Mast Cell Leukaemia – A Case Report

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Background

Mastocytosis occurs due to a clonal, neoplastic proliferation of mast cells in one or more organs or tissues. The WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues divides the disease into cutaneous mastocytosis (CM), systemic mastocytosis (SM) and mast cell sarcoma. SM with associated haematological neoplasm (SM-AHN) fits the criteria for both SM and a non-mast cell haematological neoplasm.

We herein report the clinical and histopathological features of a local case of mast cell leukaemia with associated myelodysplastic syndrome, and the extensive pathologic investigations undertaken to reach this diagnosis.

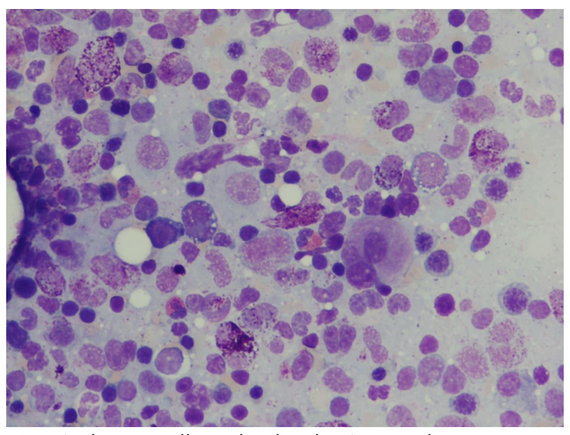
Case presentation

Clinical History

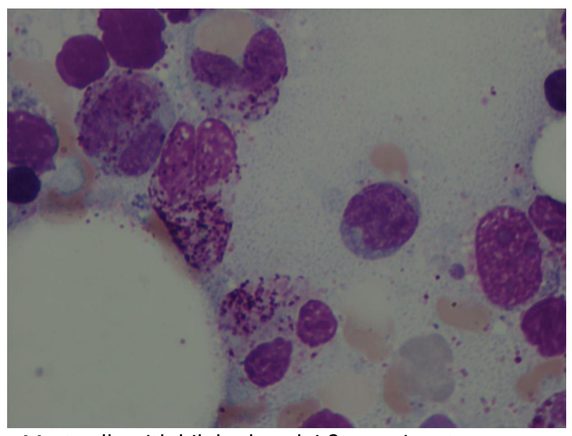
An 83-year-old man with beta thalassaemic trait and congestive heart failure presented with anaemic symptoms, bruising, constitutional symptoms and low grade fever for one week. Complete blood count showed bicytopenia (Hb 6.1 g/dL, WBC 2.5 x 10^9/L, Plt 12 x 10^9/L) with a few circulating blasts and nRBCs. Physical examination revealed hepatosplenomegaly. Bone marrow aspiration and trephine biopsy were performed for further evaluation.

Pathologic features

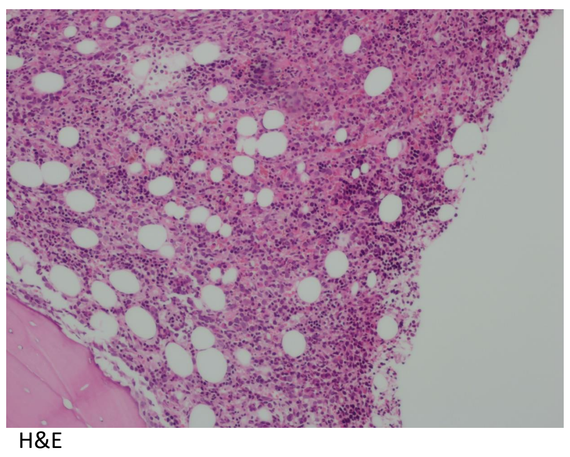
Bone marrow aspirate showed infiltration by medium-sized atypical cells (38%) with indented, bi-lobed or multi-lobed nuclei, clear cytoplasm and prominent metachromatic granules, resembling immature mast cells. Flow cytometric analysis found them to be positive for CD13, CD33, CD25, CD117 (strong) and CD123; negative for CD2 and CD34. Dyserythropoiesis, dysmegakaryopoiesis and increased blasts (8%) were also evident. Immunophenotyping confirmed them to be CD34+ myeloblasts. Bone marrow trephine showed similar atypical infiltrates that were positive for CD25, CD117 and mast cell tryptase on immunohistochemistry.



