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Myeloid/lymphoid neoplasm with *ZMYM2::FGFR1* rearrangement: A complex trilineage phenotypic and clonal evolution with associated genomic alterations

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ABSTRACT

We report a case of myeloid/lymphoid neoplasm with *ZMYM2::FGFR1* rearrangement ($MLN^{ZMYM2::FGFR1}$) exhibiting a complex disease evolution. This neoplasm initially presented as T-lymphoblastic lymphoma (T-LBL) in lymph node and myeloproliferative neoplasm (MPN) with eosinophilia in bone marrow, then transitioned to systemic mastocytosis (SM) likely accompanied by additional *JAK3* and other mutations and finally transformed to acute myeloid leukemia (AML) accompanied by additional/secondary genetic abnormality (gain of chromosome 21, der(13)t(8;13), and *RUNX1* mutation). To our knowledge, this is the first case of $MLN^{ZMYM2::FGFR1}$ with a complex trilineage/phenotypic [T-cell (T-LBL), mast cell (SM), and myeloid (MPN and AML)] lineage evolution.

1. Introduction

Myeloid/lymphoid neoplasm with fibroblast growth factor receptor 1 gene (*FGFR1)* rearrangement (MLN^{FGFR1}), as defined by the 5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours, arises from a pluripotent hematopoietic stem cell with *FGFR1* rearrangement and constitutive *FGFR1* activation [1,2].

Up to 50 cases of $MLN^{ZMYM2::FGFR1}$ have been reported in the literature. This neoplasm often presents with chronic myeloid neoplasm, and/or blast phase disease of T-cell (more common than B-cell), myeloid or mixed phenotype origin with associated eosinophilia [1–3]. Additionally, this neoplasm has a high potential for phenotypic and clonal evolution, followed by rapid disease progression. An association with systemic mastocytosis (SM) is extremely rare, only 2 cases of $MLN^{ZMYM2::FGFR1}$ with associated SM reported to date. One patient presented with SM and myeloproliferative neoplasm (MPN) in blast phase (acute myeloid leukemia) involving bone marrow (BM) [4] and the other patient presented with T-lymphoblastic leukemia (T-LBL) in LN, and MPN, lymphoblasts, and SM in BM [5]; SM in one case carried *ZMYM2::FGFR1* fusion but both cases lacked comprehensive genetic characterization by next-generation sequencing (NGS).

Herein, we report the first case of $MLN^{ZMYM2::FGFR1}$ with a complex trilineage phenotypic and clonal evolution from initial T-LBL in lymph node and MPN in BM to SM and AML in BM. Sequential cytogenetic/NGS studies in various stage of disease progression permit detection of stepwise acquisition of secondary genomic alterations.

2. Case summary

A 56-year-old African American man presented with lymphadenopathy and biopsy confirmed involvement by T-LBL. The BM biopsy one month after initial presentation showed a hypercellular bone marrow (BM) with granulocytic hyperplasia, 1% lymphoblasts, and eosinophilia. Karyotyping and NGS performed on the bone marrow aspirate revealed an abnormal male karyotype t(8:13)/(p11.2;q12), *ZMYM2::FGFR1* fusion, and *DNMT3A* mutation. These findings confirmed a diagnosis of myeloid/lymphoid neoplasm with *ZMYM2::FGFR1* rearrangement ($MLN^{ZMYM2::FGFR1}$, Fig. 1). The patient received cycles of hyper-CVAD treatment and achieved complete clinical remission. 5 months after presentation, the patient had relapse of T-LBL; he was treated with

