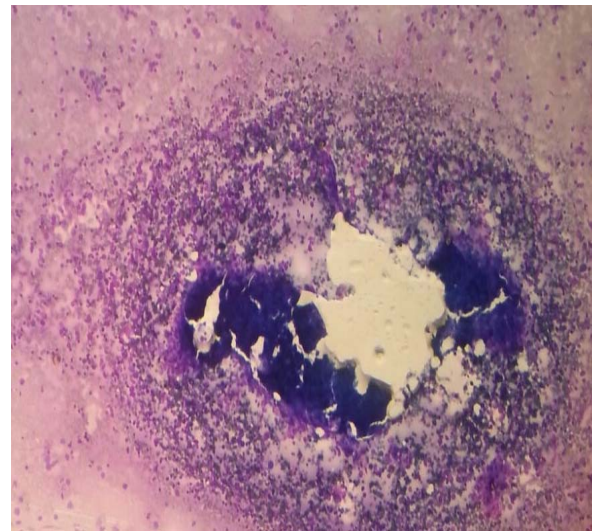


Figure.1. Photomicrograph of hypercellular bone marrow fragment (10X)

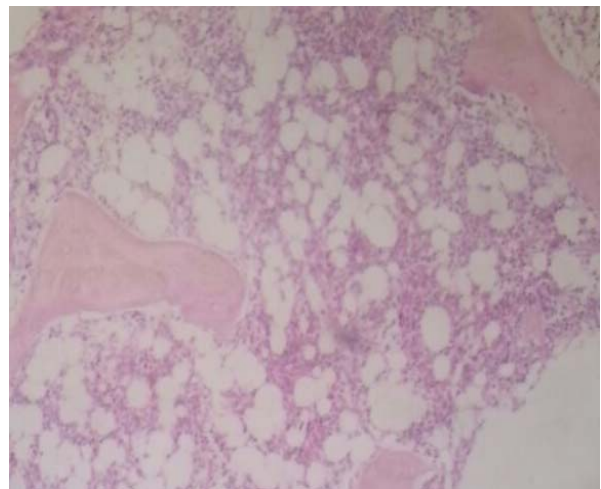


Figure.2. Photomicrograph of cellular bone marrow trephine with prominent fat spaces (10X).

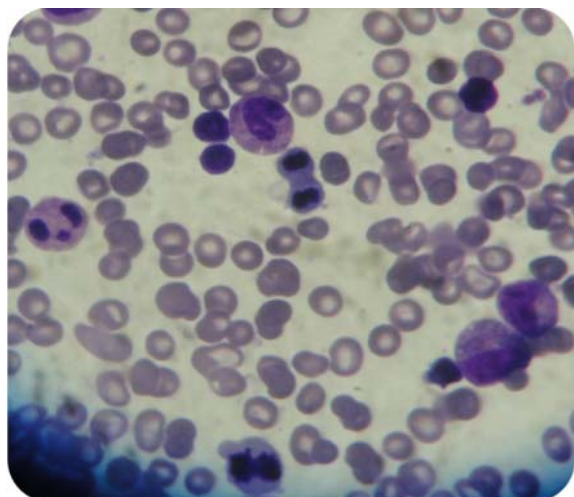


Figure. 3 .Mitosis in erythroid series (100X).

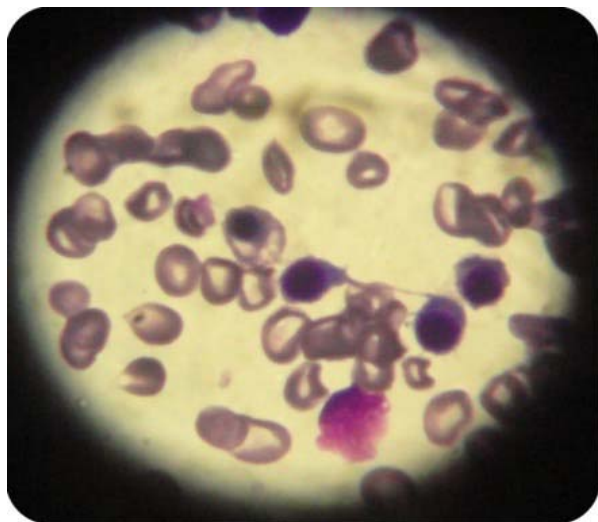


Figure.4. Photomicrograph of Intercytoplasmic bridging (100X).

