*Case Report:*

# Systemic mastocytosis associated with acute myeloid leukaemia

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## Abstract:

***Bacground:*** The pathogenesis of systemic mastocytosis with associated haematological neoplasm (SM-AHN) is not well understood. Both diagnoses heavily rely on morphological evaluation because SM is rarely suspected in clinical practise. ***Objective:*** This case highlighted a possible delay in diagnosis due to underlying conditions or diseases. ***Case Report:*** We present a case of a patient with acute myeloid leukaemia (AML), acute myelomonocytic subtype, and concurrent mastocytosis according to World Health Organization (WHO) classification. Due to an extensive accumulation of AML blast cells that obscured the mast cell infiltrates, mastocytosis was not evident at the first diagnosis. ***Discussion and conclusion:*** The diagnosis, in this case, was established only in the third bone marrow biopsy after chemotherapy. A high index of suspicion with morphological and immunohistochemical evaluations for neoplastic mast cell populations should be considered. The optimal treatment approach should be chosen based on these two disease entities.

**Keywords**: *systemic mastocytosis; acute myeloid leukaemia; mastocytosis; haematological neoplasm.*

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## Introduction:

Systemic mastocytosis (SM) with associated haematological neoplasm (SM-AHN) is a haematological malignancy that manifests with a non-mast cell haematological neoplasm. It is characterised by the accumulation of functionally defective mast cells in one or more extracutaneous organs (typically the bone marrow). The World Health Organization (WHO) first suggested SM-AHN as a unique entity in 2008. [1] Systemic mastocytosis with associated

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clonal haematological non-mast-cell-lineage disease (SH-AHNMD), which was its original name, was changed to SM-AHN in 2016. [2] The most frequent type of AHN found is chronic myelomonocytic leukaemia, and the associated malignancy is typical of myeloid lineage (CMML). [1]

Acute leukemia was more prevalent than chronic leukemia[3] and AML has been concurrently identified with SM in 32% of patients, which is more than is typically thought to occur.[4] The disease should not be diagnosed solely based on the SM condition, but also the presence of AHN cells. The activating KIT D816V mutation is found in most cases (e.g., AML blasts or CMML monocytes). Additional oncogene mutations (e.g., TET2, SRSF2, ASXL1, CBL, RUNX1, and RAS) may also be involved depending on the type of AHN, and their presence is thought to have prognostic significance[1]. Here, we present a patient diagnosed with AML, not otherwise specified (acute myelomonocytic subtype based on the most recent WHO classification), and whose coexisting mastocytosis became apparent only after a successful chemotherapy cycle.

## Case report:

A 24-year-old male presented with a persistent fever for 12 days, associated with appetite and weight loss, lethargy, and night sweats. He was afebrile and his vital signs were stable. Abdominal examination found no obvious hepatosplenomegaly. Other system examinations were unremarkable. Initial full blood count (FBC) indicated anaemia with a haemoglobin level of 11.7 g/dL, neutropenia (0.92 x $10^9$/L) and thrombocytopenia (platelet count of 46 x $10^9$/L). Full blood picture (FBP) revealed pancytopenia and a presence of 20 % circulating blast cells, which suggested acute leukaemia. Serum lactate dehydrogenase (LDH) was 447U/L.

Bone marrow aspirate (BMA) at diagnosis displayed a hypercellular marrow for age with 40 % blasts. The blast cells were composed of two populations: the first was small-sized cells, with scanty to moderate amount of cytoplasm without granules and inconspicuous nucleoli. The other cell population was moderate to large in size, with a moderate amount of granular cytoplasm and prominent nucleoli (Figure 1). Phenotypically, the blast cells showed expression of $CD13^+$, $CD33^+$, $CD64^+$, $nTdT^+$, $CD117^+$, $HLA\text{-}DR^+$, $CD34^+$, $CD7^+$ and $CD123^+$. Trephine biopsy revealed hypercellular bone marrow with homogenous blast cells that were positive for CD117, MPO, TdT, CD68 and CD34. Therefore, the bone marrow examination was concluded with a diagnosis of AML of the myelomonocytic subtype. However, additional IHC staining of trephine biopsy done retrospectively at diagnosis showing presence of mast cells (Figure 2).

