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Diagnosis and management of myelodysplastic syndrome in a Fanconi anemia patient

Arash Alghasi[1], Homayon Yousefi[1], Reza Khedri[2], Mohammad-Reza Mahmoudian-Sani[1]

[1]Thalassemia and Hemoglobinopathy Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Clinical Research Development Unit, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

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Correspondence:
Mohammad-Reza Mahmoudian-Sani, Assistant Professor of Molecular Medicine, Thalassemia & Hemoglobinopathy Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences
E-mail: mohamadsani495@gmail.com

An uncommon genetic condition known as Fanconi anemia (FA) is characterized by bone marrow failure, chromosomal instability, and a high susceptibility to cancer. We report a case study of a patient diagnosed with FA who subsequently developed myelodysplastic syndrome (MDS). Informed consent was obtained from the patient's parents/legal guardians. Consent for publication was obtained from the patient's parents/legal guardians. We present a case of a 10-year-old boy with a known diagnosis of FA who experienced a decline in platelet count and subsequent bone marrow abnormalities suggestive of MDS. Cytogenetic analysis confirmed the diagnosis of FA with multiple chromosomal breaks, and flow cytometric analysis supported the diagnosis of MDS with excess blasts. The patient underwent a stem cell transplantation from a full matched donor (his father). Stem cell transplantation from a fully matched related donor can be effective in treating FA and associated complications. The transplantation was complicated by graft-versus-host disease and cytomegalovirus infection, however the child achieved complete normalization and exhibited no signs of diarrhea or dependence on immunosuppressive drugs at the six-month follow-up. The case report emphasizes the significance of multidisciplinary care and close follow-up for pediatric FA and MDS patients, suggesting further research and standardization of diagnostic procedures.
Key words: *Fanconi anemia, myelodysplastic syndrome, stem cell transplantation, graft-versus-host disease, cytogenetic analysis, flow cytometry*

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Fanconi anemia (FA) is an extremely uncommon type of anemia. On average, it affects 1 in every 136,000 children, varying between 1 in 100,000 and 250,000 births [1]. According to the European registries and data, the prevalence of FA is only 4–7 per million live births [2]. Guido Fanconi first characterized three brothers who had pancytopenia and birth abnormalities in 1927 [3]. The chromosome breakage test (CBT), which uses DNA cross-linking chemicals such as mitomycin C and diepoxybutane, is the gold standard for diagnosing FA and reflects increased sensitivity to bifunctional cross-linking agents. No further testing is required if a patient has a negative CBT, unless there is significant clinical suspicion [4]. Although the outcomes of hematopoietic stem cell transplantation (HSCT) in patients with FA have significantly improved over the past 20 years, HSCT increases the risk and accelerates the development of late malignancies in addition to the increased procedure-related mortality. When carried out in optimal conditions (moderate cytopenia shifting to severe, prior to transfusion dependence and before clonal evolution or myelodysplasia/acute myeloid leukemia) [5], HSCT is associated with the best outcomes. Myelodysplastic syndromes (MDS) are a group of clonal blood disorders characterized by ineffective hematopoiesis, peripheral cytopenia, multilineage dysplasia and a variable propensity to progress to acute myeloid leukemia. Pediatric MDS are rare and account for 4–9% of all hematologic malignancies. At present it is clear, that in children MDS is mostly associated with inherited conditions, and FA is one of the most common conditions, predisposing to the development of MDS [6].

