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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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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 or 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 eosinophlia. 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

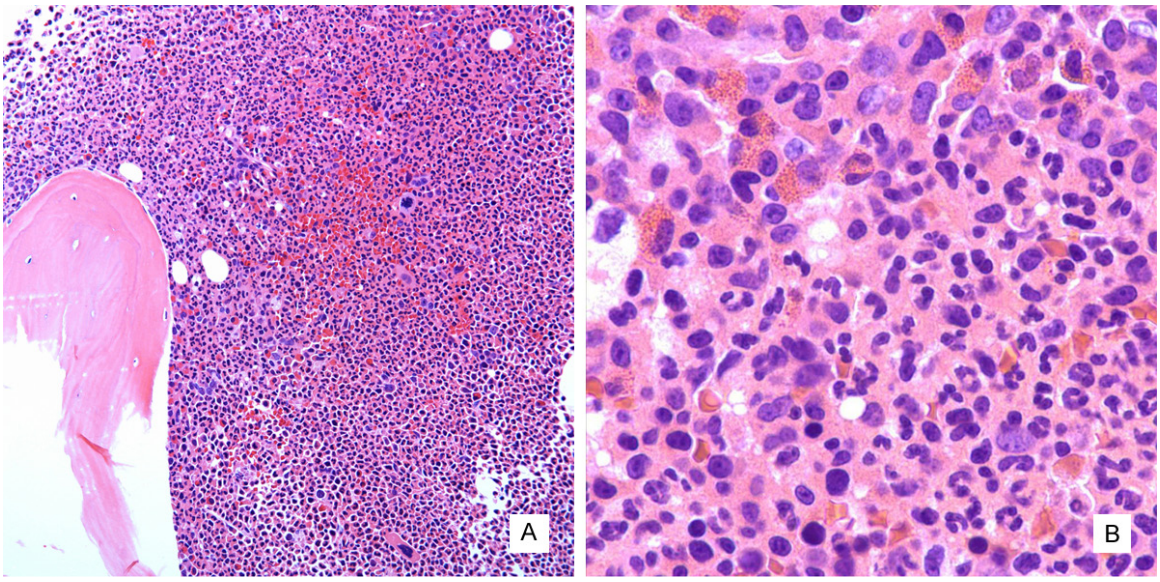

Figure 1. Histomorphology of bone marrow biopsy. The marrow is hypercellular with increased myeloid to erythroid ratio and atypical megakaryocytes (A, hematoxylin and eosin stain, 100x). Eosinophils including immature eosinophilic myelocytes are focally increased (B, hematoxylin and eosin stain, 400x).

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-

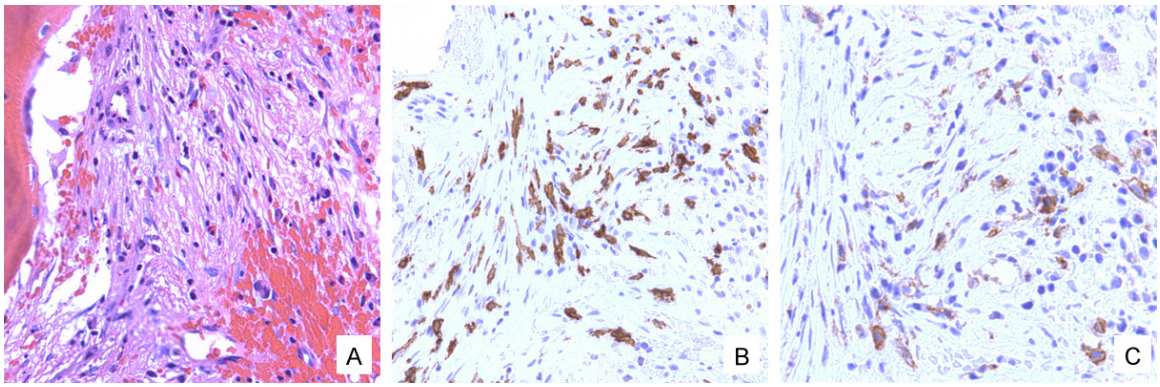

Figure 2. A representative aggregate of atypical spindle-shaped mast cells in the bone marrow (A, hematoxylin and eosin stain, 200x) that are positive for CD117 (B, 400x) and CD25 (C, 400x).

sis (**Figure 2B**, **2C**). A *KIT* D816V activating point mutation was detected by allele-specific polymerase chain reaction (PCR) analysis (Roche Molecular Systems, Inc.). Real time quantitative allele-specific PCR analysis for *JAK2* V617F mutation was negative. PCR analysis of *BCR/ABL1* (reverse transcription real-time quantitative PCR) and *BCL2/IGH* translocation (real-time PCR with capillary electrophoresis) were both negative.