After initial treatment with one cycle of the standard induction regime (cytarabine and idarubicin), subsequent FBP revealed persistently circulating blast cells (18 %) and eosinophilia. At the same time, BMA showed hypercellular marrow with 25 % blast cells, which suggested that the cancerous marrow did not go into remission, and the corresponding trephine

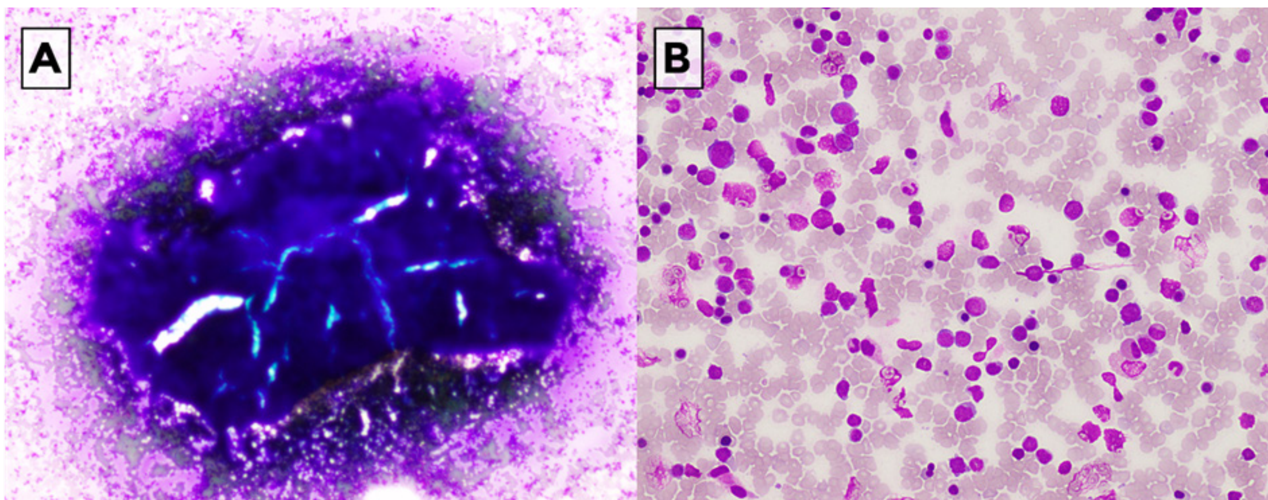


**Figure 1:** Bone marrow aspirate at diagnosis of AML M5 under a light microscope [A] (x10) showing hypercellular marrow fragments [B] (x 20) showing the presence of blast cells with mast cells.

