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Case Report

Clinical, hematological and cytogenetic profile in fibroblast growth factor receptor 1 rearranged hematoloymphoid malignancies

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ABSTRACT

The background of this study is FGFR1 belongs to a family of four, high-affinity receptor tyrosine kinase and is a legitimate oncogene associated with uterine, cervical, prostate, bladder, colorectal and lung cancers. It is rarely concomitant in myeloid and lymphoid neoplasms but has an aggressive clinical course with a high mortality rate when present. Cytogenetic abnormalities involving the FGFR1 gene is most frequently observed in AML, MPN with eosinophilia, T-ALL and T-LBL with ZMYM2 gene being the most common fusion partner. Methods of this study was to authors report a series of 4 cases with FGFR1 rearrangements. Results is three patients presented as T-cell Lymphoblastic lymphoma (T-LBL) and one as mixed phenotype acute leukemia (MPAL). The T-LBL cases harboured the FGFR1/ ZMYM2 fusion and the MPAL case harbored the CNTRL/FGFR1 fusion as identified by conventional cytogenetics and confirmed by molecular studies. Conclusion is authors herewith describe the clinical, biochemical, molecular and cytogenetic features observed in these cases.

Keywords: CNTRL gene codes for the protein centriolin, Fibroblast growth factor receptor 1, Mixed phenotype acute leukemia, T-lymphoblastic lymphoma, Zinc ginger MYM-type protein 2

INTRODUCTION

The World Health Organization 2016 (WHO) classification of hematolymphoid neoplasms distinctly places lymphoid neoplasms with fibroblast growth factor receptor 1 (FGFR1) and platelet derived growth factor receptor (PDGFRα, PDGFRβ) rearrangements apart from myeloproliferative neoplasms (MPN) due to their lymphoid preponderance.[1] These neoplasms are highly heterogeneous both genetically and hematologically and are derived from pluripotent progenitor cells. Being a stem cell disorder an underlying molecular abnormality is common and most affected patients develop a bilineal disease with both lymphoid and myeloid components. Patients with FGFR1 rearrangements most frequently present as T-cell lymphoblastic leukemia/ lymphoma or MPN in both instances with eosinophilia usually having a poor prognosis and there is no established standard therapy; rarely they present as acute myeloid leukemia (AML).[1-4] A study showed a 1-year overall survival (OS) of 43.15% in MPN, MDS and LBL with FGFR1 gene rearrangements.[5]

In this study, the authors present four patients with FGFR1 rearrangements where three cases presented as T-cell lymphoblastic lymphoma (a rare form of aggressive non-Hodgkin's lymphoma.) and one case as MPAL. The FGFR1 aberration was identified by cytogenetics and confirmed by next generation sequencing. Of the four cases, three T-LBL cases showed t(8;9)(p11;q33) i.e. FGFR1/ZMYM2 fusion and the MPAL case showed t(8;9)(p21;q33) i.e. CNTRL/FGFR1. So far, approximately 15 FGFR1 translocation partner genes have been identified- ZMYM2, CNTRL, FGFR1OP1, BCR, FGFR1OP2, TIFI, MYO18A, CPSF6, LRRFIP1, NUP98, HERVK, CUX1, TPR, RUNX1 in AML, MPN with eosinophilia, aCML, MPN+T-ALL, PV, B-ALL, MPAL, MDS, systemic mastocytosis and other types of leukemias.[5-7] According to literature, t(8;13)(p11;q12) (i.e. FGFR1/ ZMYM2) is most common and is seen in 50% cases, followed by t(8;22)(p11;q11) (i.e. BCR/FGFR1) in 18%, t(8;9)(p11;q33) (i.e. FGFR1/CNTRL) in 15% and t(6;8)(q27;p11) (FGFR1OP2/FGFR1) seen in around 10%.[2,8-9] All karyotypes stated in the study are according to The International System of Human Cytogenomic Nomenclature (ISCN) 2016.[10]

