

## Acute Myeloid Leukemia “Cup-Like”: About A Case and Litterature Review

H. Yahyaoui<sup>1\*</sup>, A. Jahdaoui<sup>1</sup>, A. Raissi<sup>2</sup>, E. Boufrioua<sup>1</sup>, M. Oujidi<sup>1</sup>, M. Ait Ameer<sup>1</sup>, M. Chakour<sup>1</sup>

<sup>1</sup>Laboratory of Hematology of Avicenna Military Hospital & Faculty of Medicine and Pharmacy of Marrakech, Morocco

<sup>2</sup>Departement of Clinical Hematology of Avicenna Military Hospital of Marrakech, Avenue Al Mouqaouama, Marrakech 40000, Morocco

DOI: [10.36347/sjams.2020.v08i03.003](https://doi.org/10.36347/sjams.2020.v08i03.003)

| Received: 17.02.2020 | Accepted: 01.03.2020 | Published: 07.03.2020

\*Corresponding author: Hicham Yahyaoui

### Abstract

### Case Report

Cup-like acute myeloid leukemia (CL AML) is a rare form of acute myeloid leukemia, but its frequency is probably underestimated because it is a poorly understood and little described entity. Characterized by a particular biological profile: hyperleukocytosis, massive blastosis, disseminated intravenous coagulation, nuclei marked by a clear nuclear invagination, relatively stereotyped immunophenotype: CD34- / HLA-DR- / MPO + / CD117 + / CD13 +. Often associated with a normal karyotype, CL AML cytology is highly predictive of molecular abnormalities affecting NPM1 and FLT3.

**Keywords:** Acute leukemia - cup like - diagnosis - immunophenotyping - mutation – prognosis.

**Copyright © 2020:** This is an open-access article distributed under the terms of the Creative Commons Attribution license which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use (NonCommercial, or CC-BY-NC) provided the original author and source are credited.

## INTRODUCTION

Acute myeloid leukemia is defined by a malignant proliferation leading to the accumulation in the blood and bone marrow of precursor cells of the myeloid lineage.

Acute myeloid leukemia cup-like, a rare form of AML, has specific cytological, phenotypic, cytogenetic and molecular characteristics distinct from other types of AML. Its diagnosis is based on a bundle of cytological, immunological and genetic arguments.

We report a case of acute cup-like leukemia whose interest lies in the similarities with variant hypogranular acute promyelocytic leukemia.

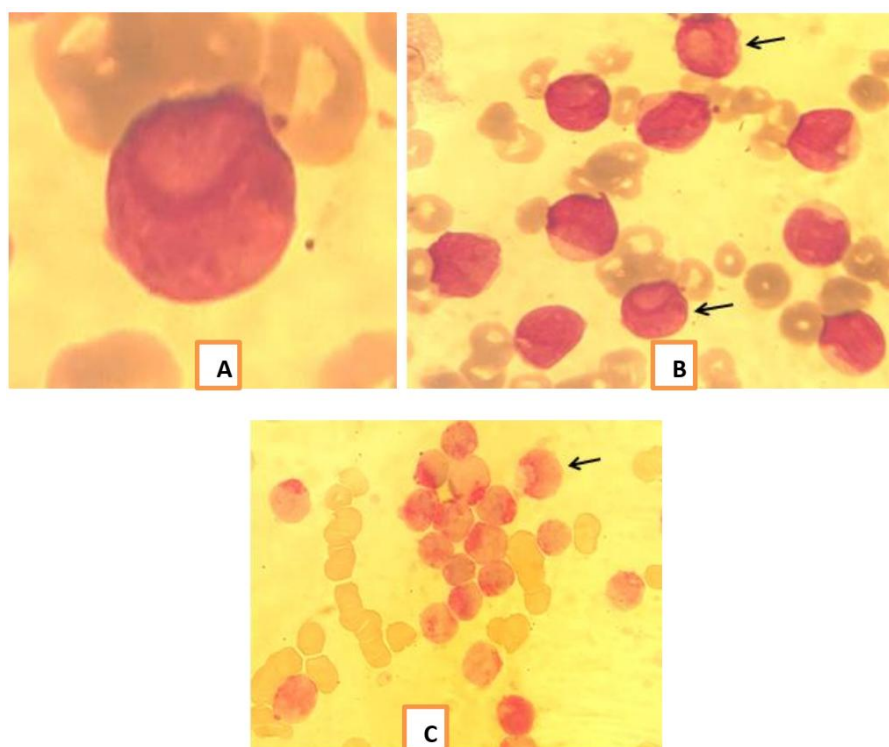
Recognizing this entity is important to avoid confusion with variant hypogranular acute promyelocytic leukemia and to guide molecular assays.

