Mast cell leukemia (MCL) is an extremely rare and aggressive form of systemic mastocytosis (SM), accounting for <1% of all adult SM, with ≥20% atypical and immature mast cells (MC) in bone marrow. There are two known forms of presentation for MCL, the classic case in which MCs account for ≥10% of the peripheral white blood cells and the more frequent aleukemic variant with less than 10% MCs in peripheral blood. De novo MCL should be distinguished from secondary MCL, evolving from other advanced SM. Diagnostic criteria and classification of SM have been updated in the 2017 World Health Organization classification. Most cases of MCL have markedly high levels of serum tryptase, peripheral cytopenia, and/or leukocytosis with eosinophilia. Patients can develop any of the typical clinical features of SM due to organ impairment or MC activation, although skin lesions are not usually detectable. Atypical MCs show an abnormal antigen expression, characteristically CD2 and/or CD25 with the expression of concurrent immaturity markers. Furthermore, most cases of aggressive SM harbor c-Kit tyrosine kinase domain mutations, most frequently D816V, without recurrent chromosomal aberrations detected to date. Therapeutic approaches are limited and, in general, prognosis of MCL is poor with less than one-year survival in most patients.

We report a de novo aleukemic form of MCL with a complex monosomic karyotype with LOH for multiple chromosomes and TP53 mutation. Additionally, whereas D816V KIT was not found, the c-Kit transmembrane domain p.M541L variant was detected which is the most common SNP of KIT gene in humans with controversial pathogenic role. In these cases, it is crucial to perform a rapid broad molecular study for an accurate diagnosis which could help to initiate targeted therapy.

**Keywords**

acute leukemia, genomics, molecular biology, systemic mastocytosis

---

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2019 The Authors. Clinical Case Reports published by John Wiley & Sons Ltd.
Bone marrow was diffusely infiltrated by 60% of large atypical cells with loose chromatin and centric and round nuclei, atypical mast cell type I (MC I), and occasionally even larger ones with polylobed nuclei (promastocytes or atypical MC II) distributed in multiple aggregates. Most of the atypical MCs exhibited a characteristic wide cytoplasm with azurophilic granules and multiple heavy inclusions or bizarre-looking vacuoles, not stained with May–Grünwald–Giemsa (MGG) (Figure 1A,B). Dysplastic features were absent in the peripheral blood and the bone marrow. These cells were positive for c-Kit (CD117) and CD2 by immunohistochemical staining. Myeloperoxidase was negative, chloroacetate esterase weakly positive, and toluidine blue stain revealed metachromatic granulated blast-like cells (Figure 1C,D). Electronic microscopy disclosed three distinct types of MCs (immature, mature, and activated MCs) characterized by its cytoplasmic granules which appear during their maturation (Figure 1E-G).

The immunophenotype of the neoplastic cells assessed by multiparametric flow cytometry was as follows: CD117,
CD2, CD25, CD34, HLA-DR, and CD123 were positive, whereas CD45, MPO, and TdT were negative. Conventional cytogenetic studies revealed a complex monosomic karyotype: 35,XY,−1,−3,−5,add(5)(q32),−7,−10,−11,−12,−13,−15,−16,−17,−18,+mar1[2]/35,XY,i(1)(q10),−3,−5,add(5)(q32),−7,−10,−11,−12,−13,−15,−16,−17,−18[2]/46,XY[16] (Figure S1). DNA arrays performed with an Affymetrix platform and Cytoscan 750K confirmed these findings along with the detection of loss of heterozygosity regions (LOH) (Table 1A).

Mutation screening with conventional PCR techniques, as previously described, ruled out mutations in KIT, FLT3, NPM1, CEBPA, MLL, IDH1, IDH2, as well as the rearrangements CBFB-MYH11 and RUNX1-RUNXIT1.

An amplicon-based targeted next-generation sequencing (NGS) myeloid panel of 42 genes (Haloplex TM, Agilent Technologies) routinely used in our institution based on published studies of Bullinger et al group detected a KIT M541L variant in exon 10 (transmembrane domain) and a TP53 missense pathogenic mutation that was confirmed by Sanger sequencing (Figure 1H). Other concurrent allelic variants of GATA2, EZH2, and ANKRD26 genes were detected (Table 1B). All these variants have previously been described and reported as polymorphisms of uncertain pathogenic significance.

Therefore, the patient was diagnosed with de novo aleukemic MCL, according to the 2017 WHO criteria. Due to a rapid clinical deterioration, midostaurin was started, before obtaining the final molecular studies results. Despite this, the clinical status worsened and the patient died one month after diagnosis.

To sum up, we report an aleukemic form of MCL case with a complex monosomic karyotype. We also identified LOH regions of chromosomes 3, 5, 7, 9, and 10. Of note, our patient harbored a TP53 mutation which has already been defined as an early transforming event in hematologic malignancies. As it has been reported, our patient lacked the D816V KIT mutation; however, a c-Kit transmembrane domain p.M541L variant was detected and it could modify the phenotype of a neoplastic myeloid progenitor transformed by TP53 mutation. In fact, this KIT allelic variant in exon 10 is the most common SNP found in the KIT gene in humans and its pathogenic role is controversial. The contributing effects of the other variants remain to be elucidated.

