Human Pathology: Case Reports 5 (2016) 6–9

Contents lists available at ScienceDirect

Human Pathology: Case Reports

journal homepage: http://www.humanpathologycasereports.com

Chronic eosinophilic leukemia, NOS with t(5;12)(q31;p13)/ETV6-ACSL6 gene fusion: A novel variant of myeloid proliferative neoplasm with eosinophilia

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ARTICLE INFO

Article history:
Received 30 August 2015
Received in revised form 17 October 2015
Accepted 20 October 2015

Keywords:
Chronic eosinophilic leukemia, NOS
Novel ETV6-ACSL6 gene fusion
Myeloid proliferative neoplasm with eosinophilia

ABSTRACT

The 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues introduced a category for myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1. Many of these patients are responsive to tyrosine kinase inhibitor (TKI) therapy. In this *case report*, we report a unique case of chronic eosinophilic leukemia with novel t(5;12)(q23-31;p13)/ETV6-ACSL6 gene fusion, in which patient was resistant to TKI therapy. This important finding is a novel addition to the above entity in WHO 2008 classification. The ACSL6 gene encodes a long-chain acyl-CoA synthetase, an enzyme that plays an essential role in lipid metabolism and ATP generation pathways in cells. The ETV6-ACSL6 rearrangement is present in diverse types of hematopoietic malignancies. As yet, it is not clear how ACSL6, a gene involved in fatty acid synthesis, contributes to clonal expansion of myeloid progenitor cells. Therefore, elucidating the contribution of ACSL6 to leukemogenesis may allow the development of novel treatment for those resistant to TKI therapy.

1. Introduction

Clonal eosinophilia is frequently associated with myeloid neoplasms. Cytogenetic analysis has identified four distinct recurrent breakpoint clusters that target PDGFRA at 4q12, PDGFRB at 5q31-33, FGFR1 at 8p11-12 and JAK2 at 9p24. As a consequence of balanced reciprocal translocations or rare insertions or complex translocations, fusion genes similar to FIP1L1-PDGFRA are created, including ETV6-PDGFRB in t(5;12)(q31-33;p13), ZNF198-FGFR1 in t(8;13)(p11;q12) or PCM1-JAK2 in t(8;9)(p11;p24). The 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues introduced a new category for myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1. Many of these cases present as a myeloproliferative neoplasm, usually with eosinophilia [1].

Translocations involving band 12p13 are one of the most common chromosomal abnormalities in leukemia and myeloproliferative/myelodysplastic disorders. These translocations frequently result in rearrangements of the ETV6 gene. ETV6 fuses to diverse (at least 30 partner) genes in myeloid neoplasms [2]. One of the partner genes is ACSL6 (ACS2 – acyl-CoA synthetase long-chain family member 6), with which ETV6 can rearrange with and lead to cell transformation and leukemogenesis. The ACSL6 gene encodes a long-chain acyl-CoA synthetase that catalyzes the formation of acyl-CoA from fatty acids, ATP, and CoA [3]. ACSL6 is predominantly expressed in the bone marrow (BM), fetal liver and brain [4], and it plays an essential role in lipid metabolism [3,5]. Several transcript variants encoding different isoforms have been identified for this gene [5].

The t(5;12)(q31;p13) has been described as a recurrent translocation inducing an ETV6-ACSL6 fusion gene and occurring in variety of myeloid malignancies, often associated with eosinophilia [4,6,7]. Almost 10 years ago, six cases of t(5;12)(q23-31;p13) with ETV6-ACSL6 gene fusion were summarized in *Leukemia*, including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute eosinophilic leukemia (AEL) and polycythemia vera (PV) [7]. Here, we report a case of t(5;12)(q31;p13) translocation with ETV6-ACSL6 rearrangement in a patient with chronic eosinophilic leukemia (CEL).

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http://dx.doi.org/10.1016/j.ehpc.2015.10.001

