

## A rare case of systemic mastocytosis with t(8;21) acute myeloid leukaemia in a young girl: a case report

Salfarina Iberahim<sup>1</sup>, Noor Haslina Mohd Noor<sup>2\*</sup>, Mohd Nazri Hassan<sup>3</sup>, Zefarina Zulkafli<sup>4</sup>, Marne Abdullah<sup>5</sup>, Razan Hayati Zulkeflee<sup>6</sup>, Marini Ramli<sup>7</sup>, Rosnah Bahar<sup>8</sup>, Shafini Mohamed Yusoff<sup>9</sup>, Hisham Atan Edinur<sup>10</sup>, Wan Suriana Wan Ab Rahman<sup>11</sup>

### ABSTRACT

Mastocytosis is a rare disorder due to the abnormal proliferation of clonal mast cells. Mast cells exist in most tissues, mature in situ from hematopoietic stem cells and develop unique characteristics of local effector cells. It manifests as two main categories: cutaneous mastocytosis and systemic mastocytosis (SM). Patients presenting with SM–acute myeloid leukaemia (AML) often have the worst outcome. Here we present a patient with the simultaneous diagnosis of SM associated with t(8;21) (q22;q22) acute myeloid leukaemia, M2 subtype in the French-American-British (FAB) classification, carrying a population of immature mast cell precursors. Initially, she was diagnosed with AML with t(8;21) (q22;q22) and was started on induction chemotherapy. Subsequent trephine biopsy evaluation post-induction chemotherapy showed no increase in blast cells. However, abnormal mast cells were seen distributed throughout the marrow spaces, which expressed mast cell tryptase, CD117 and CD68. She was then diagnosed as SM associated with t(8;21) (q22;q22) AML. Unfortunately, she succumbed to death due to severe neutropenic sepsis post-induction chemotherapy. By sharing the knowledge, hopefully it will help the clinicians as the diagnosis of SM is difficult to establish because the associated malignancy may obscure the morphological features of SM. However, a reduction in blast cell percentage at the time of a post-induction marrow evaluation helps in diagnosis.

### Keywords

Acute myeloid leukaemia; systemic mastocytosis; systemic mastocytosis with an associated acute myeloid leukaemia

### INTRODUCTION

Mastocytosis is a heterogeneous group of disorders due to clonal and neoplastic infiltration of the mast cells (MC). The manifestation ranges from the skin lesion (cutaneous mastocytosis) to the aggressive form that can invade the organ and cause organ failure (SM). The 2016 classification system from the World Health Organization (WHO) categorizes (SM) into five morphological/clinical groups with prognostic significance: indolent (ISM), smouldering (SSM), SM with an associated haematological neoplasm (SM-AHN), aggressive SM, and mast cell leukaemia (MCL)<sup>1</sup>.

AML has been concurrently identified with SM in 32% of patients, which is more than is

1. Salfarina Iberahim, Department of Haematology, School of Medical Science, Universiti Sains Malaysia, Kubang Kerian, 16150 Kubang Kerian, Kelantan, Malaysia.
2. Noor Haslina Mohd Noor
3. Mohd Nazri Hassan
4. Zefarina Zulkafli
5. Marne Abdullah
6. Razan Hayati Zulkeflee
7. Marini Ramli
8. Rosnah Bahar
9. Shafini Mohamed Yusoff
10. Hisham Atan Edinur, School of Health Science, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
11. Wan Suriana Wan Ab Rahman, School of Dental Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.

### Correspondence

Dr Noor Haslina Mohd Noor, Associate Professor.

Email: [drhaslina@usm.my](mailto:drhaslina@usm.my)

typically thought to occur. The disease should not be diagnosed solely based on the SM condition, but also the presence of AHN cells<sup>2</sup>.