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Time (at month)	1	5	6	7	8	9	10	11	12	13	14	15
Treatment	Hyper CVAD	Imatinib	Fludarabine		Cladribine, Imatinib		TAS-120		TAS-120, ponatinib	Cytarabine		
FISH *FGFR1*^{rearranged}					81%	18%	99%	95%			99%	
NGS *ZMFM2::FGFR1* (fusion read count)	56644	20006	6951		34847				34847	30240		
NGS (allele frequency)	**DNMT3A (46%)*	*DNMT3A (45%)*	*DNMT3A (33%)*		*DNMT3A (44%)* ***JAK3 p.G491R (49%)*** *BAP1 p.T444a (49%)* *RICTOR p.I190V (49%)* *FAT1 p.Y827C (49%)* ***RUNX1 p.P325Tfs*275 (19%)*** *RUNX1 p.G367Afs*227 (12%)*				*DNMT3A (41%)* ***RUNX1 p325Tfs*275 (41%)***	*DNMT3A (45%)* ***RUNX1 p325Tfs*275 (51%)***		
Karyotype	**46,XY, t(8;13)**	**46,XY, t(8;13)**	**46,XY, t(8;13)**		**46,XY, t(8;13) 47,XY,idem, +21**		**46,XY, t(8;13)**	**46,XY, t(8;13) 47,sl,+der(13) t(8;13) 48,sdl,+21**	**46, XY, t(8;13) 47, 48, idem, +der(13)t(8;13)**		**46,XY, t(8;13)**	
Diagnosis	LN:T-LBL BM:MPN 1% blast	LN: T-LBL BM: MLN	BM: Atypical mast cells		BM: SM (30%)		BM: AML(40%)		BM: AML(70%)	PB: AML(80%)	AML	Pt died

* *DNMT3A* mutation: p.R736H

Fig. 1. Summary of disease progression with cytogenetics, FISH, and molecular findings Summary of disease progression, treatment, and cytogenetic/molecular results (fluorescence *in situ* hybridization, cytogenetic study, and next generation sequencing), and biopsy results (lymph node and bone marrow/peripheral blood).

imatinib and fludarabine-based induction and achieved clinical remission. A restaging bone marrow biopsy at month 6 showed no residual lymphoblasts but featured an atypical mast cell proliferation that progressed to SM with an associated MPN (SM-AHN) by month 8. This progression was accompanied by additional/secondary *JAK3* and other mutations. Finally at month 10, acute myeloid leukemia (AML) developed and was refractory to treatment. This transformation to blast phase disease was accompanied by additional chromosomal abnormalities including trisomy 21 (+21), der(13)t(8;13) and *RUNX1* mutation. During the entire disease progression, t(8;13)/*ZMYM2::FGFR1* fusion and *DNMT3A* mutation were persistently present.

The patient was treated with cladribine and imatinib at the SM+MPN stage and with an FGFR1–4 inhibitor (TAS-120) and ponatinib at the AML stage but neither hematologic nor cytogenetic remission was achieved. Due to severe neutropenia secondary to treatment, TAS-120 was discontinued after two months and replaced by cytarabine. The patient passed away 15 months after the initial T-LBL diagnosis.

3. Pathologic examination, flow cytometry, cytogenetic and NGS studies

At initial presentation, a lymph node biopsy showed a monomorphic population of medium-sized lymphoblasts. By flow cytometry, neoplastic cells were shown to be positive for cytoplasmic-CD3, CD2/CD4/CD5/CD7/CD56/TdT, but negative for surface-CD3 or MPO. By immunohistochemistry, the neoplastic cells were positive for CD99, CD1a, and TdT but negative for CD34. The overall findings were diagnostic of T-LBL.

The bone marrow biopsy at month 1 revealed a hypercellular bone marrow (90%) with granulocytic hyperplasia, 1% T-lymphoblasts and eosinophilia. Karyotyping revealed an abnormal male karyotype 46,XY,t(8;13)(p11.2;q12)[20] and NGS revealed *ZMYM2::FGFR1* fusion and mutation of *DNMT3A*, pR736H c2207G>*A* (variant allelic frequency (VAF) of 46%.

The constellation of T-LBL in lymph node and MPN with minimal T-ALL in BM with t(8;13)(p11.2;q12)/*ZMYM2::FGFR1* fusion led to a diagnosis of myeloid/lymphoid neoplasm with *ZMYM2::FGFR1* (MLN$^{ZMYM2::FGFR1}$).