CASE PRESENTATION

Informed consent was obtained from the patient's parents/legal guardians. Consent for publication was obtained from the patient's parents/legal guardians. A 10-year-old boy, previously diagnosed with FA, presented with a decline in platelet count and subsequent bone marrow abnormalities suggestive of MDS. This child had been under observation for the past few years, with routine hematology tests conducted every 6 months that showed no problems. However, in the most recent routine test, the platelet count dropped to 90,000/mm^3. Two weeks later, the platelet count was rechecked and found to be 50,000/mm^3, which further decreased to 20,000/mm^3. The hemoglobin level was 11 grams per deciliter (g/dl), while other blood counts were within the normal range. Cytogenetic analysis revealed multiple chromosomal breaks consistent with the diagnosis of FA. A total of 20 metaphase spreads were studied from routine culture,

100 spreads from culture were prepared with the addition of two different concentrations of mitomycin C, which were then compared with 100 spreads from an age-related normal control. The culture of the proband showed 189 breaks and 10 radials in 75 cells, yielding an average of 2.09 breaks per metaphase. In contrast, the healthy control showed 14 breaks (an average of 0.14 per metaphase) in 10 cells. From a cytogenetic standpoint, breakage equal to or greater than 10-fold that of the control is considered clinically significant. Analysis at 500–550 band resolution level revealed no chromosomal aberrations (*figure 1*). A cytogenetic analysis confirmed the diagnosis of FA with multiple breaks (*figure 2*). The patient underwent a bone marrow test, which confirmed the presence of MDS with excess blasts. A flow cytometry analysis was also conducted (the results are presented in *table*) and showed dysplastic changes in myeloid cells, supporting the diagnosis of MDS with excess blasts. The bone marrow smear showed myeloid dysplasia, with blast cells accounting for 12% of the total. Immunophenotyping of bone marrow leukocytes by flow cytometry (Attune NxT Flow Cytometer) demonstrated positive expression of CD13, CD33, CD34, CD117, CD38, and HLA-DR in 12% of the cells analyzed. These findings, together with morphological features (*figure 3*), are consistent with MDS with excess blasts (the first test). Another bone marrow smear showed myeloid dysplasia with a few blast cells. Immunophenotyping of bone marrow leukocytes by flow cytometry revealed positive expression of CD13, CD34, CD117, and CD38 in 12% of the cells (a repeat test). These results, along with the morphological findings, support the diagnosis of myeloid dysplasia with excess blasts. The child was hospitalized 28 days before stem cell transplantation (SCT) and received chemotherapy according to the mini-FLAG-Ida (fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin) regimen. The intensity of FLAG was reduced before SCT. The patient received stem cells from his father, a fully matched donor. After the transplantation, the child developed severe gastrointestinal graft-versus-host disease (GvHD), which lasted for two months. Treatment involved immunosuppressive medications (mycophenolate mofetil, tacrolimus, and budesonide) to manage the symptoms. Chimerism analysis performed 1 month after the transplantation showed 100% donor cells. A bone marrow test performed 2 months after the transplantation revealed complete normalization. Fortunately, two months later, the child's diarrhea decreased and completely ceased by the third month. the third month after the transplantation, the child developed cytomegalovirus infection, which was successfully treated with ganciclovir. A subsequent bone marrow test showed myeloid dysplasia with toxic granulation. Flow cytometry immunophenotyping of the bone marrow displayed no abnormalities in the CD markers (*table*). Six months after the transplantation, the child's condition is entirely normal, with no diar-

Figure 1
G-band metaphase chromosome analysis revealed no abnormalities in the 46 XX chromosomes

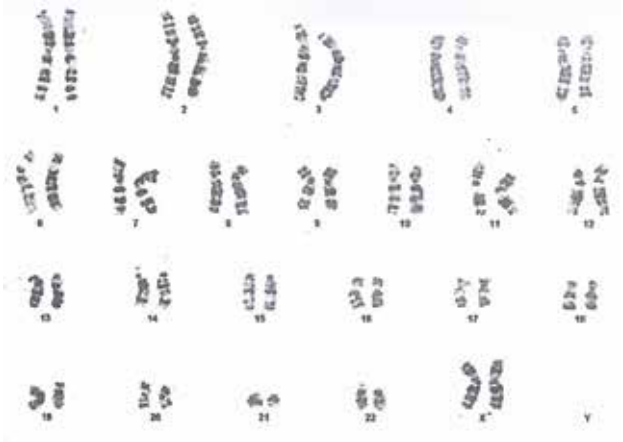


Figure 2
Metaphase spread from the patient exhibiting multiple chromosomal breaks and radial formations (some of which are indicated by arrows)