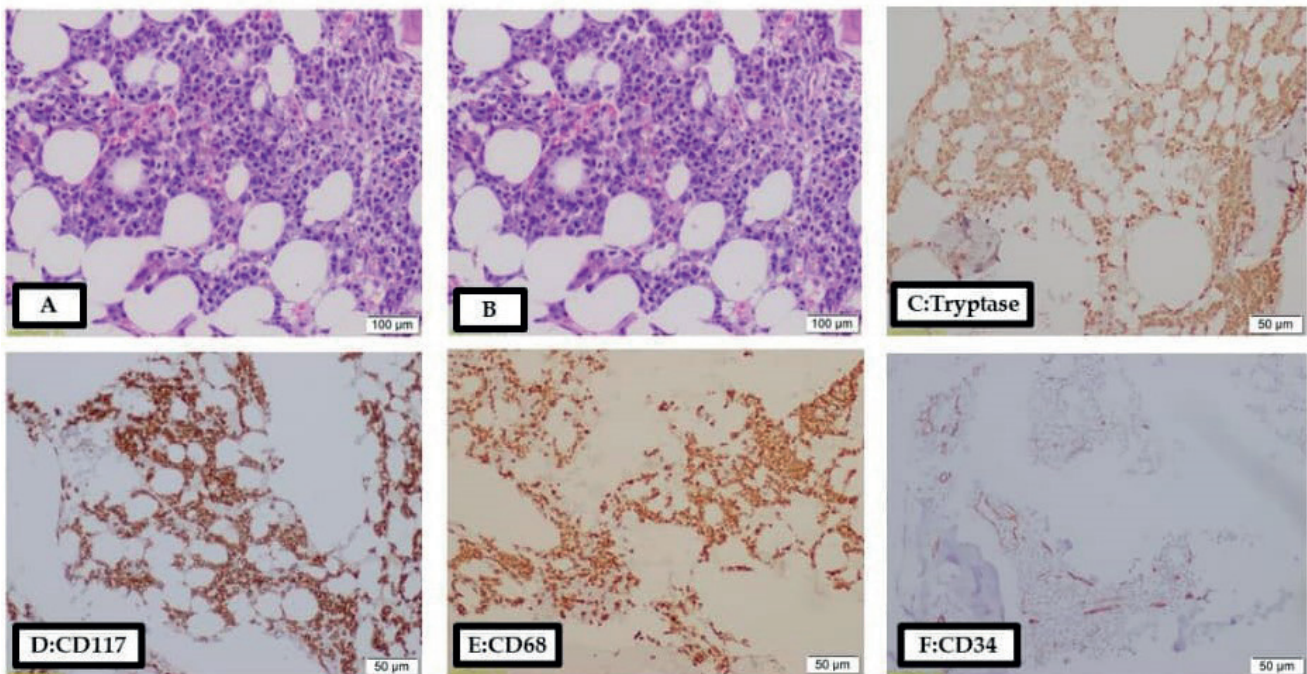
The diagnosis of mastocytosis was confirmed on the basis of one major criterion (presence of multifocal clusters of abnormal MC in the bone marrow) and two minor criteria according to the WHO classification. Minor diagnostic criteria include elevated serum tryptase level, abnormal MC CD25 expression, and presence of KITD816V mutation<sup>3</sup>. Mastocytosis has a bimodal distribution, often presenting in children from birth to 2 years of age and in those over 15. About 55% of cases present from birth to 2 years of age, 10% in children younger than 15 years old, and 35% in those over 15<sup>4</sup>. Treatment of SM-AHN primarily targets the AHN component if an aggressive disease such as AML is present<sup>3</sup>.

To the best of our knowledge, SM-AML with a t(8;21) translocation in young girls is rarely reported in our country.

## CASE PRESENTATION

A 4-year-old girl presented with a one-week history of fever associated with bleeding tendencies (i.e. gum bleeding, epistaxis, petechial rashes and bruises). Physical examination showed pallor with multiple small lymphadenopathy and hepatomegaly. The patient did not show evidence of skin involvement.

Laboratory examinations showed a normal leukocyte count ( $6.0 \times 10^9/L$ ) with haemoglobin of 6.1 g/dL and platelet count of  $5.0 \times 10^9/L$ . Peripheral blood smear showed the presence of 69% blast cells. Bone marrow was hypercellular and showed myeloid predominance with dyspoiesis along with relative suppression of erythroid and megakaryocytic series. Bone marrow aspiration showed the presence of 83% blasts, with few showing Auer rods. Immunophenotyping by flow cytometry revealed that the blasts were positive for CD34, HLA DR, CD117, cyMPO, CD33, CD13, CD64, Tdt and CD19. The blast were negative for cyCD79a, cyCD3, CD4, CD10, CD20, CD22, CD11b, CD14, CD35 and CD300e. Trephine biopsy showed a homogenous population of blast cells which were



**Figure 1:** (A and B) Heterogeneous population of hematopoietic cell with diffused mast cells in marrow spaces. The cells were positive for tryptase (C), CD117 (D) and CD68 (E). Negligible amount of CD34 positive blast cell was seen (F).

positive for CD34, MPO and CD117. Cytogenetic analysis revealed 46, XX, t(8;21)(q22;q22) which consistent with the diagnosis of AML with t(8,21); AML with recurrent cytogenetic abnormalities based on WHO classification 2016.

