J Hematopathol (2013) 6:161–165
DOI 10.1007/s12308-012-0168-2

CASE REPORT

Precursor T acute lymphoblastic leukemia from myelodysplastic syndrome in Fanconi anemia

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Received: 12 July 2012 / Accepted: 26 September 2012 / Published online: 9 October 2012

Abstract Fanconi anemia is a rare autosomal recessive disease which is associated with an increased risk of malignancy. Acute myeloid leukemia and myelodysplastic syndrome are the most common malignancies. This case report is on an infant who was diagnosed with Fanconi anemia and developed myelodysplastic syndrome in his first year of life which later likely transformed into T acute lymphoblastic leukemia. These findings were demonstrated by FISH. The case highlights a rare lymphoid neoplasm in an FA patient and also the increased incidence of T lineage neoplasms when MDS transforms into a lymphoid leukemia.

Keywords Fanconi anemia · Precursor T acute lymphoblastic lymphoma · Myelodysplastic syndrome · BRCA

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Introduction

Fanconi anemia (FA) is a rare autosomal or X-linked recessive disease characterized by a highly variable phenotype with multiple congenital malformations, pancytopenias, progressive bone marrow failure, and predisposition to hematologic malignancies and solid tumors. Almost all patients develop hematologic abnormalities with a 90 % cumulative incidence of bone marrow failure by age 40 [1]. The most frequent malignancies are acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) [1]. Bone marrow clonal cytogenetic abnormalities increase with age and are usually complex. Gains in 1q, monosomy 7, and losses in 7q are the most commonly seen abnormalities [2].

We describe a patient with FA who developed precursor T acute lymphoblastic leukemia (T-ALL) arising in a background of MDS. A review of the literature suggests that this case is unique in that T-ALL arising in a background of MDS is rare and development of ALL following MDS in a patient with FA has not been previously described.

Case report

An infant boy was born after 31 weeks of gestation with multiple congenital anomalies including an imperforate anus, hydrocephalus, dysplastic right kidney, microphthalmia, and glaucoma. At birth, as well as throughout his life, his length and head circumference were less than the third percentile. He had a normal male karyotype; however, an increased amount of chromosome breakage and rearrangements were noted. Diepoxybutane exposure testing demonstrated increased breakage with a mean of 14.4 chromatid breaks per cell involving 100 % of cells. Based on these

findings, he was diagnosed with FA at 1 month old. Sequence analysis of the *FANCC* gene was normal. *FANCD1*/BRCA2 gene analysis demonstrated two heterozygous *FANCD1* mutations: the L3101R mutation, which has uncertain significance, and the D2723H mutation, which is a known deleterious mutation. Interestingly, the patient's paternal grandmother has a history of breast cancer and carries the *FANCD1* D2723H mutation. Also, five out of nine of this grandmother's siblings have a history of cancer, although none have had genetic testing. No cancers have been noted in this patient's first-degree relatives.

Due to the patient's increased risk for bone marrow failure, at 14 months he had a bone marrow biopsy which showed a normocellular marrow with trilineage dysplasia, including hypogranular neutrophils in the peripheral blood, irregular nuclear contours of erythroid precursors in the aspirate smears, and clustered small hypolobate megakaryocytes within the biopsy and particle preparation (Fig. 1a, b). CBC obtained at the time of biopsy showed WBC 7,900/μL, platelets 332,000/μL, and hemoglobin 11.8 g/dL. Cytogenetic studies showed a complex karyotype including loss of 7q and addition 17p. Fluorescent in situ hybridization (FISH) using probes for 7cen(D7Z1) and 7q31(D7S486) showed a monosomy for 7q31 in 17 out of 200 cells. Taken together, the morphologic and genetic findings were consistent with an evolving MDS. Subsequent bone marrow biopsies showed similar findings and cytogenetics.