CASE REPORT

Case 1

A 32-year-old Radiologist presented in March 2019 with asymptomatic generalized lymphadenopathy, erythematous painful skin rash over both lower limbs with waxing and waning pattern for three months and weight loss. He was prescribed antibiotics and had moderate relief in symptoms. Bone marrow aspirate (BMA) in April 2019 suggested panmyeloid hyperplasia. He later registered at this centre in May, with generalized lymphadenopathy- cervical and bilateral auxiliary nodes (2x2) and hepatosplenomegaly (each 2cm palpable below subcostal margin). Investigative workup revealed elevated peripheral blood and bone marrow eosinophilia. PET-CT scan showed low-grade metabolism in supra and infradiaphragmatic adenopathy with largest retroperitoneal lymph node 4.2x2.6cm (SUVm-5.4). Co-morbidities included Folate, vitamin D and vitamin B12 deficiency. Hepatosplenomegaly was present without any obvious metabolically active lesions. Diffused low-grade metabolism was present in marrow, which was most likely reactive. Bone marrow biopsy was indicative of hypercellular marrow showing trilineage hematopoiesis, reduced erythroid series, abnormal myeloid maturation and interstitial increase in eosinophilia. Clinical biochemistry revealed high serum LDH (196 U/L), globulin (8.44 g/dL), CRP (4.92 g%) and low serum calcium (8.39 mg/dL), AST (14 UL), ALT (17.6 UL). Bone marrow aspirate showed 2% blasts, eosinophilia, myeloid:erythroid ratio of 3.52:1 and increased mast cells. Flow cytometry of bone marrow confirmed T-cell acute lymphoblastic lymphoma (T-LBL) (Figure 1, Table 1). Cytological examination and flow cytometry confirmed no involvement of CSF. Considering peripheral blood outcomes (elevated leucocyte) and eosinophilia, the possibility of an underlying myeloproliferative syndrome (MPS) was also considered.

Cytogenetics was performed on direct harvesting/ overnight (short-term) unstimulated cultures of BMA. Fluorescence in situ hybridization (FISH) studies did not show any evidence of T-ALL markers- TCR-α (14q11), TCR-β (7q34), TLX1 (10q24), TLX3 (5q35) (Cytocell, Milton, Cambridge, UK), ALK (2p23) and 9p21 deletion (Abbott Molecular, Abbott Park, IL, USA). However, conventional cytogenetics revealed a karyotypic abnormality- 46,XY,t(8;13)(p11;q12)[15]/46,XY[1] (Figure 2, Table 2). This abnormality was confirmed by FISH using the FGFR1 dual color rearrangement probe (8p11.2) (MetaSystems, Altlussheim, Germany) which showed a signal pattern of 1F1R1G in 90% cells (Figure 3). UGT1A analysis showed sample to be homozygous for the UGT1A1 allele.

Bone marrow and lymph node aspirate analyzed by next-generation sequencing also confirmed sample to be positive for ZMYM2/FGFR1 fusion, as a result of a translocation between exon 17 of ZMYM2 gene on chromosome 13 and exon 11 of the FGFR1 gene on chromosome 8 (Table 2). After semen cryopreservation, the patient was started on induction chemotherapy with mBFM90 regimen (prednisone, vincristine, asparaginase, cyclophosphamide, cytarabine, daunorubicin, doxorubicin, methotrexate and 6-mercaptopurine).

Post phase 1 induction, PET-CT scan revealed complete metabolic response with a significant morphologic response. Bone marrow aspiration revealed a minimal residual disease (MRD) of 0.05%. FISH showed a 1F1R1G signal pattern in 20/200 cells suggesting FGFR1 rearrangement in 10% cells. However, post phase 2 induction the bone marrow was in morphological remission (negative MRD) which was concurrent with FISH (showed 2F signal pattern) and NGS results. The patient was continued on M-phase and is being planned for allogenic hematopoietic stem cell transplant.

Case 2

A 42-year-old farmer from Ahmednagar (Western India) presented with low-grade intermittent fever for 10 days, loss of appetite, weight loss (approx.10 kgs in 2 months) and generalized lymph node enlargement in July 2019. He has been a tobacco addict, was ECOG-PS-1 with generalized lymph node swelling (largest right cervical conglomerative mass in level 3 and 4- 8x4cm, bilateral auxiliary lymph node (right side- 5x5cm, left side-3x3cm), inguinal and femoral lymph nodes). He had gross splenomegaly- 10cm below the subcostal margin, bilaterally enlarged testis and no hepatomegaly. Oral cavity testing showed bilaterally enlarged tonsils and respiratory examination showed normal vesicular breath sound. PET-CT scan showed low grade metabolically

