Acquired *STAT5B* Mutation in a Myeloid Neoplasm with Dysplasia and Hypereosinophilia: A Case Study and Literature Review

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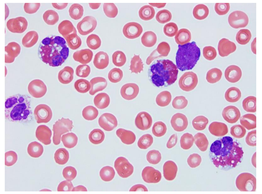
Introduction

- *STAT5B* mutation, mostly commonly at codon pN642H, is a recently reported driver mutation in myeloid neoplasms with eosinophilia, however, its exact underlying mechanism is unknown. Herein we reported an interesting case with STAT5B mutated myeloid neoplasm, highlighting the significance of acquired *STAT5B* mutation in the disease course of a myeloid neoplasm.

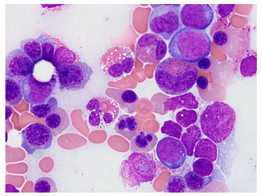
Case report

- A 52-year-old male presented with fever, chills hemoptysis and painful adenopathy in the groin for 1 month. Imaging study revealed mild splenomegaly (15 cm) and enlarged bilateral iliac nodes.
- An initial bone marrow biopsy (BMBx) showed increased myeloblasts (52%), consistent with acute myeloid leukemia (AML) with plasmacytoid dendritic cell differentiation (CD34/CD123+).
- NGS detected mutations in *RUNX1, FLT3, DNMT3A, SRSF2.*
- The patient received induction chemotherapy (Cytarabine/Anthracycline/Midostaurin) followed by 4-month maintenance therapy with complete hematologic response (CR) and free of molecular MRD (mCR).
- However, he developed relapsed disease 6 months post 3 cycles of chemotherapy.
- The NGS study AT RELAPSE was positive for *DNMT3A, RUNX1, SRSF2, FLT3 and **STAT5B**.*
- **Current Admission Work-Up:**
- PERIPHERAL BLOOD: Leukocytosis (25.07 x 10 ^{9}/L), neutrophilia, prominent eosinophilia (80%, with absolute eosinophil count of 20.06 x 10 ^{9}/L) and 3% blasts. Moderate anemia (hemoglobin: 9.1g/dL). Severe thrombocytopenia (platelet count: 9.0 x 10 ^{9}/L).
- Bone marrow biopsy showed hypercellularity (70%), with increased dysplastic hematopoiesis, 6% blasts and 5% reactive mast cells, consistent with residual acute myeloid leukemia.
- Karyotyping: normal male karyotype, 46,XY[20]
- FISH: negative for *PDGFRA, PDGFRB, and FGFR1*
  Flow cytometry AML MRD: Positive for MRD.

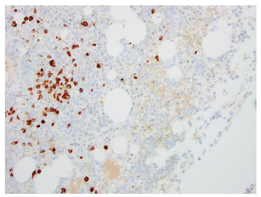
Results



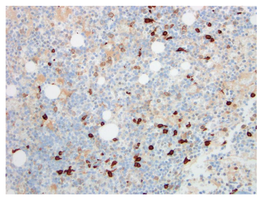
Peripheral Blood (Wright x1000): High-power view shows prominent eosinophilia.



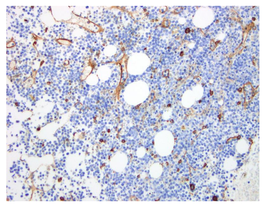
BM Aspirate (WG, x1000): Increased eosinophils. Overt dysplastic erythroid precursors. Dysgranulopoiesis with nuclear hyposegmentation & hypogranulation (not shown).



Tryptase+ (5% mast cells)



CD117 (blasts/mast cells)



CD34 (6%blasts)

Results (Continued)

Next Generation Sequencing (NGS)

Gene	Variant	DNA Change	Freq (%)	Reads	Chromo-some
STAT5B	p.N642H	c.1924A>C	22.1	3490	17

The hot-spot mutation site: p.N642H

Literature Review vs Current Case Study

Clinicopathological features	Literature Review	AML
Age in years, median (range)	73.3	52
Sex, M/F (ratio)	13M/8F	Male
WBC, x 10^{9}/L, median (range)	2.7	12.9
Hb, g/dL, median (range)	8.2 (5.7-13.8)	3.94
Platelets, x 10^{9}/L, median (range)	43 (5-220)	9
AEC, x 10^{9}/L, median (range)	22 (0-706)	8.64
PB Eosinophils >5%, N (%)	1 (5)	0
ABC, x 10^{9}/L	0 (0-57)	0.25
PB Basophils > 2%, N (%)	0 (0)	No
Eosinophilia and/or basophilia, N (%)	1 (5)	Yes
Increased LDH, N/N (%)	8/16 (50)	N/A
BM Blasts >5%, N/N (%)	21 (100)	Yes
Myelofibrosis grade >2, N/N (%)	2/17 (12)	No
FU in months, median (range)	9.4 (1-59)	>10 months
Died, N (%)	11 (52)	Alive

Cytogenetic and molecular features	Literature Review	CASE -AML
Cytogenetics • Normal or –y only • Complex or -7/-7q, -17/-17p, -5/-5q • All others	11 (55) 5 (25) 4 (20)	NORMAL
STAT5B detection • At diagnosis • Acquired • Unknown	8 (38) 10 (48) 3 (14)	ACQUIRED
STAT5B N642H	17 (81)	YES
STAT5B VAF %	7 (1.1-53)	43.3%
STAT5B VAF >5%	15 (71)	YES
Co-mutated genes, median	5 (2-8)	3
STAT5B as dominant /co-dominant clone	4 (19)	YES
Common co-mutations	*RUNX1, TET2, ASXL1*	*RUNX1, DNMT3A, SRSF2*

ABC-Absolute Basophil Count; AEC-Absolute Eosinophil Count; PB-Peripheral Blood; WBC-White Blood Cells; M-Male, F-Female

Discussion

- **Significant morphologic dysplasia** could lead to a misdiagnosis of MDS, MDS/MPN, AML-MR, or therapy-related AML.
- **Hypereosinophilia** could lead to a misdiagnosis of Relapsed AML with Myeloid Eosinophilia and tyrosinase kinase gene rearrangements, AML-MR, Systemic Mastocytosis with Associated Myeloid Neoplasm (SM-AMN), therapy-related AML.
- **Insufficient/misdiagnoses** can affect treatment options.
- **Literature review** of 82 myeloid neoplasms with *STAT5B* mutation showed 21 cases of AML with associated hypereosinophilia (5%), *STAT5B* mutation at the hot-spot mutation site, p.N642H (71%) and had shortest follow up of 9.4 months.
- Unfortunately, treatment was limited for the patient. He has persistent fever, nausea, chronic headaches (CNS involved) and depends on platelet-transfusion. He is ineligible for allogeneic transplant given his hepatitis C and lack of caregivers and has been enrolled in hospice.

Conclusion

1. Identification of the *STAT5B* mutation either at diagnosis or acquired with significant dysplasia, basophilia and eosinophilia requires contextual incorporation to ensure accurate diagnosis and therapy.
2. The hot-spot mutation, **p. N642H** is known to be associated with more aggressive disease
3. NGS study including *STAT5B* should be included for myeloid neoplasms with eosinophilia.

References & Acknowledgements

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