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Original Research Article

Acute Myelomonocytic Leukemia Eosinophilic Variant: Epidemiological, Clinical, and Biological Profile at the Hassan II University Hospital of Fez

Jarnige Khadija[1,2*], Issaka Amidou Rabi[1,2], El yaacoubi Raounak[1,2], Tlamçani Imane[1,2], Amrani Hassani Monçef[1,2,3]
[1]Service d'hématologie, Laboratoire Central d'Analyse Médical, Centre Hospitalier Universitaire Hassan II, Fès, Maroc
[2]Faculté de Médecine, de Pharmacie et de médecine dentaire, Université Sidi Med Ben Abdellah, Fès, Maroc
[3]Chef de Service d'hématologie, Laboratoire Central d'Analyse Médical, Centre Hospitalier Universitaire Hassan II, Fès, Maroc

***Corresponding author:** Jarnige Khadija
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Abstract: ***Introduction*:** Acute myelomonocytic leukemia with an eosinophilic component (AML4Eo) is a particular and rare hematological entity, representing between 5% and 8% of all acute myeloid leukemias. The aim of our work is to highlight the clinical and cytogenetic epidemiological particularities of this pathology at the Hassan II University Hospital in FES. ***Patients and Methods*:** Retrospective descriptive study spread over 14 years (January 2009-January 2023) including all patients diagnosed with LAM4Eo.Myelogram reading as well as immunophenotyping by flow cytometry on Cytomic FC500 were performed at the central hematology laboratory and cytogenetics at the genetics laboratory CHU HASSAN II of FES. Clinical data were collected from patients' medical charts. ***Results*:** Thirteen patients were enrolled. The mean age at diagnosis was 20.4 years, with a predominance of males (54%) most patients presented with an altered general condition, signs of cytopenia and a tumor syndrome. All patients presented with profound anemia associated with thrombocytopenia and hyperleukocytosis. Blood smears showed the presence of peripheral blasts in 80% of cases. All medullograms met the morphological criteria established by the FAB (Franco-American-British) classification for the diagnosis of LAM4Eo.Cytochemical staining with myeloperoxidase was performed on all medullograms and was positive in all cases. Immunophenotyping was carried out in 56% of patients, showing the existence of very immature blasts expressing myeloblast and monoblast markers. Four of our patients underwent cytogenetic studies, with no translocation or inversion of chromosome 16. Three patients died immediately after diagnosis. The other patients were put on chemotherapy, two of whom died during treatment. ***Discussion/Conclusion*:** LAM4Eo is a rare hematological malignancy with a better prognosis than other myeloid leukemias. Despite the development of cytogenetics and molecular biology techniques, morphological examination of the blood smear and myelogram by the biologist remains central to the early diagnosis of AML4Eo.

Keywords: Acute Myelomonocytic Leukemia Eosinophilic Variant, Epidemiological profile, Biology, Cytogenetics.

INTRODUCTION

Among malignant hematologic disorders, acute myeloid leukemias (AML) represent a heterogeneous group of aggressive tumor pathologies characterized by the malignant proliferation of immature myeloid cells, known as blasts, that have lost their ability to differentiate. Several subtypes exist, including acute myelomonocytic leukemia with eosinophilic component (AML-M4Eo), which is a rare and specific hematological entity, accounting for 5 to 8% of all acute myeloid leukemias [1].

According to the 2016 WHO classification, it is part of AMLs with recurrent cytogenetic abnormalities because it is associated with a rearrangement of chromosome 16 [2, 3]. In addition to the myeloid blast proliferation and monocytic component, AML-M4Eo is characterized by the presence of abnormal medullary eosinophils, which are typically absent or very rare in peripheral blood. The particularity of this entity is that it represents a cytogenetic group that can occur at any age, can present with various clinical manifestations, and is associated with a good response to chemotherapy, with a remission rate of approximately 70% to 80% [4, 5].

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This study is undertaken with the aim of highlighting the epidemiological, clinical, and cytogenetic characteristics of this pathology within the Hassan II University Hospital of Fes.

PATIENTS AND METHODS

This is a retrospective descriptive study covering a period of 14 years, from January 2009 to January 2023, including all patients diagnosed with AML-M4Eo at the Hematology Unit of the Central Medical Analysis Laboratory of Hassan II University Hospital in Fes.

For the diagnosis of AML-M4Eo, a bone marrow biopsy and a blood smear were performed on all patients. Immunophenotyping by flow cytometry on a Cytomic FC500 was conducted to detect antigens expressed by myeloblasts (CD33, CD13, CD65) and those expressed by monoblasts (CD14, CD4, CD11c).