active (SUVm-3.22) supra and infradiaphragmatic nodes with Waldeyer's ring involvement. Splenic involvement was observed. The baseline, white blood cell (WBC) count was 157x10e9/L (high), platelet count was 202x10e9/L (normal) and the haemoglobin level was 14.8 g/dL (normal). Peripheral blood smear showed promyelocyte-2%, myelocytes-17%, metamyelocytes-10%, neutrophils-49%, lymphocytes-3%, Eosinophils-17% and basophils-2%. Biochemical examination showed elevated serum uric acid (11.9 mg/dL), serum globulin (3.8g/dL), serum LDH (898 U/L) and serum phosphorous (5.6 mg/dL), low serum sodium (135 mmol/L) and serum chlorides (95mmol/L) and normal serum creatinine (1.3 mg/dL) and serum calcium (9.5 mg/dL). There was no transaminitis, but serum bilirubin was 1.6mg/dL (high) and PT-INR was 1.5. Microscopic analysis of the bone marrow aspiration showed hypercellular marrow with myeloid: erythroid ratio-11.25:1, adequate megakaryocytes and myeloid series showing- myelocytes-17%, metamyelocytes-10%, neutrophils- 49%, lymphocytes-3%, eosinophils-17% and basophils- 2%. Biopsy of the left iliac lymph node showed scanty preserved marrow with myeloid and erythroid cells. Independent immunophenotypic analysis revealed 1.1% abnormal lymphoid blasts and 1.5% abnormal myeloid blasts. The possibilities considered were- 1. CML with extramedullary T-lymphoid blast crisis 2. myeloid/lymphoid neoplasm with eosinophilia.

Immunohistochemistry showed the tumor cells to be positive for CD3 and Tdt and the left axillary lymph node biopsy was also suggestive of T-LBL. Microbiology analysis showed sample non-reactive for Hepatitis B surface antigen, Hepatitis C antibodies and HIV antibodies. Immunophenotype results by flow cytometry showed 2% blasts and were indicative of T-LBL (Figure 1, Table 1). Bone marrow biopsy showed hypercellular marrow, myeloid preponderance with left shift, erythroid series absent, increased megakaryocytes with megakaryodyspoiesis, eosinophilia and clusters of blasts.

Molecular cytogenetic examination included FISH using BCR/ABL1 dual colour dual fusion translocation probe (Zytovision, Bremerhaven, Germany), PDGFRα, PDGFRβ (Leica Biosystems, Nussloch, Germany) and FGFR1 (Metasystems, Altlussheim, Germany) dual colour break apart probes. The sample tested positive for the FGFR1 rearrangement in 90% cells (Figure 2, Table 2). Chromosome analysis using GTG-banding was performed according to standard procedure. A total of 20 metaphases from unstimulated, short-term (Overnight/ 24 hours) bone marrow cultures were analyzed using the GenASIs software, Netser-Sereni, Israel and a karyotype-46,XY,t(8;13)(p11;q12)[9]/46,XY[11] was ascertained according to ISCN 2016 (Figure 2, Table 2).

The patient was initially managed with anti-TLS measures and Hydroxyurea, after which the leucocyte count dropped to 47x10e9/L. He was then started on methotrexate and 6-mercaptopurine with palliative intent.

