

# Fanconi anemia with the presentation of abdominal rhabdomyosarcoma followed by acute myeloid leukemia

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## ABSTRACT

The objective of this study is to present an unusual case of Fanconi anemia (FA) with an initial presentation of abdominal rhabdomyosarcoma followed by acute myeloid leukemia (AML). Although epithelial cancers are more often seen in FA patients, rarities such as osteosarcomas, soft-tissue tumors and brain cancers have been reported in the literature. The present case was treated with VACA treatment (vincristine, actinomycin D, cyclophosphamide and adriamycin) and radiotherapy following initial assessment through surgery and histopathological evaluation. A second malignancy AML developed 17 months after completion of initial treatment and the patient died at 2 months remission and 6 months survival following the diagnosis of AML. [Turk J Cancer 2007;37(4):154-157]

**KEY WORDS:** Rhabdomyosarcoma, Fanconi anemia, acute myeloid leukemia

## INTRODUCTION

Fanconi anemia (FA) characterized by aplastic anemia is associated with a variety of congenital anomalies (hyperpigmentation of the skin, café-au-lait spots, abnormalities of fingers, short stature, microcephaly, deformities of the ear, renal anomalies, hypogenitalism, etc.), increased risk of malignancy and chromosomal instability (1-4). Clinical features of FA are heterogeneous. Congenital malformations without anemia have also been reported in the members in a number of families (3,5).

Diepoxybutane (DEB) test remains as a classical “gold standard” test for diagnosis, involving the detection of chromosomal breaks, gaps, rearrangements, radials, exchange, endoreduplications in peripheral blood cells following culturing with clastogenic agents (such as DEB or mitomycin-C) (6,7). Complementation studies have provided evidence for at least 11 distinct genes for 8 groups and are characterized as FANCA, C, D1, D2, E, F, G, L (8,9).

Patients with FA are at a high risk for developing specific solid tumors located at the head, neck, esophagus, liver and female genitalia. Literature search has revealed 6 patients with two solid tumors and 2 patients with four such primaries. Furthermore, acute leukemia has been diagnosed terminally in 5-20 % of FA patients (8-10).

An unusual case of intraabdominal rhabdomyosarcoma with liver metastases in a patient with FA who subsequently developed AML is presented.

## CASE REPORT

A six-year-old boy was initially admitted to the hospital with a suprapubic intraabdominal mass and a palpable liver, exceeding the costal margin for 4 cm. Having had no further abnormality detected at routine blood and urine tests, investigation for abdominal imaging revealed a tumoral mass of 10 cm diameter, behind the urinary bladder, pushing the rectum dorsally, and further numerous masses ranging from 3 mm to 3 cm in both lobes of the liver. Incisional and excisional biopsies at laparotomy were diagnosed as rhabdomyosarcoma (Stage IV). Severe cytopenias and serious pulmonary infections developed during the multidisciplinary therapy; including surgery, VACA treatment (vincristine, actinomycin D, cyclophosphamide and adriamycin) and 2,000 cGy radiation. Full doses of chemotherapy were given to the patient because he was not yet diagnosed of Fanconi anemia at this time.

A year after the treatment, during the follow-up; signs of growth retardation, microcephaly, skin hiperpigmentation, *café-au-lait* spots and a unilateral undescended testis led to cytogenetic laboratory tests which revealed Fanconi aplastic anemia with positive mitomycin-C tests (46% chromosomal breaks after incubation with mitomycin-C) (Figure 1). Hematological values remained within normal limits at this time.



Fig 1. Chromosomal structure abnormalities in the patient

A massive bleed from decayed tooth extraction requiring hospitalization, 17 months after completion of initial treatment, blood count revealed Hb: 7.4 gr/dl, WBC: 7,000/ $\mu$ L with 18% blast cells and Auer body positivity, and a platelet count: 21,000/ $\mu$ L ( Figure 2). Bone marrow aspirate showed 33% presence of blast cells, myeloperoxidase and non-specific esterase tests positivity and acid phosphatase and PAS negativity. Acute non-lymphoid leukemia (M4) diagnosis was established. The patient was treated with Denver protocol (CCG-213) which includes remission induction, consolidation, prevention of central nervous system leukemia and maintenance therapy. Briefly summarised, remission induction consists of VP16-213, adriamycin, Ara-C, 6 TG, dexamethasone and intrathecal Ara-C; consolidation regimen involves two stages. The first stage includes Ara-C and L-Asp and the second one comprises 6TG, VCR, Ara-C and CTX. In this protocol, the drugs in the second stage are used as a maintenance therapy for 18 times. Doses of all drugs were used by decreasing 50% in our patient. The patient achieved complete remission following modified Denver treatment protocol with advanced supportive care and remained in remission for the following two months, before finally dying with relapse and massive bleeds.