At 22 months, the patient presented with new onset of bruising and bleeding gums. CBC at this time showed WBC 40,400/μL with 38.3 % blasts, platelets 40,000/μL, and hemoglobin 10.9 g/dL. Bone marrow biopsy demonstrated increased blasts of intermediate size with dispersed chromatin, scant blue cytoplasm, and distinct nucleoli (Fig. 1c, d). Flow cytometry characterized these blasts as T lymphoblasts comprising 57 % of total cells expressing CD45, CD3, TdT, CD2, CD7, dim CD5, and dim CD52. The blasts did not express, CD19, CD33, CD4, CD8, CD25, CD16, CD56, CD30, CD57, gamma–delta or alpha–beta TCR. Cytogenetic studies performed on the bone marrow aspirate demonstrated an abnormal karyotype featuring der(2) and del(7q) in 16 cells, complex changes in 3 cells, and 1 normal cell. FISH studies performed on the bone marrow aspirate examining 200 cells demonstrated positive FISH results for: three copies of MLL (38.5 % of cells), loss of 21q22(58 %), loss of 5q31(48 %), and loss of 7q31(40.5 %). These findings are consistent with a diagnosis of T-ALL arising in a background of MDS, but did not conclusively demonstrate that the leukemic blasts arose from the dysplastic clone.To determine if the loss of 7q seen in the patient's myelodysplasia was also present in the neoplastic T lymphoblasts, a sample of peripheral blood was sorted for blasts that express CD3, CD2, and CD5 but were negative for CD4 and CD8. This sample could not be further tested for purity as it was too small. Fluorescent in situ hybridization testing was performed on this sorted sample using D7Z1 and D7S486 probes and revealed a monosomy 7q31 in 20.5 % of cells (Fig. 2). The finding of the same genetic abnormalities in the patient's T lymphoblastic leukemia as his

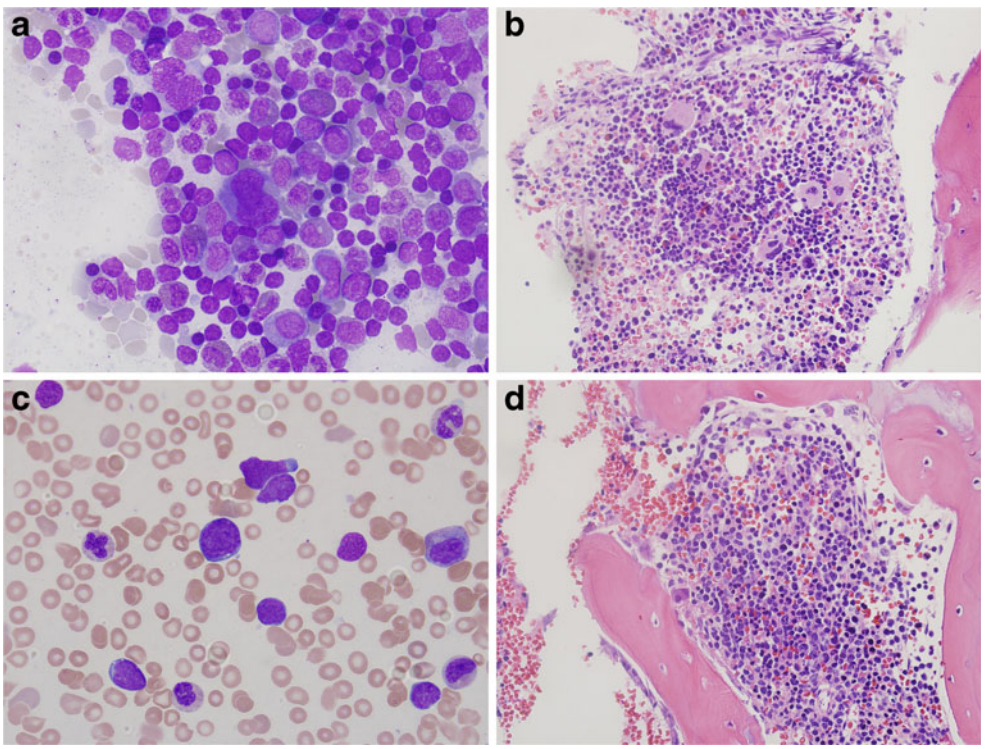

Fig. 1 Erythroid and megakaryocytic dysplasia in the aspirate smear (**a**). Trilineage dysplasia of the bone marrow (**b**). Lymphoblasts present in the blood smear (**c**) and bone marrow (**d**); original magnifications ×20 and cropped (**a**), ×10 (**b** and **d**), and ×40 (c)

