Managing Patients with Systemic Mastocytosis with Associated Haematological Neoplasm: UK Single Centre Experience

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BACKGROUND

Advanced systemic mastocytosis (AdvSM) is a rare haematological neoplasm sub-classified into either aggressive SM, SM with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia.

Approximately 60-70% of patients with AdvSM are categorised as having SM-AHN. The AHN may precede, be concurrent with or follow the diagnosis of SM. AHNs span the entire spectrum of haematologic malignancies, including MDS/MPN overlap syndromes (CMML being the most common), MDS, AML, and less commonly lymphomas and plasma cell dyscrasias.

AHN is a heterogeneous disorder with regard to both clinical phenotype and prognosis. SM-AHN is associated with significant therapeutic challenges and elucidating ways to inform management is crucial in this complex group.

Here we discuss the characteristics of our AHN patients from our SM database and outline cases that illustrate our management approach in this group.

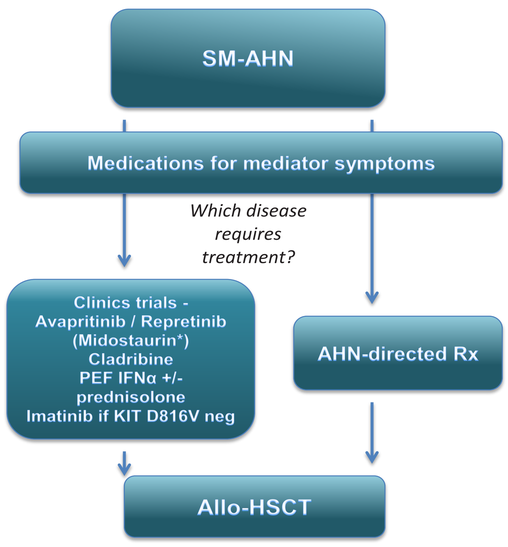
PROGNOSIS IN AHN

The diagnosis of an AHN in patients with SM is prognostically significant. Identification of the presence of an AHN in patients first diagnosed with SM infers a worse prognosis compared with indolent disease and should be actively looked for by examining the FBC differential and bone marrow.

Patients with AHN with additional secondary mutations, in particular *SRSF2*, *ASXL1* & *RUNX1* in addition to *KIT* D816V, have a worse prognosis and risk of leukaemic transformation to secondary mast cell leukaemia or AML. Prognostic models have been developed to risk stratify these patients. Myeloid gene panels (MGPs) are used to identify these mutations. This is of importance in informing management strategy.

MANAGEMENT

Fig 1: Treatment options for patients with AHN Adapted with permission from Radia et al, 2020.



Management of SM-AHN depends on:

- The symptom profile
- Whether the SM or the AHN are the cause of organ damage
- The risk of leukaemic transformation

Factors determining whether SM or AHN is predominant:

- The mast cell & c-*KIT* allelic burdens
- Tryptase levels
- Degree of dysplasia or fibrosis in MDS and MF

Allogeneic HSCT:

- HSCT should be considered in eligible patients with high risk disease
- Annual MGPs looking for secondary mutations can be helpful in timing allo-HSCT

CASE 1

Background:

- 50 year old male with rash
- Diagnosed with **indolent SM** (D816V+)

Clinical challenge:

- Developed **thrombocythaemia** with *JAK2* V617F positivity & reclassified as AHN (ET)
- Complicated by **cerebral sinus thrombosis**

Management approach:

- AHN component causing organ damage
- Treated with **cytoreduction** (pegylated IFN, hydroxycarbamide) & anti-coagulation

CASE 2

Background:

- 60 year old female presenting with **indolent SM** (D816V+) requiring anti-mediator treatment

Clinical challenge:

- Noted to have a **raised PCV**
- Diagnosed with *JAK2* V617F mutated **polycythaemia** and treated with venesections
- Progressed to **post-PV myelofibrosis (PPVMF)** with anaemia and splenomegaly

Management approach:

- AHN component causing organ damage
- Treated with **ruxolitinib**

CASE 3

Background:

- 77 year old male presenting with fatigue, weight loss, cytopaenias & raised tryptase (593 ug/L)
- Diagnosed with **AHN: SM+MDS/MPNu**

Clinical challenge:

- High symptom burden
- High risk of leukaemic transformation - **D816V, JAK2 V617F, SRSF2, ASXL1 and RUNX1 mutated**

Management approach:

- SM component causing organ damage.
- Treated with **midostaurin**

CASE 4

Background:

- 49 year old female presenting with rash, weight loss & fatigue
- Diagnosed with AHN: CMML-0
- Treated with KIT directed therapy (**avapritinib**) on a clinical trial with excellent response

Clinical challenge:

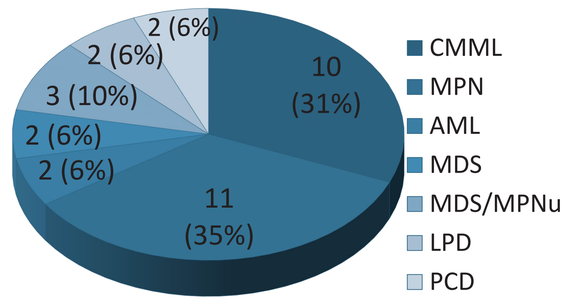
- **Secondary mutations** (DNMT3A, TET2, TP53)
- Transformation to **AML**

Management approach

- **MUD allogeneic SCT** - disease free at 3 months
- MRD monitoring for AML + SM post BMT

RESULTS

Fig 2: Number of patients by AHN subtype.



31 patients identified from the database had an AHN. Their subtype breakdown is depicted in Figure 2, with myeloid AHNs predominating.

13/31 patients had a MGP available and the additional mutations seen are illustrated in Table 1 and show 'SAR' and TET2 mutations to be common in SM-CMML. As expected patients also showed *KIT* D816V positivity and MPN patients were mostly *JAK2* V617F positive.

Table 1	*SRSF2*	*ASXL1*	*RUNX1*	*TET2*
CMML				
CMML				
CMML				
CMML				
CMML				
CMML				
CMML				
CMML				
CMML				
MDS/MPNu				
MPN				
MPN				
MPN				

CONCLUSIONS

Patients with SM can develop AHN or *vice versa*. Patients diagnosed with SM need long term follow up with comprehensive haematological and clinical reviews. Management of patients with SM-AHN requires personalised therapeutic stratification incorporating both clinicopathological and mutational features.

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