OLGU SUNUMU CASE REPORT

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Childhood Myelodysplastic Syndrome Progressing to Pre-B Acute Lymphoblastic Leukemia in Two Children with Trisomy 5 and Trisomy 8

Trizomi 5 ve Trizomi 8'li İki Çocukta Pre-B Akut Lenfoblastik Lösemiye İlerleyen Çocukluk Çağı Miyelodisplastik Sendromu

Barış YILMAZ[a], Ahmet KOÇ[a]

[a]Department of Pediatric Hematology and Oncology, Marmara University Pendik Training and Research Hospital, İstanbul, TURKEY

ABSTRACT Myelodysplastic syndrome (MDS) is a rare disorder in childhood. It is often characterized by cytopenias, morphological dysplastic changes, functional abnormalities in hematopoietic cells, and an increased risk for acute myeloid leukemia (AML). Transformation of MDS into AML can often be seen, but the transformation into acute lymphoblastic leukemia (ALL) is extremely rare in childhood. Previously only a few cases have been reported in the literature. In this article, we presented a 7-year-old female patient with trisomy 5 cytogenetic abnormality who developed ALL 9 months after the diagnosis of MDS, and a 6-year-old female patient with trisomy 8 cytogenetic abnormality who developed ALL 4 months after the diagnosis of MDS.

Keywords: Acute lymphoblastic leukemia; childhood; myelodysplastic syndrome; trisomy 5; trisomy 8

ÖZET Miyelodisplastik sendrom (MDS), çocukluk çağında nadir görülen bir hastalıktır. Genellikle sitopeniler, morfolojik displastik değişiklikler, hematopoietik hücrelerde fonksiyonel anormallikler ve akut miyeloid lösemi (AML) için artmış risk ile karakterizedir. MDS'nin AML'ye dönüşümü sıklıkla görülebilir, ancak çocukluk çağında akut lenfoblastik lösemiye (ALL) dönüşme oldukça nadirdir. Literatürde daha önce sadece birkaç olgu bildirilmiştir. Bu yazıda, MDS tanısı konulduktan 9 ay sonra ALL gelişen ve trizomi 5 sitogenetik bozukluğu olan 7 yaşında bir kız hasta ve MDS tanısı konulduktan 4 ay sonra ALL gelişen ve trizomi 8 sitogenetik bozukluğu olan 6 yaşında bir kız hasta sunuldu.

Anahtar Kelimeler: Akut lenfoblastik lösemi; çocukluk çağı; miyelodisplastik sendrom; trizomi 5; trizomi 8

Myelodysplastic syndrome (MDS) is a clonal disease arising from hematopoietic stem cells and rare in childhood. It is generally characterized by cytopenias, morphological dysplastic changes, functional abnormalities in hematopoietic cells, and an increased risk for acute myeloid leukemia (AML).[1,2] Transformation of MDS into AML can often be seen, but transformation into acute lymphoblastic leukemia (ALL) is extremely unusual. Previously only a few cases have been reported in the literature.[1,3-6] In this article, we wanted to share two pediatric MDS cases that transformed into ALL, who had trisomy 5 and trisomy 8 cytogenetic abnormalities.

CASE REPORTS

CASE 1

A seven-year-old female patient who had pneumonia was consulted by another clinic due to high fever and

Correspondence: Ahmet KOÇ
Department of Pediatric Hematology and Oncology, Marmara University Pendik Training and Research Hospital, İstanbul, TURKEY/TÜRKİYE
E-mail: ahmetkoc1@hotmail.com

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pancytopenia. Her physical examination findings were normal except 1.5x1.5 cm of cervical lymphadenomegaly. Complete blood count (CBC) revealed that white blood cell count (WBC) was 1,700/µL, absolute neutrophil count (ANC): 1,000/µL, platelet count: 26,000/µL, hemoglobin: 8.8 g/dL, red blood cell count (RBC): 3,200,000/µL, MCV: 82 fL. On the peripheral blood smear, erythrocytes were normochromic and anisocytic.

Pneumonia and the high fever have resolved in 10 days, but pancytopenia had persisted. After four weeks, bone marrow aspiration and biopsy were performed because of persistent pancytopenia. On light microscopic examination, bone marrow was hypoplastic and dysplastic changes were observed in all serial of hematopoietic cells. Three percent of all bone marrow cells were lymphoblasts. Trisomy 5 was revealed by karyotype and confirmed by FISH analysis technique. [5q31 (EGR1) and 5p13.31 Deletion Probe (Cytocell Cambridge-UK)] (Figure 1). The patient was diagnosed with MDS (refractory cytopenia with multilineage dysplasia).

