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Vol: 1, Issue: 2

Journal of Cancer Epidemiology & Treatment

A Pediatric Myelodysplastic Syndrome with Chromosome 5q Deletion

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Article Type: Research, **Submission Date**: 30 July 2015, **Accepted Date:** 04 September 2015, **Published Date:** 23 September 2015.

Citation: Hasan Acar, Umran Calıskan and Huseyin Toksoz (2015) A Pediatric Myelodysplastic Syndrome with Chromosome 5q Deletion. J Can Epi Treat 1(2): 1-4. doi: https://doi.org/10.24218/jcet.2015.09.

Abstract

Myelodysplastic syndromes (MDS) are rare haematopoietic stem cell diseases in pediatric age group. Pediatric MDS patients have a more progressive course and rapidly transform to acute myeloblastic leukemia (AML). In this study, we report a 3-year-old de novo male pediatric patient who presented with refractory anemia with excess blasts and transformed into acute myelocytic leukemia (AML) in 4 months after the initial diagnosis. At the time of referral, a bone marrow aspirate revealed myelodysplastic changes. Cytogenetic analysis showed the following abnormalities: 46,XY[4]/46,XY,del(5q31)[11] karyotype which was confirmed by FISH analysis. At the follow-up stage, a chloromal lesion occurred at the level of 2nd lumbar spine. Bone marrow aspiration revealed a leukemic transformation with 40% of myeloblasts. Cytogenetic and FISH analysis showed still the presence of 46,XY,del(5q31)[7]/46,XY,del(5q31),+mar [6] karyotypes. This patient is also the youngest to be reported with RAEB and chromosome 5q deletion and also showed a distinct clinical feature and progression to AML.

Keywords: Childhood MDS, Chromosome 5q deletion, Fluorescence in situ hybridization, Chloroma, AML.

Introduction

Myelodysplastic syndromes (MDS) are a group of immature blood cell cancer affecting hematopoietic stem cell precursors and their progeny [1,2]. This syndrome represents a variable degree of cytopenia, and an increased risk for developing acute leukemia [2,3]. Paediatric MDS is not very common disorder accounting for <5% of haematopoietic neoplasia in childhood. The initiating events of MDS are not clearly understood, research evidence suggests that an ineffective haematopoiesis is attributed to heterogeneous defects in haematopoietic stem cells [4]. In pediatric age group, MDS is not simply a counterpart of the adult type. Although both childhood and adult MDS types share morphologic features, peripheral cytopenias and eventual transformation to myeloid leukemia, the clinical course in childhood MDS is much more variable [5]. The main clonal chromosomal abnormalities may be observed in bone marrow cells of 30-50% de novo MDS cases [6,7], suggesting a pathogenic mechanism based on loss of tumour suppressor genes or the other genetic rearrangements necessary for normal myelopoiesis and also epigenetic changes [8]. Monosomy 7 or partial loss of the long arm of chromosome 7 is the most common abnormalities, but 5q deletion is very rare and often seen in middle aged to old aged group [6,7]. In children, all types of MDS are very rare and 5q deletion syndrome is exceptionally rare. There is only limited number of 5q deletion pediatric cases [9-13]. In the present study, we report a 3-year-old patient with MDS from de novo 5q deletion and the clinical and laboratory findings of the patient having 5q deletion.

Materials and methods

Case

A 3-year-old boy admitted to our hospital with a 3-month history of weakness, fever, weakness, and epistaxis. Physical examination of the patient revealed a massive paleness, hepatosplenomegaly, bruises on his legs and arms. Informed consent was obtained from the patient's parents.

Hematologic and bone marrow study

Peripheral blood smear, complete blood count and other hematologic tests, bone marrow aspirations and flow cytometric analysis were done at the diagnosis and at follow-up stages. The cell surface antigen profile of leukemic blasts of case were determined on fresh cells obtained from bone marrow sample using standard two-color flow cytometric analysis with a panel of monoclonal antibodies as previously described [14]. The mononuclear cell component was seperated and washed, then incubated in staining media with directly-conjugated either fluorescein isothiocyanate (FITC) or phycoerythrin (PE) monoclonal antibodies (MoAbs) CD45, CD34, CD117, HLA DR, CD33, CD13, CD15, MPO (Becton Dickinson, USA) for 15 minutes at room temperature. Cell was stained determined by using isotype controls (FITC-or PE-conjugated IgG1 and PE-conjugated IgG2). After washing, samples were analyzed immediately with a Becton Dickinson FACS Calibur flow cytometer (BD Biosciences, USA).