## DISCUSSION

FA is a rare cancer susceptibility syndrome with increased predisposition to leukemias and squamous cell carcinomas of the head and neck or female genitalia as well as liver tumors (8,11). One thousand three hundred

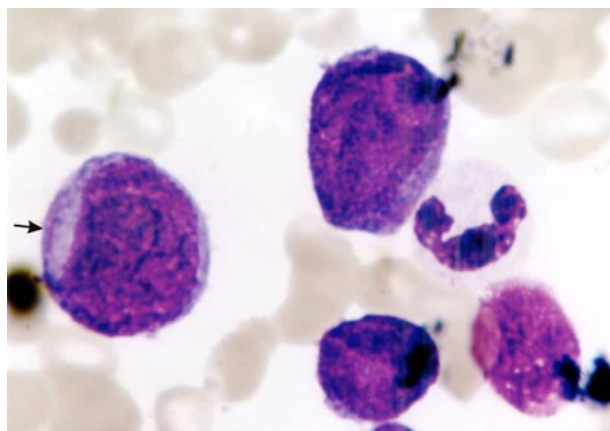


Fig 2. Blast cells and Auer body positivity

cases of FA were evaluated by Alter BP (12) during the years between 1927-2001. Nine percent of these cases had leukemia, 7% had myelodysplastic syndrome, 5 % had solid tumors and 3 % had liver tumors. It is unclear which patients are prone to develop such tumors.

Rosenberg et al. (13) have 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. The overall excess also includes nonsignificant increases in osteosarcomas, soft-tissue sarcomas and brain tumors. The median age at onset of leukemias was 11.3 years, which showed a significantly lower age compared to those of the onset for the median 28.9 years for solid tumors (13).

FA presented with aplastic anemia leads to the development of solid tumors later in life (12). Soft tissue sarcomas were diagnosed very rarely in the patients with FA but FA-D1 subgroup can be associated with a high incidence of solid tumors of early childhood (13,14). Most interestingly, our case represents an abdominal rhabdomyosarcoma with metastasis as the first manifestation of FA in a six-year-old-boy who subsequently developed AML as a second malignancy.

The recent identification of the breast and ovarian cancer susceptibility gene BRCA2, as the FANCD1 gene, implicates the FA/BRCA pathway in homology-directed DNA repair and suggests that disruption of the pathway may promote breast and ovarian cancer (11).

The types of leukemia which occur in FA are primarily non-lymphocytic leukemias although a few lymphoblas-

tic types have also been reported (15,16). The incidence of AML in FA patients is more than 15,000 times than those observed in children in the general population (17). In these patients, all FAB subtypes occur except promyelocytic type (M3); the myelomonocytic (M4) and acute monocytic (M5) types are the most common (18). Auerbach et al. (17) suggested that all FA patients may be considered preleukemic and this disorder represents a model for study of the etiology of AML. Altay et al. (4) reported that 5 of the 52 FA patients developed malignancies. Three had AML and one developed a squamous cell carcinoma of the gingiva and another a hepatocellular carcinoma. There was increased risk for AML and for other cancers among family members of FA patients (4). In our series, 4 of the 39 FA patients developed AML and one had two malignancies as reported in the presented case (19).

AML in FA is generally very difficult to treat and survival has been very poor as observed in the presented case. 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 (15). Our patient achieved complete remission following modified Denver treatment protocol and remained in remission for the following two months, before finally dying with relapse and massive bleeds.

The clinician should be aware of and alert for other concomitant leukemias and solid tumors especially when congenital malformations encountered in FA are present. On the other hand, the prognosis in the patients with FA and AML is still poor. The effective treatment modalities have to be further developed.

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