Pancytopenia of the patient deepened at the 9th month of her follow-up. CBC showed that hemoglobin was 6.6 g/dL, RBC: 2,850,000/µL, WBC: 1,100/µL, ANC: 500/µL, platelet count: 13,000/µL, MCV 75.3 fL. The peripheral blood smear was concordant with CBC. Bone marrow aspiration and biopsy showed that 35% of bone marrow nucleated cells were lymphoblasts. Flow-cytometric investigation showed that blast cells were positive for CD34, TDT, CD10, CD19 and intracellular CD79a. Cytogenetic analysis revealed hyperdiyploidy and complex karyotype abnormality with trisomy 5. The patient was diagnosed with pre-B ALL secondary to MDS and treated with St Jude Total Therapy XV chemotherapy regimen (standard-high risk group).[7] Bone marrow aspiration was repeated after induction chemotherapy, and full remission had been obtained. Stem cell transplantation (SCT) was performed from a human leukocyte antigen (HLA) full match sibling at the 24th week of maintenance while she was in complete remission. The patient is in a good clinical status without any important complications after 74 months of SCT.

CASE 2

A six-year-old female visited the general pediatric outpatient clinic of our hospital with fever and with symptoms of upper respiratory tract infection. CBC revealed thrombocytopenia and neutropenia. Although fever and infection symptoms had resolved, bicytopenia persisted for a month and the patient was referred to our clinic. In admission, CBC showed that WBC was 2,600/µL, ANC: 1,200/µL, platelets: 26,000/µL hemoglobin: 9 g/dL, RBC: 3,850,000/µL and MCV: 83.2 fL. Morphological assessment of the peripheral blood film revealed hypogranuler changes in polymorph nucleated cells, anisocytosis and hypocromia in erythroid cells and severe thrombocytopenia. Bone marrow was hypoplastic, myeloid and erythroid series cells were dysplastic and relatively decreased. Karyotype analysis established trisomy 8, and it was also confirmed by FISH analysis [Centromeric 8 (D8Z2) Probe, 8p11.1-q11.1 Green (Cytocell Cambridge-UK)] (Figure 1).

The patient was diagnosed with MDS (refractory cytopenia). Bone marrow examination was repeated at 1-2 monthly intervals because of persistent bicytopenia. The fourth month examination established that 80% of bone marrow nucleated cells were HLA-DR, CD10, CD19, CD20, intracellular CD79a positive lymphoblasts. The patient was diagnosed with CALLA (+) pre-B ALL secondary to MDS. St Jude Total Therapy XV ALL standard-high risk group treatment protocol was given to the patient.[7] The patient responded well to chemotherapy and achieved complete remission after the induction phase. At the 26th week of maintenance treatment, SCT was performed from a full match HLA unrelated donor. Engraftment was successful, but unfortunately, 160 days after the SCT, the patient died due to infectious complications.

Both patients' family histories were negative for familial MDS/AML, ALL, or other familial cancers. Written informed consent was obtained from both patients' families.

DISCUSSION

MDS may transform into AML, but progression to ALL is rare and seen in less than 1% of adult cases,

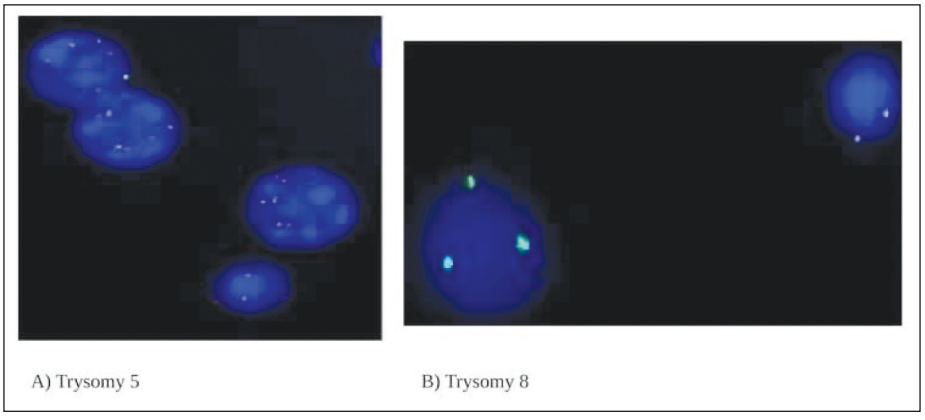

FIGURE 1: FISH analysis of patients before ALL diagnosis. A. Case 1, trisomy 5.85% of all analyzed bone marrow cells. Nine months before ALL diagnosis. Del (5q) Deletion Probe (Cytocell UK). B. Case 2, trisomy 8.46% of all analyzed bone marrow cells. Four months before ALL diagnosis. Centromeric 8 (D8Z2) Probe , 8p11.1-q11.1 Green (Cytocell UK).