Cytogenetic and FISH study

Conventional cytogenetic analysis of bone marrow and fluorescence in situ hybridization (FISH) studies were done at diagnosis and follow up by using standard direct, 24, 48 and 72

hours cultures without using mitotic stimulant. Conventional cytogenetic studies from the direct and 72 hours were done, but 24 and 48-hour cultures did not show the analyzable quality metaphase spreads. FISH analysis with the LSI CSF1R/D5S23 and D5S721 probes (Vysis, USA) was done on the same sample, according to conventional procedure.

Results

At the diagnosis, complete blood count showed that his hemoglobin level was 5.3 gr/dL; the mean corpuscular volume was 94 fl, white blood cell, $8.8x10^9$/L; platelets, $19x10^9$/L. Peripheral blood smear showed normochromic and machrocytic anemia and myeloblasts (4%), metamyelocytes, normoblasts, promyelocytes, myelocytes and monocytes (11%), indicating the picture of 'leukoerythroblastosis'. Vitamin B12 and folic acid levels in serum were within normal range. In follow up period of 4 months, complete blood count showed that hemoglobin level was ranged between 5-9 g/dl, platelet count between 10-50 x 10^9/L, and normal leukocyte count.

At the diagnosis, bone marrow aspiration smears revealed 16% myelocytes and metamyelocytes, 10% myeloblasts, 8% promyelocytes, 26% normoblasts, 21% stab and neutrophils, and 19% lymphocytes. Hypersegmentation, hypogranulation and pseudo-pelger-huet anomalies were seen in the myeloid series, indicating dysgranulopoiesis. Erythroid series were normal. There was a small number of progenitors of megaloblastic erythroid and 10% erythroblasts; showing binuclearity, nuclear bridging and segmentation. There were mononuclear megakaryocytes with excentric position of nucleus, indicating dysmegakaryopoiesis (Figure 1). Bone marrow biopsy also revealed three-lineage dysplasia. There was no ringed sideroblast in the biopsy.

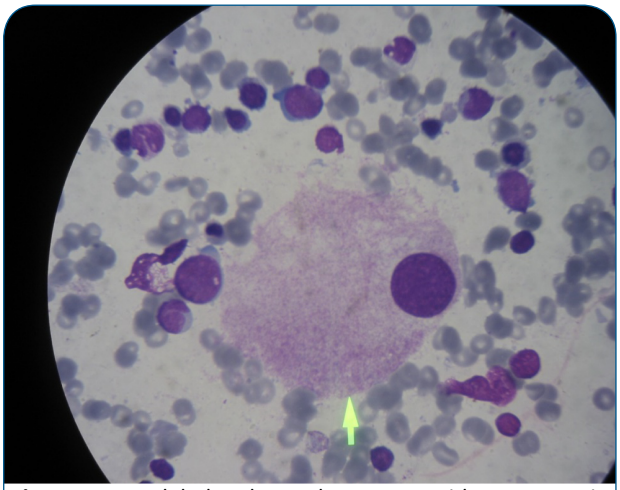

Figure 1: Hypolobulated megakaryocytes with an excentric nucleus position in bone marrow smear (arrow) (x100).

Karyotype was a 46,XY[4]/46,XY,del(5q31)[11] in a direct bone marrow culture. FISH with the LSI CSF1R/D5S23, D5S721 FISH probes (Vysis, USA) confirmed both clones having 46,XY/46,XY,del(5q31) karyotypes on the bone marrow cultures at the diagnosis (Figure 2). Other cytogenetic abnormalities including t(9;22) were all negative at diagnosis. The cytogenetic results were confirmed by FISH analysis, at diagnosis. At remission stage, there was no the 5q31 deletion on the follow up samples. At relapse stage, cytogenetic analysis revealed 46,XY,del(5q31)[7]/46,XY,del(5q31),+mar [6] karyotype on the follow up samples.