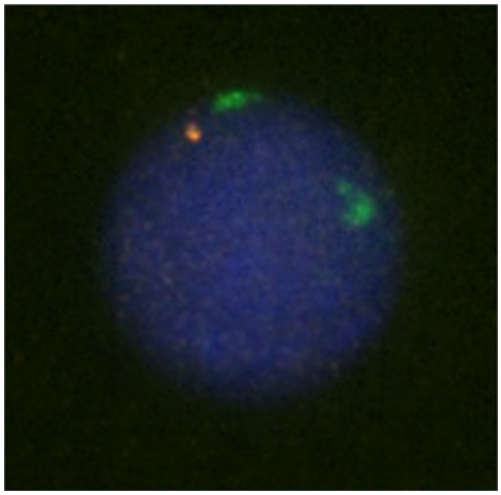

Fig. 2 Fluorescent in situ hybridization testing on peripheral blood sorted for CD3+, CD2+, CD4-, and CD8-blasts. The probes D7Z1 for locus 7p11.1-q11.1 (*green fluorophore*) and D7S486 for locus 7q31 (*orange fluorophore*) demonstrate a monosomy 7q31 in 20.5 % of blasts

myelodysplasia supports the hypothesis that the T lymphoblastic leukemia represents a progression of his myelodysplasia.

The patient received induction chemotherapy and passed away 2 months after the diagnosis of T-ALL.

Discussion

Fanconi anemia (FA) is a rare autosomal or X-linked recessive disease associated with defects in 13 distinct genes [2]. These genes encode proteins that are part of a pathway for repair of DNA interstrand crosslinks and double-strand breaks, where a complex composed of FA proteins are thought to prepare damaged DNA for repair by a series of proteins including BRCA1 and FANCD1/BRCA2. As a result of these defects in cell repair, there is genomic instability that increases the risk of cancer in FA. These patients are often diagnosed after presenting with aplastic anemia, MDS, or leukemia with characteristic congenital physical abnormalities.

AML is the most common malignancy seen in FA, while lymphoid neoplasms are rare [1]. In 2003, Alter et al. looked at 1,301 cases of FA from 1927 to 2001 and reported 116 cases of acute leukemia, of which 7 were ALL [3]. There were 89 cases of MDS, of whom 13 progressed to AML and none to ALL.

This is the first reported case of ALL evolving from MDS in a patient with FA. An extensive literature search found case reports of 10 FA patients who developed lymphoblastic neoplasms, of which eight presented as ALL and two as lymphoblastic lymphoma (Table 1). None of the patients had prior myeloid neoplasms, including MDS. The mean

Table 1 Eleven cases of lymphoblastic leukemia or lymphoma developing in Fanconi anemia patients reported in the literature

	Age at diagnosis	Sex	Diagnosis	Outcome	Comment
1[a]	22 months	Male	T-ALL with underlying MDS	Death 2 months after diagnosis	
2 [8]	Not stated	Not stated	ALL	Received chemotherapy; died 7 months after diagnosis	Donor originated ALL 18 months after BMT
3 [7]	4.9 years	Female	T-ALL	Not stated	Biallelic *BRCA2* mutations
4 [7]	4.9 years	Female	T-ALL	Diagnosed with AML at 6.3 years and Wilms' at 6.6 years	
5 [7]	5.2 years	Male	T-ALL	Not stated	Biallelic *BRCA2* mutations
6 [9]	5.3 years	Male	ALL (FAB L1)	Received chemotherapy; died 1 month after diagnosis	Probable FA based on brother with similar anomalies who had FA; prior treatment with growth hormone
7 [10]	8 years	Male	ALL (FAB L1)	Complete remission of ALL, developed AML 38 weeks after chemotherapy was started and received a BMT	
8 [11]	9 years	Male	T-ALL	Complete remission	
9 [12]	10 years	Female	ALL	Treated and died	
10 [13]	2.5 years	Male	T cell lymphoblastic lymphoma	Received induction chemotherapy; died 2 months after diagnosis	
11 [14]	12 years	Male	Precursor T lymphoblastic lymphoma	Received chemotherapy; died	Received BMT at age 11