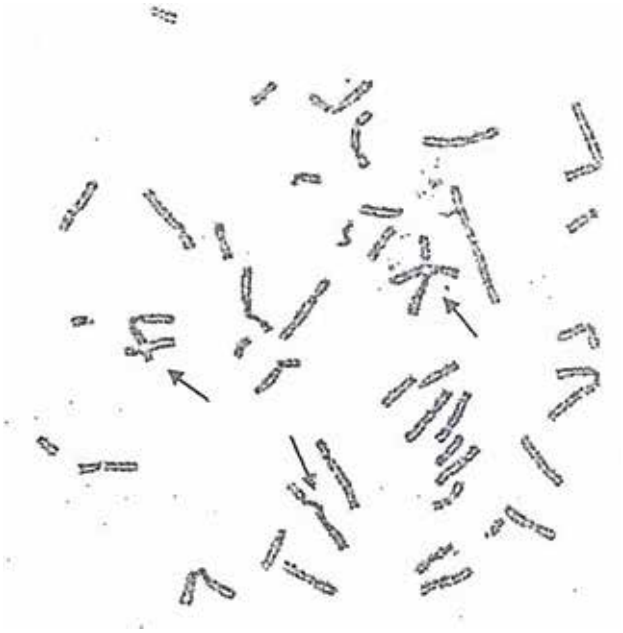
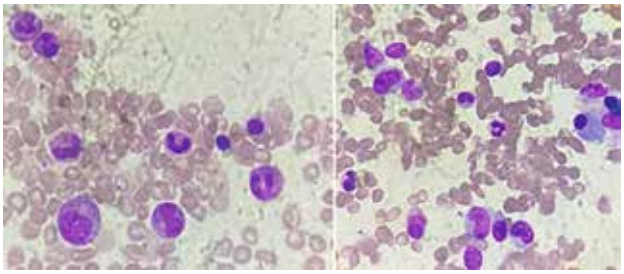


Figure 3
Cellular bone marrow aspirate smears in MDS showing dysplastic features, abnormal cellularity, increased blasts, abnormal myeloid and erythroid maturation, and the presence of ring sideroblasts. These findings raise suspicion for MDS and guide further diagnostic investigations (BMA Leishman Giemsa stain 9 1009)



rhea, and the immunosuppressive drugs have been discontinued.