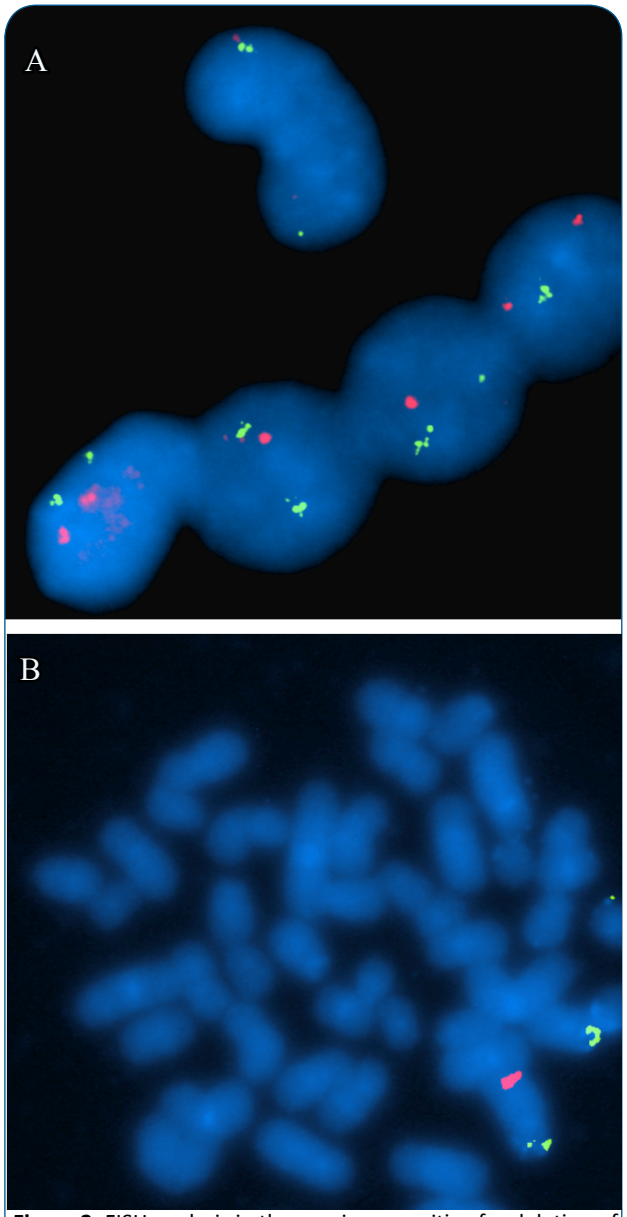

Figure 2: FISH analysis in the specimen positive for deletion of chromosome 5q.

(**A**) Interphase nuclei having single red signal and two green signals as control probe on interphase nuclei, demonstrating presence of the deletion of chromosome 5q.

(B) Metaphase spread having single red signal and two green signals as control probe on chromosome 5, demonstrating presence of the deletion of chromosome 5q.

As a result, according to the French-American-British (FAB) criteria [15], the patient was diagnosed as MDS (refractory anemia excess blast, RA-EB). The patient was then treated the AML-MDS treatment protocol as Cytosine arabinoside, methyl prednisolone, etaposide and mitoxantrone [16]. After the first cure of the treatment, the patient's bone marrow was in remission. However, for hematopoietic stem cell transplantation (HSCT), there were no HLA matched related or unrelated donors and HSCT has not been performed. After 4 months of remission, the patient applied to our clinic with severe back pain. The examination of thoracolomber vertebra MRI revealed a presence of chloroma

at the level of 2nd lumbar spine. Complete blood count revealed that leukocyte count 5000/mm3, hemoglobin 6.3 g/dl platelet count 12x10^9/L. Peripheral blood smear revealed the picture of leukoerythroblastosis (3% myeloblast, 2% promyelocyte, 10% metamyelocytes, 21% neutrophils, 2% normoblasts, 50% lymphocytes, 12% monocytes) with similar dysplastic findings. Furthermore, the bone marrow aspiration revealed a leukemic transformation with 40% of myeloblasts and also dysplastic findings in erythroid and megakaryocytic series. Flow cytometric analysis of bone marrow revealed that these blastic cells had CD45, CD33, CD13, CD15, MPO, HLA DR, CD34, CD117 marker, showing acute myeloid leukemia (AML) M0-M1 (Figure 3). The induction therapy of Berlin Frankfurt Munich (BFM) 98 high-risk AML treatment protocol (cytarabine, etoposide, and idarubicin) was applied to the patient [17]. In addition to systemic chemotheraphy, radiotherapy directed to chloroma was also applied. After this treatment protocol, a remission could not be achieved. Therefore, refractory-AML treatment protocol including fludarabine, ARA-C, and idarubicin (FLAG-IDA regimen) was used for the patient. Unfortunately, he did not have any satisfactory response to FLAG-IDA regimen and remission could not be achieved. The patient died of neutropenic sepsis at the 3rd week of the regimen.

