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Journal Title: International Journal of Clinical and Experimental Pathology
Volume: Volume 7, Number 2
Publisher: e-Century Publishing | 2014, Pages 801-807
Type of Work: Article | Final Publisher PDF
Permanent URL: http://pid.emory.edu/ark:/25593/fm62k

Final published version: http://www.ijcep.com/V7_No2.html

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Accessed January 5, 2020 11:51 PM EST
Case Report
Systemic mastocytosis with associated myeloproliferative neoplasm with t(8;19)(p12;q13.1) and abnormality of FGFR1: report of a unique case

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Received November 20, 2013; Accepted December 23, 2013; Epub January 15, 2014; Published February 1, 2014

Abstract: Systemic mastocytosis is a neoplastic proliferation of mast cells that frequently presents with associated clonal hematological non-mast cell lineage disease. Myeloid and lymphoid neoplasms with abnormalities of the FGFR1 gene are a heterogenous group of rare and aggressive hematopoietic stem cell disorders. About a dozen of chromosome changes involving the FGFR1 gene, presenting as myeloid and lymphoid neoplasms, have been described in the literature. To date, only 2 cases of myeloid and lymphoid neoplasms with abnormalities of the FGFR1 gene have been reported in association with systemic mastocytosis, one with t(8;13) and one with t(8;17) involving the FGFR1 gene. Here we describe another case of myeloproliferative neoplasm with chromosome translocation t(8;19) involving FGFR1 gene associated with systemic mastocytosis.

Keywords: Myeloproliferative neoplasm, systemic mastocytosis associated with clonal hematological non-mast cell lineage disease, FGFR1, eosinophilia

Introduction

Systemic mastocytosis, defined as a clonal proliferation of mast cells characterized by the accumulation of multifocal clusters of abnormal mast cells within multiple organ systems, is a distinct entity of myeloproliferative neoplasm in the 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues [1]. As many as 40% cases of systemic mastocytosis are associated with clonal hematological, non-mast cell lineage disease (SM-AHNMD) [2]. Genetically, a somatic activating point mutation of the KIT proto-oncogene is seen in the majority of cases of systemic mastocytosis. The prognosis of SM-AHNMD is dependent on the associated hematological neoplasm, therefore, recognizing the AHNMD is critical when diagnosing systemic mastocytosis [2, 3].

An uncommon group of myeloid and lymphoid neoplasms have been associated with eosinophilia and chromosome rearrangements involving the platelet derived growth factor receptor alpha (PDGFRA), platelet derived growth factor receptor beta (PDGFRB), or fibroblast derived growth factor receptor 1 (FGFR1) gene, each encoding a tyrosine kinase. The tyrosine kinase becomes constitutively activated when a fusion gene is formed due to a chromosome translocation or insertional mutation. To help recognize this unique group of neoplasm for better clinical management, they are separately classified in the 2008 WHO as “myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB and FGFR1”, although the peripheral blood and bone marrow eosinophilia is not invariably present [4].

Abnormalities of FGFR1 on chromosome 8p11-12 result in rare and aggressive disorders presenting as B or T lymphoblastic leukemia/lymphoma, acute myeloid leukemia, mix phenotype acute leukemia or myeloproliferative neoplasms. The majority of these patients also have blood or bone marrow eosinophilia. These disorders are sometimes referred to as the 8p11-12 myeloproliferative syndrome (EMS) [5]. Patients affected are typically young adults, with a slight male predominance. The peripheral blood usually shows leukocytosis, and blood
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or bone marrow eosinophilia is seen in 80-90% of cases. The bone marrow generally shows increased cellularity; the liver, spleen, and lymph nodes often contain infiltration by neoplastic cells.

While neoplasms associated with abnormalities PDGFRA and PDGFRB have shown a good response to tyrosine kinase inhibitors, the neoplasms associated with FGFR1 abnormalities appear to be refractory to this mode of treatment. Although rare reports have shown that interferon [6] and tyrosine kinase inhibitors such as PKC142 [7] may potentially be effective in some patients, the prognosis is poor with traditional chemotherapy. Therefore, hematopoietic stem cell transplantation is an earlier consideration for these patients, even for those in the chronic phase of the disease. Here we report the unique case of myeloproliferative neoplasm with chromosome translocation t(8;19)(p12;q13.1) involving the FGFR1 presenting as AHNMD of SM.