Finally, a cytogenetic examination was performed at the Genetics Laboratory to search for chromosomal abnormalities (inversion (16) (p13.1q22) or translocation (16;16) (p13.1q22)). For all patients, demographic data, clinical and hematological signs were studied, and a complete blood count along with a lysis panel were conducted.

Clinical data were collected from the patients' medical records using the Hosix database. Quantitative variables were expressed as means, while qualitative variables were expressed as percentages.

RESULTS

During our study period, thirteen (13) patients were included. The average age at diagnosis was 20.4 years, with an age range from 7 to 40 years. We observed 6 females (46%) and 7 males (54%), with a male-to-female ratio of 1.17.

Most patients presented with general deterioration, signs of cytopenia, and a tumor syndrome. All patients had severe anemia associated with thrombocytopenia and leukocytosis on the blood count. Peripheral blood smears showed the presence of blasts in 80% of cases.

All bone marrow biopsies met the morphological criteria established by the FAB (French-American-British) classification for the diagnosis of AML-M4Eo.

A myeloperoxidase (MPO) cytochemical stain was performed on all bone marrow biopsies and was positive in all cases.

Immunophenotyping was conducted for 56% of the patients, revealing the presence of very immature blasts expressing myeloblast markers CD33, CD13, CD65, CD117, and monoblast markers CD14, CD4, CD11c.

Cytogenetic studies were performed on 4 of our patients, all of whom showed no translocation or inversion of chromosome 16.

Three patients died following the diagnosis (23%). The remaining 10 patients were treated with chemotherapy, and 2 of them died during treatment (15.38%). The remaining 8 patients achieved complete remission (61.53%).

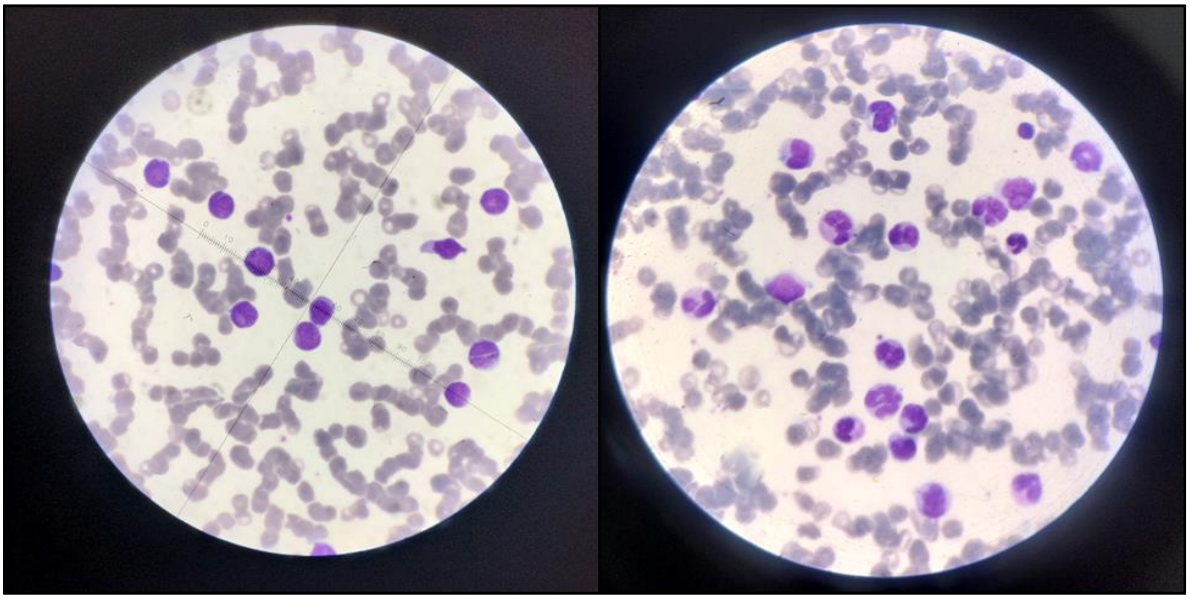

Figure 1 : Peripheral blood smear (May-Grünwald-Giemsa stain, ×100 objective) showing the presence of peripheral blasts of the monoblast type