## OBSERVATION

A 64-year-old female patient, followed for type 2 diabetes treated with insulin and high blood pressure treated by antihypertensive drugs. Admitted for an incomplete spinal cord syndrome with an anemic syndrome made of asthenia and cutaneous mucosal pallor and a hemorrhagic syndrome made of ecchymotic spots the whole evolving in a context of deterioration of general state.

The blood count reveals a normochromic normocytic anemia at 7 g/dl, a major leukocytosis at 101 G/l and a deep thrombocytopenia at 10 G/l, the blood smear examined objective a 90% swelling of blasts of myeloid appearance with a nuclear invagination.

The bone marrow smear reveals a blastic overwhelming 96% with a nuclear invagination in more than 15% of blasts (Figure 1A &1B), staining with myeloperoxidase returned positive in more than 90% of blasts recalling the myeloid nature (Figure-1C).



**Fig-1: A. Photomicrograph of bone marrow aspiration specimen (May-Grunewald-Giemsa stain,  $\times 1000$ ) showing blasts with cup-like invagination. B. The cup-like nuclear phenotype was defined by the presence of nuclear Invaginations (arrows) of  $\geq 15\%$  of the nuclear diameter ( $\times 1,000$ , Wright stain). C. Myeloperoxidase activity (arrows) was observed in a distinctive granular pattern within the areas of nuclear invagination ( $\times 1,000$ , MPO stain)**

Immunophenotyping reveals a population blastic with CD45 +, CD34 -, HLA -, DR -, partial CD117, MPO +, CD13 - and CD33 +, this profile evoked an acute myeloid leukemia "cup-like".

Molecular assays revealed positive FLT3 and NPM1 mutations in our patient.

The patient received hydro-urea-based cyto-reducing treatment (50 mg / kg / day) without response, then 2 aracytine flashes of 100 mg / day (D1 and D2) with hyperhydration 3L / m<sup>2</sup> / 24h.

The patient presented on day 11 an infectious syndrome made of fever encrypted at 40 °C, she was put on dual antibiotic therapy (3rd generation cephalosporin + Amikacin). The patient died after 3 days with septic shock.

## DISCUSSION

The CL-AML is part of acute leukemia classified by the 2016 edition of the classification of hematological tumors of the world health association (WHO) that aims to integrate recent information concerning the clinic, prognosis, morphology, immunophenotyping and genetics [1].

The CL-AML, described for the first time in 1994 [2], is defined according to the authors by the presence of nuclear invagination in at least 5% [3], 7% [4] or more commonly accepted value of 10% blasts [5-

7]. In our case, they were detected in more than 15 % of the blasts.

The nuclear invagination is prominent and extends over at least 25% of the nuclear diameter [3, 5-7]. It is then designated by its cup-like appearance or fish mouth. The final stage of nuclear invagination can go as far as clear cleavage, giving a bilobed nuclear appearance [2-7], which can be the source of confusion with variant acute promyelocytic leukemia, with absence or weak expression of CD34 and HLADR as well as a particular morphological aspect of the blasts (prominent nuclear invagination). Thus in our case immunophenotyping was the element of orientation by absence of the expression of CD34 and HLA.

The formal diagnosis of APL requires identification of a specific genetic mutation of the PML-RARA transcript and is closely correlated with specific immunophenotypic and morphological features [8, 9].

Recently, cup-like were strongly associated with mutations of the nucleophosmin (NPM1), fms-like tyrosine kinase (FLT3)-internal tandem duplication (ITD), and tyrosine kinase domain (TKD) genes as well as with negativity for the MHC class II cell surface receptor HLA-DR [10-14].

These morphological and genetic associations can be used to screen for specific genetic mutations.

However, whether cup-like nuclei are associated with mutation of NPM1 alone or co-occurring mutations of both NPM1 and FLT3 is controversial [10, 11, 14].

In our study, the cytogenetic study has found a combination of the two mutations FLT3 and NPM1.

The bad prognosis related to this form and reported in the literature [14] corresponded to our case, in fact resistance to cytoreductive treatment even before receiving the results of immunophenotyping and cytogenetics was in favor of the diagnosis, which has leads to the search for FLT3 and NPM1 mutations.

## CONCLUSION

In view of our case report and data from the literature, we recall the interest of recognizing this entity, not only because of the possible cytological confusion with variant acute hypogranular promyelocytic leukemia, but also because of the diagnostic guidance it can provide.