At month 5, the biopsy of a right neck lymph node revealed a recurrent T-LBL. The restaging bone marrow biopsy at month 6 revealed a persistent MPN and an atypical mast cell proliferation (negative for *KIT* mutation) with no evidence of residual T-ALL (no FISH results). The bone marrow biopsy at month 8 revealed SM (accounting for 30% of marrow cellularity) in a background of persistent MPN; the high percentage of *FGFR1* fusion (81%) by FISH suggests both MPN and SM harboring *ZMYM2::FGFR1* rearrangement. Karyotyping revealed an additional abnormality (+21): 46,XY,t(8;13)(p11.2;q12)[13]/47,XY,idem,+21[2]. NGS study showed persistence of *ZMYM2::FGFR1* fusion and *DNMT3A* mutation, and additional mutations in *JAK3* (pG491R c1471G>C), *BAP1* (pT444A c1330A>*G*), *FAT1*, (pY827C c2480A>*G*), and *RICTOR* (pI190V c568A>*G*) at a similar VAF level (~50%), and *RUNX1* mutations (pG367fs*227 c1100delG; *RUNX1* p325Tfs*275 c972dupA) at a much lower VAF (~15%).

From months 10 to 14, the bone marrow biopsy revealed MPN progressing to blast phase (AML) and refractory to treatment (blast count ranging from 40 to 80%) with moderate to severe marrow fibrosis but without SM. Karyotyping and FISH showed additional/secondary complex abnormalities (der(13)t(8;13) and trisomy 21): 46,XY,t(8;13)(p11.2;q12)[1]/ 47,sl,+der(13)t(8;13)[16]/48,sdl,+21[3] with *FGFR1* rearrangement in ~95% of cells. NGS detected persistent *ZMYM2::FGFR1* fusion and *DNMT3A* mutation and increased VAF for the *RUNX1* mutation (~45% at AML stage, p325Tfs*275 c972_973insA, Fig. 1).

4. Discussion

The unique findings in this case of MLN$^{ZMYM2::FGFR1}$ are the *ZMYM2::FGFR1* rearranged neoplastic clone undergoing trilineage phenotypic evolution (from T-LBL, MPN, to SM and finally AML); this evolution was accompanied by stepwise gains of secondary chromosomal abnormalities [der(13)t(8;13) and trisomy 21] and gene mutations (*JAK3, RUNX1,* and others).

The t(8;13)/*ZMYM2::FGFR1* rearranged MLN is extremely rare, with only up to 50 cases (~30 cases with confirmed fusion transcript) reported in the literature. This neoplasm has a male predilection (male: female = 2:1), a wide age range (from 5 months to 68 years old), and poor survival (median overall survival of ~ 15 months). Progression to acute leukemia with rapid deterioration is present in ~40% of MLN$^{ZMYM2::FGFR1}$ cases (most as AML), which is accompanied by genetic progression. At least 14 partner genes have been reported in MLN^{FGFR1}[2]. *ZMYM2* at 13q12.11 (also known as *ZNF198*) is the most common partner gene, and trisomy 21 and *RUNX1* mutation are common secondary genetic abnormalities [3]. Our case is generally comparable to this described profile with the additional complexity of clonal evolution to SM; the latter is rare and has only been reported in two cases without comprehensive genomic characterization [4,5].