Chromosome analysis demonstrated the presence of abnormal metaphases with a reciprocal translocation between the short arm of chromosome 8 and the long arm of chromosome 19, consistent with t(8;19)(p12;q13.1) (**Figure 3A**). Fluorescence in-situ hybridization (FISH) testing on directly-prepared bone marrow aspirate smear with *FGFR1* dual color breakapart probe (Kreatech Diagnostics North America, Durham, NC) confirmed the presence of *FRGR1* gene rearrangement secondary to chromosome translocation t(8;19). FISH analysis using a panel of 6 DNA probes [*D5S630* and *EGR1* for deletion 5q or monosomy 5; *D7Z1* and *D7S486* for deletion 7q or monosomy 7; *D8Z2* for trisomy 8; and *MLL* for translocation involving 11q23 (Abbott Molecular, Inc., Cytocell, Ltd.)] failed to detect these common abnormalities associated with myeloid neoplasms.

Taken together, in the background of a myeloproliferative neoplasm associated with t(8;19), this patient concurrently had systemic mastocytosis best diagnosed SM-AHNMD. The patient has since undergone HLA-matched, allogeneic stem cell transplantation following conditioning with fludarabine/melphalan. He is currently in clinical and cytogenetic remission, eighteen months after transplantation and two and half years after initial diagnosis.

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

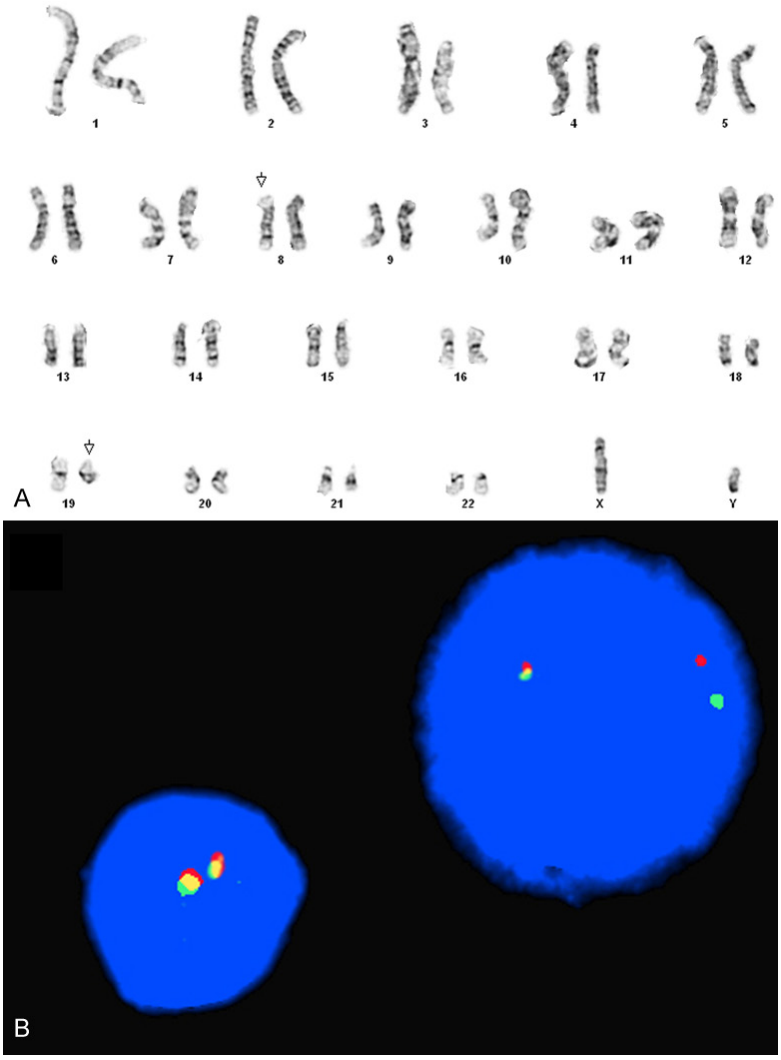

Figure 3. Chromosome analysis of the bone marrow aspirate demonstrated an abnormal karyotype with chromosome translocation t(8;19)(p12;q13.1) (A). FISH analysis confirmed the presence of *FGFR1* gene rearrangement as shown by an interphase nucleus with one red, one green and one fusion signal pattern (B).

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;q13.3) 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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