A Case with *ZNF198-FGFR1* Gene Rearrangement Presenting as Acute Eosinophil Myeloid Leukemia

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A previously healthy 47-year-old Chinese man presented in January 2009 with extreme fatigue, fever, and night sweats. Hepatomegaly (palpable, 2 cm in the right hypochondrium) and splenomegaly (palpable, 2 cm in the left hypochondrium) were identified, and axillary lymph nodes were swollen. A laboratory investigation showed a white blood cell (WBC) count of 39.8 × 10^9/L with eosinophils 52% (absolute eosinophil count of 20.7 × 10^9/L), hemoglobin level of 14.9 g/dl and platelet count of 50.0 × 10^9/L. Bone marrow (BM) aspirate revealed hypercellular and occupied by approximately 22.0% blasts; eosinophils comprised 23.5% of total cellularity [Figure 1a]. Flow cytometry of these blast cells demonstrated expression of CD13, CD33, CD34, CD117, CD14, CD15, and human leukocyte antigen-DR indicating that myeloblasts were presented. Cytogenetic studies on BM showed a 46, XY, t (8;13)(p11.2;q12.1)[15]/46, idem,-7, der (14), +Mar[5] karyotype [Figure 1c]. Reverse transcriptase-polymerase chain reaction (RT-PCR) was performed to detect gene rearrangements of *BCR/ABL*, *FIPIL1/PDGFRA*, *TEL/PDGFRB* were all negative as well as *c-KIT* and *JAK2V617F* mutations. Fluorescence *in situ* hybridization using a dual-fusion probe confirmed *FGFR1* gene rearrangement [Figure 1b], the *ZNF198-FGFR1* fusion test was done by RT-PCR using *ZNF198*-and *FGFR1*-specific primers (5′-TCCCTGTGCCTGTG TATATCCC-3′ and 5′-CGGGAAGCTCATACTCAGAGAC-3′, respectively) and showed a specific amplification product of 195 bp [Figure 1d]. Sequencing identified an in-frame fusion of exon 17 of *ZNF198* to exon 9 of *FGFR1* [Figure 1e], which was indicative of 8p11 myeloproliferative syndrome (EMS, World Health Organization [WHO] 2008, myeloid and lymphoid neoplasms with *FGFR1* abnormalities[1]). Treatment was started with imatinib (400 mg once daily) plus urbason (40 mg once daily) at day 5, about 2 weeks after initiating treatment, WBC count (30.43 × 10^9/L) did not achieve a significant decrease and the level of hemoglobin and platelet count gradually reduced to 8.6 g/dl and 10.0 × 10^9/L, respectively. Therefore, imatinib and urbason therapy was stopped. Subsequently, the patient received AA (aclacinomycin plus cytarabine) regimen and had a marked initial response to the first cycle of chemotherapy: The WBC and platelet count returned to normal. However, 25 days later, the patient again developed worse, his WBC rose to 52.7 × 10^9/L. BM study revealed inadequate aspirate due to dry tap. At the time, a bone biopsy was performed and revealed a hypercellular with marked hypereosinophilia. High-dose cytarabine therapy was recommended and completed. Nonetheless, the patient failed to respond to aggressive chemotherapy and supportive treatment. He died in May 2009, 5 months after the initial diagnosis.

Discussion

The EMS is an extremely rare, aggressive hematologic malignancy involving the *FGFR1* gene at chromosome 8p11 and is now classified by the WHO as myeloid and lymphoid neoplasm with *FGFR1* abnormality.[1] In cases with t (8;13) (p11;q12), the *FGFR1* gene at chromosome band 8p11 is fused with the *ZNF198* (or *ZMYM2*) gene on 13q12.37.[2] The *ZNF198-FGFR1* fusion protein is found in the cytoplasm and appears to foster *FGFR1* dimerization and constitutively activate the *FGFR1* tyrosine kinase domain, thereby promoting activation of multiple signal transduction

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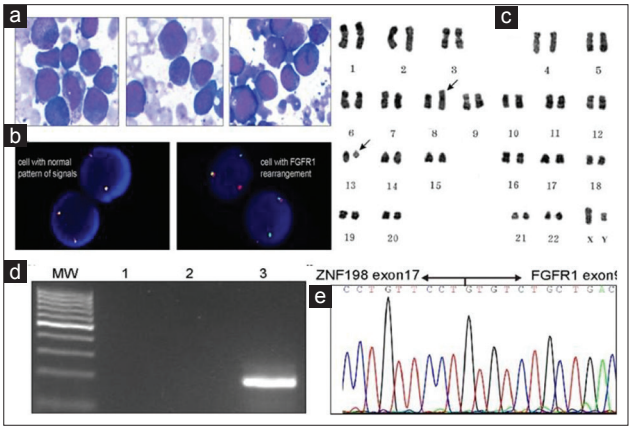

Figure 1: (a) Morphologic changes of bone marrow (BM) smear (Wrighte Giemsa, 1 000) showed markedly increased abnormal myeloblasts with eosinophils. (b) Fluorescence *in situ* hybridization analysis of BM cells with an *FGFR1* break-apart DNA probe revealing *FGFR1* disruption and rearrangement (The distal 5′ end of *FGFR1* is labeled red, the proximal 3′ end of *FGFR1* is labeled green). The normal *FGFR1* gene appears as juxtaposed red and green, or sometimes yellow signal. The translocation is demonstrated by separation of the red and green signals. (c) G-banded karyotype of the BM cells demonstrated the t (8;13)(p11.2;q12.1) translocation. Arrows show the chromosomes harboring the translocations. (d) Detection of the *ZNF198-FGFR1* fusion transcript by reverse transcriptase-polymerase chain reaction (RT-PCR); Lane M: The DNA of 100-bp ladder as a size marker; lane 1: Blank; lane 2: Normal cell from healthy donor; lane 3: BM mononuclear cells at initial diagnosis. (e) Nucleotide sequence analysis of the PCR product demonstrating an in-frame *ZNF198-FGFR1* fusion mRNA in BM at presentation with a breakpoint at exon 17 of the *ZNF198* gene and exon 9 of the *FGFR1* gene.

pathways involved in oncogenesis.[2-4] All reported cases with *ZNF198-FGFR1* in blastic phase at diagnosis showed confirmative phenotypic alterations of neoplastic cells/blasts derived from B or T cell lineage with or without CD34, and the occurrence of hypereosinophilia in blood and marrow of patients with AML was usually found in association with *CBFβ-MYH11* fusion gene in AML-M4Eo with inv (16); t (16;16) or in a minority of patients with a *AML1-ETO* fusion gene in AML-M2 with a t (8;21).[5] However, we have reported here, the case of acute eosinophil myeloid leukemia (*AML-Eo*), *ZNF198-FGFR1* rearrangement positive, *BCR-ABL* negative, presenting marked peripheral blood, and BM eosinophilia, that is extremely rare. To date, the promising approaches designed for patients with chronic myelogenous leukemia or other myeloproliferative neoplasms, has not been achieved in patients with EMS. Most of the cases, including this report, had a fatal outcome. The only potentially therapeutic intervention for this clinically aggressive disease is allogeneic-hematopoietic stem cell transplantation,[4] which indicates that the pathogenesis associated with t (8;13) (p11;q12)/*ZNF198-FGFR1* is worthy of further exploration and better treatment strategies are needed.

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