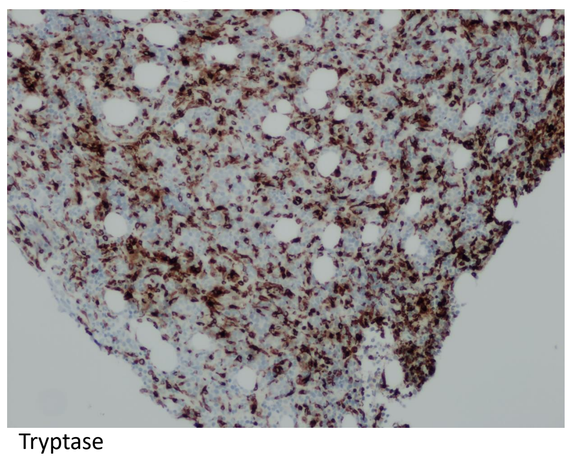
Atypical mast cells and a dysplastic megakaryocyte



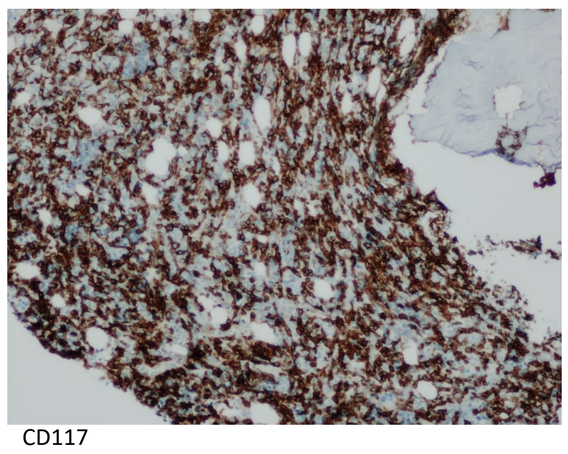
Mast cells with bilobed nuclei & prominent metachromatic granules



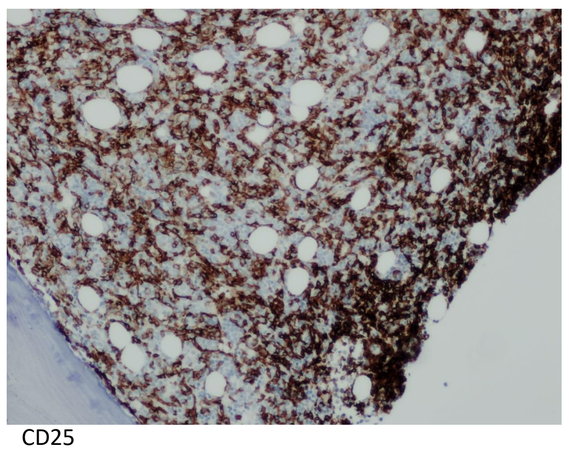
H&E



Tryptase



CD117



CD25

Molecular and cytogenetic studies

DNA sequencing revealed a missense mutation in exon 17 of KIT gene (KIT D816V mutation). BCR::ABL1 fusion transcripts and JAK2 V617F mutation were absent by PCR. Karyotyping detected trisomy 8 in 7 out of 20 metaphases.

Discussion

MCL must meet WHO criteria for SM and diffuse bone marrow infiltration by ≥20% immature or atypical mast cells. The leukaemic variant (circulating mast cells ≥ 10%) is most classical but the aleukaemic variant (circulating mast cells <10%) is more common.

Important differential diagnoses of MCL include myelomastocytic leukaemia, chronic myeloid leukaemia in disease acceleration or blast phase, chronic eosinophilic leukaemia, tryptase-positive acute myeloid leukaemia and basophilic leukaemia. Combined morphological examination, immunophenotyping and genetic studies are necessary to reach the correct diagnosis.

