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Acute lymphoblastic leukemia in a child with Fanconi’s anemia

Naureen Mushtaq  
*Aga Khan University*

Rabia Wali  
*Shaukat Khanum Cancer and Research Hospital*

Zehra Fadoo  
*Aga Khan University*

Ali Faisal Saleem  
*Aga Khan University*

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INTRODUCTION

Fanconi anaemia (FA) is a constitutional pancytopenia of childhood with mostly autosomal recessive inheritance with diverse clinical heterogeneity including congenital malformations, progressive bone marrow failure and high propensity for cancer in long-term, mostly solid tumours and carcinoma of head, neck and upper oesophagus followed by carcinoma of vulva and/or anus and lower oesophagus; however, it is also associated with acute leukemia with marked predisposition with acute myeloid leukemia (AML) and rarely acute lymphoblastic leukemia (ALL).1,2 Myelodysplastic syndromes may follow clinically overt aplastic anaemia or develop without a detectable antecedent.3 The incidence of AML or myelodysplastic syndrome in FA is approximately 15%.4 All patients have underlying abnormal chromosome fragility seen in metaphase preparations which was enhanced by adding clastogenic agents such as diepoxybutane.4,5 Growth hormone (GH) therapy for FA can also lead to ALL.6 Sensitivity to DNA damaging agents limits therapy in patients with FA; however, severe toxicity and marrow aplasia without haematological recovery has also been described in the literature.7

FA transformation into ALL is a rare phenomenon. There are very few case reports in the literature. Here we present this rare entity of FA with ALL.

CASE REPORT

The patient was a 13 years old girl at presentation to the haematology and oncology clinic with prolonged history of blood transfusion since last 6 years. She had no previous records available. However, she was on regular once fortnightly packed cell transfusion and weekly platelet transfusion. On examination, she was short statured with microcephaly, having triangular facies and areas of hyperpigmentation. There was no organomegaly or lymphadenopathy. She had six siblings and they were healthy when she presented to us. Because of FA suspicion her laboratory workup was done. Her complete blood count showed pancytopenia, with < 20% cellularity of bone marrow on trephine biopsy and chromosomal breaks was positive. She was kept on supportive management and planned for haematopoietic stem cell transplantation (HSCT). Her human leukocyte antigen (HLA) typing along with her siblings was also done. Unfortunately, the patient's HLA matched donor was found to have chromosomal breaks as well. Later on, her peripheral smear showed blast cell. Bone marrow showed pre-B ALL. She was started on chemotherapy but died shortly due to complications of the treatment. For this rare condition conservative management is indeed essential, however, safe and appropriate chemotherapy regimen is needed.

Key words: Fanconi anaemia. Acute lymphoblastic leukemia. Bone marrow failure.
therapy (vincristine, L-asparaginase, prednisolone and daunorubicin) as per ALL protocol, but because of her severe diastolic dysfunction daunorubicin was omitted from the chemotherapy. She succumbed to infection and died on the 7th day of induction therapy with septicaemia; however, none of her cultures were positive.

DISCUSSION

Fanconi anaemia (FA) is a genetic disorder characterized by congenital abnormalities, cancer predisposition, and progressive pancytopenia. The cellular phenotype of FA is characterized by increased sensitivity to DNA cross-linking or alkylating agents that block DNA replication and RNA transcription.8

FA children typically present in the first decade of life on recognition of aplastic anaemia.1 The classic features of FA consist of thumb and radial absence malformations; less obvious features include a deeper cleft between the first two digits. The gold standard for FA quantify chromosomal breakage in cells exposed to cross-linking agents to which FA cells are hypersensitive.2

FA patients have a very high risk of developing progressive bone marrow failure along with an increased risk of future long-term malignancies. The most frequent malignancy in FA is acute myeloid leukemia (AML) with a cumulative incidence of 33% by 40 years of age.8

This patient developed ALL which is rare, but possible acute leukemia in FA. The FA-related leukemias differ from leukemia in the general population in several important ways.9 In FA patients, 94% of the acute leukemias are myeloid and only 6% are lymphoid compared with 84% of the acute leukemias being lymphoid in general paediatric population. The age distribution for acute leukemia in FA was normally distributed around a mode of 14 years; however, in the general population in which the incidence of AML is higher in infants, it was declined to around age 10, and then rises slightly in the late teens.2 The age of this patient was 13 years when she diagnosed as ALL.

Cancer risk assessment was done for FA. Table I showed the three studies with their haematological malignancies distribution. First was a literature review of 1300 reported cases of FA from 1927 to 2001;10 second was of 754 FA patients from the International Fanconi Anaemia Registry (IFAR) ascertained from 1982 to 2001,8 while the third was a cross-sectional study of 145 North American patients during 2000.11 It was seen that the cumulative incidence of ALL in FA was 0.5% (12/2200 patients).

<table>
<thead>
<tr>
<th>Studies</th>
<th>Total cases of Fanconi anaemia</th>
<th>Haematological malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alter BP (2003) (10)</td>
<td>1301</td>
<td>109 89 07 205</td>
</tr>
<tr>
<td>Kutler DI (2003) (8)</td>
<td>754</td>
<td>60 53 05 120</td>
</tr>
<tr>
<td>Total cases</td>
<td>2200</td>
<td>– – 12++ –</td>
</tr>
</tbody>
</table>

**Table I:** Studies with FA cases along with their haematological malignancies distribution.

This patient was also planned for four-drug induction therapy with vincristine, daunorubicin, steroids and L-asparaginase; but as patient had sub-optimal cardiac function anthracyline was omitted for the time being. The patient died on 7th day of her induction therapy due to septicemia.

In conclusion, the existence of ALL in patients with FA is rarely reported and further work is needed to determine the appropriate chemotherapy regimen in these patients.

REFERENCES


