Research Article

Acute myeloid leukemia in Turkish children with Fanconi anemia. One center experience in the period between 1964-1995

Fanconi anemili Türk çocuklarında akut miyeloid lösemi. 1964-1995 döneminde bir merkezin deneyimleri

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Abstract

Objective: Fanconi's anemia (FA) is an autosomal recessive disorder characterized by a progressive pancytopenia,variable congenital abnormalities and an increased risk for the development of acute myeloid leukemia (AML). The objective of this study is to evaluate AML in the patients with FA diagnosed and followed-up in the Department of Pediatric Hematology at Ankara University School of Medicine in the period between 1964-1995.

Methods: A total of 39 patients within the age range 2-14 years (mean 8.2±3.16), 28 male and 11 female were diagnosed as FA on the basis of congenital abnormalities, pancytopenia, bone marrow aplasia and diepoxybutane induced chromosomal abnormalities that observed in all patients. The hereditary and familial basis of FA was apparent in this series.

Results: Common abnormalities were growth retardation, café- au- lait spots, hyperpigmentation, microcephaly, finger and thumb deformities,mental retardation and hypogenitalismus. Four AML (10.2%) were observed in our series. Cytogenetic analysis of these cases revealed 46/ XX, dup(3)(q22;q26) t(7;17) (p11;p11) in one where it was unsuccessful in three. Two cases could not achieve remission and died. The other two achieved complete remission and remained in remission for 2 and 6 months

Conclusion: Acute myelomonocytic leukemia in three cases and acute monocytic leukemia in one patient were diagnosed in our series. The patients with FA should be followed with regard to AML and solid tumors. AML and solid tumors should be taken into the consideration as the first manifestation of FA. *(Turk J Hematol 2009; 26: 118-22)*

Key words: Fanconi, acute myeloid leukemia, congenital abnormalities, diepoxybutane

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Özet

Amaç: Fanconi anemisi progresif pansitopeni,çeşitli konjenital anomaliler,akut miyeloid lösemi ve solid tümor gelişme riski çok yüksek olan bir sendromdur.Bu çalışmanın amacı bölümümüzde 30 yıl içinde izlenen Fanconi anemili hastalarda gelişen AML'nin özelliklerini incelemektir.

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Yöntemler: Yaşları 2-14 yaş (mean 8,2±3,16) arasında değişen 28'i erkek,11'i kız toplam 39 hasta materyelimizi oluşturdu. Hastalara tanı konjenital anomalilerin varlığı, pansitopeni, kemik iliği aplasia ve diepoksibutan testi ile kromozom kırıklarının gösterilmesiyle kondu.
Bulgular: Hastalarımızda görülen konjenital anomaliler gelişme geriliği, sütlü kahve renginde lekeler, hiperpigmentasyon, mikrosefali, baş parmak ve parmak anomalileri, hipogenitalya ve mental retardasyondu. Hastaların dördünde AML (%10,2) gelişti. Sitogenetik incelemelerde bir hastada 46/XX,dup (3) (q22;q26) t(7;17) (p11;p11) saptandı, diğer üç hastada üreme olmadı. İki hasta remisyona girmedi, diğer iki hastada iki ay ve altı ay süren tam remisyon sağlandı.
Sonuç: Serimizde 3 olguda akut miyelomonositik lösemi ve 1 hastada akut monositik lösemi teşhis edildi. FA'li hastalar AML ve solid tümörler açısından izlenmelidir. AML ve solid tümörler FA'li hastanın ilk bulgusu olabilir. Hastanın aile bireyleri de malignite yönünden incelenmelidir. FA'lı ve AML'li hastalarda prognoz kötüdür. Yeni ve etkin tedavi yöntemleri geliştirilmelidir. *(Turk J Hematol 2009; 26: 118-22)*
Anahtar kelimeler: Fanconi, akut miyeloid lösemi, konjenital anormallikler, diepoksibütan
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Introduction

Fanconi's anemia (FA) is a rare autosomal recessive disorder characterized by variable congenital abnormalities, increased spontaneous and DNA cross-linker-induced chromosome instability, progressive pancytopenia, and a predisposition to leukemia and solid tumors. X-linked inheritance was reported in FA complementation group B [1]. The clinical manifestations of FA are heterogeneous, ranging from multiple birth defects to completely normal appearance. Congenital malformations without anemia have also been mentioned in a number of family members [2-8].