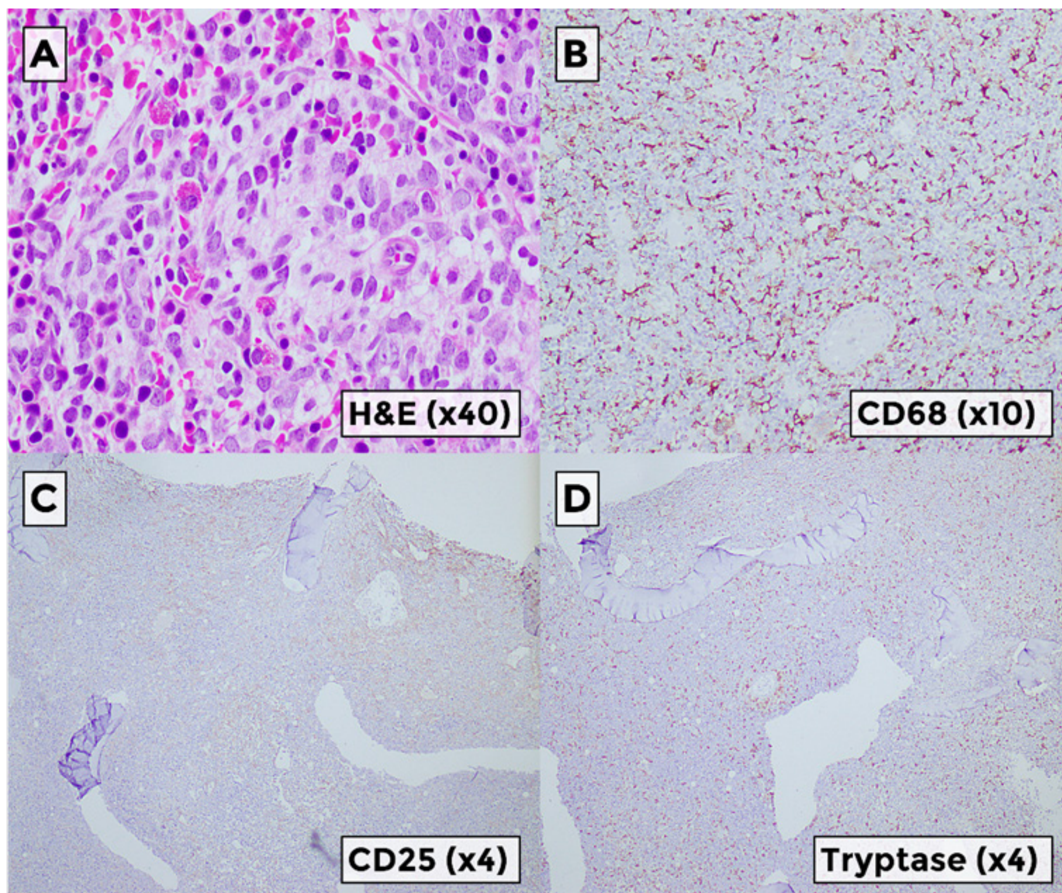


**Figure 2:** Trephine biopsy at diagnosis showing mast cells highlighted by (B) CD68, (C) CD25 and (D) tryptase

biopsy confirmed this. The patient's chemotherapy regime was then changed to fludarabine, cytarabine and idarubicin. Subsequent FBP displayed anaemia with no circulating blast cells and mast cells, but there was persistent eosinophilia.

The BMA exhibited a normocellular marrow with no increase in blast cells. However, trephine biopsy revealed a few foci of granuloma-like lesions, composed of 15 small-to-medium-sized cells, with oval to spindle nuclei and a moderate amount of cytoplasm in the intertrabecular areas. These cells were surrounding the blood vessels. These cells were immunoreactive towards CD25, tryptase, CD117, CD45, CD68, MPO and S100, but were negative for CD1a, pan-CK, CD34, CD30 and Toluidine blue (Figure 3), which were suggestive of mast cells. The eosinophils had increased in number, but the blast cells were not in excess. The initial diagnosis of AML of the myelomonocytic subtype was then changed to SM-AML based on the results of this trephine biopsy. Apparently, the mast cells had been present in previous trephine biopsies, but most were inconspicuous and loosely scattered. The patient was scheduled to undergo an allogeneic haematopoietic stem cell transplant after completing his chemotherapy with high dose of cytarabine.

## Discussion:

The pathogenesis of the uncommon disease SM-AHN has not yet been fully elucidated. The dual diagnosis would mostly depend on morphological evaluation because the SM component was rarely suspected in clinical settings. In a few articles, a case with a similar appearance to ours was recorded, in which the physicians only detected the presence of SM in AML after a few chemotherapy cycles. [5,6,7] It is possible that the component of the non-mast cell lineage does not exhibit the same c-kit mutation as neoplastic mast cells. Two explanations for the pathogenesis of SM associated with myeloid neoplasm have been proposed: an acquired c-kit mutation that transformed