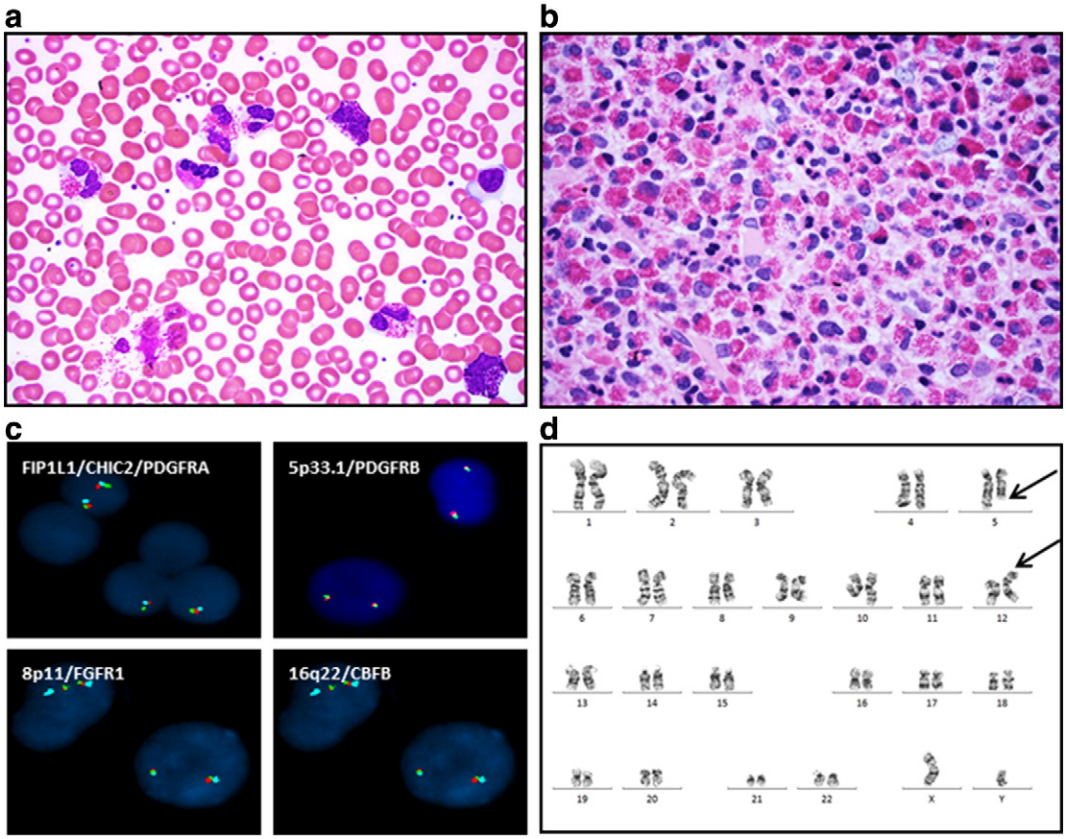

Fig. 1. Marked eosinophilia is detected in patient's peripheral blood smear (a) and bone marrow core biopsy (b). Fluorescence *in situ* hybridization analysis (FISH) of rearrangements of FIP1/CHIC2/PDGFRA, 5p33.1/PDGFRB, 8p11/FGFR1 and 16q22/CBFB is negative (c). Representative G-banded karyotyping reveals translocation of chromosomes 5 and 12 from peripheral blood cells at metaphases. The breakpoints are identified as 5q31 and 12p13 (arrows) (d).

2. Case report

A 52-year-old man presented with progressive eosinophilia for two years. His initial eosinophilia was mild, with absolute eosinophils of 2400/mm^3, but the absolute eosinophil count increased to 13,300/mm^3 two years later. This was associated with mild normocytic anemia, normal platelet count and no neutropenia or monocytosis. The patient complained of fatigue and muscle pain. Physical examination and imaging studies showed no organomegaly or lymphadenopathy. An extensive workup for infectious diseases was negative for trichinosis, strongyloides, toxoplasma, HIV, schistosomiasis and parasitic infection. The peripheral blood smear showed leukocytosis with marked eosinophilia, mild basophilia and mild normocytic, normochromic anemia (Fig. 1a). Bone marrow biopsy revealed a hypercellular (~90% cellularity) marrow with marked eosinophilia. No increase in immature myeloid precursors, blasts or basophils was detected. There was no overt dysplasia in the remaining trilineage hematopoiesis (Fig. 1b). No abnormal mast cells were detected by staining of CD117, CD2, CD25 and tryptase immunostains. Florescence *in situ* hybridization (FISH) for MDS markers [−5/del(5q), −7/del(7q), +8 and del(20q)], t(9;22)(q34;q11)/BCR/ABL1, t(15;17)(q24;q21)/PML-RARA, t(8;21)(q22;q22)/RUNX1T1-RUNX1, and inv(16)(p13.3q22)/CBFB was negative. FISH was also negative for rearrangements of FIP1L1/CHIC2/PDGFRA, 5p33.1/PDGFRB, 8p11/FGFR1 and 16q22/CBFB (Fig. 1c). No c-KIT (D816V) mutation or T cell receptor gamma gene rearrangement was detected. Metaphase cytogenetic analysis on the bone marrow aspirate detected a t(5;12)(q31;p13) translocation in 9/20 (45%) metaphases (Fig. 1d). ETV6-ACSL6 gene fusion was further confirmed by FoundationOne™ Heme assay (Foundation Medicine, Cambridge, MA), a next-generation sequencing (NGS) based assay. The current assay utilizes DNA sequencing to interrogate 405 genes as well as selected introns of 31 genes involved in rearrangements, in addition to RNA sequencing of 265 genes. Targeted RNA-seq found 246 reads supporting the fusion event: fusion: 5′-ETV6(ex1-1 NM_001987)-ACSL6(ex2-21 NM_015256). No other fusion transcripts were identified. Therefore, a diagnosis of CEL, NOS with t(5;12)(q31;p13) resulting in a ETV6-ACSL6 gene fusion was rendered. Pending the NGS data, the patient was treated for 3 months with imatinib, but developed progressive anemia without improvement in the leukocytosis and eosinophilia. After confirming the ETV6-ACSL6 fusion, therapy was changed to hydroxyurea, which led to an improvement in eosinophils, anemia and clinical symptoms. Allogeneic stem cell transplant is being considered.

3. Discussion

Yagasaki et al. identified an ETV6-ACSL6 chimeric gene in three patients with t(5;12)(q31;p13), including refractory anemia with excess blasts (RAEB) with basophilia, AML and AEL [4]. Different fusion genes were identified by cytogenetic and FISH analysis in these patients: a short in-frame fusion of exon 1 of ETV6 to the 3′UTR of ACSL6, an out-of-frame fusion of exon 2 of ETV6 to exon 11 of ACSL6, and an out-of-frame fusion of exon 1 of ETV6 to exon 1 of ACSL6 [4]. FISH with bacterial artificial chromosomes (BACs) specific probes for the ETV6 and ACSL6 genes were performed on two patients with t(5;12)(q31;p13)-associated PV and demonstrated the involvement of ETV6 and the 5′ region of the ACSL6 in the translocation [7]. In the current case, FISH for t(5;12)(q31;p13) was negative, most likely due to PDGFRB (5p33.1)