Case report

A 68-year-old male presented to his primary care physician with a two year history of fatigue, night sweats, early satiety, and a 45 pound weight loss. He denied any history of infection, allergies, autoimmune diseases, or medication use. Blood counts revealed leukocytosis [white blood cell count (WBC) 41,100/µL], erythrocytosis and thrombocytopenia; and an ultrasound showed splenomegaly (16.7 cm). The patient was referred to Emory University Hospital for further workup and management. A repeat complete blood count showed WBC 41,300 cells/µL, with 26% myelocytes, 2% metamyelocytes, 16% band form neutrophils, 49% segmented neutrophils, 4% lymphocytes, 3% monocytes; hemoglobin 16.6 g/dL, hematocrit 49.6%; and platelet count 106,000/µL. The peripheral blood showed mild red blood cell anisopoikilocytosis, and no significant dysgranulopoiesis. The myeloid to erythroid ratio on bone marrow aspirate smear was 16:1; eosinophils, including eosinophilic myelocytes, as well as mast cells were slightly increased but blasts were not. Flow cytometric immunophenotyping failed to reveal any abnormal cell populations. The bone marrow biopsy showed a cellularity of more than 95%; megakaryocytes were mildly increased with slight nuclear atypia (Figure 1A and 1B). There was no significant fibrosis. Eosinophils were mildly increased. Multiple foci of spindle-shaped cells with moderate amount of eosinophilic cytoplasm were identified (Figure 2A). Immunohistochemistry revealed clusters of spindle-shaped cells to be CD117 (DAKO, Carpinteria, CA) positive mast cells that co-express CD25 (Leica Microsystems, Buffalo Grove, IL), consistent with systemic mastocyto-
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**Discussion**

Systemic mastocytosis is a clonal neoplastic proliferation of mast cells involving multiple organs. According to the 2008 WHO, its diagnosis requires one major criterion and one minor criterion or at least three minor criteria [1]. The major criterion is defined as the presence of multifocal dense mast cell infiltrates (15 or more mast cells per aggregate) detected histologically in the bone marrow or another extracutaneous organ(s). The three minor criteria include: (1) 25% or more of the mast cells in the infiltrate are spindle-shaped or atypical or 25% or more of the mast cells are immature or atypical on bone marrow aspirate smear; (2) persistent elevation of serum tryptase level greater than 20 ng/mL; (3) demonstration of the characteristic KIT D816V mutation; and (4) expression of CD2, CD25 or both in the neoplastic mast cells. Systemic mastocytosis associated with clonal hematological, non-mast cell lineage disease (SM-AHNMD) is the most common subtype [1-3, 8], comprising up to 40% of systemic mastocytosis.

Myeloid and lymphoid neoplasms with FGFR1 abnormalities are rare, with approximately 80 cases reported in the literature. The translocation partners of FGFR1 are quite variable. About a dozen of fusion partners have been identified deriving from 8p11-12 translocations. These include TPR at 1q25, RANBP2 (NUP358) at 2q12, LRRFIP1 at 2q37, FGFR1OP1 (POP) at conditioning with fludarabine/melphalan. He is currently in clinical and cytogenetic remission, eighteen months after transplantation and two and half years after initial diagnosis.
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6q27, CUX1 at 7q22, TRIM24 (TIF) at 7q34, CEP110 at 9q33, NUP98 at 11p15, FGFR1OP2 at 12p11, CPSF6 at 12q15, ZMYM2 (ZNF198) at 13q12, MYO18A at 17q23, HERVK at 19q13 and BCR at 22q11 [5, 8-19]. The transforming potential of the abnormal FGFR1 fusion proteins has been confirmed by experimental studies in several fusion proteins derived from the commonly associated rearrangements: ZMYM2(ZNF198)-FGFR1 from t(8;13)(p11;q12), CEP110-FGFR1 from t(8;9)(p11;q33), FGFR1OP1-FGFR1 from t(6;8)(q27;p11-12), and BCR-FGFR1 from t(8;22)(p11;q11) [20-25]. The other fusion partners are rarer, with only one or two reported cases associated with each of them. Most cases of myeloid and lymphoid neoplasms associated with FGFR1 rearrangement were diagnosed by cytogenetic analysis; some were confirmed by molecular studies. Only one case of a myeloid neoplasm with t(8;19)(p12;q13.1) has been reported thus far. The patient presented with a paraneoplastic syndrome and was diagnosed with acute myeloid leukemia with minimal differentiation (AML-M0), probably secondary to a myeloproliferative disorder, with a high hemoglobin level (17 g/dL), but without leukocytosis or eosinophilia. The chromosome location was identified as 8p12, nonetheless, the involvement of FGFR1 in the reciprocal translocation was confirmed by dual-color FISH with the FGFR1-specific probes [15]. The partner gene located at 19q13.3 was later recognized as human endogen retrovirus gene (HERVK), although the transforming activity has not yet been confirmed in any study [16].