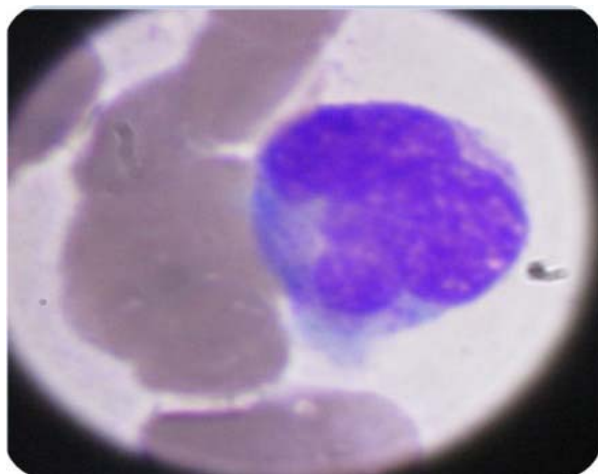


Figure. 5 Dysplasia in myeloid series cells (10X).

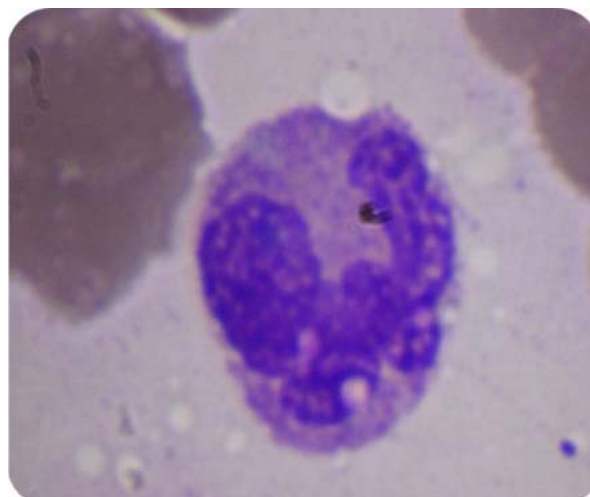


Figure. 6 Dysplasia in myeloid series cells (100X)

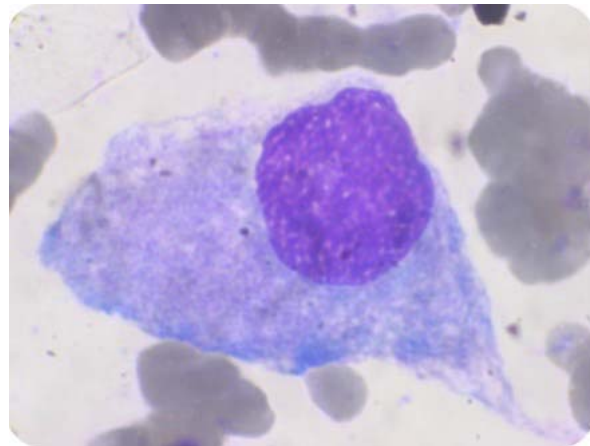


Figure. 7 Mononuclear megakaryocyte (40X).

Discussion

MDS in childhood is rarely seen. There is lack of understanding about genetic events which lead to this entity. The childhood Acute Myeloid Leukemia (AML) cannot be differentiated from MDS, on blast count only, therefore cytogenetics and clinical features are also taken into consideration for diagnosis. Allogeneic hematopoietic stem cell transplantation is often the only option. Cure rate of stem cell transplantation is around 60%.³ Incidence of pediatric MDS in Europe and Canada varies from 1 to 4 cases per million per year and it is equal in males and females.⁴ Median age at presentation in children is 6.8 years.⁵ It is difficult to differentiate MDS with low blast counts from aplastic anemia and MDS with excess blasts from AML.⁶ Both myelodysplastic syndrome (MDS) and severe aplastic anemia can present with

very hypocellular bone marrows. It is important to distinguish these two conditions because although pancytopenia is present in both, MDS has higher risk of progression to acute leukemia. In hypoplastic MDS fat spaces are increased in bone marrow with one or more clusters of erythroid precursors. Proerythroblasts are increased and increased numbers of mitoses are seen. Granulopoiesis is always decreased. There are markedly decreased or absent Megakaryocytes. In Severe aplastic anemia all three hematological cell lineages are decreased with focal increase in lymphocytes, plasma cells, and mast cells. Increased number of immature erythroblasts, particularly proerythroblasts and micromegakaryocytes are absent in aplastic anemia. If Cytogenetic abnormalities like abnormalities of chromosome number are present, these will help to differentiate between Refractory cytopenia and Aplastic anemia or congenital bone marrow failure syndromes.⁷