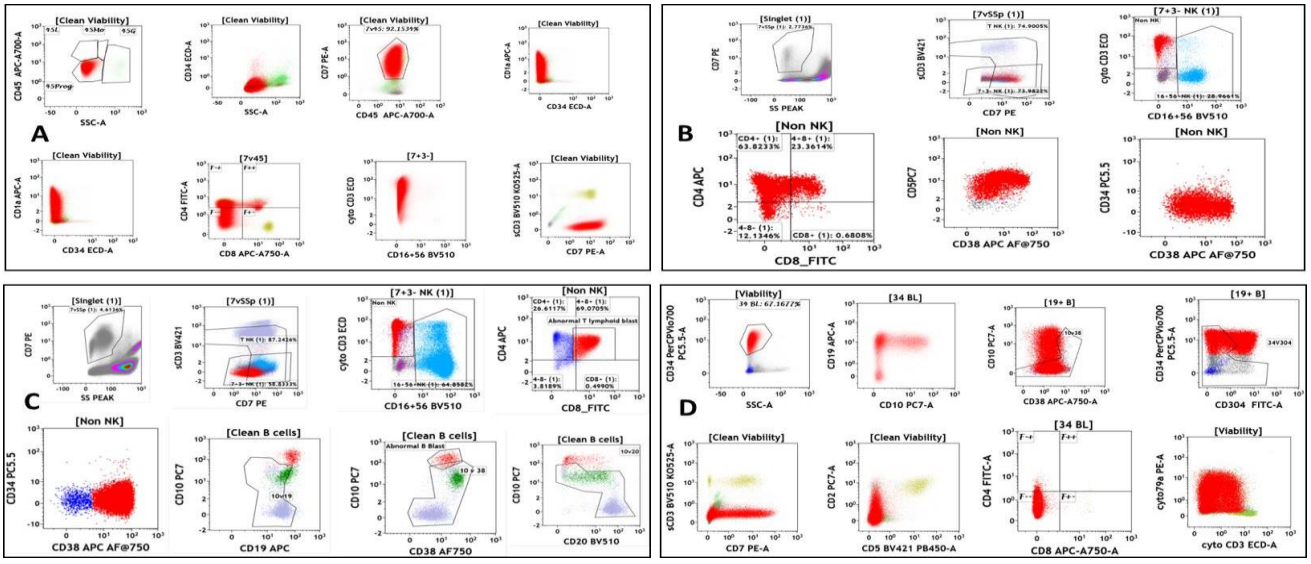

Figure 1: (A): The abnormal T-lymphoid blasts on immunophenotyping highlighted by red dots positive for CD7, CD1a, CD5, cytoCD3, CD4 heterogeneous, double positive for CD4 and CD8 in a subset and negative for CD34, sCD3,CD16 and CD56. (B): Sequential gating strategy showing abnormal T-lymphoid blasts (red dots) positive for cytoCD3, CD7, CD5, CD4 and CD8 heterogeneous, CD8 variable and negative for CD38, sCD3, Cd16 and CD56. (C): Abnormal blasts (red dots) positive for mixed B and T lineage-specific markers. (D): Abnormal T-blasts (red dots) positive for CD7, cytoCD3, double positive for CD4 and 8; a separate population of B-Blasts (red dots) show bright CD19, CD10 expression; whereas, dim for CD38 and dim to negative for CD20; also normal hematogone maturation highlighted by green dots.

Case 3

A 23-year-old boy presented with fever, weakness, generalized lymphadenopathy, loss of appetite and weight loss for 4 months. On examination, he was ECOG-PS-1, had multiple cervical/axillary nodes (largest 2cmx1cm). Physical examination showed liver ~3cm and spleen ~4cm below the costal margin. PET CT scan revealed hypermetabolic supra and infradiaphragmatic adenopathy (SUVm-17). Metabolically active bilaterally enlarged tonsils (SUVm-9) were suspicious of disease involvement. Diffuse low-grade metabolic activity was seen involving marrow, likely reactive. Spleen and liver were uninvolved.

Table 1: Baseline clinical and hematological manifestation in patients with FGFR1 rearrangements.

Baseline presentation	Case 1	Case 2	Case 3	Case 4
Lymphadenopathy	Present	Present	Present	Present
Splenomegaly	Present	Present	Present	Present
Hepatomegaly	Present	Absent	Present	Present
Hb (g/dl)	14.7	14.8	19.1	10.2
TLC (x109/L)	19.1	157	32.8	7.3
Platelet (x109/L)	191	202	175	23
Peripheral Smear	Myelocytes-07%, Neutrophils- 63%, Lymphocytes- 06% Eosinophils- 15% Monocytes- 09%.	Promyelocyte-2%, Myelocyte-17%, Metamyelocyte-10%, Neutrophil-49%, Lymphocyte-3%, Eosinophil- 17% Basophil-2%.	Myelocytes-02%, Metamyelocytes-05%, Basophils-05%, Neutrophils-64%, Lymphocytes: 9% Eosinophils-11% Monocytes-04%	Blast-38% Basophils-01%, Neutrophils-12%, Lymphocytes: 36% Eosinophils-01% Monocytes-12%
LDH (U/L)	196	898	430	603
Creatinine (mg/dl)	1.18	1.3 (high)	0.9	0.9
Bone marrow aspiration	Hypercellular marrow Eosinophilia Increased mast cells	Hypercellular marrow Reduced erythroid cellularity	Mildly hypercellular	Hypercellular marrow. reduced Erythroid Cellularity
Flow cytometry	cCD 3 Positive CD 34 Negative CD 4 Variable CD 7 Mod-Dim CD 8. Subset CD 5 Moderate CD 16+CD 56 Negative CD 45 Dim-Mod CD 1a Variable	cCD 3 Positive CD 34 Negative CD 4. Moderate CD 7 Bright CD 8 Variable CD 5 Dim CD 16 Negative CD 56 Negative sCD 3. Negative CD 38 Variable	cCD 3 Positive CD 34 Negative CD 4 Moderate CD 7 Dim-Mod CD 8 Variable CD 5 Moderate CD16+CD 56 Negative sCD 3 Negative CD 38 Bright CD10 Bright CD19 Bright CD20 Negative	cCD3 Positive CD 34 Moderate CD 4 Negative CD 7 Variable CD 8 Negative CD 5 Negative CD 16 Negative CD 56 Negative sCD 3 Negative CD 38 Variable CD 10 Partial CD 19 Moderate CD 304 Partial CD 2 Subset cCD79α Positive

Initial investigation revealed polycythemia (Hb-19.1gm/dL), leucocytosis with left shift and eosinophilia (11%). Bone marrow biopsy showed hypercellular marrow, normal erythropoiesis with few showing megaloblastic reactions, left shift of the myeloid series with an increase in the eosinophilic precursor, megakaryocytes with features of dysmegakaryopoiesis and no increase in blast cells.