## REFERENCES

- Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016 May 19;127(20):2391-405.
- Scott AA, Head DR, Kopecky KJ, Appelbaum FR, Theil KS, Grever MR, Chen IM, Whittaker MH, Griffith BB, Licht JD. HLA-DR-, CD33+, CD56+, CD16-myeloid/natural killer cell acute leukemia: a previously unrecognized form of acute leukemia potentially misdiagnosed as French-American-British acute myeloid leukemia-M3. *Blood*, 1994; 84:244-55.
- Kroschinsky FP, Schäkel U, Fischer R, Mohr B, Oelschlaegel U, Repp R, Schaich M, Soucek S, Baretton G, Ehninger G, Thiede C. Cup-like acute myeloid leukemia: new disease or artificial phenomenon?. *Haematologica*. 2008 Feb 1;93(2):283-6.
- Bennett JM, Pryer J, Laughlin TS, Rothberg PG, Burack WR. Is the Association of “Cup-like” nuclei with mutation of the NPM1 gene in acute myeloid leukemia clinically useful? *Am Journal Clin Pathol*, 2010; 134:648-52.
- Kussick SJ, Stirewalt DL, Yi HS, Sheets KM, Pogossova-Agadjanyan E, Braswell S, Norwood TH, Radich JP, Wood BL. A distinctive nuclear morphology in acute myeloid leukemia is strongly associated with loss of HLA-DR expression and FLT3 internal tandem duplication. *Leukemia*. 2004 Oct;18(10):1591-8.
- Chen W, Rassidakis GZ, Li J, Routbort M, Jones D, Kantarjian H, Medeiros LJ, Bueso-Ramos CE. High frequency of NPM1 gene mutations in acute myeloid leukemia with prominent nuclear invaginations (“cuplike” nuclei). *Blood*. 2006 Sep 1;108(5):1783-4.
- Chen W, Konoplev S, Medeiros LJ, Koeppen H, Leventaki V, Vadhan-Raj S, Jones D, Kantarjian HM, Falini B, Bueso-Ramos CE. Cuplike nuclei (prominent nuclear invaginations) in acute myeloid leukemia are highly associated with FLT3 internal tandem duplication and NPM1 mutation. *Cancer*. 2009 Dec 1;115(23):5481-9.
- Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Willman CL. Hypergranular promyelocytic leukemia: correlation between morphology and chromosomal translocations including t(15;17) and t(11;17). *Leukemia*, 2000;14(7):1197-1200.
- Orfao A, Chillon MC, Bortoluci AM, Lopez-Berges MC, Garcia-Sanz R, Gonzalez M, Tabernero MD, Garcia-Marcos MA, Rasillo AI, Hernandez-Rivas J, San Miguel JF. The flow cytometric pattern of CD34, CD15 and CD13 expression in acute myeloblastic leukemia is highly characteristic of the presence of PML-RARalpha gene rearrangements. *Haematologica*, 1999; 84(5):405-412
- Scott AA, Head DR, Kopecky KJ, Appelbaum FR, Theil KS, Grever MR, Chen IM, Whittaker MH, Griffith BB, Licht JD. HLA-DR-, CD33+, CD56+, CD16- myeloid/natural killer cell acute leukemia: a previously unrecognized form of acute leukemia potentially misdiagnosed as French-American-British acute myeloid leukemia-M3. *Blood*, 1994; 84(1):244-255
- Kroschinsky FP, Schakel U, Fischer R, Mohr B, Oelschlaegel U, Repp R, Schaich M, Soucek S, Baretton G, Ehninger G, Thiede C. Cup-like acute myeloid leukemia: new disease or artificial phenomenon? *Haematologica*, 2008; 93(2):283-286.
- Chen W, Konoplev S, Medeiros LJ, Koeppen H, Leventaki V, Vadhan-Raj S, Jones D, Kantarjian HM, Falini B, Bueso-Ramos CE. Cuplike nuclei (prominent nuclear invaginations) in acute myeloid leukemia are highly associated with FLT3 internal tandem duplication and NPM1 mutation. *Cancer*, 2009; 115(23):5481-5489.
- Bennett JM, Pryor J, Laughlin TS, Rothberg PG, Burack WR. Is the association of “cup-like” nuclei with mutation of the NPM1 gene in acute myeloid leukemia clinically useful? *Am Journal Clin Pathol*, 2010; 134(4):648-652.
- Chen W, Rassidakis GZ, Li J, Routbort M, Jones D, Kantarjian H, Medeiros LJ, Bueso-Ramos CE. High frequency of NPM1 gene mutations in acute myeloid leukemia with prominent nuclear invaginations (“cuplike” nuclei). *Blood*, 2006; 108(5):1783-1784.