Diepoxybutane (DEB) test remains the classical "gold standard" test for diagnosis involving the detection of chromosomal breaks, gaps, rearrangements, radials, exchange, and endoreduplications in peripheral blood cells following culturing with clastogenic agents such as DEB or mitomycin-C [9,10]. FA can be divided into 12 complementation groups (A, B, C, D1, D2, E, F, G, I, J, L and M) defined by cell fusion studies and 11 of the 12 responsible FA genes have been identified [11-13]. Recently, a new FA gene, PALB2, also known as subtype FA-N, has been discovered as the 13th, and it has been found that mutations in this gene caused a very severe phenotype with cancer developing in early childhood [14].

Children with FA have a very high risk of developing acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). The incidence of AML is 15,000 times more than that observed in children in the general population [15]. Acute leukemia has been the terminal event in about 5-20% of the patients with FA. MDS was reported as 7% and the overall incidence of solid tumors was estimated at about 2%. Patients with FA are at a high risk for developing specific solid tumors located in the head, neck, esophagus, liver, and female genitalia [16-18].

The objective of this study is to report AML in the patients with FA diagnosed and followed up in the Department of Pediatric Hematology at Ankara University School of Medicine in the period 1964-1995.

Materials and Methods

A total of 39 patients with a mean age of 8.2 ± 3.16 (range: 2-14 years), 28 males and 11 females, were diagnosed as FA during 30 years on the basis of congenital abnormalities, pancytopenia, bone marrow aplasia and DEB-induce chromosomal abnormalities. The hereditary and familial characteristics of FA were existent in this series. Common abnormalities were growth retardation, café-au-lait spots, hyperpigmentation, microcephaly, finger and thumb deformities (Figure 1), Sprengel deformity, and hypogenitalism. These 39 patients were followed up from one month to 4.5 years (median: 2.5 years) after diagnosis.

The patients with FA were evaluated with regard to the development of AML and their prognosis. The characteristic findings of the patients with AML and the hematologic parameters at diagnosis are summarized in Tables 1 and 2.

Results

AML developed in four of the patients (10.2%) in our series. These patients were treated by androgens, steroids and immunotherapy during the aplastic anemia. Myelomonocytic type (Figure 2) developed in three cases and acute monocytic type in one patient (Figure 3). AML was observed in the follow-up period of three patients after the development of aplastic anemia. Rhabdomyosarcoma as the first manifestation of FA was noticed in a six-year-old boy who was treated with VACA protocol and 2000 cGy radiotherapy to the abdomen. Full doses of chemotherapy with advanced supportive care were given to the patient because he was not yet diagnosed as FA at that time. Severe complications such as pneumonia, urinary tract and skin infections developed during this period. One year

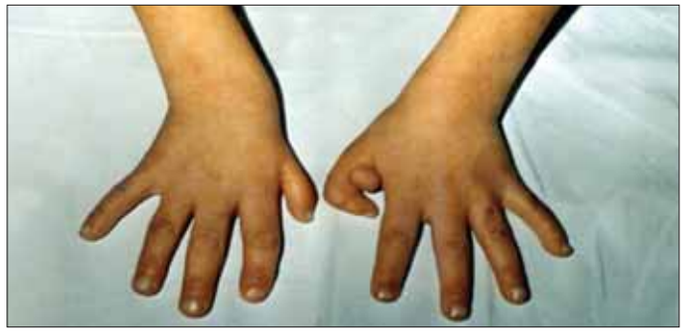

Figure 1. Radial ray defects in case 1

Table 1. Characteristics of the patients with AML

Case	Age (year)/ sex	Findings	Age at first admission	Cytogenetic at AML	Treatment before AML	Treatment
1. RAG	11 / M	growth retardation café-au-lait spots radial ray defects (thumbs) pallor bruising and epistaxis hepatomegaly (5cm) splenomegaly (3cm)	8	-	corticosteroid testosterone	AML developed three years after FA Exitus within 4 days
2. YK	9 / M	café-au-lait spots growth retardation microcephaly right-sided undescended testis pallor, bruising hepatomegaly (4 cm) splenomegaly (5 cm)	6	-	VACA 2000 cGy radiotherapy	Modification of Denver protocol CR: 2 months Relapse - exitus within 2 weeks
3. CD	12 / M	café-au-lait spots ear abnormalities clinodactyly hypogenitalism pallor hepatomegaly (6cm) splenomegaly (4cm)	8	-	corticosteroid testosterone	Modification of Denver protocol No obtained CR-exitus
4. ZS	12 / F	café-au-lait spots growth retardation microcephaly hypoplastic thumb, clinodactyly Sprengel deformity pallor splenomegaly (3 cm) hepatomegaly (5 cm)	10	46 XX dup (3) (q22;q26) t(7;17) (p11;p11)	oxymetholone ALG	Modification of CCG-2961 CR: 6 months Relapse - exitus within 1 month