The right supraclavicular lymph-node biopsy however favored T-lymphoblastic leukemia/lymphoma as microscopically the sections showed effaced architecture and sheets of monotonous atypical medium-sized,

lymphoid cells with hyperchromatic nuclei (coarse chromatin) and scanty cytoplasm. Immunohistochemistry also showed cells positive for CD3 and CD99. Immunophenotyping suggested T-cell lymphoblastic lymphoma with B lymphoid subset (Figure 1, Table 1).

Conventional cytogenetics in 20 metaphases from unstimulated bone marrow aspirate culture revealed karyotype- 46,XY,t(8;13)(p11;q12)[13]/46,XY[7] (Figure 2, Table 2) according to ISCN 2016. FISH on directly harvested bone marrow aspirate showed 90% cells with FGFR1 rearrangement (8p11.2) (Figure 3, Table 2). RNA sequencing also revealed FGFR1/ZMYM2 fusion. The patient was started initially on Hydroxyurea which slightly improved the regression of lymph nodes. After confirmation of diagnosis, he was started on mBFM90 protocol and is about to complete induction.

Case 4

A 27-year-old technician, with a history of fever (Tmx 102), skin lesions, pallor, generalized weakness and hypochondrium heaviness for a month was referred to this centre. He was ECOG-PS-1, had tachycardia and oral cavity showed multiple erythematous ulcers and candidiasis.

Physical examination showed bilateral vesicular breath sound, P/A soft tender, Liver ~8cm, spleen ~4cm below the costal margin and enlarged left testis.

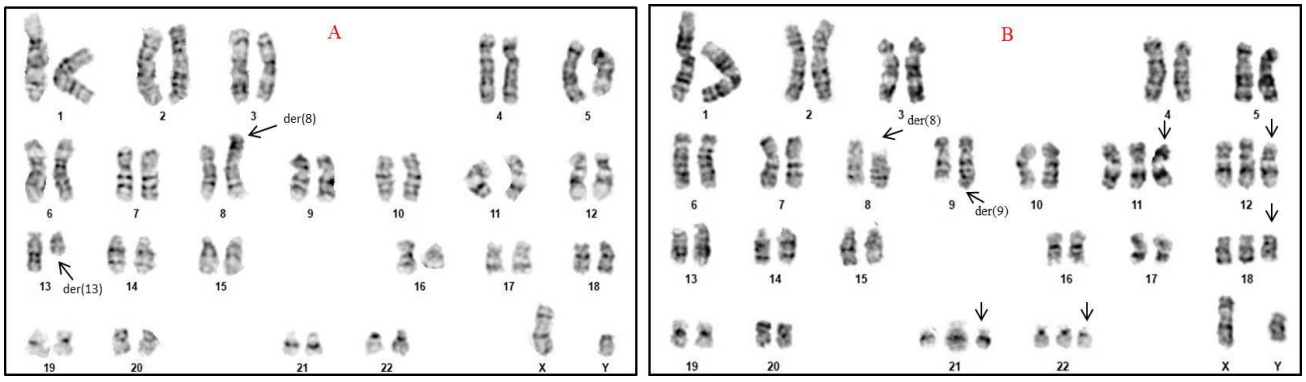

Figure 2: (A): Karyotype: 46,XY,t(8;13)(p11.2;q12); (B):Karyotype:50,XY,t(8;9)(p11.2;q33),+11,+12,+18,+21,+22.