She was started on AML 12 protocol. Post Course 1 AML 12 protocol, she was planned for follow-up bone marrow before starting Course 2. However, the procedure was done after one month completed course 1 chemotherapy due to neutropenic sepsis and splenic microabscesses.

The surveillance bone marrow evaluation following induction chemotherapy revealed hypocellular marrow with no increase in myeloblasts. Trepine biopsy showed no increase in blast cells; however, abnormal mast cells were seen distributed throughout the marrow spaces. The mast cells were round to oval-shaped, with abundant cytoplasm, purple cytoplasmic granules and diffused chromatin pattern. Immunohistochemical staining demonstrated expression of mast cell tryptase, CD117 and CD68 but negative for CD25. A negligible amount of CD34 positive blast cells was seen. (Figure 1) The diagnosis at this time was SM associated with t(8;21)(q22;q22) AML. She started on induction therapy again, unfortunately, she succumbed to death due to severe neutropenic sepsis post-induction chemotherapy

## DISCUSSION

Mastocytosis is an uncommon disorder with an estimated prevalence of 1 in 10,000 persons, characterized by abnormal proliferation and accumulation of clonal mast cells<sup>5</sup>. The t(8;21)(q22;q22) associated AML with SM in the paediatric population is extremely rare with few case reports in literature describing this entity<sup>6</sup>.

Concurrent development of SM with AML is exceedingly rare. A previous study reported that a definitive diagnosis of SM was made after chemotherapy when the mast cell infiltrates were prominent in the majority of the cases<sup>7,8</sup>.

Paediatric patients with t(8;21) AML-SM may represent a high-risk group despite favourable cytogenetics<sup>7,9</sup>. Patients with concurrent SM and AML t(8;21) are often refractory to induction chemotherapy and have a high relapse rate<sup>8</sup>. Therefore, detection of concurrent SM at diagnosis of t(8;21) AML has important prognostic

implications.

According to the WHO classification 2016, this case is classified into SM associated with clonal hematologic non-mast cell lineage disease. The diagnosis of SM-AHN may be difficult to establish because the associated malignancy may mask the histological and cytological features of SM<sup>10</sup>. In our case, the diagnosis of SM was missed/masked at the time of diagnosis, mainly due to the excess number of blasts and tendency of mast cells to localize within the stroma of bone marrow particles. As the number of leukemic blasts decreased (as evidenced by decreased CD34+ cells), the mast cells component increased. Persistence of mastocytosis at the time of post-induction bone marrow evaluation with a reduction in blast percentage helps us diagnose SM at that time/ retrospectively.

We found oval shaped MC hyperplasia in the bone marrow with immunohistochemical staining demonstrated expression of mast cell tryptase, CD117 and CD68 but negative for CD25. Mastocytosis needs to be differentiated from mast cell hyperplasia or mast cell activation states. Thus, care should be taken in the morphological bone marrow examination to rule out the presence of abnormal MCs. If SM is suspected, a careful histologic and immunophenotypic analysis of MCs is mandatory. The neoplastic nature of mastocytosis is proved either by morphology, aberrant immunophenotype, or detection of a point mutation at codon-816 of the c-kit gene<sup>11</sup>. The neoplastic mast cells often showed spindle cell morphology and may abnormally express CD2 and/or CD25, the lymphocyte-associated antigens. This helps distinguish neoplastic mast cells (CD25+ and/or CD2+) from reactive mast cells (CD2- and CD25-) <sup>8,12</sup>. Antibodies that should be applied when bone marrow trephine specimens are investigated in cases suspected for mastocytosis are tryptase, CD117 (KIT), and CD25. However, the expression of CD2 has proved to be of minor relevance because it has a significantly lower sensitivity than CD25 and is not expressed in most cases with advanced disease. All normal/reactive and neoplastic mast cells coexpress the antigens tryptase and CD117<sup>13</sup>. However, tryptase expression may be very low or missing in about 1% to 5% of patients with mastocytosis. Cells not expressing CD117 are not mast cells<sup>13,14</sup>.



Induction chemotherapy with high dose cytarabine should be started in view of presence of t (8;21). Following this, two cycles of cytosine arabinoside, daunorubicin, and etoposide (ADE) will be administered. The consolidation phase will involve cladribine with cytarabine, with plans for subsequent allogeneic stem cell transplantation<sup>6</sup>.