ALL acute lymphoblastic leukemia; *MDS* myelodysplastic syndrome; *BMT* bone marrow transplant; *FAB* French–American–British classification system; *AML* acute myeloid leukemia; *FA* Fanconi anemia

[a] Current case

age at diagnosis of all acute leukemia patients in the 2003 Alter et al. report was 14.5 years, and the mean age at diagnosis of MDS 15.7 years. Our literature search demonstrated a mean age at diagnosis for lymphoblastic leukemias in FA of 6.4 years. Our current patient was diagnosed with MDS at 14 months, and was diagnosed with T-ALL at 22 months. These trends to earlier diagnosis of ALL than AML, and in our patient earlier diagnosis of MDS, are consistent with a more aggressive FA phenotype in these ALL patients than in those progressing to AML or MDS.

It is unusual for MDS to transform into lymphoblastic leukemia, with an incidence of less than 1 % [4]. The explanation for this rarity is uncertain, but the transformation of MDS to ALL does support the hypothesis that at least some cases of MDS arise from a pluripotent hematopoietic stem cell capable of lymphoid, as well as myeloid, differentiation. Evidence for this hypothesis can be found in a study by Miura et al. of four patients with MDS which demonstrated monosomy 7 in pluripotent stem cells and B and T/natural killer progenitors [5].

In the general population, the majority of ALL patients are of B lineage, but 7 of the 11 noted FA patients progressing to a lymphoblastic malignancy developed T lineage disease. Of interest, almost half of MDS cases transforming to ALL are also T-ALL [4]. Both trends suggest that underlying leukemogenic mechanisms in FA and in MDS may differ fundamentally from those in the general population, rather than simply being an accentuation of leukemogenic mechanisms in the general population. Further, the concurrence of FA and MDS in our patient, with progression to ALL at a young age for this clinical setting, raises the possibility that the lymphoblastic leukemogenic mechanisms in FA and MDS are either the same, or may together have a synergistic leukemogenic effect.

Additionally, this patient was shown to have *FANCD1* mutations. The L3101R mutation has uncertain significance, but the D2723H mutation is known to be deleterious, showing cosegregation with breast and ovarian cancer in multiple families [6]. Due to the patient's death, further testing to determine if the mutations were on the same allele was not performed, but we presume double heterozygosity, given the diagnosis of FA. The patient's paternal grandmother carried only the D2723H mutation, which also suggests that these mutations were in *trans*.

Biallelic gene mutations of *FANCD1* have been associated with a more severe phenotype [7]. These patients are classified as FA subtype D1 (FA-D1) and have mutations distributed throughout the length of the *FANCD1/BRCA2* gene. They have an early onset and increased incidence of both leukemia and solid tumors (specifically Wilms' tumors and medulloblastomas) [7]. In a 2007 study by Alter et al., three of the 27 patients (cases 3–5 in Table 1) developed T-ALL, although one of the patient's was not genotyped [7]. These patients all developed T-ALL at a slightly older age than our patient. Patients in the FA-D1 classification have been noted to have a distinct phenotype with short stature, microcephaly, and GI abnormalities [7]. Notably, this phenotype is similar to that in the current patient. While the L3101R mutation has not been shown to have clinical significance in isolation, we hypothesize that in combination with the D2723H mutation, it portends a more severe phenotype.

In conclusion, we present a case of a 22-month-old patient with a history of Fanconi anemia and myelodysplastic syndrome who developed precursor T lymphoblastic leukemia at a young age, and have shown via FISH and cytogenetic analysis that these two processes likely arose from the same neoplastic clone. These findings both demonstrate another rare case of MDS transforming into ALL, and highlight the increased incidence of T cell lineage neoplasms compared to B cell lineage neoplasms in both FA patients and patients with MDS who transformed into ALL.

Conflict of interest The authors declare that they have no conflict of interest.

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