A morphologic classification of neoplastic mast cells based on distinct stages of their maturation has been published. Atypical MC type II/promastocyte (bi- or multi-lobed nuclei) and metachromatic blasts (myeloblast with few or several metachromatic granules) are most common in MCL. Immunophenotypically, aberrant expression of CD2, CD25 and CD30 suggests their neoplastic nature. Other markers e.g. HLA-DR, CD52 and CD123 may also be more abundantly expressed in MCL.

KIT D816V mutation is pathognomonic of SM and is present in 50% of MCLs. Other non-D816V codon mutations at exon 8, 9, 10, 11, 13, and 17, and a small subset where no KIT mutations are reported. The presence of any activating KIT mutation is a minor diagnostic criteria for SM by WHO classification. Apart from diagnostic purpose, its presence also has prognostic and therapeutic implications – its VAF correlates with disease activity and different types of KIT mutations respond differentially to KIT inhibitors.

There is an associating AHN in 10-70% MCL cases by different studies, with the AHN component being MDS, MPN, MDS/MPN or AML in up to 90%. Cytogenetic study and myeloid genes sequencing should be considered to characterize the ANH component for therapeutic and transplant decisions.

In a systematic review of 51 MCL cases, MCAS (mast cell activation symptoms) were frequently observed e.g. flushes (60%), fever (52%) and malaise (36%). Other symptoms include asthenia (78%), severe weight loss (38%) and anorexia (20%). Hepatosplenomegaly was the most common physical finding. GI manifestations frequently included GU and complicated by haemorrhage (64%). Interestingly, GU seems to be more frequently associated with KIT D816V mutation than other KIT mutations. Lymphadenopathy and skin involvement were only present in one-third of MCL cases.

Follow up

The patient was started on midostaurin, a multi-target tyrosine kinase inhibitor active against non-mutant and mutant KIT D816V. He remained pancytopenic and suffered from severe GU bleed and intracranial haemorrhage. He succumbed three months after diagnosis.

Conclusion

Mast cell leukaemia is an extremely rare disease, often with an aggressive clinical course and dismal prognosis. Differentiating it from other diagnoses necessitate meticulous morphological examination, extensive immunophenotyping, molecular and cytogenetic studies. Its AHN component, if present, should also be thoroughly evaluated.

References:
1. Valent P, Sotlar K, Sperr WR, et al. Refined diagnostic criteria and classification of mast cell leukemia (MCL) and myelomastocytic leukemia (MML): a consensus proposal. Ann Oncol. 2014;25(9):1691-1700.
2. Leguit R, Hebeda K, Kremer M, et al. The Spectrum of Aggressive Mastocytosis: A Workshop Report and Literature Review. Pathobiology. 2020;87(1):2-19.
3. Georgin-Lavialle S, Lhermitte L, Dubreuil P, Chandesris MO, Hermine O, Damaj G. Mast cell leukemia. Blood. 2013;121(8):1285-1295.
4. Sperr WR, Escribano L, Jordan JH, et al. Morphologic properties of neoplastic mast cells: delineation of stages of maturation and implication for cytological grading of mastocytosis. Leuk Res. 2001;25(7):529-536.
5. Pozdnyakova O, Kondtratiev S, Li B, Charest K, Dorfman DM. High-sensitivity flow cytometric analysis for the evaluation of systemic mastocytosis including the identification of a new flow cytometric criterion for bone marrow involvement. Am J Clin Pathol. 2012;138(3):416-424.
6. Jawhar M, Schwaab J, Meggendorfer M, et al. The clinical and molecular diversity of mast cell leukemia with or without associated hematologic neoplasm. Haematologica. 2017;102(6):1035-1043.
7. Galura GM, Cherukuri SV, Hakim N, Gaur S, Orazi A. Acute aleukemic mast cell leukemia: Report of a case and review of the literature. Leuk Res Rep. 2020;14:100230.
8. Lopes M, Teixeira MDA, Casais C, et al. KIT D816V Positive Acute Mast Cell Leukemia Associated with Normal Karyotype Acute Myeloid Leukemia. Case Rep Hematol. 2018;2018:3890361.