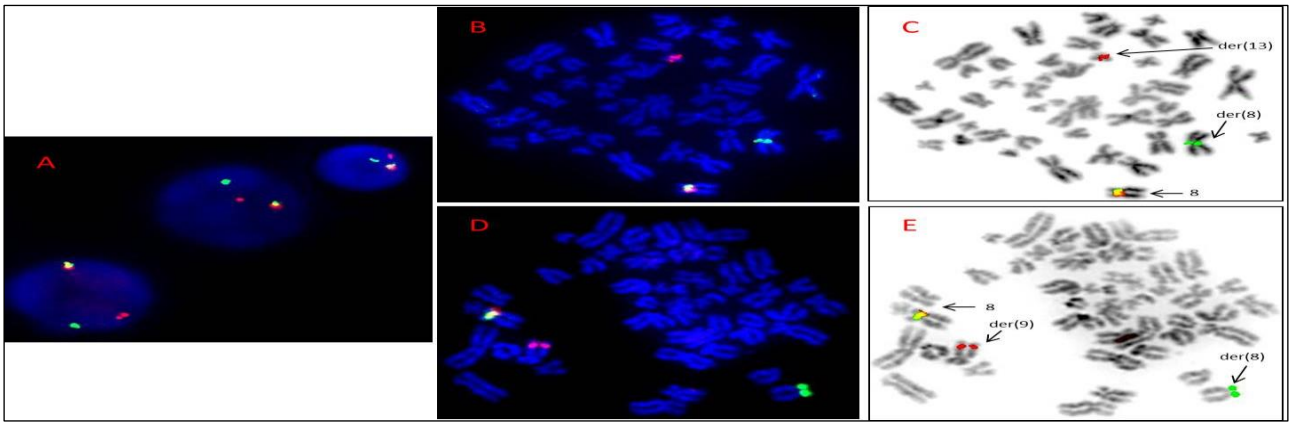

Figure 3: (A): Interphase FISH showing FGFR1 rearrangement (1F1R1G signal pattern) using the FGFR1 rearrangement probe. (B and C): DAPI and reverse DAPI FISH images confirming t (8;13) (11;q12). (D and E): DAPI and reverse DAPI FISH images confirming t(8;9) (p11;q33).

His baseline CBC showed leukemia with thrombocytopenia. The coagulation profile was observed to be normal and detailed microbiology of blood tested negative for gram-positive and negative bacilli and cocci. The sample was also negative for Hepatitis B core IgH antibodies, Hepatitis B surface antigen, Hepatitis C antibodies and HIV antibodies. Biochemical evaluation showed low serum sodium (135mmol/L), serum albumin (3.3g/dL), serum calcium (8.5mg/dL) and high serum CRP (3.59 mg/dL), serum globulin (3.7g/dL) and serum LDH (603U/L).

Both, serum folate (12.4ng/mL) and serum vitamin B12 (335pg/mL) were normal. Histopathology report of the bone marrow showed hypercellular marrow with near-total replacement by blast cells and thus was suggestive of acute leukemia. The microscopic examination of the cerebrospinal fluid showed no involvement of CSF. Bone marrow aspirate was hypercellular with 86% blasts, MPO negative and suggested reduced erythroid series. Immunophenotyping analysis was consistent with mixed phenotype acute leukemia (MPAL- B/T) (Figure 1, Table 1). On immunohistochemistry CD3, CD7, TdT were positive, CD10 focally expressed with negative PAX5 and CD20.

The conventional cytogenetic analysis performed on BM cells cultured for 24 hours revealed a complex karyotype-50~51,XY,t(8;9)(p11;q33),+11,+12,+19,+21,+22 (Figure 2, Table 2).

Simultaneously, FISH on bone marrow specimen (AML panel) showed a signal pattern of 2R3G for RUNX1/RUNX1T1 (Abbott Molecular, Abbott Park, IL, USA) and BCR/ABL1 (Zytovision, Bremerhaven, Germany) dual colour translocation probe, 3F for MLL (Abbott Molecular, Abbott Park, IL, USA) break apart rearrangement probe suggesting sample to be negative for translocation however with trisomy of 11, 21 and 22 in 90-92% cells. Trisomy 11, 21 and 22 was further confirmed by FISH using CEP 11, 21 and 22. All other AML FISH markers- monosomy 5/del(5q) (Leica Biosystems, Nussloch, Germany), monosomy7/del(7q) (MetaSystems, Altlussheim, Germany), CBFβ rearrangement (Abbott Molecular, Abbott Park, IL, USA), trisomy 8 and Tp53 deletion (Zytovision, Bremerhaven, Germany) were negative. Translocation involving the FGFR1 gene was confirmed by FISH using FGFR1 rearrangement probe (MetaSystems, Altlussheim, Germany) (Figure 3, Table 2).

Table 2: Cytogenetic and molecular analysis at baseline and time to first follow-up.