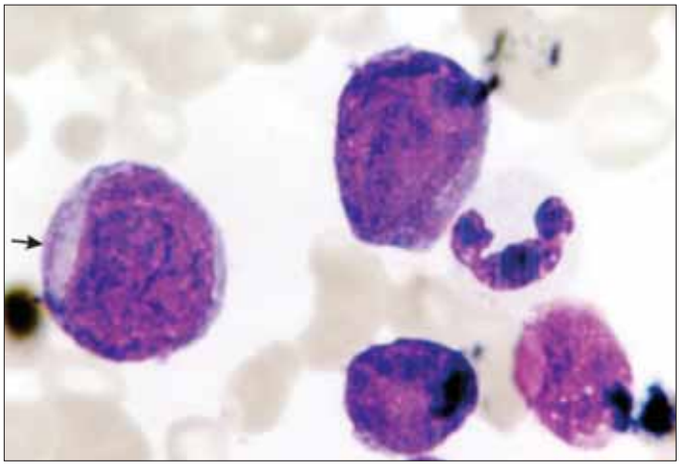

Figure 2. Myeloblast with Auer rods in the bone marrow in case 2

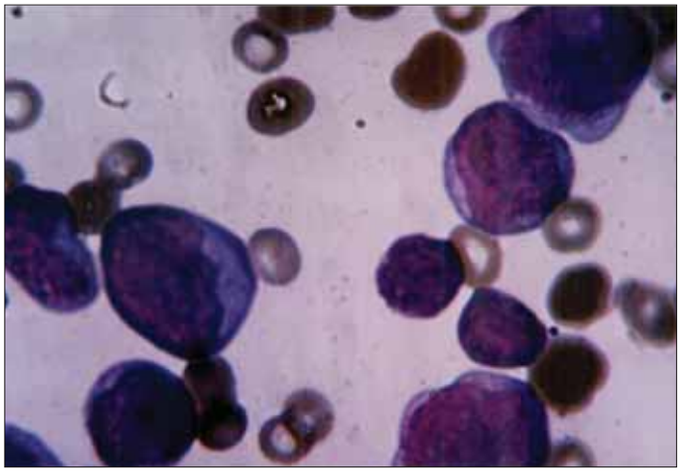

Figure 3. Monoblasts in the bone marrow in case 1

after the end of the treatment, DEB test was applied because of growth retardation, hyperpigmentation and microcephaly and it revealed that the patient had FA. Hematologic parameters and bone marrow examination were normal at that time; 17 months later, after the end of solid tumor treatment, AML, M4 subtype, developed. Cytogenetic analysis of these patients revealed 46/XX,dup (3) (q22;q26) t (7;17) (p11;p11) in one (Figure 4), whereas it was unsuccessful in three. Two cases could not achieve remission and died. The other two patients achieved complete remission following modified Denver treatment protocol and remained in remission for the following two and six months respectively (Table 1).

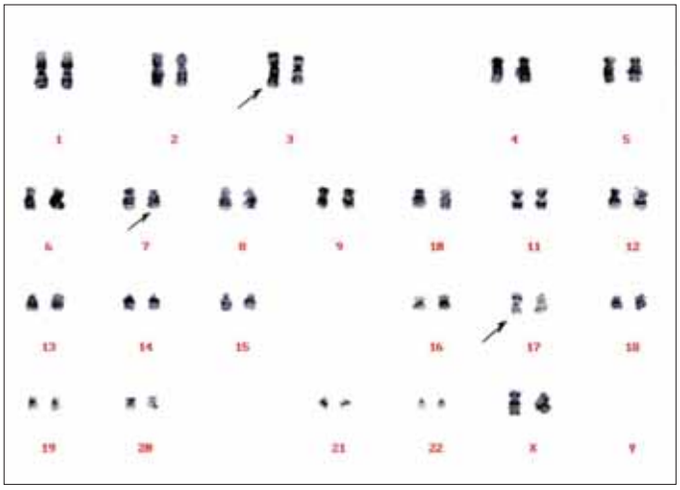

Figure 4. Cytogenetic abnormalities in the metaphase plaque in case 4: 46XX, dup (3) (q22;26), t(7;17) (p11;p11)