DISCUSSION

This article presents a case report of a 10-year-old boy with FA who developed MDS and underwent a successful SCT from his HLA-matched father. Despite the challenges of GvHD and cytomegalovirus infection post-transplantation, the child achieved complete normalization and exhibited no signs of complications at the six-month follow-up. Patients diagnosed with FA face a significantly increased risk of various conditions, including bone marrow failure, MDS, leukemia, head and neck squamous cell carcinoma, and other types of cancer [7]. The criteria for identifying MDS in FA individuals are not well defined, and the significance of clonal chromosomal abnormalities is still uncertain. MDS diagnosis relies on comprehensive assessments that include blood smear analysis, bone marrow aspirate smears and biopsies. Cytogenetic analysis can also provide valuable diagnostic information. Flow cytometry has also become useful in the study of MDS, aiding in the diagnosis and prognosis of the disease. In the majority of MDS cases, bone marrow cellularity is increased at diagnosis, often with hyperplasia of the erythroid or granulocytic series, or both [8]. However, approximately 30–40% of cases display normal bone marrow cellularity, while around 10% of patients have hypocellular bone marrow aspirates. People with MDS sometimes have non-specific reactive changes in the bone marrow, such as increased lymphocytes, plasma cells, mast cells, or hemosiderin-laden macrophages with some hemophagocytosis [9]. Patients with MDS show abnormal erythrocyte development, which is often characterized by nuclear irregularities. Neutrophils may also exhibit hypogranularity and abnormal nuclear segmentation. Dysmegakaryopoiesis, characterized by small and hypolobated megakaryocytes, is another common feature. Cytogenetic testing also provides valuable information [10]. In the mentioned case, the bone marrow aspirate and biopsy revealed increased marrow cellularity and granulocytic proliferation. Dysplastic features are typically observed in one or more myeloid cell lines in MDS. To be considered significant, the requisite percentage of cells displaying dysplasia in a specific cell line should be at least 10%. Dysplastic erythroid cell lines (caused by dyserythropoiesis), dysplastic granulocytic cell lines (caused by dysgranulopoiesis), and dysplastic megakaryocytic cell lines (caused by dysmegakaryopoiesis) are the three subtypes of dysplastic presentation in MDS [11]. The CBT, which uses DNA cross-linking agents including mitomycin C and diepoxybutane, is the gold-standard diagnostic procedure for FA. If a patient's CBT results are negative, additional testing might not be required unless there is a significant clinical suspicion [12]. Significant advancements have been made in the utilization of flow cytometry for studying MDS since the World Health Organization's 2008 classification of myeloid neoplasms was proposed [13]. Flow cytometry immunophenotyping makes it possible to find, count, and describe different types of hematopoietic cells and their stages of development in both bone marrow and peripheral blood samples. For this reason, flow cytometry plays a unique role in the diagnosis and prognosis of individuals suspected or confirmed to have MDS [14]. Even though there is a lot of evidence that flow cytometry is highly sensitive in diagnosing MDS, appropriate markers and immunophenotypic patterns still need to be confirmed in prospective studies and standardized across multiple centers. By standardizing flow cytometry in the context of MDS, it is possible to enhance the accuracy of diagnosis and improve prognostication in the future [15]. Allogeneic HSCT may be able

Table
Flow cytometric immunophenotyping of the bone marrow

Parameter	Value
The first test	
CD4	45%
CD7	41%
CD8	27%
CD10	15%
CD19	8%
CD20	10%
CD56	8%
CD38	56%
CD117	15%
CD13	36%
CD33	45%
CD64	32%
CD34	15%
HLA-DR	42%
A repeat test	
CD4	20%
CD7	18%
CD19	2%
CD38	36%
CD117	12%
CD13	79%
CD33	35%
CD64	60%
CD34	15%
HLA-DR	51%
After HSCT	
CD3	10%
CD7	11%
CD10	3%
CD19	2%
CD20	2%
CD22	2%
CD13	34%
CD33	22%
CD34	1%

to treat MDS because of the strong immune-mediated graft against tumor effects and the high-dose cytotoxic treatment used during pretransplant conditioning [16]. In a study involving 119 patients with FA, 23 participants had MDS, and the most common subtype of MDS was refractory cytopenia with multilineage dysplasia. There was a high correlation between the presence of clonal aberrations and the diagnosis of MDS. On the other hand, granulocytic dysplasia and increased blast counts were always associated with the presence of a malignant clone. Patients with FA who also have cytogenetic abnormalities, MDS, or acute leukemia have high long-term survival rates [17]. Allogeneic HSCT can be a potential treatment option for MDS, despite the possible complications. Younger patients and those who receive transplants from HLA-matched related donors and only have cytogenetic abnormalities with no excess of blast cells have the highest survival rates [18].

CONCLUSION

Regular follow-up and timely intervention are crucial for FA patients at risk of developing MDS. Stem cell transplantation from a matched donor can be an effective treatment option, although complications such as GvHD and infections may arise. This case report highlights the importance of multidisciplinary care and close follow-up to achieve successful outcomes for pediatric patients with FA and MDS. Further research and standardization of diagnostic procedures, such as flow cytometry, can enhance the accuracy of diagnosis and prognostication for MDS in the future.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

ORCID
Arash Alghasi ORCID: https://orcid.org/0000-0003-3482-2195
Homayon Yousefi ORCID: https://orcid.org/0000-0002-4027-2030
Mohammad-Reza Mahmoudian-Sani ORCID: https://orcid.org/0000-0002-1096-5661

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