Baseline presentation	Case 1	Case 2	Case 3	Case 4
Cytogenetics	Karyotype: 46, XY, t (8;13) (p11; q12) [15]	Karyotype: 46, XY, t (8;13) (p11; q12) [9]	Karyotype: 46, XY, t (8;13) (p11; q12) [13]	Karyotype: 50~51, XY, t(8;9)(p11;q33),+11,+12,+19,+21,+22.
	FISH: FGFR1 rearrangement in 92% cells	FISH: FGFR1 rearrangement in 90% cells	FISH: FGFR1 rearrangement in 80% cells	FISH: FGFR1 rearrangement in 90% cells and Trisomy of 11, 21 and 22 in 90-92% cells.
Molecular	RNA Sequencing: ZMYM2/FGFR1 fusion, (chr13:20633702>chr8:38275891	-	RNA Sequencing: ZMYM2/FGFR1 (chr13:20633702>chr8:38275891).	RNA Sequencing: CNTRL-FGFR1 (chr9:123933826>chr8:38275891).
	DNA Based assay: negative for any somatic mutations.		DNA Based assay: negative for any somatic mutations.	DNA Based assay: negative for any somatic mutations
Diagnosis	T cell lymphoblastic lymphoma	T cell lymphoblastic lymphoma	T cell lymphoblastic lymphoma with B lymphoid subset	Mixed phenotypic acute leukemia (B/T)
Time to first follow-up	2 months	-	-	2 months

NGS confirmed fusion between exon 38 of CNTRL gene on chromosome 9 and exon 11 on the FGFR1 gene on chromosome 8 (Table 2). No other mutations were observed.

The patient was started on induction with mBFM90 protocol. However, the course was complicated due to skin rash, fever and perianal pain. Skin biopsy showed features of leukemic cutis. Post induction BMA did not show morphologic remission. Immunophenotyping revealed 20.1% abnormal residual blasts.

Conventional cytogenetics showed karyotype- 50,XY, t(8;9)(p11;q33),+11,+12,+18,+19,+21,+22[11]/46,XY[2] and FISH confirmed trisomy 21 in 20% cells, trisomy 11 in 50% cells and trisomy 22 in 26% cells.

Bone marrow biopsy also showed hypocellular marrow, not in remission. RNA sequencing detected 51.7% MRD. He was therefore planned for 6-mercaptopurine and methotrexate with palliative intent as allogeneic stem cell transplant was not feasible.

DISCUSSION

Myeloid and lymphoid neoplasms associated with FGFR1 rearrangements are rare, clinically and cytogenetically heterogeneous but have some shared features.[2] Eosinophilia is one such prominent feature and was expressed in 2 patients. According to literature, these patients occasionally show monocytosis and/or neutropenia.[7] In this study, case 1 showed low levels of absolute eosinophils and high absolute neutrophils and monocytes, case 2 and 3 showed monocytosis and elevated absolute neutrophils and case 4 showed neutropenia and low absolute eosinophils. As described in literature, myeloid hyperplasia is common and was seen in one case.[11] Moreover, the bone marrow was hypercellular in all cases, as most often reported. FGFR1 rearranged patients most often present with a multi-lineage abnormality and are known to rapidly transform to acute leukemia, usually of myeloid phenotype.[12] Case 1 and 4 in this study showed a bi-/ tri-lineage involvement however, none showed clonal transformation. Translocation t(8;9)(p11;q34) is mostly concomitant with tonsillar enlargement and patients with t(8;13)(p11;q12) most often present with or develop lymphadenopathy.

A variety of translocations involving the 8p11 breakpoint underline this syndrome and approximately 15 partner genes have been identified. An association between the t(8;13) and the triad of T-LBL/leukemia, eosinophilia, and myeloid malignancy was first reported by Inhorn et al, in 1995.[13] In this study, three patients showed the FGFR1/ ZMYM2 fusion and one showed CNTRL/FGFR1 fusion. Both these gene fusions have been associated with poor prognosis despite extensive chemotherapy and have a low overall survival.[14] Umino et al, show a 1-year overall survival of 43.15% in MPN, MDS and LBL with FGFR1 rearrangement.[5] Authors could assess response to treatment by cytogenetics and MRD by flow cytometry in two cases. Strikingly there was a dramatic reduction in positive metaphases in case 1. This patient showed an MRD of 0.05%, FGFR1 rearrangement in 10% cells by FISH after phase 1 induction and a morphological and cytogenetic remission post phase 2 induction (2 months later). Case 4 however, showed no morphologic remission and minimal cytogenetic response after two months. Authors presume this difference in response to be a consequence of either complex karyotype in case 4 or poorer prognosis of CNTRL gene as compare to ZMYM2. The other two cases are presently under treatment and could not be followed up.