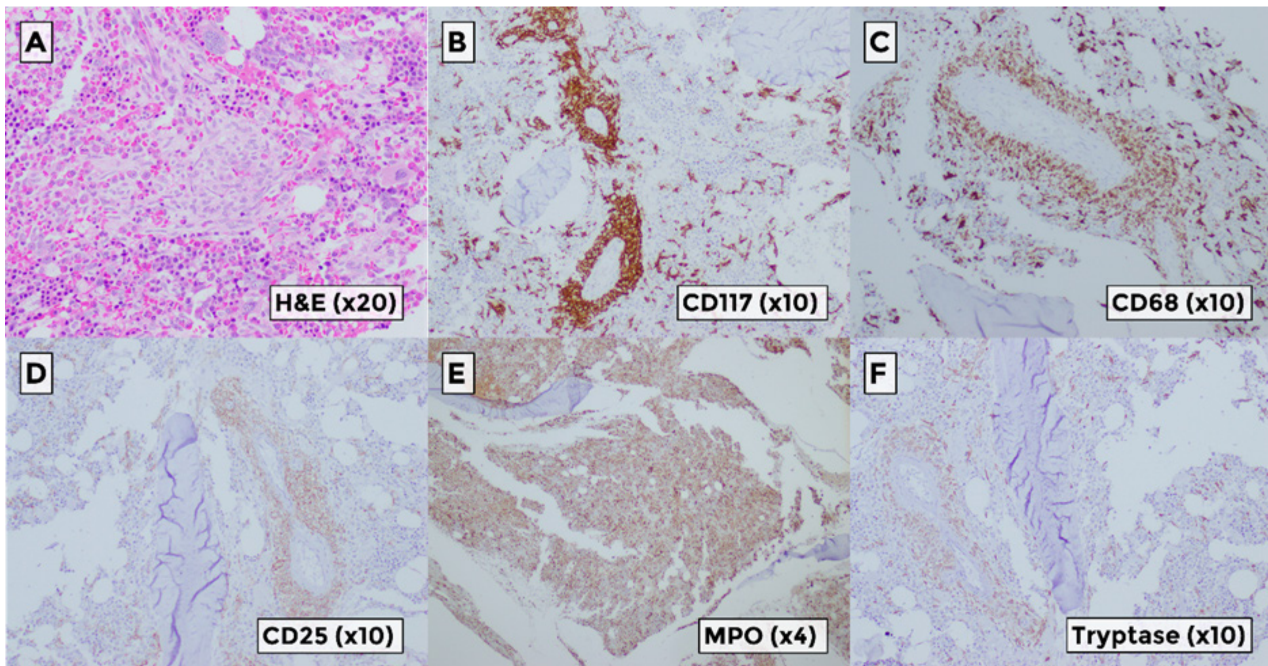


**Figure 3:** Trephine biopsy during SM-AML diagnosis established, highlighting mast cell granulomas in (B, C, D and E) and blast cells of AML in the periphery (E).

a myeloid stem cell and an activating c-kit mutation that developed in conjunction with other genetic changes and events in a myeloid stem cell.[8]

In this case, the diagnosis wasn't made until the third bone marrow sample following chemotherapy. The very hypercellular bone marrow, which was diffused, dense, and penetrated by myelomonoblast cells, must have masked the earlier diagnoses. In an aplastic bone marrow after the cytoreductive chemotherapy revealed multifocal dense infiltrates of clonal mast cells. If one major and at least one minor criterion had been present in the earlier bone marrow specimen with disseminated infiltration by blast cells, an accurate diagnosis of SM-AML would have been attainable.[1] However, compact mast cell infiltrates were not seen earlier as the sole significant diagnostic requirement for SM. By using morphological analysis and immunohistochemical staining, two minor diagnostic criteria were fulfilled. In addition to the typical mast cell markers, they were presence of spindling in more than 25% of the loosely dispersed mast cells and the expression of CD25 by those cells in the bone marrow. Unfortunately, neither the serum tryptase level nor the molecular identification of a point mutation at codon 816 of the KIT gene was available as diagnostic methods in our institution, which would have allowed us to identify the remaining two minor criteria.

The differential diagnosis for this patient included mast cell leukaemia (MCL), a severe type of SM. More than 10% of mast cells in peripheral blood or more than 20% of atypical mast cells in the bone marrow were required to diagnose MCL. [9] Complete gene sequencing is required for the diagnosis because non-KIT mutations were frequently found in patients with this condition. Myelomastocytic leukaemia (MML), which is characterised as mastocytic differentiation in advanced myeloid neoplasms without evidence of SM, was another consideration in the diagnosis of this patient. [10] However, the former scenario may be ruled out because this patient had SM with underlying AML.

## Conclusion:

This case indicated that mast cell infiltrates were sometimes underappreciated during the initial diagnosis of AML. Patients who presented with SM-AML often had the worst outcome, so early detection was still paramount for good clinical response. This required clinicians to have a high index of suspicion to carry out morphologic and immunohistochemical evaluation for neoplastic mast cell populations during diagnosis and treatment.

Conflict of Interest: No conflict of interest

**Ethical clearance:** NA

**Author Contribuition:**

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