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634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Common Pathways for Acute Myeloid Leukemia Progression in Systemic Mastocytosis with Associated Hematologic Neoplasm

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Background:
Mastocytosis is a heterogenous disease of mast cell (MC) clonal proliferation with pathologic accumulation in organ systems such as but not limited to skin, bone marrow, gastrointestinal tract, liver and spleen. Mast cells are CD34+, CD117+ (stem cell factor, KIT) with greater than 90% of people with mastocytosis harboring KIT D816V activating mutations which allows for increased proliferation and accumulation of neoplastic mast cells leading to downstream mast cell activation and intolerable symptoms.
Advanced systemic mastocytosis (advSM) is categorized into three major subtypes, aggressive SM, MC leukemia and SM with an associated hematologic neoplasm (SM-AHN). SM-AHN is the most common advSM subtype accounting for about 75% of advSM cases and typically includes myeloid neoplasms such as MDS, CMML, or MPN. In most pts with SM-AHN, clinical symptoms is driven by the MC component and the goal of treatment with KIT inhibitors is to decrease the MC burden, thus improving quality of life and overall survival (Nat Med refs), However, the median survival of SM-AHN remains poor at 2-3.5 years with many pts transforming to advanced myeloid neoplasms especially an acute myeloid leukemia (AML).
The use of next generation sequencing has helped to prognosticate patients with AdvSM. Patients with advSM typically exhibit multiple somatic mutations other than KIT D816V We describe the molecular signature of patients with SM-AHN who transformed to AML. Commonly involved genes are *TET2*, *SRSF2*, *ASXL1*, *RUNX1*, and *CBL* with inferior OS and adverse clinical characteristic associated with *SRSF2/ ASXL1/ RUNX1* (S/A/R). To better prognosticate, Jawhar and colleagues introduced the MARS score. This incorporated molecular findings in AdvSM to help estimate overall survival which identified 3 risk categories (low, intermediate, and high). The overall survival in low, intermediate and high were not reached, 4.3 years, and 1.9 respectively for patients with AdvSM. While mutational findings in the MARS score can help prognosticate overall survival in these patients, the molecular footprint of progression or transformation to acute myeloid leukemia has not been established. We describe the molecular signature of patients with SM-AHN who transformed to AML.
Methods: We analyzed 10 pts with SM-AHN who transformed to AML from 2000-2022. Of those patients, 7 were found to have full next generation sequencing at the time of initial consultation and transformation. These data were collected and descriptive analysis was performed.
Results: We identified 7 pts with SM-AHN who progressed to AML. At SM-AHN diagnosis all pts had at least 2 additional co-mutations with a maximum of 7 co-mutations along with KIT D817V. The most common co-mutations were splicing factor mutations (*SRSF2* and *SF3B1*), *TET2, RAS EZH2, CUX1* and *CBL*. Six of the seven received treatment for SM-AHN. These patients received treatment with multikinase inhibitors or hypomethylating agents.
The acquired driver mutations were *NPM1, FLT3-ITD, RUNX1*, and *RAS* pathway. In patient 1, a new *FLT3-ITD* and *RUNX1* was acquired with an increased VAF of a RAS pathway mutation (*PTPN1*) which was originally present in the SM-AHN diagnosis. Patient 3 also developed a new *RUNX1* mutation at AML transformation. Patients 4 and 5 had new *NPM1* mutations and patients 6 and 7 had a new RAS pathway mutations . Patient 2 acquired new *BCOR, RIT1* and *CBL* mutations. Upon transformation to AML, 5/7 patients had resolution or a decrease of greater than 10% of *KIT D816V* VAF. One of the seven had no change in *KIT D816V* VAF at the time of transformation, this was also the only patient to receive no prior therapy. Only 1/7 had a VAF increase of greater than 20% in *KIT D817V* at transformation.
The MARS score was calculated at the time of diagnosis of SM-AHN which showed that only 4 of 7 had a high MARS score. Time from SM-AHN diagnosis to AML progression ranged from 4-31 months. Survival was calculated from time of SM-AHN diagnosis to death which ranged from 6-47 months.