When MDS develops in a previously healthy child and is termed as "primary". When child has known predisposing condition and develops MDS, it is termed as "secondary". When MDS develops in a child who received chemo- or radiation therapy it is called as secondary MDS or therapy-related MDS. The children may have an underlying unknown genetic defect which predisposes them to MDS at young age. Therefore distinction between primary and secondary disease may become difficult sometimes.

MDS is very heterogeneous disease. Various mechanisms which initiate development of dysplasia or mechanisms which lead to progression of disease have been proposed. There is a genetic defect in pluripotential hemopoietic progenitor cell. This will give rise to genetic instability. After that numerous molecular and cellular abnormalities are acquired and this will result in development of disease.⁸

De novo and secondary MDS both occur in children. These may be the first presentation of inherited bone marrow failure syndromes. Pediatric MDS is different from adult MDS in a way as it is more frequently associated with hypocellular bone marrow and cytogenetic abnormalities.⁹

MDS has micromegakaryocytes which can be missed easily in H&E stained B.M trephine biopsy section

.These can be seen more easily by expression of platelet glycoprotein like CD61. Myeloblasts are usually < 5% in bone marrow. If 5% or more CD34, myeloperoxidase, lysozyme and CD117 positive blast cells are seen it means that disease is progressed to high grade MDS.

Karyotype is an important factor which can predict progression to high grade MDS. Patients with monosomy 7 have higher tendency of progression to high grade MDS. When trisomy 8 or normal karyotype is present, these patients have long and stable course.¹⁰

References

1. Rau ATK, Shreedhara AK and Kumar S. Myelodysplastic Syndromes in Children: Where Are We Today? *Ochsner J.* 2012;12(3):216-20.
2. Alter BP, Giri N, Savage SA, Peters JA, Loud JT, Leathwood L et al. Malignancies and survival patterns in the National Cancer Institute inherited bone marrow failure syndromes cohort study. *Br J Haematol.* 2010 ; 150(2):179-88.
3. Hasle H, Niemeyer CM. Advances in the prognostication and management of advanced MDS in children. *Br J Haematol.* 2011; 154(2): 185-195.
4. SJ Passmore, Chessells JM, Kempski H, Hann IM, Brownbill PA, Stiller CA. Paediatric myelodysplastic syndromes and juvenile myelomonocytic leukaemia in the UK: a population-based study of incidence and survival. *Br J Haematol.* 2003; 121(5):758-67.
5. Jackson GH, Carey PJ, Cant AJ, Bown NP, Reid MM. Myelodysplastic syndromes in children. *Br J haematol.* 1993; 84(1):185-6.
6. Al-Rahawan MM, Alter BP, Bryant BJ, Elghetany MT. Bone marrow cell cycle markers in inherited bone marrow failure syndromes. *Leuk Res.* 2008 ;32(12):1793-9.
7. Barret J, Sauntharajah Y, Mollderm J. Myelodysplastic syndrome and aplastic anemia: distinct entities or diseases linked by a common pathophysiology?. *Semin Hematol.* 2000; 37(1):15-29.
8. Charlotte M, Niemeyer, Baumann I. Classification of childhood aplastic anemia and myelodysplastic syndromes. *ASH hematology.* 2011; 84-9.
9. Taly G, Lisa R and Seth C. Pediatric Myelodysplastic Syndromes: They Do Exist. *Journal of Pediatric Hematology/Oncology.* 2014; 36(1):1-7.
10. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA and Stein H et al. WHO classification of tumors of haematopoietic and lymphoid tissues. 4TH edition. IARC ; 2008.p.106-7.