and extremely rare in children.[1,3-6] Bader-Meunier et al. described a 4-years-old male MDS-refractory anemia with excess blasts (RAEB) patient with 5q- who transformed to ALL.[1] Goel et al. presented a 9-year-old boy with MDS-RA that transformed into ALL after 21 months who was given cyclosporine therapy.[3] Koh et al. reported a case of an 8-year-old girl with refractory cytopenia of childhood that transformed into ALL three months after the diagnosis of MDS.[4] This patient had large interstitial deletions on 5q21, 2q31.1 and 13q14. Gupta and Bhatia reported a 5-year-old female patient who presented with RAEB and transformed into ALL four months after diagnosis.[5] Guillen et al. reported two cases of MDS at the ages of 2 and 5, (RC and RAEB respectively) which transformed to pre B-cell ALL three months and two months after MDS diagnosis. The first patient had trisomy 8.[6]

Trisomy 5 is extremely rare in childhood MDS and ALL as a sole abnormality and is commonly encountered in cases with hyperdiploidy.[8,9] No other pediatric MDS case with trisomy 5 who transformed into ALL has been seen in the literature. Trisomy 8 is one of the less common but recurrent cytogenetic abnormalities in pediatric MDS. There are a few reports associated with adult MDS cases with trisomy 8 who transformed into ALL.[10,11] There is only one pediatric MDS case with trisomy 8 who transformed into ALL in the literature (mentioned above).[6] Case 2 in our article is the second reported pediatric MDS case with trisomy 8 as the sole cytogenetic abnormality who transformed into ALL.

There are some reports in the literature associated with familial syndromes or germline mutations that cause familial MDS/AML and less commonly ALL. Many patients initially exhibiting bone marrow failure syndromes such as Fanconi anemia, dyskeratosis congenita and Shwachman-Diamond syndrome are prone to the development of MDS or AML.[1,12-14] Relatively common germline mutations that cause familial MDS/AML syndromes are mutations in the ANKRD26, CEBPA, DDX41, ETV6, GATA2, RUNX1 genes.[13-15] Germline alterations in *ETV6* and *TP53* can lead to hematopoietic neoplasms in both myeloid and lymphoid lineages.[14,15]

Familial ALL is relatively uncommon. Apart from well-defined cancer predisposition syndromes (Down syndrome, ataxia telangiectasia, and Nijmegen breakage syndrome), ALL has been considered to have a relatively low hereditary predisposition, with few familial cases. Rarely, constitutional chromosomal rearrangements may cause predisposition to ALL.[15] Germline alterations in PAX5 and IKZF1 may lead to B cell ALL.[14,15] Both of our patients had no history for familial MDS, leukemia or other cancers. There is no reported association between trisomy 5 or trisomy 8 and familial MDS or familial ALL. We could not find any report about familial MDS cases that progressed to ALL in the literature.

These rare cases support the notion that MDS originates from a multipotent cell that can differentiate into both myeloid and lymphoid lineages. Consistent with the data reported in the literature, our cases suggest that most pediatric ALL cases transformed from MDS are pre-B cell phenotype.[3-6]

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Barış Yılmaz, Ahmet Koç;* ***Design:*** *Barış Yılmaz, Ahmet Koç;* ***Control/Supervision:*** *Barış Yılmaz, Ahmet Koç;* ***Data Collection and/or Processing:*** *Barış Yılmaz, Ahmet Koç;* ***Analysis and/or Interpretation:*** *Barış Yılmaz, Ahmet Koç;* ***Literature Review:*** *Barış Yılmaz, Ahmet Koç;* ***Writing the Article:*** *Barış Yılmaz, Ahmet Koç;* ***Critical Review:*** *Ahmet Koç;* ***References and Fundings:*** *Barış Yılmaz, Ahmet Koç;* ***Materials:****Barış Yılmaz, Ahmet Koç.*

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