Various chemotherapy strategies are available for the treatment of FGFR1 lesions and there is no single accepted regimen.[5,14] In this study, all this patient were initiated on the mBFM90 regime. In literature, non-selective tyrosine kinase inhibitors have recently shown to have promising outcomes in pre-clinical studies.[15] As FGFR1 aberrations are known to not behave uniformly across cancer types and have variable outcomes; a deeper understanding of biomarker strategies is essential. Refractoriness to chemotherapy regimens has also been reported in FGFR1 rearranged neoplasms.[11] McDonald et al, suggested that only allogeneic stem cell transplantation can effectively suppress the malignant clone.[16] Thus authors present the clinicopathological feature of patients with FGFR1 rearrangement which could add to the data pool and may help efficiently sub-categorize these patients as a distinct entity and/ or may even direct novel/ optimal therapeutic approaches.

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REFERENCES

1. Bain B, Gilliland P, Horny H, Vardiman J. Myeloid and Lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1. Eds. Swerdlow S, Campo E, Harris NL, Jaffe E, Pileri S, Stein H, et al. World Health Organization classification of hematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC Press; 2016:67-74.
2. Bain B. Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1. Haematologica. 2010;95(5):696-8.
3. Patel R, Sheehan A, Finch C, Lopez-Terrada D, Hernandez V, Curry C. Fine –needle aspiration cytology of T-lymphoblastic lymphoma associated FGFR1 rearrangement Myeloproliferative Neoplasm. Diagn Cytopath. 2017;42(1):45-8.
4. Rosati R, La Starza R, Veronese A, Aventin A, Schwienbacher C, Vallespi T et al. NUP98 is fused to the NSD3 gene in acute myeloid leukemia associated with t(8;11)(p11.2;p15). Blood. 2010;99(10):3857-60.
5. Umino K, Fujiwara S, Ikeda T, Toda Y, Ito S, Mashima K et al. Clinical outcomes of myeloid/lymphoid neoplasms with fibroblast growth factor receptor-1 (FGFR1) rearrangement. Hematology. 2018;23(8):470-7.
6. Heim S, Mitelman F. Cancer Cytogenetics-Chromosomal and molecular genetic aberrations of tumour cells. 4th ed. West Sussex, UK: Wiley Blackwell; 2015: 175-197.
7. Kumar K, Chen W, Koduru P, Luu H. Myeloid and lymphoid neoplasm with abnormalities of FGFR1 presenting with trilineage blasts and RUNX1 rearrangement. Am J Clin Pathol. 2015;143:738-48.
8. Vega F, Medeiros J, Bueso-Ramos C, Arboleda P, Miranda R. Hematolymphoid neoplasms associated with rearrangements of PDGFRA, PDGFRB, and FGFR1. Am J Clin Pathol. 2015;144:377-92.
9. Patnaik M, Ketterling R, Tefferi A. FGFR1 rearranged hematological neoplasms- molecularly

defined and clinically heterogenous. Leukemia Lymphoma. 2018;59(7):1520-2.
10. McGowan-Jordan J, Simons A, Schmid M. An international system for human cytogenomic nomenclature (ISCN). Basel, Switzerland: Karger publisher; 2016.
11. Verstovsek S, Subbiah V, Masarova L, CameronYin C, Tang G, Manshouri T et al. Treatment of the myeloid/lymphoid neoplasm with FGFR1 rearrangement with FGFR1 inhibitor. Ann Oncol. 2018;29(8):1880-2.
12. Wang Y, Wu X, Deng J, Yu H, Xu R, Zhu Z et al. Diagnostic application of next-generation sequencing in ZMYM2-FGFR1 8p11 myeloproliferative syndrome: A case report. Cancer Biol Ther. 2016;17(8):785-9.
13. Inhorn RC, Aster JC, Roach SA, Slapak CA, Soiffer R, Tantravahi R et al. Asyndrome of lymphoblastic lymphoma, eosinophilia, and myeloid hyperplasia/malignancy associated with t(8;13) (p11;p11): Description of a distinctive clinicopathologic entity. Blood 1995;85:1881-7.
14. Jackson C, Medeiros J, Miranda N. 8p11 myeloproliferative syndrome: a review. Hum Pathol. 2010;41(4):461-76.
15. Sobhani N, Ianza A, D'Angelo A, Roviello G, Giudici F, Bortul M et al. Current status of fibroblast growth factor receptor-targeted therapies in breast cancer. Cells. 2018;7(7):76-89.
16. Macdonald D, Reiter A, Cross C. The 8p11 myeloproliferative syndrome: a distinct clinical entity caused by constitutive activation of FGFR1. Acta Haematol. 2002;107(2):101-7.

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