Further MCL cases should be analyzed with the newly available techniques before drawing more precise conclusions about the genomic landscape of this infrequent disease. In these cases, it is crucial to perform a rapid broad molecular study for an accurate diagnosis which could help to initiate targeted therapy.

**TABLE 1** (A) List of LOH as determined using CytoScan 750K Array; (B) Allelic variants identified by NGS

| Chrom. | Cytoband/Location | Start (Mb)a | End (Mb)a |
|--------|-------------------|-------------|-----------|
| 3      | 3p21.31-p21.2     | 47 002 139  | 50 797 870|
| 5      | 5q34-q35.2        | 167 244 759| 176 110 659|
| 7      | 7p21.2-p15.3      | 14 753 209  | 22 086 697|
| 7      | 7q11.21           | 62 569 501  | 66 530 404|
| 7      | 7q31.31           | 117 485 006| 120 694 229|
| 9      | 9q31.1-q31.2      | 107 580 656| 111 256 573|
| 10     | 10q22.1-q22.2     | 73 731 650  | 77 131 019|

| Gene   | AA variant | cDNA variant | VAF   |
|--------|------------|--------------|-------|
| KIT    | p.M541L    | c.1621A>C    | 0.57  |
| TP53   | p.G266R    | c.796G>A     | 0.075 |
| GATA2  | p.A164T    | c.490G>A     | 0.54  |
| EZH2   | p.D185H    | c.553G>A     | 0.48  |
| ANKRD26| p.Q20R     | c.59A>G      | 0.56  |

Abbreviations: AA, aminoacid; Chrom, chromosome; VAF, variant allele frequency.

A Nucleotide position of the origin and the end of the aberration in the reference genome (hg19).

**AKNOWLEDGMENTS**

This work was supported in part by grants AGAUR 2014 SGR 383 from Generalitat de Catalunya and Instituto de Salud Carlos III FIS 16/00940, Ministerio de Economía y Competitividad, Spain.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**AUTHOR CONTRIBUTIONS**

AB-V and AM-R: conceived and designed the analysis, collected the data, performed the analysis, and wrote the paper; SC-W: contributed data or analysis tools (electronic microscopy study); EB and MC: contributed data or analysis tools (molecular analysis); GO, ÁR, CM, MP, and MLB: aided in interpreting the results and worked on the manuscript. JFN: conceived the study and was in charge of overall direction and planning. All authors discussed the results and commented on the manuscript.

**ORCID**

Anna Bosch-Vilaseca https://orcid.org/0000-0002-9147-3692
REFERENCES

1. Georgin-Lavialle S, Lhermitte L, Dubreuil P, Chandesris MO, Hermine O, Damaj G. Mast cell leukemia. *Blood*. 2013;121(8):1285-1295.

2. Swerdlow SH, Campo E, Harris NL, et al. (Eds). *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, Revised 4th edn. Lyon, France: IARC; 2017.

3. Lim K-H, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood*. 2009;113(23):5727-5736.

4. Noack F, Sotlar K, Notter M, Thiel E, Horny H-P, Horny HP. Aleukemic mast cell leukemia with abnormal immunophenotype and c-kit mutation D816V. *Leuk Lymphoma*. 2004;45(11):2295-2302.

5. 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.

6. Sperr WR, Escribano L, Jordan J-H, 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.

7. Arock M, Sotlar K, Akin C, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. *Leukemia*. 2015;29(6):1223-1232.

8. Frederiksen JK, Shao L, Bixby DL, Ross CW. Shared clonal cytogenetic abnormalities in aberrant mast cells and leukemic myeloid blasts detected by single nucleotide polymorphism microarray-based whole-genome scanning. *Genes Chromosomes Cancer*. 2016;55(4):389-396.

9. Desai P, Mencia-Trinchant N, Savenkov O, et al. Somatic mutations precede acute myeloid leukemia years before diagnosis. *Nat Med*. 2018;24(7):1015-1023.

10. Hirsch P, Zhang Y, Tang R, et al. Genetic hierarchy and temporal variegation in the clonal history of acute myeloid leukaemia. *Nat Commun*. 2016;7:12475.

11. Schwaab J, Schnittger S, Sotlar K, et al. Comprehensive mutational profiling in advanced systemic mastocytosis. *Blood*. 2013;122(14):2460-2466.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Bosch-Vilaseca A, Monter-Rovira A, Cisa-Wiezczorek S, et al. Ultrastructural, cytogenetic, and molecular findings in mast cell leukemia: Case report. *Clin Case Rep*. 2019;7:1395–1398. [https://doi.org/10.1002/ccr3.2208](https://doi.org/10.1002/ccr3.2208)