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Conclusion: Acquisition of known AML driver mutations (RAS, RUNX1, NPM1, FLT3-ITD) are commonly found in SM-AHN patients at time of progression to AML. The MARS score calculated in our patients did not correlate with time to transition to AML.

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Figure 1: Oncoplot of SM-AHN at Diagnosis and at AML Progression

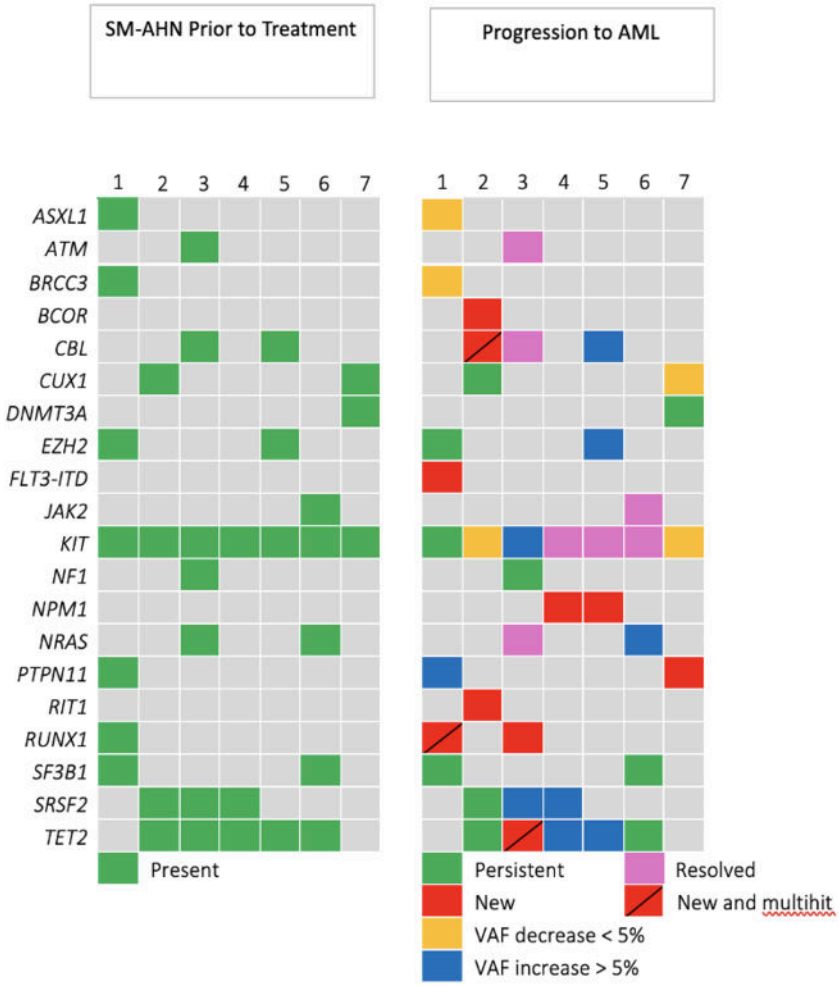

Table 1: Patient Specific Data

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age at SM-AHN	77	75	67	62	71	67	48
AHN	CMML	MPN-U	MDS-EB1	MDS/MPN-U	CMML	CMML	MDS/MPN-U
Time from SM-AHN to AML	4 months	23 months	20 months	31 months	7 months	27 months	21 months
Molecular Pathway to AML	RAS, RUNX1, FLT3ITD	BCOR, RIT1, CBL	RUNX1	NPM1	NPM1	RAS	RAS (PTPN11)
MARS Score	High (5)	High (4)	High (4)	High (3)	Low (1)	Low (1)	Low (1)
Survival*	**6 months**	**24 months**	**26 months**	**47 months**	**10 months**	**31 months**	**34 months**

*Time from SM-AHN diagnosis to death

Figure 1

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