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FMS-like Tyrosine Kinase-3 Mutation in a Child with Standard-risk ALL and Normal Karyotype

Alavi S [1]*, Kaji Yazdi M [1], Arzanian MT [1]

1. Pediatric Congenital Hematologic Disorders Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

***Corresponding Author:** Alavi S, Email: s.alavi@sbmu.ac.ir*

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Abstract

FMS-like tyrosine kinase-3 is a receptor tyrosine kinase expressed by immature hematopoietic cells and is important for the normal development of stem cells and immune system. Mutations of FMS-like tyrosine kinase-3 have been detected in about 30% of patients with acute myelogenous leukemia and a small number of patients with acute lymphoblastic leukemia. The FMS-like tyrosine kinase-3 mutations most often involve small tandem duplications of amino acids within the juxtamembrane domain of the receptor and are called internal tandem duplications. The other type of mutations in FMS-like tyrosine kinase-3 is located in the activation loop of the second tyrosine kinase domain. Multiple studies have shown that activating mutations of FMS-like tyrosine kinase-3 are common in blasts from patients with acute myeloid leukemia but are rarely found in adult patients with acute lymphoblastic leukemia. In addition, activating FLT3 mutations occur only rarely in T-ALL cases. Here we report a 3-year-old girl with acute lymphoblastic leukemia who had a mutation in FMS-like tyrosine kinase-3 / internal tandem duplications.

Keywords: FMS-like tyrosine kinase-3, mutation, acute lymphoblastic leukemia, childhood.

Introduction

The FMS-related tyrosine kinase-3 (FLT3) is a receptor tyrosine kinase expressed in early hematopoietic precursors, both myeloid and B-lymphoid lineage as well as various human cell lines that plays a central role in hematopoietic development [1, 2]. In normal bone marrow, expression is limited to early progenitors, including CD34+ cells with high levels of expression of CD117 (c-KIT) [3]. FLT3 is expressed at high levels in 70% to100% of cases of AML [4].

Report of the case

A 3-year-old girl was referred with fever and pancytopenia for 3 weeks. On examination she was ill and febrile. Organomegaly was not noted. She underwent bone marrow aspiration through which a diagnosis of acute lymphoblastic leukemia (ALL) was given. Flowcytometry was consistent with pre B-cell ALL with increased expression of CD 10,19 and HLA-DR. Cytogenetic study by karyotype was normal 46,XX without hyper or hypodiploidy. Study for recurrent chromosomal translocations was negative; the only positive finding was having FLT-3/ITD mutation analyzed by real-time PCR. She received induction treatment for standard ALL and satisfactory remission was achieved. This was our first case of childhood ALL with FLT-3/ ITD mutation without any other accompanying cytogenetic abnormality or recurrent chromosomal translocation.

Discussion

FLT3 expression may play a role in the survival or proliferation of leukemic blasts and is the single most commonly mutated gene in AML. Multiple studies have shown that activating mutations of FLT3 are common in blasts from patients with AML but are rarely found in adult patients with ALL [1, 5]. In addition, activating FLT3 mutations occur only rarely in T-ALL cases (1–3%) (6-8). Mutations of the FLT3 gene, including internal tandem duplications (ITD) and tyrosine kinase domain (TKD) mutations are one of the most frequent somatic alterations in AML. Nakao et al. first reported the presence of ITDs in the juxtamembrane domain of FLT3 in AML [5]. In a study performed by Wang et al. in children with leukemia the occurrence of FLT3/ITD mutation was assessed in 122 with AML and 124 with ALL by PCR which indicated 80.32% of AML and 58.06% of

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ALL patients had FLT3 gene products in their bone marrow respectively [9]. FLT-3/ITD mutations were usually detected in AML but infrequently in ALL. In this study the occurrence of mutation in ALL cases were higher [9]. In a study by Karabacak et al. a total of 120 pediatric patients, 80 with ALL and 40 with AML were analyzed by high resolution PCR. FLT3/ITD mutations were found in 7.5% of the patients with ALL and 22.5% of those with AML, whereas no FLT3/TKD mutation was evident in any case. There was no difference between the ALL patients positive and negative for FLT3/ITD with regard to overall survival [10]. Xu et al. in a study on pediatric patients (87 AML patients, 60 ALL patients) in which RT-PCR method was used, found FLT3/ITD mutations rates of 13.8% in AML and 3.3% in ALL patients [11]. Armstrong et al. have recently demonstrated that FLT3 is highly expressed and mutated in ALL with rearrangement of the mixed lineage leukemia (MLL) gene on chromosome 11q23. Likewise, their data has shown that about 25% of hyperdiploid ALL samples possess FLT3 mutations [12]. There is another report indicating more cases of FLT3 mutations in the activation loop of tyrosine kinase domain in infant ALL with MLL rearrangements (18.2%) or pediatric ALL with hyperdiploidy (21.5%) [13] . Although, our case did not show either hyperdiploidy or 11q23 abnormalities on cytogenetic studies, yet still was positive for FLT3/ITD mutation. FLT3-ITD is associated with leukocytosis and a poor prognosis, especially in patients with normal karyotype [14]. However, our case had a normal karyotype without leulocytosis.

Conclusion

It seems that further studies in children with ALL are needed to analyze the status of FLT3 mutations and more importantly to clarify its correlation with prognosis.

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