Myeloid and lymphoid neoplasms with FGFR1 abnormalities presenting as clonal hematological, non-mast cell lineage disease of systemic mastocytosis are extremely rare. Lewis et al reported the first association in a 29-year-old woman who initially presented with urticaria pigmentosa [26]. She then progressed to systemic mastocytosis about 3-4 years later, and shortly after that she was diagnosed with atypical chronic myeloid leukemia, BCR-ABL1-negative. Cytogenetic studies demonstrated the presence of chromosome translocation t(8;17) in all 20 bone marrow metaphases analyzed, presumably involving FGFR1 gene at 8p11-12. More recently, Mayeur-Rousse et al reported another case of systemic mastocytosis with associated myelo-
proliferative neoplasm in blast crisis and chromosomal translocation t(8;13)(p11;q12) [ZMYM2(ZNF198)-FGFR1] [27]. The patient was a 31-years-old man who presented with leukocytosis and absolute eosinophilia. A bone marrow biopsy demonstrated myeloproliferative neoplasm in myeloblast crisis. Cytogenetic analysis demonstrated chromosome translocation t(8;13)(p11;q12). Molecular studies confirmed the presence of ZMYM2(ZNF198)-FGFR1 fusion gene. In addition, a spindled mast cell population was identified in the bone marrow as well as in a cervical lymph node. These atypical mast cells were positive for CD25. Though KIT D816V mutation was not detected, the morphologic and immunohistochemical findings were diagnostic of systemic mastocytosis. The patient expired shortly after initial diagnosis.

Our case was diagnosed as a myeloproliferative neoplasm based on the clinical presentation of splenomegaly, and laboratory findings of leukocytosis with myeloid precursors in the peripheral blood, hypercellular bone marrow with myeloid hyperplasia, and clonal evidence of reciprocal chromosome translocation t(8;19) (p12;q13.1). Blasts and eosinophils were not significantly increased in either blood or bone marrow though focal increase in eosinophils was noted on the bone marrow core biopsy. Systemic mastocytosis was diagnosed according to published WHO criteria; one major criterion and two minor criteria (abnormal phenotype of mast cells, and KIT D816V mutation) were present at diagnosis.

Our case reported here has a reciprocal translocation t(8;19)(p12;q13.1) with involvement of FGFR1 gene confirmed by FISH analysis. The breakpoint on chromosome 19 is at q13.1, suggesting that the same fusion gene FGFR1-HERVK would most likely be derived from the reciprocal translocation. Whether the concurrent systemic mastocytosis is biologically associated with t(8;19)(p12;q13.1) or is simply coincidental has yet to be determined. However, the question cannot be answered until there are more clinical cases diagnosed with this specific translocation.

Myeloid and lymphoid neoplasms with FGFR1 abnormalities usually have poor prognoses. It is predicted that most patients with the myeloproliferative neoplasm will eventually transform to acute leukemia. Hematopoietic stem cell transplantation is currently the only chance to cure the neoplasm. The patient described in this case report received HLA-matched related donor allogeneic stem cell transplantation and is currently in clinical and cytogenetic remission. Long term followup will be required to monitor whether the malignant clone is actually eradicated by transplantation.

Disclosure of conflict of interest

None.

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