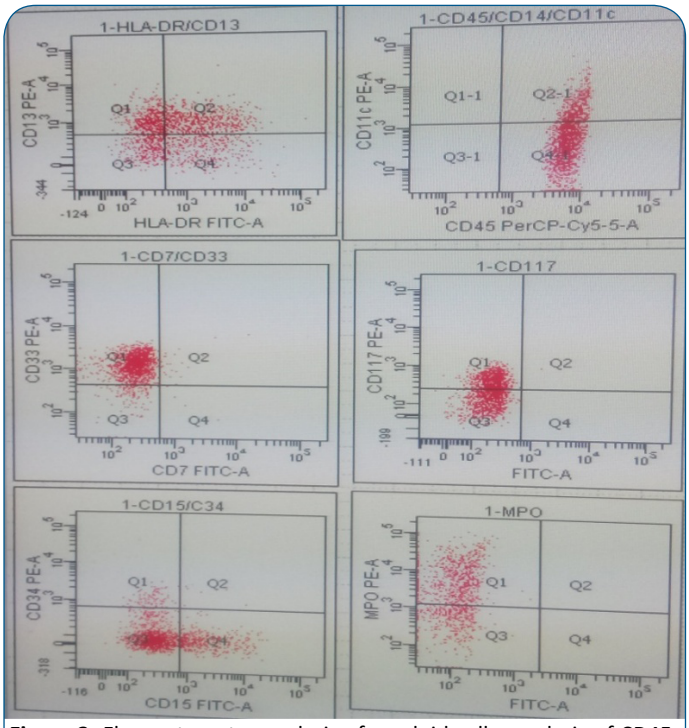

Figure 3: Flow cytometry analysis of myeloid cells: analysis of CD45, CD33, CD13, CD15, MPO, HLA DR and CD117 markers pattern. Increased blastic cells in bone marrow have CD45, CD33, CD13, CD15, MPO, HLA DR, CD117 markers, indicating acute myeloid leukemia (AML) M0-M1.

Discussion

MDS constitute a poorly understood heterogeneous group of disorders that show number of characteristics such as cytopenias, morphologic dysplasia. Childhood MDS is relatively rare in comparison to adult MDS. Most of cases with adult MDS who may remain asymptomatic for a long time, most of the pediatric patients are symptomatic and have a more aggressive and also significant risk of progression to acute leukemia [11, 18]. Neutropenia and thrombocytopenia are more prominent in pediatric cases. Unlike the adult patients, pediatric MDS cases have male predominance to female [19,20]. In the present report, the patient had several characteristics of 5q deletion syndrome in childhood. These are macrocytic anemia with megaloblastoid erythropoiesis, thrombocytopenia, increased blast counts and typical hypolobulated megakaryocytes in bone marrow. The MDS patients with complex karyotype have a much greater tendency of leukemic transformation than those with only 5q deletion [18]. Childhood MDS varies importantly from its adult counterpart in its presenting subtypes and differing cytogenetic abnormalities. Chromosome 5q abnormalities are often seen in adults with MDS and AML. The presence of 5q deletion as the simple cytogenetic abnormality in refractory anemia is related with a favorable clinical course and also a low frequency of leukemic transformation in adult patients [13]. Although the karyotype has been reported to be of significant influence on outcome in pediatric MDS, still the impact of cytogenetics on outcome is debatable. Because chromosomal rearrangements of chromosomes such as 5q, 20q, and Y are extremely common in adults, these are extremely rare seen as a sole in pediatric MDS cases [21, 22]. A few reports regarding pediatric MDS patients with 5q deletion have been reported [9-13]. In our case, clonal cytogenetic abnormalities were seen at diagnosis and the follow up samples of the bone marrow. In the literature, there has not been published any case showing this kind of cytogenetic and clinical entity. It was recommended a supportive care for these patients with 5q deletion. In our child case, MDS was transformed into AML. In the literature, the few similar case of pediatric MDS with 5q deletion has had poor outcomes [11]. HSCT is a lifesaving treatment for this kind of patients [22]. Thus, it is recommended hematopoietic stem cell transplantation (HSCT) for this unfavorable group. However, our patient did not have any HLA-matched donors. Therefore, HSCT could not be done for him. Children with 5q deletion were significantly more likely to progress to poor disease, the remission duration was also very short and he died within 6 months. This patient with 5q deletion syndrome has been presented here, because he had an atypical and severe poor prognosis presentation. Chromosome 5q deletion syndrome seems to have a worse prognosis in childhood period. Therefore pediatric hematologist and oncologist should be aware of this syndrome progression.

Acknowledgment

We thank to the technicians in Department of Medical Genetics and Flow Cytometry laboratories.

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