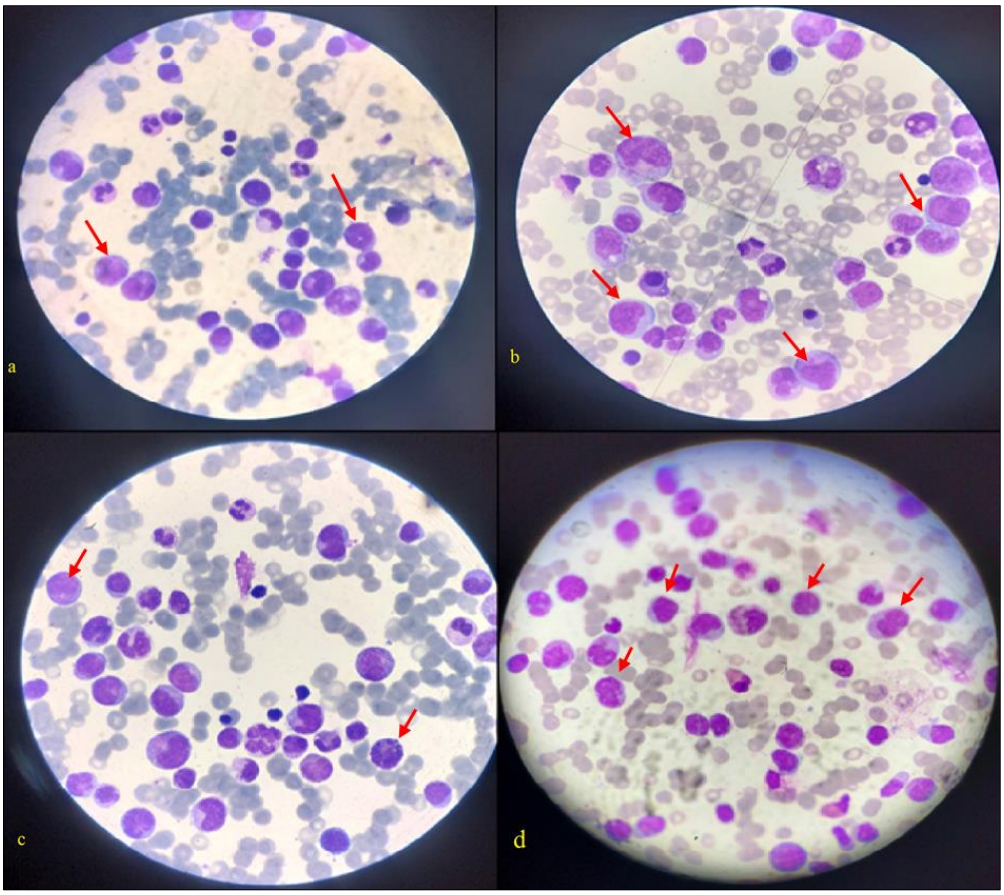

Figure 2 : Bone marrow smear (May-Grünwald-Giemsa stain, ×100 objective) showing bone marrow infiltration by myeloblasts, monoblasts, and dystrophic eosinophil precursors

a. Dystrophic blasts

b. Presence of undifferentiated blasts, monocytes, and dystrophic blasts with irregular nuclei

c. An undifferentiated blast; a dystrophic eosinophil precursor containing both normal eosinophilic granules and large basophilic granules

d. Presence of myeloblasts and monoblasts with irregular nuclei

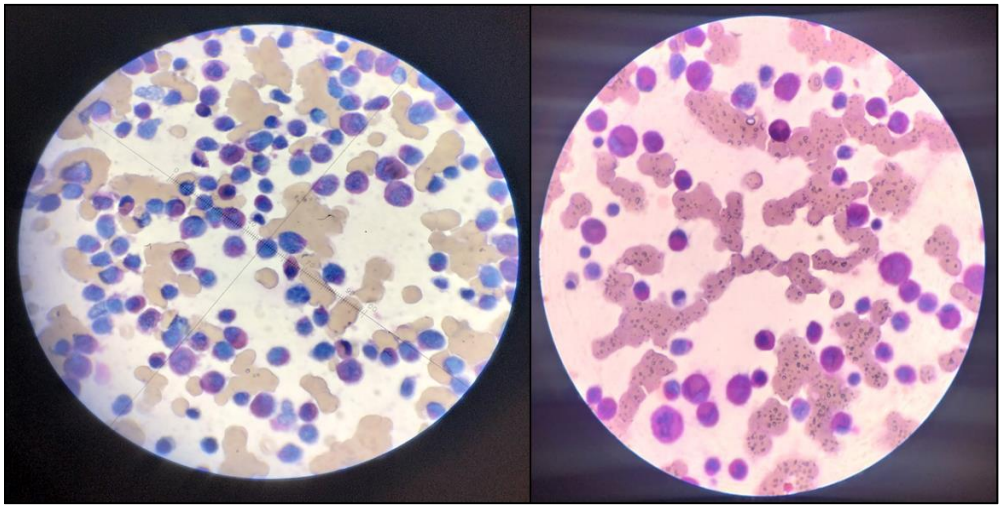

Figure 3 : Bone marrow smear (myeloperoxidase MPO stain, ×100) showing positive granulations indicative of the myeloid origin of the leukemia

DISCUSSION

Acute myeloid leukemia type M4Eo, characterized by a monocytic component associated with abnormal maturation of medullary eosinophils, represents about 20% of M4 cases and 5 to 8% of all acute myeloid leukemias [1].

