Hereditary thrombocytopenia and acute myeloid leukemia: a common link due to a germline mutation in the AML1 gene

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Ann Hematol (2009) 88:1037–1038
DOI 10.1007/s00277-009-0722-x

LETTER TO THE EDITOR

Hereditary thrombocytopenia and acute myeloid leukemia: a common link due to a germline mutation in the AML1 gene

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Received: 9 August 2008 / Accepted: 25 February 2009 / Published online: 1 April 2009

Dear Editor,

A 45-year-old woman with a longstanding history of severe hereditary thrombocytopenia was diagnosed with acute myeloid leukemia (AML) of the M1 subtype. Genetic analysis of peripheral blood samples revealed a base pair change leading to a Pro236LeufsX48 mutation in the AML1 gene which is known to confer a propensity to develop AML. The identical mutation was found in her three sons suffering from thrombocytopenia, as well, suggesting an inherited germline mutation in this family. Thus, in the rare case of AML diagnosed in a patient with familial thrombocytopenia, a germline mutation in the AML1 gene should be considered.

Analysis of families with inherited predisposition to develop malignancies has supported the multistep pathogenesis of human malignancy [1, 2]. A spectrum of genes when mutant in the germ line increase the likelihood of developing cancer during an individual's lifetime. These genes have been identified by linkage analysis and positional cloning strategies. A loss of function of the residual allele is often the result of a second mutation. This has contributed to the concept of tumor suppressor genes in which homozygous loss of function is essential for the development of a malignant phenotype. Most mutant genes causally implicated in the pathogenesis of AML have been identified by cloning acquired chromosomal translocation breakpoints in hematopoietic progenitor cells [3].

Mutations in the AML1 gene have been shown in patients with familial platelet disorders, e.g., familial thrombocytopenia. These patients are described to have a propensity to develop AML [4].

The patient, a 45-year-old teacher with macrothrombocytopenia known since her youth, was diagnosed with AML (French–American–British classification M1 with dysplastic features including ring sideroblasts). She was referred to a hospital for diagnostic workup of gastric hemorrhage due to severe thrombocytopenia. On admission, she had also been suffering from non-specific symptoms. Cytogenetic analysis of the bone marrow revealed a female karyotype with complex chromosomal alterations in chromosomes 3, 4, 5, 6, and 8. Fms-like receptor tyrosine kinase 3 (FLT3) and nucleophosmin (NPM) mutations were excluded by molecular studies. The patient was treated with three courses of chemotherapy containing cytarabine, mitoxantrone, and daunorubicin (first course—high dose cytarabine plus daunorubicin, second course—high dose cytarabine plus mitoxantrone, and third course—high dose cytarabine) and achieved a complete remission (CR). Subsequently, she underwent allogeneic transplantation from an unrelated donor in 1.CR.

Since an association between hereditary thrombocytopenia and development of leukemia has been described recently [3–6], blood samples from the patient and her three sons were examined for known mutations in the AML1 gene (Fig. 1). A Pro236LeufsX48 mutation was found, which corresponds to a heterozygous deletion of one base pair (707delC). This mutation induces a preterm stop codon which inhibits the formation of a complete AML1

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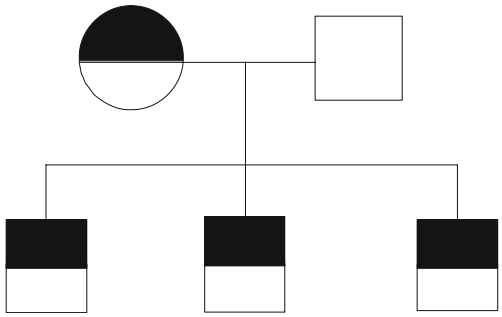

Fig. 1 Pedigree of patient's family (patient's parents were not indicated because they were not known; the patient was adopted as a child)

protein so that the transactivation domain of the AML1 protein is inactivated [6].

A potential leukemogenic impact of AML1 mutations has been described recently [5, 6]. The incidence of AML1 mutations is in the range of 10–20% in AML patients [5–8]. Additionally, the AML1 gene is important for megakaryocyte development [9].

The detection of mutations of the AML1 gene supports and extends the relevance of wild-type AML1 inhibition for leukemogenesis in AML1 fusion proteins created by chromosome translocations. The decrease in AML1 activities potentially provides an efficient mechanism for driving the initial step of leukemogenesis. It may be a common underlying mechanism for the pathogenesis in AML1-associated leukemia. However, recently generated transgenic or knock-in mice showed that AML1 mutations are critical for the development of AML, but that one or more additional mutations are necessary for leukemogenesis [10–12]. This accepted hypothesis is supported by the cytogenetic findings in the case of our patient exhibiting a complex karyotype.

It has been shown that in patients with familial platelet disorders, e.g., hereditary thrombocytopenia, mutations in the AML1 gene may occur and then lead to a propensity to develop AML. In our case, the Pro236LeufsX48 mutation must be seen as a predisposing factor for leukemogenesis not only in our patient but also in her three sons.

Thus, we suggest that the rare patients with familial thrombocytopenia and leukemia should be tested for AML1 mutations. Screening of all patients with presumed hereditary thrombocytopenia and asymptomatic family members may be debatable because of the anxiety caused by a positive test result. Furthermore, the true incidence of AML1 mutations in hereditary thrombocytopenia is not known. However, a surveillance strategy with regular blood counts may identify patients in an earlier stage of the leukemia, thus reducing the risk for bleeding and infectious complications and increase cure rates. Therefore, we suggest a stepwise diagnostic algorithm in which the most frequent causes of hereditary thrombocytopenia (e.g., May–Hegglin anomaly and Fechtner syndrome [13–16]) are excluded by clinical investigations and subsequently AML1 mutational analyses are performed.

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