## CONCLUSION

SM associated with t (8;21) AML is very rare in children and may result in a poor prognosis, despite the fact that t (8;21) AML are generally considered to

have a favourable risk. The presence of myeloblasts may obscure morphological features of SM and make the diagnosis of SM difficult to establish during the early presentation. However, a reduction in blast cell percentage during a post-induction marrow evaluation helps in the diagnosis. We recommend examining all cases of AML with t (8;21) for the presence of SM via morphology, immunophenotyping, and mutational analysis studies.

## CONFLICT OF INTEREST

The authors declared no conflicts of interest.

## REFERENCES

- Pardanani, A.; Lasho, T. L.; Reichard, K. K.; Hanson, C. A.; Tefferi, A., World Health Organization class-independent risk categorization in mastocytosis. *Blood Cancer J* 2019;**9**(3):29.
- Nazihah, M. N. D.; W. A. R. W. S., Hussain Faezahtul Arbaeyah, Systemic mastocytosis associated with acute myeloid leukaemia. *Bangladesh Journal of Medical Science* 2023;**22** (4):937-941.
- Pardanani, A., Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management. *Am J Hematol* 2019; **94**(3):363-377.
- Frieri, M.; Quershi, M., Pediatric Mastocytosis: A Review of the Literature. *Pediatr Allergy Immunol Pulmonol* 2013;**26** (4):175-180.
- Brockow, K., Epidemiology, prognosis, and risk factors in mastocytosis. *Immunol Allergy Clin North Am* 2014;**34** (2), 283-95.
- Rabade, N.; Tembhare, P.; Patkar, N.; Amare, P.; Arora, B.; Subramanian, P. G.; Gujral, S., 'Childhood systemic mastocytosis associated with t (8; 21) (q22; q22) acute myeloid leukemia'. *Indian J Pathol Microbiol* 2016;**59**(3):407-9.
- Pullarkat, S. T.; Pullarkat, V.; Kroft, S. H.; Wilson, C. S.; Ahsanuddin, A. N.; Mann, K. P.; Thein, M.; Grody, W. W.; Brynes, R. K., Systemic mastocytosis associated with t(8;21) (q22;q22) acute myeloid leukemia. *J Hematop* 2009;**2**(1):27-33.
- Xie, W.; Wang, S. A.; Yin, C. C.; Xu, J.; Li, S.; Bueso-Ramos, C. E.; Medeiros, L. J.; Tang, G., Acute myeloid leukemia with t(8;21)(q22;q22.1)/RUNX1-RUNX1T1 and KIT Exon 8 mutation is associated with characteristic mastocytosis and dismal outcomes. *Exp Mol Pathol* 2019;**108**:131-136.
- Mahadeo, K. M.; Wolgast, L.; McMahon, C.; Cole, P. D., Systemic mastocytosis in a child with t(8;21) acute myeloid leukemia. *Pediatr Blood Cancer* 2011;**57**(4):684-7.
- Khan, S.; Abid, Z.; Siddiqui, H. F.; Zahoor, S.; Haider, G., Acute Myeloid Leukemia with Occult Systemic Mastocytosis or Atypical Mast Cells Post-induction. *Cureus* 2018;**10**(12):e3734.
- Gadage, V. S.; Kadam Amare, P. S.; Galani, K. S.; Mittal, N., Systemic mastocytosis with associated acute myeloid leukemia with t (8; 21) (q22; q22). *Indian J Pathol Microbiol* 2012;**55**(3), 409-12.
- Zhrebker, L.; Cooper, B.; Krause, J. R., Systemic mastocytosis with associated acute myelogenous leukemia. *Proc (Bayl Univ Med Cent)* 2014;**27** (1):22-4.
- Hans-Peter Horny, K. S., Peter Valent, Mastocytosis: Immunophenotypical Features of the Transformed Mast Cells Are Unique Among Hematopoietic Cells. *Immunol Allergy Clin North Am.* 2014;**34** (2):315-321.
- Escribano, L.; Garca-Montero, A.; Nunez-Lopez, R.; Lopez-Jimenez, J.; Almeida, J.; Prados, A.; Orfao, A., Systemic mastocytosis associated with acute myeloid leukemia: case report and implications for disease pathogenesis. *J Allergy Clin Immunol* 2004;**114** (1):28-33.