Discussion

Initial hematologic abnormalities in FA are diverse. Thrombocytopenia 38%, pancytopenia 53%, MDS 3.9%, AML 2.1%, anemia 1.8%, neutropenia 0.3%, and ALL 0.3% were reported in an International Fanconi Anemia Registry (IFAR) study. Macrocytosis is often the first detected abnormality in FA. This is followed by thrombocytopenia, anemia and pancytopenia. According to the IFAR study, median age at detection of initial hematologic abnormality was 7 years, and actuarial risk of developing hematologic abnormality by 40 years of age was 98% [19]. In another study, Rosenberg et al. [16] showed that certain congenital abnormalities were potential risk indicators for the development of bone marrow failure; FA patients with abnormal radii had a 5.5 times increased risk of developing bone marrow failure.

Leukemia was reported in more than 100 cases representing 10% of the patients with FA in the literature [2]. The types of leukemia occurring in FA are primarily non-lymphocytic leukemias, although a few lymphoblastic types have also been reported [2,15,19, 20]. In the patients, all FAB subtypes occur except promyelocytic type (M3); the myelomonocytic (M4) and acute monocytic (M5) types are the most common [20]. Auerbach et al. [15] suggested that all FA patients may be considered as in preleukemic state.

Acute myelomonocytic type in three cases and acute monocytic type in one patient were diagnosed in our series. Interestingly, AML was developed after 17 months following the completion of initial treatment in a nine-year-old boy diagnosed of abdominal rhabdomyosarcoma at the age of six in first admission [21].

Table 2. Hematologic parameters in the patients at AML diagnosis

	Case 1	Case 2	Case 3	Case 4
Hb (g/dl)	6.0	7.3	5.4	6.2
Hct (%)	23.7	-	16.8	25
WBC/mm^3	20,700	7,000	29,900	56,100
Platelet/mm^3	12,000	21,000	52,000	13,000
Blasts				
Blood smear	44%	18%	60%	83%
Bone marrow	77% monoblasts	33% Auer rods(+) myeloblasts	62%	100%
Cytochemical features	MPO(+)	MPO(+) NSE(+) PAS(-) A. Phosphatase(-)	MPO(+) D. Esterase(+)	-
Immunophenotype	-	-	-	CD33:25% CD34:26% CyMPO:34% HLA-DR:36%

One thousand three hundred cases of FA were evaluated by Alter [18] over the period 1927-2001. Nine percent of these cases had leukemia, 7% had MDS, 5% had solid tumors, and 3% had liver tumors. In approximately 25% of the patients with cancer, the malignancy preceded the diagnosis of FA. It is unclear which patients are prone to develop such tumors [18]. On the other hand, FA-D1 subgroup can be associated with a high incidence of solid tumors of early childhood [22].

Rosenberg et al. [16] estimated the cumulative incidence of malignancies among 145 FA patients, with 9 developing leukemia and 18 solid tumors developing in 14 patients. The ratio of observed to expected neoplasm (O/E) patients was 50 for all cancers, 48 for all solid tumors and 785 for leukemias. These increased risks were calculated to be statistically significant. Median age at detection of MDS or AML was 13 years (1 month to 32 years), and actuarial risk of developing MDS or AML by 40 years of age was 52% according to IFAR [19].

Altay et al. [6] mentioned that five of the 52 FA patients developed malignancies (3 AML, 1 squamous cell carcinoma of the gingiva, 1 hepatocellular carcinoma). In our series, four of the 39 FA patients developed AML and one had two malignancies. There were no other cancers among family members in these four patients, whereas the sister of a boy with FA also developed acute leukemia in another hospital [4].

Stem cell transplantation (SCT) is often effective treatment in bone marrow failure in FA. In the patients with MDS/AML, it is best to proceed to a SCT rather than chemotherapy [17] but long–term survivors of SCT have high risks of developing solid tumors such as head and neck squamous cell carcinomas, particularly of the oral cavity, and gynecologic malignancies [23].

In conclusion, leukemia in FA is generally very difficult to treat and survival is poor. Deaths occur on average within the first two months after diagnosis. The defect in DNA repair leads to increased sensitivity to chemotherapy, and the patients are either vulnerable to treatment toxicity or may receive inadequate treatment. The effective treatment modalities have to be further developed. Patients with FA should be followed with regard to AML and solid tumors. AML and solid tumors have to be taken into consideration as the first manifestation of FA. It is also important to note that the family members of the patients with FA must be analyzed regarding cancer.

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