During our 14-year study, we identified 13 patients with M4Eo, confirming the rarity of this condition. A male predominance was observed in our cohort, consistent with literature data [6]. This predominance may be explained by increased exposure to environmental factors associated with certain occupational activities, such as pesticide use [7].

According to the 2016 WHO classification, M4Eo is classified among acute myelomonocytic leukemias with recurrent cytogenetic abnormalities, particularly within the group of AMLs involving Core Binding Factor (CBF) genes [3]. This group includes AML2 with t (8;21) (q22;q22) and M4Eo with inv(16) or t(16;16) (p13;q22). These cytogenetic abnormalities result from the fusion of the CBF beta gene located at 16q22 and the Smooth Muscle Myosin Heavy Chain (MYH11) gene coding for the heavy chain of myosin. This fusion generates 11 different transcripts, with type A being the most common [8, 9]. These events have two main consequences: first, the sequestration of the protein encoded by the AML1 gene (also known as CBFA2 or RUNX1), which plays a role in regulating hematopoietic differentiation, preventing it from entering the cell nucleus; second, the repression of transcription of factors involved in hematopoiesis, primarily through the recruitment of histone deacetylases [10-12].

These histone deacetylases block transcription complexes from accessing the DNA, leading to a blockade of differentiation [13]. However, this inversion or translocation (type II mutation) alone is generally not sufficient to induce leukemia and requires additional mutations (type I). Approximately 70% of patients with AML with inv(16) also present one of the mutations affecting tyrosine kinase receptors, including RTK, c-KIT, and FLT3, as well as mutations in RAS genes, which promote the proliferation and survival of the mutated clone [13]. The inversion of chromosome 16 is an abnormality that can be difficult to detect by standard banding karyotyping, especially if the quality of the metaphase is poor [14].

This could be the case for our four patients in whom no abnormalities were observed. The detection of the CBF beta/MYH11 gene rearrangement can be performed using fluorescence in situ hybridization (FISH) techniques, regardless of the quality of the metaphases [15]. As for its fusion transcript, it can be identified by RT-PCR, providing not only diagnostic support but also monitoring of residual disease [16].

Nevertheless, according to the FAB classification, the morphological characteristic of this hematological condition pertains not to the leukemic cells themselves but rather to the eosinophils, which may exhibit prominent, dark, and atypical basophilic granules, as well as atypical nuclei with folding patterns and chromatin reminiscent of those seen in monocytes or promonocytes.

Flow cytometry analysis of bone marrow blasts is crucial for confirming the diagnosis of acute leukemia. It relies on low expression of the CD45 marker and/or the presence of immaturity markers such as CD34 and HLADR. The presence of myeloid markers like MPO, CD13, CD33, and CD117 confirms that the blast cells belong to the myeloid lineage [17]. This analysis is conducted using a multi-color flow cytometer after labeling the blasts with fluorescent monoclonal antibodies. It helps determine whether the blasts belong to the myeloid cell lineage and assesses their level of differentiation [17]. Specific markers for the granulocytic lineage include CD11b, CD15, and CD65, while markers for the monocytic lineage include CD4, CD11b, CD14, CD36, and CD64.

These results described in the literature are consistent with those found in our patients who underwent immunophenotyping.

The management of this hematologic malignancy primarily relies on chemotherapy, which occurs in two distinct phases. First, there is an intensive induction phase based on the 3 + 7 regimen, where three days of anthracycline are combined with seven days of AraC, aiming to achieve a complete morphological remission. This is followed by a consolidation phase, involving several cycles of high-dose AraC [18]. In our study, ten (10) patients were treated according to this protocol, and eight (61.5%) of them achieved complete remission. This is consistent with the data from the European LeukemiaNet (ELN 2022) prognostic classification, which categorizes LAM4eo as a disease with a favorable prognosis [17-19].

CONCLUSION

Although the literature review was not fruitful and did not allow us to find similar cases for comparison with our results, we can still conclude that LAM4Eo is a rare malignant hematologic condition with a better prognosis compared to other myeloid leukemias. Despite advances in cytogenetics and molecular biology, the morphological analysis of blood smears and bone marrow aspirates by the hematologist remains essential for early diagnosis of LAM4Eo.

Conflict of Interest Statement: The authors declare that they have no conflicts of interest.

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