Several notable findings in our case merit further description for proposing a clonal evolution pathway (Fig. 2). First, *ZMYM2::FGFR1* rearrangement was persistently present in all disease stages, (initial presentation with T-LBL, and MPN, and later when SM and AML developed), indicating that *ZMYM2::FGFR1* fusion is the founding pathogenic molecular abnormality. Second, the VAFs of *JAK3, BAP1, FAT1,* and *RICTOR* mutations were at similar levels (~50%) in BM with 30% SM involvement but these mutations were absent from the subsequent BM with AML, which lacked evidence of SM. This finding suggests that SM is likely accompanied by these four mutations. Third, the low VAF of *RUNX1* mutation (12%) and an isolated trisomy 21 (in ~10% of metaphase cells) at SM+MPN stage (at 8th month) may have heralded impending progression of MPN to blast phase (AML) which fully developed in 2 months. At the AML stage, mutant *RUNX1* was further expanded (VAF ~45%) along with acquiring additional der(13)t(8;13) in the trisomy 21 clone (Fig. 1). These results suggest that AML is likely accompanied by *RUNX1* mutation and trisomy 21 and der(13)t(8;13).

While we are unable to describe precisely the clonal evolution pattern without single-cell genomics, the available data support a proposed clonal evolution pathway as illustrated in Fig. 1, given the notable NGS/Karyotyping/FISH findings and current knowledge of disease pathogenesis. MLN$^{ZMYM2::FGFR1}$ arises from a pluripotent hematopoietic stem cell [1,2], capable of propagating the similar founding genetic alteration of *ZMYM2::FGFR1* fusion in phenotypically distinct subpopulations (T-LBL, SM, MPN, and AML in this case) while acquisition of secondary genomic alterations further contributes to the heterogeneous phenotypic presentation [6,7]. Although it is unknown whether any additional genetic alteration contributed to pathogenesis of T-LBL due to

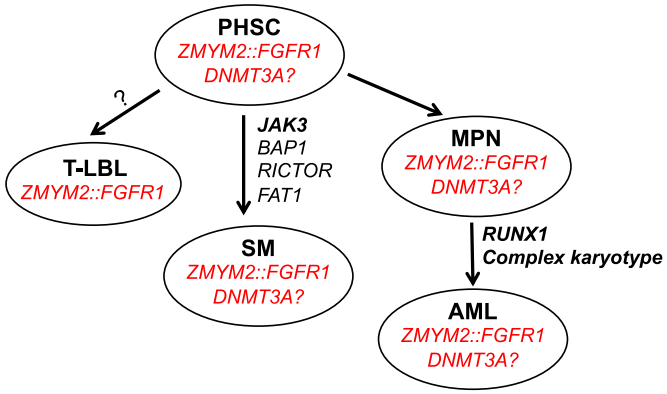

Fig. 2. Proposed phenotypic and clonal evolution pathway in myeloid/lymphoid neoplasm with *ZMYM2::FGFR1* fusion. PHSC, pluripotent hematopoietic stem cell; complex karyotype [additional +der(13)t(8;13),+21].

lack of NGS study, acquisition of secondary mutations in *JAK3, BAP1, RICTOR*, and *FAT1* likely contributed to pathogenesis of SM; of note, *JAK3* mutation has been reported in a recent case of mast cell leukemia with additional mutations (*SETBP1, TP53* and others) but without *KIT* mutation [8]. Additionally, *ZMYM2::FGFR1* fusion was detected in SM in a case of MLN$^{ZMYM2::FGFR1}$ [5]. These results suggest that *ZMYM2::FGFR1* fusion and *JAK3* in this case contributes to SM pathogenesis. Finally, acquisition of secondary *RUNX1* mutation, trisomy 21, and der (13)t(8;13) likely contribute to the pathogenesis of AML; this is not unexpected given that acute leukemias often stem from complementary mutations involving a transcription factor (*RUNX1*) and a tyrosine kinase (*FGFR1*). The *RUNX1*p325T frameshift is located in the transcription activation domain on the C-terminal (residues 291–371, one of the three main structural domains), likely behaving as loss-of-function mutation. Notably, most MLN$^{ZMYM2::FGFR1}$ cases with secondary *RUNX1* mutation (~80%) develop acute leukemias with poor outcomes [9,10], as seen in our case. Together, these stepwise secondary cytogenetic and gene mutational findings provide insight into complex trilineage phenotypic and clonal evolution with associated molecular pathogenesis.

Declaration of Competing Interest

All the authors have no conflict of interests.

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